



AGENDA OF THE PROTECTION AND POLICY COMMITTEE

**THURSDAY, NOVEMBER 19, 2020, 5:30 PM
CONTINUED MEETING**

The Protection & Policy Committee Meeting from October 8, 2020 was recessed at 9:37 p.m. The meeting will reconvene at 5:30 p.m. on November 19, 2020.

**This is a virtual meeting.
Please see the zoom instructions in the agenda.**

A. Zoom Meeting Information.

- I. This item contains instructions and information for the Zoom virtual meeting.

B. Roll Call.

C. Approval of the Agenda.

D. Regular Business.

- I. Consideration with possible action on a request by Ald. Galvin, filed on behalf of constituent Brenda Staudenmaier, that the City consider taking fluoride out of the treatment process for the City water.

E. Adjournment.

- 1) THIS MEETING IS RECORDED: THE VIDEO OF THIS MEETING AND MINUTES ARE AVAILABLE ONLINE AT www.greenbaywi.gov
- 2) ACCESSIBILITY: Any person wishing to attend who requires special accommodation because of a disability, should contact the City Safety Manager at 920-448-3125 at least 48 hours before the scheduled meeting time so that arrangements can be made.

- 3) **QUORUM:** Please take notice that a majority or quorum of the Common Council will attend this Protection and Policy committee meeting and will constitute a meeting of the Common Council for purposes of discussion and information gathering relative to this agenda.
- 4) **REPRESENTATION:** The party requesting the communication, or their representative, should be present at this meeting.
- 5) **FOR ALL LICENSING ISSUES,** the Committee may convene in closed session pursuant to §19.85 (1)(b) and/or §19.85 (1)(f) Wis. Stats., for the purpose of considering information with respect to licensing for a person, including financial, social, or personal information. The Committee will thereafter reconvene in open session pursuant to Section 19.85(2), Wis. Stats., to take action on items discussed in closed session, if appropriate, and to consider the remainder of the agenda.

Virtual Meeting Instructions



Special Meeting of Protection and Policy 2020-11-19

Zoom Meeting Information

Join Zoom Meeting

<https://us02web.zoom.us/j/87954784440>

Meeting ID: 879 5478 4440

Passcode: 112734

One tap mobile

+13017158592,,87954784440#,,,,,0#,,112734# US (Germantown)

+13126266799,,87954784440#,,,,,0#,,112734# US (Chicago)

Dial by your location

+1 301 715 8592 US (Germantown)

+1 312 626 6799 US (Chicago)

+1 929 205 6099 US (New York)

+1 253 215 8782 US (Tacoma)

+1 346 248 7799 US (Houston)

+1 669 900 6833 US (San Jose)

Meeting ID: 879 5478 4440

Passcode: 112734

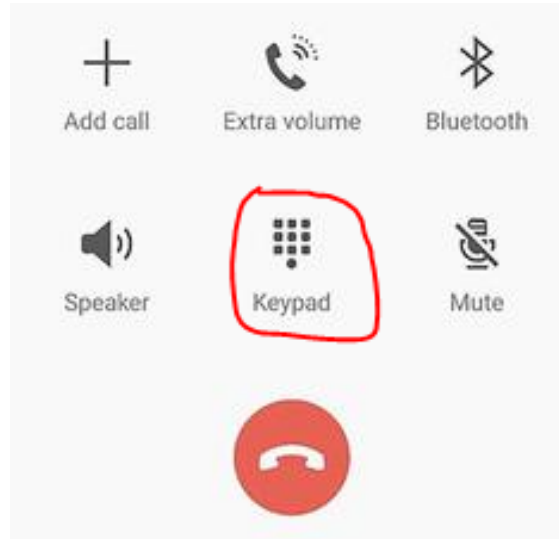
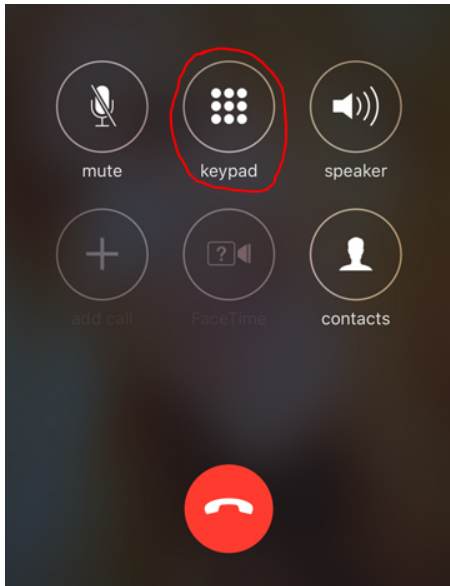
Find your local number: <https://us02web.zoom.us/j/87954784440>

Additional Information

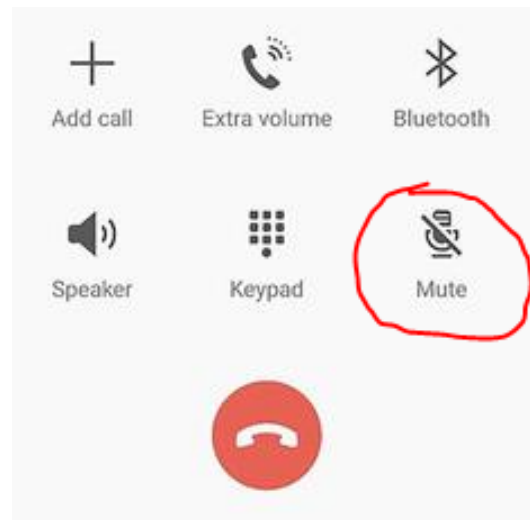
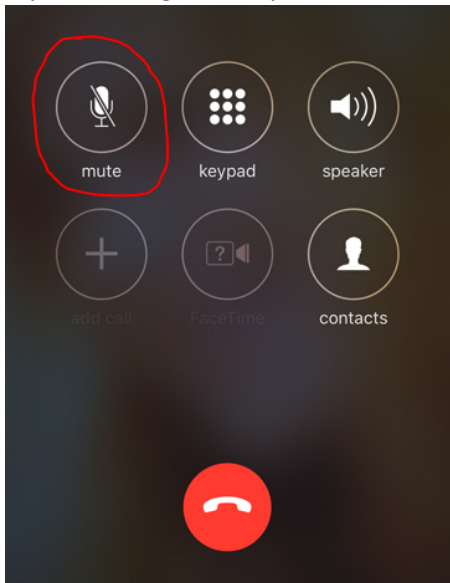
1. Wisconsin Open Meetings Law still applies
 - a. Persons interested in speaking to an item must give their name and address
 - b. Committee/Commission/Board members will still follow *Roberts Rules of Order*
2. All zoom meetings will have a password in the instructions. Please enter when prompted.
3. Please log into the Zoom meeting 10 minutes before the meeting starts to ensure proper technology is working.
 - a. If you are a Board Member, please log into [CivicClerk](#) with a computer, laptop, or tablet device.
4. Once you are in the meeting please mute yourselves.
 - a. You may unmute yourself when you are called upon to speak.
5. Waiting room
 - a. When you call in, all callers/participants will be placed in a “waiting room.”
 - b. Persons on the agenda will be admitted to the meeting, and then once the item is concluded, the host will permanently mute you from the meeting (you can still hear the meeting).
6. Using Zoom with a tablet or computer
 - a. Tablet—you will be asked to sign in. Download the app either with the Apple Store or the Play Store
 - b. Computer—you will be asked to sign in. You may download the app or click on the link to open Zoom in your browser.
7. Registering
 - a. The host may ask you to register for the meeting. A registration link will be sent to you along with the invite. You’ll receive another email confirming that you’re registered for the meeting.
 - b. If you’re using a phone, your registration will still be tied to an email.
8. Raising your hand
 - a. Committee members—you can either use CivicClerk and request to speak or you can “raise your hand” in the zoom meeting (you’d need to use a computer or tablet) to let the host know you’d like to speak. You can also un-mute yourselves and start speaking.
 - b. Persons on the agenda—you can “raise your hand” but you’d need to use a computer. You will be allowed to speak, per Wisconsin Open Meetings Rules, once the committee has “opened the floor for interested parties to speak.” Once the committee is finished with your agenda item, the host will mute you permanently, unless the committee opens the floor again.
9. What devices should I use?
 - a. Smart phone (please see more detailed instructions on page 3)
 - b. Land line
 - c. Tablet—well in advance of the meeting, please download the Zoom Meeting app before you join a meeting by using either the Apple Store or the Play Store. You will be asked to input your name, thus identifying you for the meeting. You’ll also be asked to verify your email.
 - d. Computer—well in advance of the meeting, please download the Zoom Meeting app, but you can also click on a link to open the Zoom Meeting in your browser. You will be asked to input your name, thus identifying you for the meeting.
 - e. For tablet and computer users—if you download the app you will be asked to verify your email.
10. Zoom etiquette
 - a. Muting yourselves when you’re not talking will prevent your background noise from interfering with others’ ability to listen to and participate in the meeting.
 - b. If you’re using a telephone, please identify yourself with your phone number and name before you speak. Zoom meeting hosts can see only your telephone number and will ask you to identify yourselves.
11. Closed session
 - a. Persons in the Zoom meeting will be put into a waiting room while the committee meets in Closed Session. Participants will be admitted back into the Zoom meeting once the committee reconvenes in Open Session.
 - b. Persons watching live on YouTube will see a gray screen with the City logo during closed session.
12. Persons interested in attending anonymously or listening to the meeting may call in by dialing *67 followed by the phone number above.

Calling into the Zoom meeting using a smartphone

1. Dial the phone number listed at the beginning of this document.
2. When prompted, enter the Meeting ID number followed by #
 - a. If you're using a smartphone, you can access the keypad by clicking "Keypad" on your screen



3. Once you are in the meeting, notify the meeting host that you are in and state your name.
4. If you do not need to talk, please make sure your phone is on **Mute**
 - a. If you're using a smartphone, look at your screen and click the Mute button



- b. If you're using a computer, you should see a Mute button in the Zoom application





Report to the
Protection and Policy Committee
of the City of Green Bay

MEETING DATE

November 19, 2020

PREPARED BY

AGENDA ITEM # D.I

Consideration with possible action on a request by Ald. Galvin, filed on behalf of constituent Brenda Staudenmaier, that the City consider taking fluoride out of the treatment process for the City water.

BACKGROUND

RECOMMENDATION

FISCAL IMPACT

ATTACHMENTS

1. NANCY QUIRK AGD CWF Support Letter_GB
2. Village of Ashwaubenon GB Fluoride Statement
3. Town of Scott Resolution August 2, 2020
4. Village of Hobart GB Fluoride Statement
5. Village of Wrightstown GB Floridation Statement
6. Fluoride Statement from Dr. Kevin DeGroot final
7. Fluoride Statement from Dr. Brad DeGroot final
8. WI Dental Association
9. BROWN COUNTY HEALTH STATEMENT
10. Brenda Staudenmaier
11. Brenda Staudenmaier World-Wide Movement FINAL one-pager pdf 5-30-19 (1)
12. NTP 2020_Revised Monograph
13. BILL OSMUNSON
14. DANIEL STOCKIN
15. deanmurphy
16. KARENFAVAZZASPENCER_67LANGSFORD ST GLOUCESTERMA
17. PAUL CONNETT
18. AAP CWF Letter Green Bay 10.05.20_Hollis Russinof
19. DRJOHNFBEAL
20. AMANDA JUST
21. Community Water Fluoridation - Reasons why I support it-DIONE SNITKER
22. HOLLIS RUSSINOF AAP CWF Letter Green Bay 10.05.20
23. ROBERT DICKSON-Calgary graph of cavity rates
24. For Agenda_ The Importance of Community Water Fluoridation_JULIE BOECKMAN

25. KURT FERRE 2020 10 08 Green Bay PDF
26. JOHN DANE JD Green Bay Letter
27. NINIA LINERO AGD CWF Support Letter_GB
28. DIONE SNITKER Community Water Fluoridation - Reasons why I support it
29. johnsoncommunication_partI
30. johnsoncommunicationpart2
31. JOHNSONE-MAILPART3
32. DRJOHNNY JOHNSON CWF Presentation for Agenda only
33. DR. JOHNNY JOHNSON CWF Presentation for Agenda-final
34. 07.13.2020FluoridePacketMaterials

October 6, 2020

Members of the Green Bay Protection and Policy Committee:

On behalf of the Academy of General Dentistry (AGD) and its over 40,000 members, including more than 600 that make up the Wisconsin AGD (WIAGD), I am writing to express our strong support of community water fluoridation (CWF).

The AGD was founded in 1952 and has grown to be the second largest dental association, proudly working to address the most pressing issues that face general dentistry. General dentists are the primary oral health care providers for patients of all ages, and take responsibility for the diagnosis, treatment, and coordination of services to meet patients' oral health needs. Approximately 82% of Wisconsin's licensed dentists are general dentists.

We work diligently to advocate for effective policies that will most benefit the oral health care of patients and the public. Among our top priorities is increasing access to oral health care in every community, which cannot be solved by any one silver bullet, but is a multipronged approach. Many barriers to oral health care are complex and timely in terms of identifying effective and equitable solutions. However, CWF is one of the single most effective ways proven to prevent dental caries (cavities) and accessible to every single community member regardless of other barriers to care they may face.

Through 75 years of practice and decades of research, CWF is proven to be effective and safe in reducing dental caries in both children and adults. The evidence surrounding CWF is why the Center for Disease Control and Prevention (CDC) named it one of [ten great public health achievements of the 20th century](#). Nearly all credible health organizations recognize CWF's efficacy alongside the CDC, despite the many attempts by opponents to discredit and denounce it.

Several studies have demonstrated how the removal of fluoridation from public water supplies can negatively impact members of that community. [BMC Oral Health published a peer-reviewed research article](#) that compared average caries-related procedures and treatment costs in Juneau, Alaska, before and after discontinuing their CWF. Results showed the study population in 2003, during optimal CWF, was 25.2% less likely to receive dental caries procedures than in 2012, almost six years post-CWF cessation. The difference between children seven years and younger was significantly greater than that of the entire study population.

It is most important to note that results were based off Medicaid dental claim records from Medicaid-eligible residents of Juneau. This data represents children and adolescents whose family's income is no more than 150-200% of the Federal Poverty Level: one of the most vulnerable populations in today's society. This does not even touch on adults, who States are not required to provide any oral health benefit to under their Medicaid program. This does not touch on how COVID-19 and the current state of

our nation has created additional barriers. Finally, this does not touch on the wide range of residents who may have been benefitting from CWF but simply didn't fall into this study's population.

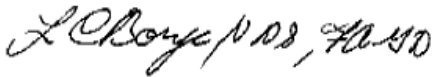
With optimal levels of water fluoridation, all members of the Green Bay community, and the four communities who purchase their water from Green Bay, have the opportunity to protect their teeth regardless of age, race, income or barriers to oral health care. We respectfully urge the Committee and City of Green Bay to continue fluoridating its public water system. We ask that you stand with us in protecting the oral health of your community.

Thank you for allowing the AGD to express our support of CWF and we appreciate your consideration in advance. If you have any questions, please contact our Government Relations staff at ninia.linero@agd.org.

Regards,



Connie White, DDS, FAGD
President
Academy of General Dentistry



Lou Boryc, DDS, FAGD
President
Wisconsin Academy of General Dentistry

DEPARTMENT OF PUBLIC WORKS
Douglas J. Martin
Director of Public Works
dmartin@ashwaubenon.com



August 19, 2020

**Green Bay Water Utility
Attn: Nancy Quirk, P.E.
PO Box 1210
Green Bay, WI 54305**

Re: Potable Drinking Water -- Fluoride Addition

Dear Nancy:

Thank you for the opportunity to discuss the topic of fluoride addition in potable drinking water. From time to time, questions come forth as to the viability of adding fluoride to public drinking water and its effectiveness in providing a measurable impact on the teeth of those drinking the water. When questions of this nature come forth, we show them the respect they are due by turning to the experts in the professions who see the end results on a daily basis. In this case, our dental professionals are the front-line viewers of what the addition of fluoride to public drinking water has on the teeth of those who drink water with versus without the addition. From our local dentists to the American Dental Association, the results, and recommendations they consistently urge is to maintain a beneficial level of fluoride in drinking so as to aid in the development and protection of teeth. The Green Bay Water Utility has followed CDC and WDNR guidelines for decades in the addition of fluoride to its drinking water to the benefit of many generations of families. In following the recommendations and results from the experts in the dental professions, as well as the national associations within that field, we continue to support the fluoride addition to potable drinking water.

Thank you very much for your time.

Sincerely,

**Douglas J. Martin, P.E.
Director of Public Works**

**SCOTT MUNICIPALITY UTILITY - BROWN COUNTY WISCONSIN
RESOLUTION 2020-08-01
SAFE DRINKING WATER**

WHEREAS, Scott Municipal Utility's (SMU's) number one objective is to provide customers with safe drinking water, and

WHEREAS, SMU strives to follow all federal, Wisconsin, and local regulatory guidelines and recommendations relative to the addition of and maintenance of recommended chemicals, including fluoride, and

WHEREAS, SMU, at the same time, recognizes the concerns of customers relative to save levels of said chemicals in their drinking water, and

WHEREAS, SMU will continue to depend on the medical experts, scientific community, and regulatory agencies to establish the safe level for each chemical found in or added to the drinking water provided to our customers, and

WHEREAS, SMU is a wholesale customer of the Green Bay Water Utility.

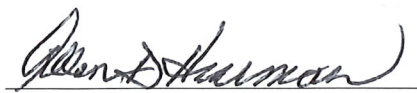
NOW THEREFORE BE IT RESOLVED the SMU strongly encourages the Green Bay Water Utility to follow all federal, Wisconsin, and local regulatory guidelines and recommendations relative to the addition of and maintenance of recommended chemicals, including fluoride, and

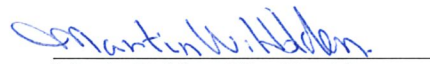
FURTHER, SMU strongly encourages Green Bay Water Utility to depend on the medical experts, scientific community, and regulatory agencies to establish the safe level for each chemical found in or added to the drinking water provided to their wholesale and retail customers.

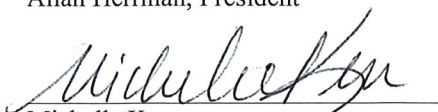
Adopted this 3rd day of August, 2020.

I hereby certify that the foregoing resolution was duly adopted by the Scott Municipal Utility Commission at a legal meeting on the 3rd day of August, 2020.

ADOPTED THIS 3rd DAY OF AUGUST, 2020

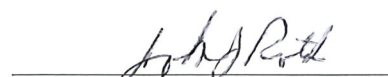

Allan Herrman, President


Martin Holden, Vice-President


Michelle Kerr


Mark Verbeten


Scott May


ATTEST: John Roth, Clerk/Treasurer



2990 S. Pine Tree Rd.
Hobart, WI 54155
Phone (920) 869-3807
Fax (920) 869-3808

Jerry Lancelle
Public Works Director
Email Jerry@Hobart-WI.org

RE: Green Bay Water Utility Fluoride Levels

August 11, 2020

The Village of Hobart, purchasing water from Green Bay Water Utility for about a decade, has been very satisfied with the quality of the water and levels of Fluoride in that water.

It has been our experience that Green Bay Water Utility, being a member of the AWWA, keeps current with the applicable research and recommendations for optimal Fluoride levels in the drinking water. The recommendations of AWWA in turn follow the science and research conducted by the CDC, AMA, and WHO among others, for beneficial and safe levels of Fluoride in our drinking water.

The proven benefits from Fluoride to aid in strengthening teeth and preventing tooth decay has been well documented worldwide as nearly all developed countries practice fluoridation. The 25% reduction in tooth decay estimated from the use of low levels of fluoride is a safe and cost effective means of aiding our residents in maintaining a healthy lifestyle while potentially saving money in health care costs.

The Village of Hobart does not wish to see a deviation in levels of Fluoride in our water supply from the Green Bay Water Utility. I believe changes from the AWWA recommended levels they have followed in the past will decrease the value of the water supplied to our residents.

Respectfully,

Jerry Lancelle
Public Works Director
Village of Hobart
920-655-3719

8/14//2020

Dear Green Bay Common Council,

On behalf of the Village of Wrightstown, I write to express our overwhelming support for community water fluoridation. The Green Bay Water Utility supplies us with treated water that contains fluoride at the appropriate level to promote dental health for our customers, and we would like to be able to continue this offering as a wholesale customer of the Green Bay Water Utility.

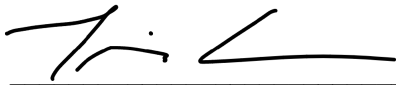
The science behind fluoridation of water and decades of success, with agreement from every major health organization from the Centers for Disease Control and Prevention (CDC) to the American Dental Association (ADA), concluded that fluoridated water protects teeth without posing risks to health. While fluoride is naturally occurring in almost all water supplies, we appreciate that Green Bay Water Utility has adjusted the level by adding fluoride to achieve the right amount to reduce tooth decay.

Before the common practice of fluoridation, health organizations believe lack of fluoride is one of the major reasons that many people needed dentures, which were quite common before widespread fluoridation. Science and studies prove that dental costs are lower and oral health problems have declined in fluoridated communities, having an important impact on our overall health and lowered many families' dental budgets.

Many times misleading information associates fluoride with fertilizer and industrial waste. The reality is that fluoride is extracted from phosphate rock, and so is phosphoric acid, an ingredient in name brand soft drinks such as Pepsi and Coca Cola. Neither one of them comes from fertilizer. It is important to base decision-making on true and corresponding health related information and the science behind water treatment.

Dental disease is the most common childhood disease and is associated with diabetes, adverse pregnancy outcomes, heart disease and lost school and work hours.

Science and health stats show fluoridated water decreases tooth decay by nearly 25 percent in children as well as in adults. The science behind this treatment has also proven to save communities money, by reducing costs and lost work hours spent on repairing tooth decay. For most communities, every \$1 invested in water fluoridation saves \$38 in unnecessary dental treatment costs. Green Bay Water Utility has been wise to use this proven intervention and we urge its continuation to benefit all of the people who drink Green Bay water.



Travis Coenen, Village Administrator

8/14/2020

Date

Dr. Kevin DeGroot
Madison No Fear Dentistry
344 S. Yellowstone Dr.
Madison, Wisconsin 53705

July 20th, 2020

To Whom it May Concern:

When my aunt asked me to write a statement regarding my perspective on community water fluoridation, I got excited. Not because writing a public health statement is what I want to do with my one hour of free time each night after I get my two kids to bed. Rather, I got excited to offer a very human perspective on the subject. I want to offer two distinct perspectives: a dentist and a father of two young children.

The first perspective I want to present is my professional take on the subject matter. I am a general dentist who sees many children in my practice in Madison, Wisconsin. What I know to be true is that dental decay in our pediatric population is an epidemic. According to peer-reviewed published articles, over 60% of our children in the United States experience dental decay by age five. By age 17, the percentage increases to 78 percent. The reality of this situation is that 60% of our under-five population is receiving multiple fillings/crowns/extractions. Of these patients, some handle it well in an out-patient setting while others are treated in the hospital under general anesthesia. This is the reality of the disease. I spend approximately 15% of my time doing fillings, extractions and crowns on these under-five patients. This is just the pediatric population. The adult population numbers get even worse.

Fluoride is not a cure-all for this problem. However, it has been demonstrated that community water fluoridation can reduce the rate of decay from 15-50% depending on the specific source you are citing. This means that we need to perform 15-50% less dental surgery on our under-five population. This may seem insignificant, but I would challenge you to face the reality that our system cannot handle a 15-50% increase in treatment for this population. We also cannot handle a 25-35% increase in necessary treatment for adult dental disease. The bottom line is that community water fluoridation is the most cost-effective way to manage dental decay. It is not the only way, but it is the most cost-effective way to combat this epidemic. It reaches everyone in Green Bay by simply turning on the faucet.

The second perspective I want to offer is that of a father. I have two children. One is age two and the other is two months old. My children eat organic, healthy foods (at least the two year-old). They also drink tap water that is fluoridated at the appropriate level of 0.7ppm. I choose to give them this water because I have yet to find a legitimate scientific study that demonstrates any negative health effects of fluoride levels of 0.7 ppm in our drinking water. The overwhelming preponderance of epidemiological studies that we have demonstrates no elevated levels of any systemic diseases linked to community water fluoridation at the level of 0.7ppm. Over 75 years of fluoridation in the U.S. and over 6,000

studies and research papers published have shown that fluoridation is effective at reducing decay for everyone and causes no adverse health effects in anyone. If that ever changes, I will be the first to change my tune. Until then, my children will benefit from the decay prevention provided by this public health measure. The alternative to this simple, preventive measure is too real for me. Earlier today, I struggled to treat two cavities on a 5-year-old girl. Ultimately, she would not allow me to treat the two cavities and we referred her to a pediatric specialist. I fear the she will not cooperate with them and require a trip to the hospital under general anesthesia to treat these cavities. This is, unfortunately, a weekly occurrence at our office. I am not in favor of ceasing fluoridation of our water and making these experiences a daily occurrence.

Prevention of disease is always the best practice. Treating a preventable disease is not going to rid us of this any disease. COVID-19 is a prime example that we are all facing right now. If we had a vaccination immediately available for COVID-19, the world would be immeasurably better. Water fluoridation is the closest thing that we have to a vaccination for dental cavities.

For the good of all of your families, please keep water fluoridation in place.



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Re: Community water fluoridation

To whom it may concern,

Community water fluoridation is one of the most cost-effective and safe ways to improve oral health throughout a population. It has been in use since 1945 and has an incredibly long track record of success in reducing the caries rate of a population. Additionally, controlled water fluoridation has not been associated with any systemic health issues outside of fluorosis in a few uncontrolled cases. Finally, there have been a number of systematic reviews evaluating the cost-effectiveness of community fluoridation and they have all come to the same conclusion: it saves money.

There is unequivocal evidence supporting the efficacy, safety, and cost-efficiency of community water fluoridation. There is no substantiated evidence to the contrary. While I do not envy the political role of sorting through all of the misinformation provided by a vocal minority, I do feel that this debate was scientifically settled years ago.

I have included citations for you if you would like to review some of the evidence. Please let me know if you would like any additional information.

Sincerely,

Bradley S. DeGroot, DDS, MS
Diplomate, American Board of Periodontology

Ran T et al. Economic Evaluation of Community Water Fluoridation: A Community Guide Systematic Review. Am J Prev Med. 2016 Jun;50(6):790-796.

O'Connell JM, Rockwell J, Ouellet J, Tomar SL, Maas W. Costs and Savings Associated with Community Water Fluoridation in the United States. Health Affairs. 2016. 1;35(12):2224-2232.

Public Health Service. Review of fluoride: benefits and risks. Report of the Ad Hoc Subcommittee on Fluoride of the Committee to Coordinate Environmental Health and Related Programs. Washington, DC: US Department of Health and Human Services; 1991.

McDonagh MS, Whiting PF, Bradley M, et al. A Systematic Review of Public Water Fluoridation. University of York, York: NHS Centre for Reviews and Dissemination; 2000.

Community Preventive Services Task Force. Guide to Community Preventive Services: Preventing Dental Caries: Community Water Fluoridation website. <https://www.thecommunityguide.org/oral/fluoridation.html>

Executive Office
6737 W. Washington Street
Suite 2360
West Allis, Wisconsin 53214
414.276.4520
414.276.8431 FAX



Legislative Office
122 W. Washington Avenue
Suite 600
Madison, Wisconsin 53703
608.250.3442
608.282.7716 FAX

September 28, 2020

Re: Advocacy for Community Water Fluoridation

Dear Protection & Policy Committee and Green Bay City Council:

As your office considers Green Bay's budget, the Wisconsin Dental Association urges you to maintain support for community water fluoridation, which is one of the most equitable and impactful public health programs available today.

The COVID-19 pandemic has led communities across the country to appreciate the value of having a strong public health infrastructure. Dental offices have implemented new workflows and processes to keep patients, staff and themselves safe and healthy. All these measures have been in the name of health, but also come with unexpected costs to our public health budgets. The Wisconsin Dental Association understands that public health budgets have been under additional scrutiny since COVID-19 has impacted allocations of public health dollars. As these budgets are given a closer look, one of the most equitable and impactful public health programs is at risk in countless communities: community water fluoridation.

This is an issue that will directly impact the oral health in Green Bay. Community water fluoridation's power to prevent dental caries (the disease that causes cavities) is well worth the state's continued investment in public health. Because of the increased hesitancy by many Wisconsinites concerned about COVID-19 to access medical and dental providers, community water fluoridation may be one of the only preventive oral health measures they have access to in these uncertain times.

The economic benefits of community water fluoridation are also clear. The average cost per year for U.S. communities to fluoridate the water ranges from 50 cents per person for large communities to \$3.00 per person for small communities. The latest studies continue to demonstrate water fluoridation is effective in reducing dental decay by at least 25% in children and adults, including older adults. This remains true even when fluoride is widely available from other sources, such as fluoride toothpaste. Community water fluoridation is foundational in maintaining Wisconsin's oral health. According to the Centers for Disease Control and Prevention, (<https://www.cdc.gov/oralhealth/fast-facts/community-water-fluoridation/index.html>) communities of 1,000 or more see an average estimated return on investment of \$20 for every \$1 spent on water fluoridation. In addition, Communities served by fluoridated water save an average of \$32 per person a year by avoiding treatment for cavities.

Advocate...Educate...Empower...Serve

For more information on this issue, please reference tools at ada.org/fluoride and the 2018 "Fluoridation Facts" book (<https://www.ada.org/en/public-programs/advocating-for-the-public/fluoride-and-fluoridation/fluoridation-facts>).

We recognize that you will be considering many budget obligations in the near future. Community water fluoridation is the best low-cost, high-impact way for you to maintain optimal oral health in our communities. We urge you to fully fund community water fluoridation in any upcoming budget considerations.

Regards,

A handwritten signature in blue ink, appearing to read "Mark Paget", with a stylized, flowing script.

Mark S. Paget
Executive Director

BROWN COUNTY HEALTH & HUMAN SERVICES DEPARTMENT
Public Health Division

111 N JEFFERSON ST
P. O. BOX 23600
GREEN BAY, WI 54305-3600



Anna Destree, MS, Public Health Officer

PHONE: (920) 448-6400 FAX: (920) 448-6449 / 448-6479 WEB: www.browncountywi.gov FACEBOOK: @BrownCountyPublicHealth

September 18, 2020

Green Bay Protection and Welfare Committee,

We, the appointed Board of Health, wish to submit this letter in support of continued fluoridation of our local water. We understand that this topic has again been brought forward for consideration.

At our August 11, 2020 meeting, two constituents spoke against fluoridation and were supported by two individuals calling from other states identifying as experts. Water fluoridation was supported and evidence was cited by Dr. Russell Dunkel, State Dental Director as well as an outside caller, Dr. Johnny Johnson. Nancy Quirk, Green Bay Water Utility General Manager, with expertise in water safety gave reassurance of the support and evidence of benefit to fluoridation. We are grateful for the interested participation of our community on this and all topics and are committed to examining credible new data and research as it becomes available.

According to the Center for Disease Control website (CDC.gov), community water fluoridation is recommended by nearly all public health, medical, and dental organizations. It is recommended by the American Dental Association, American Academy of Pediatrics, US Public Health Service, and World Health Organization. The CDC goes on to say that because of its contribution to the large decline in cavities in the United States since the 1960s, CDC named community water fluoridation one of 10 great public health achievements of the 20th century.

With this firm endorsement of water fluoridation by these prominent and recognized experts, we are confident that water fluoridation is the right public health provision for our community. We are taking this opportunity to reaffirm our support, as the Board of Health, for continued fluoridation of water.

Please feel free to reach out to us for any reason.

Respectfully submitted,

Respectfully,

A handwritten signature in black ink, appearing to read "Richard Schadewald".

Richard Schadewald, Chair
Brown County Board of Health

A handwritten signature in black ink, appearing to read "Karen Sanchez".

Karen Sanchez, Vice Chair
Brown County Board of Health



Public Health
Prevent. Promote. Protect.

Brown County
Health & Human Services

Ingestion of infant formula constituted from fluoridated water associated with IQ deficit

Till C, Green R, Flora D, Hornung R, Martinez-Mier EA, Blazer M, et al. Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. *Environ Int* 2020;134:105315.

Question Among otherwise normal preschool children, what is the association between fluoridated water used to constitute formula as infants/toddlers and IQ?

Design Multicenter, prospective study drawn from participants in the Maternal-Infant Research on Environmental Chemicals (MIREC) program.

Setting 6 cities across Canada.

Participants 398 mother-child dyads, the children of which were 3-4 years old.

Intervention Wechsler Primary and Preschool Scale of Intelligence-III.

Outcomes IQ score.

Main Results 38% of the dyads lived in cities with fluoridated water. An increase of 0.5 mg/L in water fluoride concentration corresponded to a 9.3- and 6.2-point decrement in Performance IQ among both formula-fed (95% CI: -13.77 to -4.76) and breast-fed children (95% CI: -10.45 to -1.94), respectively.

Conclusions Ingestion of formula constituted from fluoridated water is associated with Performance IQ deficits.

Commentary This study by Till et al used data from the MIREC Study to demonstrate that fluoride intake from infant formula constituted from tap water is associated with lower performance IQ at age 3-4 years. Despite some limitations, eg, the use of estimated vs directly measured exposures to fluoride, the possibility of bias or confounding appears low. The results are consistent with increasing evidence suggesting that early life exposure to fluoride (prenatal and infancy) is associated with adverse neurobehavioral impacts. Evidence includes experimental studies in rodents as well as 3 recent longitudinal birth cohort studies (1 involving MIREC and 2 involving ourselves and colleagues) demonstrating significant associations between individual measures of prenatal fluoride exposure and lower performance on offspring measures of intelligence and behavior.¹⁻³ Overall, these studies inform the ongoing debate over the benefits vs risks associated with the fluoridation of water. Clearly, more research is needed. Meanwhile, since the beneficial effects of fluoride predominantly occur at the tooth surface after teeth have erupted, whereas fluoride is not essential for growth and development, a cautious step could be avoidance of fluoridated products and water by women during pregnancy and by infants during the first 6 months of life.

Morteza Bashash, PhD, MS
University of Toronto
Toronto, Ontario, Canada

Howard Hu, MD, MPH, ScD
University of Washington
Seattle, Washington

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Mandatory vaccine policies associated with increased vaccination rates and decreased measles incidence

Vaz OM, Ellingson MK, Weiss P, Jenness SM, Bardají A, Bednarczyk RA, et al. Mandatory Vaccination in Europe. *Pediatrics* 2020;145: pii e20190620.

Question Among children living in Europe, what is the association between mandatory vaccination and vaccine-preventable disease reduction?

Design Data analysis from the data banks of the European Centre for Disease Prevention and Control and the World Health Organization.

Setting 29 European countries.

Participants Children vaccinated.

Intervention Vaccination rates from 2006 to 2015 for measles, 2006 to 2016 for pertussis, and mandatory vaccination policies.

Outcomes Measles and pertussis vaccine coverage and the annual incidence of these diseases.

Main Results Mandatory vaccine policies were associated with higher vaccination prevalence, 3.71% (95% CI, 1.68 - 5.74) and 2.14% (95% CI, 0.13 to 4.15) for measles and pertussis, respectively. Some countries imposed a monetary penalty for non-compliance. Every €500 increase in the maximum penalty demonstrated an increase of 0.8% and 1.1% for measles pertussis vaccination prevalence, respectively ($P < .0001$ for both). Only countries without non-medical exemptions demonstrated an association with a lower measles rate compared with countries without a mandatory vaccine policy, adjusted incidence rate ratio, 0.14 (95% CI, 0.05 to 0.36). Pertussis rates were not statistically different.

Conclusions Mandatory vaccination policies were associated with higher vaccination rates and a decreased measles incidence.

A new perspective on metals and other contaminants in fluoridation chemicals*

Phyllis J. Mullenix

Andover, MA, USA

Background: Fluoride additives contain metal contaminants that must be diluted to meet drinking water regulations. However, each raw additive batch supplied to water facilities does not come labeled with concentrations per contaminant. This omission distorts exposure profiles and the risks associated with accidents and routine use.

Objectives: This study provides an independent determination of the metal content of raw fluoride products.

Methods: Metal concentrations were analyzed in three hydrofluorosilicic acid (HFS) and four sodium fluoride (NaF) samples using inductively coupled plasma-atomic emission spectrometry. Arsenic levels were confirmed using graphite furnace atomic absorption analysis.

Results: Results show that metal content varies with batch, and all HFS samples contained arsenic (4.9–56.0 ppm) or arsenic in addition to lead (10.3 ppm). Two NaF samples contained barium (13.3–18.0 ppm) instead. All HFS (212–415 ppm) and NaF (3312–3630 ppm) additives contained a surprising amount of aluminum.

Conclusions: Such contaminant content creates a regulatory blind spot that jeopardizes any safe use of fluoride additives.

Keywords: Fluoride additives, Metal contaminants, Drinking water regulations

Background

Prior studies have linked human ingestion of heavy metals to agricultural applications of municipal wastes and commercial fertilizers.^{1–3} However, fluoride additives used in the water fluoridation process are another potential source for metal ingestion by humans and have not yet been adequately investigated. The production of fluoride additive involves phosphate rock, which contains cadmium (Cd), arsenic (As), lead (Pb), chromium (Cr), mercury (Hg), nickel (Ni), vanadium (V), uranium (U), and other radionuclides and metals at levels that vary by geographical origin.^{2–4} Metal contaminants in fluoride additives are a potential contamination source of the water supply.

In an attempt to limit hazardous exposures via drinking water, the US Environmental Protection Agency (EPA) requires that quality and safety assurance programs screen the metal content of drinking water after the use of additives like fluorosilicic acid (H_2SiF_6 or hydrofluorosilicic acid [HFS]), sodium fluorosilicate (Na_2SiF_6), and sodium

fluoride (NaF). The EPA recommends that finished drinking water have fluoride at the desired levels of ≤ 1.2 mg/l (less than one-third the EPA Maximum Contaminant Level, MCL), while other contaminants stay at or below levels considered safe ($<$ one-tenth the respective EPA MCL).^{5,6} Silicate has no MCL, but there is a 16 mg/l maximum drinking water level (MDWL) restriction, and radionuclide levels are not to exceed detection limits of EPA Test Method 900.0.^{5–7}

Both the American Water Works Association (AWWA) and the National Sanitation Foundation International (NSF) provide guidelines for the selection and use of fluoride additives. Quality controls consist of multiple standards (i.e., ANSI/NSF Standards 60 and 61, ANSI/AWWA B701–B703) and testing and certification programs.^{5,6,8} When an NSF certified additive is dosed into water according to the specified maximum use level (MUL) (typically 6.0 mg/l for HFS; 2.3 mg/l for NaF; 2.0 mg/l for Na_2SiF_6), the dilution process should limit the doses of metals delivered to the public via fluoridation. However, data from 2000 to 2006 and 2007 to 2011 show that controlled dilution procedures resulted in detectable levels of up to 13 metal contaminants and that in finished drinking water samples 43–50% had detectable As; <1 –2% had Pb; 0–1% had Cd; and

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Correspondence to: Phyllis J. Mullenix, Post Office Box 753, Andover, MA, USA. Email: pjmtox@gmail.com

<1% had Cr.^{5,6} Controlled dilution is intended to restrict contaminants to concentrations at or below the ANSI/NSF Standard 60 single product allowable concentration (SPAC) limits (0.1 MCL for contaminants except fluoride) and thereby lessen concern for metal exposure originating from fluoridation.

The controlled dilution process does not protect public safety in the case of accidents and therefore it is necessary to shift focus from regulation of diluted fluoride products to raw fluoride additives – which are never contaminant free. In the United States, state and local agencies are responsible for regulating the use of raw fluoride additives and on numerous occasions these authorities have had to deal with mishandling accidents.^{9–22} Such accidents fall into one of three categories: water distribution overfeeds (fluoride levels ≥ 4 or ≥ 7 mg/l in school systems); non-overfeeds (fluoride levels >1.2 mg/l but <4 or <7 mg/l in school systems); and industrial accidents during the handling, transport, or storage of additives at or near water treatment facilities. Regardless of category, fluoride is typically the only contaminant identified or monitored during accidents. Overfeed accidents occur when the MUL is exceeded and excess fluoride additive enters the drinking water. This can result in illnesses in children and adults, attributed to fluoride and not to fluoride combined with other contaminants such as As and Pb.^{23–26} In non-overfeed accidents, the public may not be informed for up to 12 months that their drinking water has fluoride levels >1.2 mg/l as long as the MCL of 4 mg/l is not exceeded. Furthermore, the public is never informed about the concentration levels of the other contaminants also present in the water.

In an industrial accident in Utah where a water facility storage tank ruptured and released 300 gallons of HFS, authorities anticipated the high levels of fluoride (495 ppm) in the nearby waterway, but did not anticipate the coexisting 42.6 ppb arsenic discovered during the follow-up investigation. The manufacturer's material safety data sheet (MSDS) on file for the spilled HFS did not warn of any potential arsenic content.²⁷ This example demonstrates how gaps in regulation allow unreported metal content to become potential health risks during accidental exposure to raw or improperly diluted fluoride additives.

Contaminant content defines exposure and determines health impact. It is well established that batch-to-batch variation in contaminant content can change biological response and that even trace amounts of contaminants can lower the threshold dose for an effect, particularly when there are synergistic interactions and the overall effect is greater than the sum of effects caused by contaminants acting alone.²⁸

Synergism between contaminants fosters an underestimation of risks, like that occurring with combinations of Pb, As, Cd, and Cr or fluoride coexisting with aluminum or beryllium.^{29–35} Combinations of contaminants can also trigger chemical degradation, generating decomposition products with toxicity greater than that of the original compounds. In a previous trace contaminant study of commercially available HFS samples, one in four samples had signs of decomposition where an unexpectedly high level of hydrofluoric acid (3.3%) exceeded the AWWA standard (1%).³⁶

The MSDS's for fluoride additives do not specify threshold limit values for decomposition products such as hydrogen fluoride. While they do warn against combining fluoride with metals to avoid corrosion, they do not describe the risks that decomposition creates for workers as a result of airborne contamination. Although the MSDS's for HFS and NaF additives list a threshold limit value (TLV) of 2.5 mg(F)/m³, they avoid the 0.5 ppm TLV (0.41 mg(F)/m³ at 25°C and 760 Torr) for occupational exposure to hydrogen fluoride.³⁷ This incomplete disclosure can result in unexpected outcomes, like that encountered by manufacturers of fluoroether compounds (i.e. sevoflurane) when trace amounts of metal oxides from metallic or glass surfaces of containers or medical devices initiated chemical degradation to form highly toxic levels of hydrogen fluoride, hydrofluoric acid, and silicon tetrafluoride.^{38–41} Any metal initiated degradation of fluorinated compounds is important to consider, especially since drinking water increasingly contains fluorinated pharmaceuticals.^{42,43} Beryllium oxyfluoride, barium fluoride, or magnesium fluoride are acutely more toxic than compounds such as sodium fluoride, calcium fluoride, or magnesium oxide.^{44–46} Given established hierarchies in potential toxicity, it is important to consider the risks associated with the combination of metals and fluoride in an exposure scenario.

To understand the risks associated with using fluoride additives, it is necessary to first evaluate the metal content of the raw fluoride product before the application of controlled dilution procedures. While NSF programs require annual unannounced inspections of fluoride additive suppliers, inspection results are kept private by nondisclosure agreements to protect business interests. There is no routine screening for discrepancies between inspection results and the manufacturer's Certificate of Analysis or MSDS sent with each additive batch.^{5,6} Description of the metal content of raw additives is typically limited to total percent levels (i.e., heavy metals such as lead, $<0.0200\%$) and not the actual concentration of metal per batch. Furthermore, many of the additives imported to the US have errors in their Certificates

of Analyses.²⁷ Regardless, there are currently no routine measures of metal content per additive batch before use. Currently, fluoride additive purchases are based on AWWA and NSF Standard 60 certification, availability, and cost, but not on metal contaminant content. As of 2013, only one New Hampshire water facility had a low arsenic requirement for fluoride additives (personal communication, D. Paris, Manchester Water Treatment Plant). Utah recently passed legislation (HB 72) requiring the full disclosure of metal contaminant levels in raw fluoride additives.⁴⁷

The aim of this study was to analyze the metal content of NSF certified raw fluoride additives. Unlike previous studies of additive chemical composition, the analyses presented in this study are independent of chemical supplier data, address both liquid (HFS) and solid (NaF) forms of fluoride additives, and focus on multiple metals, not just arsenic.^{36,48} This paper also expands on safety considerations in the event of an accident, arguing that NSF's dilution approach, which focuses on one contaminant at a time, is inadequate. Such data are crucial as water facilities that fluoridate are adding potentially harmful contaminants, some carcinogenic, to drinking water.

Methods

Fluoride additives

All the fluoride additives analyzed in this study were commercially available products intended for fluoridation use at US water facilities.

Three HFS additives (HFS-1, HFS-2, and HFS-3) from different batch shipments were selected for study. Each sample was a clear liquid and consisted of 23–25% acid. The HFS additives originated from the US or Mexico (Juarez) and were labeled as AWWA/NSF certified. The origin of individual samples could not be established because manufacturer shipments were stored in common bulk tanks not cleaned between batches. The HFS samples selected for laboratory study were shipped and stored in polyethylene containers prior to analysis.

Four samples of solid fluoride additives were obtained for laboratory testing. One NaF sample (NaF-1) was in white powder form, while the remaining samples (NaF-2, NaF-3, and NaF-4) were in granular form. Each sample was taken from a different batch shipment and all samples selected for laboratory analysis were shipped and stored in individual Teflon containers. All NaF samples originated from Shanghai, China and met AWWA and NSF Standard requirements. Cross-contamination between domestic and foreign made dry additives was unlikely because US production ceased years ago. In contrast, cross-contamination between shipments of different fluoride compounds, some

intended for purposes other than fluoridation, could not be ruled out. Cross-contamination between fluoride salts originating from different countries could also not be ruled out. US suppliers repackage foreign made fluoride salts using the same equipment regardless of source and there is no wet cleaning between uses.

Analytical procedures

All fluoride additive samples required dilution in order to be within the analytical range of the testing instruments. Concentration levels of aluminum, antimony, arsenic, barium, beryllium, cadmium, calcium, chromium, copper, iron, lead, magnesium, manganese, molybdenum, nickel, potassium, selenium, silver, thallium, vanadium, and zinc were determined using EPA's Method 200.7 for inductively coupled plasma-atomic emission spectrometry (ICP).⁷ Percentage levels of fluoride and sodium were determined for all additive samples and the percentage of silicon dioxide was determined in the NaF samples and in the samples of HFS-1 and -2. The ICP determined arsenic results were confirmed by reassessment of levels using Graphite Furnace Atomic Absorption (GFAA) analysis.

Report values

Concentration values (micrograms per milliliter for liquid additives and micrograms per gram for solid additives) were expressed as parts per million (ppm) and reported when they equaled or exceeded the method detection limit (MDL) established per analyte. All concentration levels presented in the results, including those for MDL determinations, were from the raw (undiluted) fluoride additive. Each concentration value reported was an average of duplicate measures for intra-laboratory verification.

Results

Some of the results from the chemical analysis were consistent with the content expected of an AWWA and NSF certified fluoride additive. The 23–25% HFS samples contained 18–19% fluoride and sodium content of the four NaF samples met expectations (56%, NaF-1; 56.8%, NaF-2; 54.9%, NaF-3; and 57.4%, NaF-4). The sodium content of the HFS additives was 0.11% (HFS-1), 0.14% (HFS-2), and 0.05% (HFS-3). Based on two measurements, the SiO₂ content of the HFS samples ranged from 16.15% (HFS-2) to 16.55% (HFS-1). The SiO₂ content of the NaF samples was higher than expected: 24.6% in NaF-1, 26.6% in NaF-2, 26.0% in NaF-3, and 25.7% in NaF-4.

Of the 21 metal contaminants analyzed, 12 had concentration levels that were below established MDL's in the raw HFS and NaF additive samples. The contaminants with insignificant concentrations

Table 1 Contaminants with concentration levels below MDL's in raw 23–25% hydrofluorosilicic acid (HFS-1, -2, and -3) and sodium fluoride (NaF-1, -2, -3, and -4) additive samples

Analyte	MDL* (ppm)
Antimony	10.0
Beryllium	1.5
Cadmium	2.0
Chromium	10.0
Copper	10.0
Manganese	20.0
Molybdenum	10.0
Nickel	15.0
Selenium	25.0
Silver	10.0
Thallium	20.0
Vanadium	10.0

*Method detection limit

and the established MDL's per contaminant are provided in Table 1.

The remaining contaminants, including aluminum, arsenic, barium, calcium, iron, lead, magnesium, potassium, and zinc, had concentration levels that exceeded MDL's in at least one of the fluoride additive samples tested. The contaminant concentrations for the liquid HFS samples are presented in Table 2. Contaminant concentrations for the dry salt NaF additives are listed in Table 3.

Arsenic, lead, and zinc were found only in HFS additives. Arsenic in particular was present most consistently. The GFAA analysis confirmed reportable levels of arsenic in the three HFS additive samples (4.9, 34.0, and 56.0 ppm, Table 2). The HFS sample with the lowest arsenic level also contained a reportable level of lead (10.28 ppm, HFS-3, Table 2).

Barium was the only metal contaminant found exclusively in NaF additive samples (13.3 ppm, NaF-1 and 18.0 ppm, NaF-3; Table 3). Reportable levels of aluminum, calcium, iron, magnesium, and potassium were found in both the liquid and dry salt fluoride additives and concentration levels were similar in HFS and NaF samples. Concentration levels of potassium and aluminum were higher in the dry salt additives; with aluminum concentrations in the NaF samples nearly 10-fold higher than those in HFS samples. In general, aluminum was the contaminant with the highest concentration levels.

Discussion

This study demonstrates that the metal contaminant content of raw fluoride additives is highly batch-dependent. There was as much as a 10-fold difference between batches in the concentration levels of arsenic, lead, and barium, contaminants classified as a risk to human health by the National Primary

Table 2 Metal contaminant concentrations found using ICP analysis of raw 23–25% hydrofluosilicic acid additives (HFS-1, -2, and -3). Values are not corrected for density of 1.2 g/ml

Analyte	MDL* (ppm)	HFS-1 (ppm)	HFS-2 (ppm)	HFS-3 (ppm)
Aluminum	10.0	415.0	385.0	212.2
Arsenic	15.0	38.1	20.6	<15.0
	2.0 [†]	56.0 [†]	34.0 [†]	4.9 [†]
Barium	5.0	<5.0	<5.0	<5.0
Calcium	25.0	84.5	89.3	90.9
Iron	5.0	714.0	173.0	27.6
Lead	10.0	<10.0	<10.0	10.3
Magnesium	25.0	30.9	31.6	32.2
Potassium	50.0	80.0	68.0	<50.0
Zinc	10.0	27.3	<10.0	<10.0

*Method detection limit.

[†]Value determined using GFAA and a dilution of 0.1 ml/100 ml.**Table 3** Metal contaminant concentrations found using ICP analysis of raw sodium fluoride additives (NaF-1, 2, -3, and -4)

Analyte	MDL* (ppm)	NaF-1 (ppm)	NaF-2 (ppm)	NaF-3 (ppm)	NaF-4 (ppm)
Aluminum	10.0	3393.0	3630.0	3397.0	3312.0
Arsenic	15.0	<15.0	<15.0	<15.0	<15.0
	2.0 [†]	<2.0 [†]	<2.0 [†]	<2.0 [†]	<2.0 [†]
Barium	5.0	13.3	<5.0	18.0	<5.0
Calcium	25.0	87.6	69.6	67.8	64.8
Iron	5.0	94.3	60.9	82.6	58.7
Lead	10.0	<10.0	<10.0	<10.0	<10.0
Magnesium	25.0	41.4	49.4	40.8	43.6
Potassium	50.0	192.0	221.0	346.0	171.0
Zinc	10.0	<10.0	<10.0	<10.0	<10.0

*Method detection limit.

[†]Value determined using GFAA and a dilution of 1 g/100 ml.

Drinking Water Regulations.^{49,50} As no two additive samples were found to have the same exposure profile in this study, assumptions about metal content are unreliable if based on manufacturer source or certification by NSF. Although the AWWA affirms the HFS purchasers' right to know the source of a raw product when manufactured outside North America,⁸ such information is meaningless when there is cross-contamination between HFS shipments stored in common tanks. Likewise, cross-contamination may impact metal content when all imported salt additives, regardless of source, chemical form, or intended usage are handled in the same repackaging equipment. The fact that NaF samples in this study were obtained from bulk supplies not yet repackaged, suggests that the unexpectedly high SiO₂ levels were more a function of mislabeling than cross-contamination. Contrary to label and lot number information, this analysis revealed that salt samples were likely an unidentified mix of NaF and Na₂SiF₆, two frequently used fluoride additives with different MUL's and chemical properties. Whether mislabeling or cross-contamination, the findings here indicate that users of fluoride additives can expect unpredictable amounts of metal contamination.

The only consistencies observed among the additives was that certain contaminants were always

absent (e.g., antimony, silver, and vanadium), while others were always present (e.g., aluminum, magnesium, and iron). The absent contaminants are consistent with those absent in EPA test samples of tap, pond, and well water.⁷ When compared to the content reported for other substances (Table 4), contaminant concentration levels of raw HFS additives were typically much higher than those found in tap water or in industrial or sewage treatment primary effluents.^{5-7,51} Moreover, contaminant concentration levels in raw NaF additives were much lower than those reported for contaminated solids with two notable exceptions. Barium and aluminum levels approached those that the EPA found in samples of electroplating sludge, river sediment, and hazardous soils (Table 4). The high and unpredictable contaminant levels found in the samples indicate the upper limits of possible exposures during fluoridation accidents when dilution's mitigating influence is inaccurate or altogether absent. Thus, the results here indicate that NSF's dilution approach is inappropriate. Employees who handle fluoride additives require a fail-safe strategy that takes into account the variable and hazardous metal content of the additives, both for their safety and the safety of consumers.

Arsenic has been reported as the "limiting constituent" for HFS dosage when controlling contaminants

Table 4 Measured contaminant levels in raw fluoride additives compared with measurements in environmental test samples

Analyte	Concentration levels (ppm) in raw fluoride additives*	Concentration levels (ppm) in aqueous and solid matrices reported in the literature
Arsenic		
HFS	4.9–56.0	0.0006 or 0.00166 average in tap water fluoridated by NSF certified HFS [†] ; <0.02 in industrial effluent [‡]
Lead		
HFS	<10.0–10.3	0.0006 or 0.0011 average in tap water fluoridated by NSF certified HFS [†] ; 0.251 in industrial effluent [‡] ; 0.015 in sewage treatment primary effluent [‡]
Barium		
NaF	<5.0–18.0	39.8 in electroplating sludge [§] ; 54.8 in river sediment [§] ; 111 in hazardous soil [§]
Aluminum		
HFS	212.2–415.0	0.185 in tap water [‡] ; 1.19 in sewage treatment primary effluent [‡]
NaF	3312–3630	4980–5160 in electroplating sludge, hazardous soil, and river sediment [§]
Calcium		
HFS	84.5–90.9	35.2 in tap water [‡] ; 500 in industrial effluents [‡]
NaF	64.8–87.6	28 000–85 200 in river sediment, electroplating sludge, and hazardous soil [§]
Magnesium		
HFS	30.9–32.2	8.08 in tap water [‡] ; 6.84 in industrial effluent [‡] ; 22.7 in sewage treatment primary effluent [‡]
NaF	40.8–49.4	1950–24 400 in electroplating sludge, river sediment, and hazardous soil [§]
Iron		
HFS	27.6–714.0	0.008 in tap water [‡] ; 1.28 in sewage treatment primary effluent [‡]
NaF	58.74–94.3	16 500–84 800 in river sediment, electroplating sludge, and hazardous soil [§]

*Data from Tables 2 and 3 of this study.

[†]Data from NSF's Tables 1 and 2.^{5,6,51}

[‡]Data from EPA's Table 6.⁷

[§]Data from EPA's Table 7.⁷

in finished drinking water.³⁶ The range of arsenic levels found in raw HFS samples was 4.9–56 ppm, similar to previous research analyzing raw HFS additives (9.4–58.5⁵² and 28–60 ppm⁴⁸). Dilution reduces the parts per million arsenic levels of raw HFS additives, to parts per billion ($\mu\text{g/l}$) arsenic levels in finished drinking water, allowing concentrations to meet established enforceable drinking water regulations. The current NSF/ANSI standard for arsenic is 0.001 ppm (1 ppb based on an MCL of 0.010 ppm).^{5,6,49,50} Table 5 provides the arsenic levels expected in finished drinking water when HFS is used for fluoridation. For example, Weng *et al.* calculated that 60 ppm arsenic in raw HFS additives would contribute 0.245 $\mu\text{g/l}$ arsenic in finished drinking water fluoridated at 1 ppm (Table 5).⁴⁸ Using this calculation, the 56.0 ppm arsenic found here in one HFS sample would become 0.224 $\mu\text{g/l}$ arsenic in finished drinking water when fluoridated at 1 ppm. As long as dilution is controlled and fluoridation stays at 1 ppm, arsenic levels (0.019–0.245 ppb in Table 5) in finished drinking water stay below the 1 ppb Standard 60 level. However, during fluoride overfeeds only the HFS additives with the lowest arsenic levels (4.9 $\mu\text{g/l}$ in Table 5) can produce drinking water where arsenic meets the Standard 60 level of 1 ppb. Moreover, fluoride non-overfeeds risk exceeding the Standard 60 level of 1 ppb arsenic when HFS additives contain high levels of arsenic (56.0–60 $\mu\text{g/l}$). The risk is even greater when there are multiple sources (e.g., natural erosion or non-fluoride water treatment chemicals) contributing arsenic to finished drinking water. Water treatment chemicals other than fluoride additives can contribute up to 0.061 μg arsenic/l of finished drinking water.⁴⁸ Combine this 0.061 $\mu\text{g/l}$ arsenic with the 0.956 or 0.873 $\mu\text{g/l}$ arsenic contributed by fluoride additives (raw additives containing 56 or 60 ppm arsenic; Table 5), and the total either exceeds the 1 ppb standard or comes close enough that there is no allowance for input from natural sources. Fluoride, but

not arsenic, is typically monitored daily when treated water enters the water delivery system. In contrast, arsenic levels are only checked quarterly or annually, depending on individual facility protocols. While HFS related non-overfeeds mean that fluoride levels are below the 4 ppm MCL/MCLG standard, it does not necessarily mean that arsenic is below the 1 ppb standard, or that arsenic is even the highest concentration contaminant of concern. The low arsenic HFS additive identified in this study (4.9 ppm arsenic) also contained 10.3 ppm lead (current NSF/ANSI standard=0.0015 ppm; MCL=0.015 ppm). The NaF additives contained neither arsenic nor lead, but did contain up to 18.0 ppm barium (current NSF/ANSI standard=0.2 ppm; MCL=2 ppm).^{5,6,49,50} Therefore, the use of arsenic as the “limiting constituent” may not be appropriate.

The arsenic, lead, and barium content of raw fluoride additives pit health risks against technological feasibility and drinking water regulations. For these contaminants, standards are based on health concerns, technology, and cost.^{49,50} Technological allowances are for geogenic sources that contribute substantially to source water contamination. In short, standards are relaxed to allow for arsenic, lead, and barium to be introduced into drinking water via erosion of natural deposits.^{49,50} When present in fluoride additives, these contaminants are added to natural sources of contaminants, complicating control over site-specific erosion problems and in turn the estimation of total contaminant exposure. Without such allowances, the standards would be solely health-based and provide margins of safety adequate to protect against adverse health effects. Such health-based standards are the EPA’s Maximum Contaminant Level Goals (MCLG’s), which are set at 0 ppm for arsenic and lead, and 2 ppm for barium.^{49,50} The 0 ppm MCLG for arsenic was established because arsenic exposure is associated with skin and cardiovascular damage, lung cancer,

Table 5 Raw HFS additive arsenic content converted to concentration levels expected in finished drinking water with fluoridation at desired (1 ppm), non-overfeed (3.9 ppm), and overfeed (24–200 ppm) dilutions

Raw HFS additives – analytical results for arsenic (ppm)	Finished drinking water – calculated estimate* of arsenic concentrations ($\mu\text{g/l}$) during desired, non-overfeed, and overfeed fluoride situations		
	Desired F-level 1.0 ppm	Non-overfeed F-level 3.9 ppm [‡]	Overfeed F-level 24 ppm [§]
56.0 [†]	0.224	0.873	5.38
34.0 [†]	0.136	0.530	3.26
4.9 [†]	0.019	0.076	0.470
60	0.245 [†]	0.956	5.88
28	0.114 [†]	0.446	2.75

*Calculation method of Weng *et al.*⁴⁸

[†]HFS solution designated as 24.0%.

[‡]Fluoride non-overfeed range=1.2–4.0 mg/l.

[§]Reported accidental fluoride overfeed level.¹³

^{||}Reported HFS analytical result for arsenic⁴⁸ (24.5% HFS solution).

[†]Reported finished drinking water arsenic level.⁴⁸

and bladder cancer. Similarly, the 0 ppm MCLG was established for lead because lead exposure can cause physical and mental developmental delays, attention and learning deficit disorders, kidney damage and hypertension. The 2 ppm MCLG for barium was created because of its hypertensive effects. The MCLG of zero indicates that any amount of lead or arsenic in drinking water, whether derived from natural or artificial sources, poses a risk to human health.

While it is known that arsenic in HFS increases the numbers of lung and bladder cancers in the United States,⁵³ no consideration has been given to the arsenic and lead levels in HFS overfeeds and non-overfeeds. Non-overfeeds are a particularly insidious exposure since they are unreported for months and total contaminant contribution is ignored. As water operators continue to focus only on desired fluoride levels (1 ppm), health consequences will be systematically underestimated and potential carcinogens may enter into the public water system.

The high levels of aluminum in raw fluoride additives raise questions about the adequacy of current drinking water regulations. Along with calcium, iron, and magnesium, aluminum is regulated under the National Secondary Drinking Water Regulations as a technical and a esthetic nuisance, not as a risk to human health.^{49,50} Some nuisance contaminants are considered essential and possibly protective against cardiovascular and cerebrovascular mortality.^{54,55} In drinking water, aluminum and iron can cause undesirable color, tastes, and/or odors, but neither has an enforceable MCL for health-based concerns. Federal regulations do not require state health agencies and public water systems to monitor aluminum levels in water supplies, and aluminum levels are not determined when an NSF certified fluoride additive is dosed into water at a MUL.^{5,6,49,50} Aluminum is not a limiting constituent for any water treatment chemical and is only restricted when an aluminum-based flocculant is used to remove naturally occurring excess fluoride and/or unwanted color and turbidity from water supplies.^{36,56,57} After this removal process, residual aluminum levels should not exceed 0.2 ppm. This concentrations is low enough that drinking water contributes a much smaller proportion of the lifetime burden of aluminum than food.^{49,50,58,59} However, this flocculation limit does not relate to the later process of fluoridation, which is the last step in water treatment before drinking water is delivered. It is assumed that NaF additives contain only small amounts of aluminum.⁶⁰ This is not a safe assumption given the 212–415 ppm aluminum found in the HFS samples and the near electroplating sludge levels (3312–3630 ppm) found in the NaF samples (Table 4). Findings from this study indicate that

fluoride additives deliver a larger proportion of the daily aluminum intake than previously realized, and unknown concentrations of aluminum fluoride complexes are reaching consumers via fluoridation.

Concerns that aluminum in drinking water threatens health are countered by claims of low toxic potential due to poor gastrointestinal (GI) absorption.⁶¹ The level of aluminohydroxide complexes in city water supplies ($21.8 \pm 10 \mu\text{g/l}^{58}$) seems trivial compared to the 400 mg of aluminum hydroxide found in one over the counter antacid tablet. However, this comparison is misleading. Although only a small portion of the antacid aluminum gets absorbed, it is enough to accumulate and cause premature osteoporosis, encephalopathy, and proximal myopathy during renal insufficiency.⁶² Manufacturers of antacids counterbalance aluminum with magnesium hydroxide in order to cancel the adverse effects the two metals have on the bowel.⁶² Furthermore, patients are warned not to take antacids concomitantly with certain medications because aluminum hinders essential drug absorption by forming Al-drug insoluble complexes.⁶² This exceptional binding strength is why aluminum is no longer used as a phosphate binder to treat renal osteodystrophy. It promotes adynamic bone disease (low bone turnover), anemia, myopathy, and dementia.⁶³ In short, aluminum exposure via antacids is not comparable to exposure from drinking water. Antacids contain aluminum in the hydroxide form. Aluminum in food additives is usually in the form of a sulfate, silicate, or phosphate,⁶⁴ and human absorption of aluminum sulfates and silicates is largely unknown, while that of relatively insoluble aluminum phosphates depends upon the amounts consumed.⁶⁵ Gastrointestinal absorption of aluminum varies by quantity and chemical form.^{66,67} Drinking water contains multiple forms of aluminum, including aluminum-fluoride complexes, which are readily absorbed in the GI tract and cross the blood-brain barrier.^{32,68,69} It is the aluminum-fluoride complex form that has the greatest potential for biological impact, where toxicity stems from mimicking gamma-phosphate, altering enzyme activity and activating guanine nucleotide-binding proteins (G-proteins), which are integral to endocrine and nervous system functions.^{60,70–78} Al-fluoride complexes have been shown to be markedly more toxic than fluoride alone regarding deposition of aluminum in the brain and kidney and cerebrovascular and neuronal integrity.³² The much greater biological impact of the Al-fluoride complex, or fluoride coexisting with aluminum or beryllium, constitutes a threat to human health no longer dismissible on the basis of poor GI absorption.

Contaminant interactions should be considered in determining drinking water regulations. The finding of high aluminum levels in raw fluoride samples

underscores the inadequacy of regulations based on SPAC limits. There is no justification for the disparate limits, 0.2 ppm for aluminum and 1.2 ppm for fluoride, especially when the greatest toxic concern is the Al-fluoride complex. To build in a margin of safety, other contaminants have limits that are one-tenth their MCL. In contrast, the 1.2 ppm fluoride limit is less than one-third its MCL, providing no margin of safety to cover the potential toxicity of Al-fluoride complexes. While prior studies have investigated the potential link between Alzheimer's disease and aluminum in drinking water at levels as low as 0.1–0.2 ppm,^{79–82} it may be more important to investigate the association between Alzheimer's and levels of Al-fluoride complexes.

While many variables influence Al-fluoride complex formation, control over the formation starts with the disclosure of aluminum content in raw fluoride additives. When aluminum is only regulated as a water quality nuisance, only fluoride is considered for its potential health effects. Too narrow a focus on fluoride artificially limits populations at risk to those with compromised fluoride excretion (renal insufficiency), excluding those with higher than normal aluminum absorption (e.g., the elderly, Alzheimer and Down's syndrome patients^{83,84}). This shortsighted exclusion is avoidable if drinking water regulations addressed exposures to Al-fluoride complexes in addition to individual aluminum or fluoride levels.

In summary, raw fluoride additives contain significant levels of arsenic, lead, barium, and aluminum not addressed by current regulations with health-based standards. These raw product levels establish the upper limits of exposure in the event of fluoride overfeeds, non-overfeeds, and industrial accidents. Although the findings of this study are limited by small numbers of samples and manufacturing sources, they highlight flaws in the quality control of NSF certification. Controlled dilution procedures needed to meet NSF/ANSI standards camouflage the fact that metal contaminants are being removed from water sources only to be returned to finished water supplies via fluoridation. The use of fluoride additives assures that some risk is passed to the consumer, especially with regard to arsenic, lead, and non-overfeed levels of fluoride (1.2–4 ppm) that can persist undisclosed up to a year. Since January 2011, there has been a proposed recommendation to lower the optimum fluoridation level to 0.7 ppm. This proposal remains without regulatory standing and has been ignored. Considering this study's findings, the following recommendations outline controls needed to fill the gaps in current regulations:

1. All metal contaminants with concentrations that reach or exceed MDL's of analytical instrumentation should be identified per batch shipment,

regardless of source, before being used as a treatment chemical in public water supplies. Records of actual contaminant concentrations should be kept and made available to the public on request and to first responders during accidental spills.

2. Fluoridation levels should not exceed 0.4 ppm (one-tenth the fluoride MCL) in order to provide a margin of safety for interacting contaminants. Fluoridation above 0.4 ppm should not be attempted unless the aluminum and beryllium in raw additives are at levels below MDL's.
3. Raw additives with low arsenic, lead, and barium levels should be used when source waters contain these contaminants in naturally high concentrations. If such additives are unobtainable, the use of fluoride additives should be discontinued.
4. In conjunction with the use of fluoride additives, aluminum should have an established MCL and be regulated under the National Primary Drinking Water Regulations.

There must be a concerted effort to improve transparency with respect to the contaminant content of raw fluoride additives. Adopting the above recommendations would be a major step in alleviating the growing concerns for safety.

Disclaimer statements

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Is Water Fluoridation Effective?

According to most major sources, estimates of fluoridation effectiveness amount to at most a reduction of only one-half cavity per child. Low end estimates find **no significant reduction at all**. Children aged 6-17 average 2.1 cavities in their permanent teeth¹:

- Cochrane Collaboration² (2015): 26% (**0.5 cavity per child**)
- CDC³ (2018): 25% (**0.5 cavity per child**)
- Iowa Fluoride Study⁴ (2018): **No significant reduction**
- World Health Organization data⁵ (2005): **No evidence of fluoridation's effectiveness**



There is already a consensus including CDC, Cochrane Collaboration, the Iowa Fluoride Study and others that fluoride's effectiveness in preventing cavities is mainly topical (not swallowed).

The **Cochrane Collaboration** is considered the gold standard of evaluating effectiveness. It said the cavity reduction referenced above was **"based predominantly on old studies and may not be applicable today."**

"Over 97% of the 155 studies were at a high risk of bias, which reduces the overall quality of the results... We did not identify any evidence... to determine the effectiveness of water fluoridation for preventing caries in adults... There is insufficient evidence to determine whether water fluoridation results in a change in disparities in caries levels across socio-economic status."

The **Iowa Fluoride Study (IFS)**, funded by the National Institutes of Health, is the most comprehensive, ongoing research project in the U.S., the only one measuring all sources of fluoride ingestion. The 2018 study from IFS referenced above found no significant correlation between ingested fluoride and cavity reduction, further validating a 2009 study⁶ from IFS that stated:

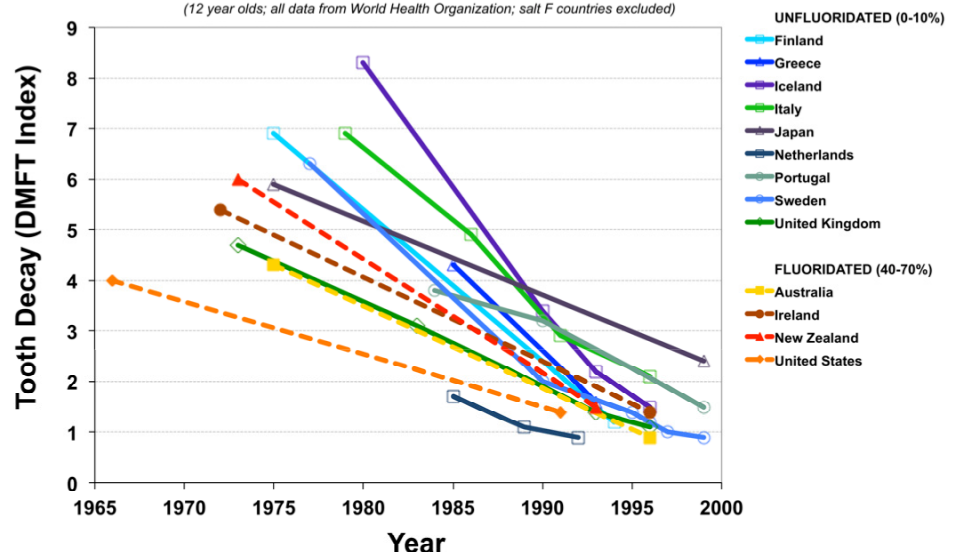
*"... achieving a caries-free status may have relatively little to do with fluoride **intake** (emphasis in the original) ... recommending an 'optimal' fluoride intake is problematic."*

Finally, World Health Organization data show cavity rates in children (age 12) have dropped as much in nations that don't fluoridate (darker solid lines) as in nations that do (red/yellow dotted lines). (See graph)

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**Tooth Decay Trends:
Fluoridated vs. Unfluoridated Countries**

(12 year olds; all data from World Health Organization; salt F countries excluded)





November 22, 2016

Gina McCarthy, Administrator
Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Administrator McCarthy:

Pursuant to section 21 of the Toxic Substances Control Act ("TSCA"), 15 U.S.C. § 2620, the Fluoride Action Network, Food & Water Watch, Organic Consumers Association, American Academy of Environmental Medicine, International Academy of Oral Medicine and Toxicology, Moms Against Fluoridation, and undersigned individuals (collectively, "Petitioners") hereby petition the U.S. Environmental Protection Agency to protect the public and susceptible subpopulations from the neurotoxic risks of fluoride by banning the addition of fluoridation chemicals to water.

Under Section 6 of TSCA, EPA is invested with the authority to prohibit the "particular use" of a chemical substance if the use presents an unreasonable risk to the general public or susceptible subpopulations. 15 U.S.C. § 2605(a). EPA has recognized that its authority to regulate chemical substances under TSCA includes the authority to prohibit *drinking water additives*.

EPA should exercise its authority under TSCA to prohibit fluoridation additives because application of the Agency's own *Guidelines for Neurotoxicity Risk Assessment* to the existing database on fluoride shows that (1) neurotoxicity is a hazard of fluoride exposure, and (2) the reference dose that would reasonably protect against this hazard is incompatible with the doses now ingested by millions of Americans in fluoridated areas. In fact, the amount of fluoride now regularly consumed by many people in fluoridated areas *exceeds* the doses *repeatedly* linked to IQ loss and other neurotoxic effects; with certain subpopulations standing at elevated risk of harm, including infants, young children, elderly populations, and those with dietary deficiencies, renal impairment, and/or genetic predispositions.

The risk to the brain posed by fluoridation additives is an unreasonable risk because, *inter alia*, it is now understood that fluoride's predominant effect on tooth decay comes from *topical* contact with teeth, not *ingestion*. Since there is little benefit in *swallowing* fluoride, there is little justification in exposing the public to *any* risk of fluoride neurotoxicity, particularly via a source as essential to human sustenance as the public drinking water and the many processed foods and beverages made therefrom. The addition of fluoridation chemicals to water thus represents the very type of unreasonable risk that EPA is duly authorized to prohibit pursuant to its powers and responsibilities under Section 6 of TSCA, and Petitioners urge the Agency to exercise its authority to do so.

THE PETITIONERS

ORGANIZATIONS:

American Academy of Environmental Medicine (AAEM) was founded in 1965, and is an international association of physicians and other professionals that provides research and education in the recognition, treatment and prevention of illnesses induced by exposures to biological and chemical agents encountered in air, food and water.

Fluoride Action Network (FAN), was founded in 2000 as a project of the American Environmental Health Studies Project, Inc. FAN is an organization of scientists, doctors, dentists, environmental health researchers, and concerned citizens working to raise awareness about the impact of current fluoride exposures on human health.

Food & Water Watch (FWW) is a national non-profit public interest consumer organization, based in Washington, D.C. that works to ensure safe food and clean water. FWW has worked on many emerging technologies that impact our food supply, by educating consumers, the media, and policymakers about the impact on the food system and public health and by calling for appropriate regulation.

The **International Academy of Oral Medicine & Toxicology (IAOMT)** has been dedicated to its mission of protecting public health through the practice of biological dentistry since it was founded in 1984. A worldwide organization of over 800 dentists, physicians, and research professionals in more than 14 countries, IAOMT's mission is accomplished by funding and promoting relevant research, accumulating and disseminating scientific information, investigating and promoting non-invasive scientifically valid therapies, and educating medical professionals, policy makers, and the general public.

Moms Against Fluoridation is a national nonprofit with a mission to increase awareness of the unsafe and unethical practice of artificial water fluoridation in America today.

Organic Consumers Association is a nationwide grassroots public interest organization dealing with issues of food safety, industrial agriculture, and genetic engineering while promoting organic and sustainable agriculture.

INDIVIDUALS:

Audrey Adams, a resident of Renton, Washington (individually and on behalf of her son Kyle Adams); **Jacqueline Denton**, a resident of Asheville, North Carolina (individually and on behalf of her children Tayo Denton and Rumi Denton); **Valerie Green**, a resident of Silver Spring, Maryland (individually and on behalf of her children Joseph Scribner, Paxton Scribner, Savannah Scribner, Talia Scribner, and Violet Scribner); **Kristin Lavelle**, a resident of Berkeley, California (individually and on behalf of her son Neal Lavelle); and **Brenda Staudenmaier** from Green Bay, Wisconsin (individually and on behalf of her children Ko Staudenmaier and Hayden Staudenmaier).

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	THE TOXIC SUBSTANCES CONTROL ACT (TSCA).....	1
III.	REGULATORY BACKGROUND: FLUORIDE IN DRINKING WATER.....	2
IV.	THE RESEARCH DEMONSTRATING FLUORIDE’S NEUROTOXICITY INCLUDES OVER 180 STUDIES PUBLISHED SINCE THE NRC’S 2006 REVIEW.....	3
V.	FLUORIDE POSES NEUROTOXIC RISKS AT LEVELS RELEVANT TO U.S. POPULATION... 5	
	a. Fluoride Repeatedly Linked to Reduced IQ at “Safe” Water Fluoride Levels.....	5
	b. Fluoride Linked to Cognitive Impairment at Levels of Individual Exposure Seen in Western Fluoridated Populations.....	6
	i. Daily Fluoride Intake	7
	ii. Urine Fluoride Level	9
	iii. Serum Fluoride Level	11
	iv. Dental Fluorosis Level	12
VI.	NEUROTOXIC RISK OF LOW DOSE FLUORIDE IS FURTHER SUPPORTED BY ANIMAL AND CELL STUDIES.....	14
VII.	RECENT EPIDEMIOLOGICAL STUDIES CORROBORATE NEUROTOXIC RISK FROM FLUORIDATED WATER IN WESTERN POPULATIONS.....	16
VIII.	SUSCEPTIBLE SUBPOPULATIONS ARE AT HEIGHTENED RISK TO FLUORIDE NEUROTOXICITY AND NEED PROTECTION	17
IX.	A REFERENCE DOSE PROTECTIVE AGAINST FLUORIDE NEUROTOXICITY IS INCOMPATIBLE WITH WATER FLUORIDATION IF STANDARD RISK ASSESSMENT PROCEDURES ARE APPLIED.....	19
X.	THE BROADBENT STUDY DOES NOT ESTABLISH THE SAFETY OF FLUORIDATION.....	21
XI.	THE BENEFITS OF PREVENTING FLUORIDE NEUROTOXICITY DWARF THE COSTS OF RESTRICTING FLUORIDE CHEMICALS	23
XII.	IT IS IN THE PUBLIC INTEREST FOR EPA TO TAKE ACTION UNDER TSCA.....	27
XIII.	CONCLUSION.....	29
XIV.	BIBLIOGRAPHY.....	30
XV.	APPENDICES	
	A. Post-NRC Human Studies - Fluoride’s Impact on Cognition.....	55
	B. Post-NRC Human Studies - Fluoride’s Impact on Fetal Brain.....	60
	C. Post-NRC Human Studies - Fluoride’s Impact on Other Parameters of Neurotoxicity....	61
	D. Post-NRC Animal Studies – Fluoride’s Neuroanatomical & Neurochemical Effects.....	62
	E. Post-NRC Animal Studies – Fluoride’s Effect on Learning/Memory.....	70
	F. Post-NRC Animal Studies – Fluoride’s Effect on Other Behavioral Parameters.....	73
	G. Post-NRC Cell Studies – Fluoride’s Effect on Brain Cells.....	75

I. INTRODUCTION

The addition of industrial-grade fluoride chemicals at a concentration of 0.7 to 1.2 mg/L to public water supplies for the purpose of preventing tooth decay is a common practice in the United States, with approximately 200 million Americans now consuming artificially fluoridated water. This practice, known as “water fluoridation,” is hailed as an effective practice by public health institutions in the U.S., but has been rejected by most of continental Europe without any demonstrable adverse effect on childhood caries rates.¹

Water fluoridation began in the U.S. in the 1940s on the premise that fluoride’s primary benefit to teeth comes from *ingestion*. (Fejerskov 2004). The consensus among dental researchers today, however, is that fluoride’s predominant benefit is *topical* not systemic. (NRC 2006, at 13; CDC 2001, at 4; Featherstone 2000). It is also now recognized that fluoride is not an essential nutrient. (NRC 1993, at 30; NRC 1989, at 235). Fluoride does not need to be swallowed, therefore, to prevent any disease, including tooth decay. By contrast, fluoride’s risks to health come from ingestion, including the spectrum of neurotoxic effects discussed below. Accordingly, a reasonable use of fluoride for caries prevention would aim to maximize its topical contact with teeth, while minimizing its ingestion. Topical fluoride products like toothpaste are compatible with this goal; fluoridating water supplies is not.

II. THE TOXIC SUBSTANCES CONTROL ACT (TSCA)

Section 6 of the Toxic Substances Control Act (TSCA) invests EPA with the authority and duty to take certain actions if it determines that “the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance . . . presents an unreasonable risk of injury to health.” 15 U.S.C. § 2605(a). In making this determination, TSCA commands that EPA consider not only risks to the general public, but to “susceptible subpopulation[s]” as well. 15 U.S.C. § 2605(b)(4)(A). Further, TSCA commands that EPA conduct the risk evaluation “without consideration of costs or other nonrisk factors.” *Id.*

If EPA determines that a chemical substance presents an unreasonable risk to the general public or susceptible subpopulation(s), the Agency “shall” take action “to the extent necessary to protect adequately against such risk using the least burdensome requirements.” 15 U.S.C. § 2605(a). The actions that EPA may take include: (1) a complete prohibition on the manufacture, processing, and distribution of the substance or (2) a prohibition on a “particular use” of the substance. 15 U.S.C. § 2605(a)(1)–(3).

EPA’s authority to prohibit and regulate the use of chemical substances under TSCA encompasses drinking water additives. EPA recognized this in its June 12, 1979 Memorandum of Understanding with the FDA, in which the Agency stated unequivocally that it has authority “to regulate direct and indirect *additives to drinking water* as chemical substances and mixtures under TSCA.”² (EPA/FDA 1979)

¹ Tooth decay rates declined precipitously throughout the western world during the second half of the twentieth century, in both the *minority* of western countries that fluoridate water (e.g., Australia, Canada, Ireland, New Zealand, and the U.S.), and the majority of western countries that do not. (Cheng et al. 2007; Pizzo et al. 2007; Neurath 2005; Bratthall et al. 1996; Diesendorf 1986).

² As EPA explained, “[a]lthough Section 3(2)(B) of TSCA excludes from the definition of ‘chemical substance’ food and additives as defined under FFDCA, the implicit repeal by the [Safe Drinking Water Act] of FDA’s authority over

EPA may not consider costs when determining whether a risk exists, but it must do so when determining the appropriate course of action to protect against the risk. Specifically, EPA must consider: (1) “the effects of the chemical substance,” (2) “the magnitude of the exposure of human beings,” (3) “the benefits of the chemical substance,” and (4) “the reasonably ascertainable economic consequences of the rule.” 15 U.S.C. § 2605(c)(2)(A). The EPA shall also consider “whether technically and economically feasible alternatives . . . will be reasonably available as a substitute when the proposed prohibition or other restriction takes effect.” 15 U.S.C. § 2605(c)(2)(C).

Finally, EPA is authorized to take action under TSCA, *even if it has authority under other laws to address the risk*, so long as “it is in the public interest” to do so. 15 U.S.C. § 2608(b)(1). In determining whether it is in the public interest to take action under TSCA, EPA “*shall consider . . . all relevant aspects of the risk and a comparison of the estimated costs and efficiencies of the action to be taken under [TSCA] and an action to be taken under such other law to protect against such risk.*” 15 U.S.C. § 2608(b)(2) (emphases added).

Although EPA has certain authorities to regulate fluoride in drinking water under the Safe Drinking Water Act (SDWA), there is an important distinction between TSCA and SDWA that permits EPA to take the requested action under TSCA in a more targeted, efficient, and less expensive manner than would be the case under SDWA. Namely, TSCA permits the EPA to differentiate between fluoride that is *added* to water versus fluoride that is *naturally occurring*. As explained in Section XII below, prioritizing regulatory action against fluoridation *additives* is further justified on policy and scientific grounds. It is therefore in the public interest for EPA to take the requested action under TSCA, instead of SDWA.

III. FLUORIDE IN DRINKING WATER: RECENT REGULATORY BACKGROUND

In 2003, the EPA asked the National Research Council (NRC) to review the scientific merits of EPA’s Maximum Contaminant Level Goal (MCLG) for fluoride, which then and now is set at 4 mg/L. In response, the NRC reviewed the existing research on fluoride toxicity and concluded, in March 2006, that the MCLG is not protective of public health and should be lowered. (NRC 2006). The NRC’s conclusion was based on fluoride’s adverse effects on bone and teeth, but the NRC also raised numerous concerns about the potential for fluoride to cause other systemic harm, particularly to the nervous and endocrine systems.

With respect to the nervous system, the NRC concluded: “On the basis of information largely derived from histological, chemical, and molecular studies, it is apparent that fluorides have the ability to interfere with the functions of the brain.” (NRC 2006, at 222). The NRC’s conclusion about fluoride’s interference with the brain rested primarily on its review of animal studies, since—at the time of NRC’s review—few human studies were available. The situation today, however, is much different as many studies linking fluoride exposure to cognitive deficits in humans have now been published. The number of human studies published subsequent to the NRC review that have found significant relationships between fluoride and adverse cognitive outcomes (n = 46) dwarfs the number of such studies that were available to the NRC (n = 5).³

drinking water enables EPA to regulate direct and indirect additives to drinking water as chemical substances and mixtures under TSCA.” (EPA/FDA 1979)

³ The 46 post-NRC human cognitive studies are cited in Appendix A. The five human cognitive studies that NRC cited are: Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a,b); and Qin et al. (1990).

The evidence linking fluoride to neurotoxicity in humans, therefore, is far more compelling today than it was when NRC published its review. Indeed, in 2014, fluoride was added to the list of chemicals “*known to cause developmental neurotoxicity in human beings*” in a review published by *Lancet Neurology*. (Grandjean & Landrigan 2014, at 334, Tbl 2). Only 12 chemicals are on this list.

It has been 10 years since the NRC concluded that the MCLG for fluoride be lowered, but the EPA has yet to do so. Further, despite the voluminous post-2006 research on neurotoxicity, and despite the Safe Drinking Water Act’s mandate that EPA protect against “known or *anticipated* adverse effects,”⁴ EPA’s Office of Water (EPA OW) has indicated that it will *not* be considering neurotoxicity as an endpoint of concern when promulgating the new MCLG. Specifically, in its December 2010 risk assessment of fluoride’s non-cancer effects, EPA OW established a reference dose for fluoride based solely on severe dental fluorosis, and declined to add an uncertainty factor to account for the neurotoxicity hazard. (EPA 2010, at 3 & 106). EPA OW justified this decision on the grounds that NRC’s 2006 review did not draw firm conclusions about the public health relevance of fluoride neurotoxicity. (EPA 2010, at 106). Nowhere in EPA OW’s risk assessment, however, did it account for the neurotoxicity research published subsequent to NRC’s review.

The cavalier manner in which EPA’s OW dismissed the evidence of fluoride neurotoxicity stands in stark contrast to EPA’s own *Guidelines for Neurotoxicity Risk Assessment* [hereafter *Guidelines*] that EPA has stated it “*will follow in evaluating data on potential neurotoxicity associated with exposure to environmental toxicants.*” (EPA 1998, at 1). Petitioners submit that application of EPA’s *Guidelines* to the existing database for fluoride shows that neurotoxicity is a hazard of fluoride exposure, that the weight of evidence indicates neurotoxicity is a more sensitive endpoint of fluoride exposure than severe dental fluorosis,⁵ and, further, that the reference dose for fluoride that will protect the public and susceptible subpopulations against neurotoxicity is incompatible with the doses now ingested in fluoridated areas.

IV. FLUORIDE’S NEUROTOXICITY IS SUPPORTED BY OVER 180 STUDIES PUBLISHED SINCE NRC’S 2006 REVIEW

One of the striking features of the research on fluoride neurotoxicity is the large quantity of studies—animal, cellular, *and* human—that have reported an effect. In a recent review of developmental neurotoxins by EPA scientists, only 22% of suspected neurotoxins were found to have *any* supporting human data. (Mundy et al. 2015, at 25). The EPA team thus characterized chemicals, including fluoride, whose suspected neurotoxicity is backed by human data, as “gold standard” chemicals that warrant prioritization. (Mundy et al. 2015, at 27). In the case of fluoride, not only is there human data, the data is so extensive that fluoride has been classified alongside lead, mercury, and PCBs as one of only 12 chemicals “*known to cause developmental neurotoxicity in human beings.*” (Grandjean & Landrigan 2014, at 334, Tbl 2). The existence of so many human studies on fluoride neurotoxicity highlights the urgent need for a diligent risk assessment, per EPA’s *Guidelines*, to ensure that the general public, and sensitive subpopulations, are not ingesting neurotoxic levels.

⁴ 42 U.S.C. § 300g-1(b)(4)(A).

⁵ The *Guidelines* state that: “If data are considered sufficient for risk assessment, and *if neurotoxicity is the effect occurring at the lowest dose level* (i.e., the critical effect), an oral or dermal RfD or an inhalation RfC, based on neurotoxic effects, is then derived.” (EPA 1998, at 2)

Unlike EPA's 2010 risk assessment, a diligent evaluation of fluoride's neurotoxicity would consider the voluminous data that has been released since the NRC published its review in March 2006. Towards this end, Petitioners have attached an exhaustive list of human, animal, and cell studies of fluoride's neurotoxicity that have become available since NRC's review.⁶

In total, Petitioners have identified 196 published studies that have addressed the neurotoxic effects of fluoride exposure subsequent to the NRC's review, including 61 human studies, 115 animal studies, 17 cell studies, and 3 systematic reviews.

The post-NRC human studies include:

- 54 studies investigating fluoride's effect on cognition, including but not limited to IQ, with all but 8 of these studies finding statistically significant⁷ associations between fluoride exposure and cognitive deficits.⁸ (Appendix A)
- 3 studies investigating fluoride's effect on fetal brain, with each of the 3 studies reporting deleterious effects. (Appendix B)
- 4 studies investigating fluoride's association with other forms of neurotoxic harm, including ADHD, altered neonatal behavior, and various neurological symptoms. (Appendix C)

The post-NRC animal studies include:

- 105 studies investigating fluoride's ability to produce neuroanatomical and neurochemical changes, with all but 2 of the studies finding at least one detrimental effect in the fluoride-treated groups. (Appendix D)
- 31 studies investigating fluoride's effect on learning and memory, with all but one of the studies finding at least one deleterious effect in the fluoride-treated groups. (Appendix E)
- 18 studies investigating fluoride's impact on other parameters of neurobehavior besides learning and memory, with all but one of the studies finding effects. (Appendix F)

The post-NRC cell studies include:

- 17 studies, including 2 studies that investigated and found effects at fluoride levels that chronically occur in the blood of Americans living in fluoridated communities. (Appendix G)

⁶ Included among these studies are Chinese language studies that were originally published in Chinese journals prior to 2006 but were not translated and made available in the U.S. until after the NRC's review. Excluded from these studies are those that are only available in abstract form, and animal/cell studies that have not yet been published and/or translated into English.

⁷ In 4 of the 8 studies not finding statistically significant associations, the IQs of the children in the high-fluoride area were lower than in the low-fluoride area. (Eswar et al. 2011; Yang et al. 2008; Fan et al. 2007; Zhang et al. 1998) The 4 studies that did not find any association between fluoride exposure and IQ, significant or otherwise, are: Broadbent et al. 2015; Kang et al. 2011; He et al. 2010; and Li et al. 2010.

⁸ Petitioners are aware of two unpublished fluoride/IQ studies from Mexico, one which reports a significant relationship between prenatal fluoride exposure and reduced IQ (water F = 3.1 mg/L; urine F = 2.0 mg/L) (Rocha Amador et al. 2016), and one which reports no association between childhood IQ and low-level prenatal and postnatal exposures (Thomas 2014). The Thomas study failed to detect an association between IQ and urinary/serum fluoride concentrations in a population with average urinary and serum fluoride levels among pregnant women of 0.89 mg/L and 0.02 mg/L, respectively, and average urinary fluoride concentrations among children of 0.64 mg/L. The Thomas study, however, failed to find a significant correlation between urinary and serum fluoride levels, which raises questions about whether the study's spot-sample testing method reliably reflected the chronic fluoride intake among the cohort.

In addition to the above studies, Petitioners are submitting three post-NRC systematic reviews of the literature, including two that address the human/IQ literature, and one that addresses the animal/cognition literature. (NTP 2016; Choi et al. 2012; Tang et al. 2008).

V. FLUORIDE POSES NEUROTOXIC RISKS AT LEVELS RELEVANT TO U.S. POPULATION

A frequent claim made by those who continue to promote fluoridation is that the doses of fluoride associated with neurotoxicity in humans and animals so vastly exceed the levels which Americans drinking fluoridated water receive as to be entirely irrelevant. In support of this claim, proponents of fluoridation often point to the *highest* levels that have been linked to neurotoxicity, while ignoring the *lowest* levels (and even the *typical* levels) that have been associated with harm.⁹ This focus on the *highest* levels that cause harm as the starting point for analysis, rather than the lowest levels, clashes with standard tenets of risk assessment, including EPA's *Guidelines*, where the starting point for risk characterization analysis is to determine the *Lowest* Observable Adverse Effect Level (LOAEL) or No Observable Adverse Effect Level (NOAEL).¹⁰

A. Fluoride Repeatedly Linked to Reduced IQ at “Safe” Water Fluoride Levels

Contrary to the oft-repeated claim that fluoride neurotoxicity is only found at irrelevantly high doses, the existing studies of fluoride-exposed human populations have consistently found neurotoxic effects at water fluoride levels well below the current MCLG. To help clarify this issue, we examined the IQ studies that were included in the meta-review by Choi, et al. (2012). Proponents of fluoridation have dismissed the relevance of the Choi meta-review on the grounds that the IQ studies it included were in communities with fluoride levels that ranged as high as 11 ppm. As can be seen in the following table, however, the majority of waterborne fluoride studies (i.e., 13 of 18)¹¹ that Choi reviewed included communities with fluoride levels below the 4 mg/L MCLG. Further, each of the 13 studies that investigated the effect of fluoride levels below 4 mg/L (average F = **2.3 mg/L**) found these communities to have a lower average IQ than the control (average reduction = 6.3 IQ points), with the difference reaching statistical significance in 10 of the 13 studies.¹²

⁹ Another common misconception is that the endemic fluorosis/IQ studies prove the safety of fluoridated water because the control populations in these studies often have 0.7 to 1.0 mg/L fluoride in their water. Using areas with 0.7 to 1.0 mg/L as the *control*, however, says nothing about the safety of these levels since they are not compared against communities with *lower* fluoride levels.

¹⁰ As the *Guidelines* note, “Typically, estimates of the NOAEL/LOAEL are taken from the *lowest* part of the dose-response curve associated with impaired function or adverse effect.” (EPA 1998, at 58). Similarly, when the Benchmark Dose (BMD) approach is utilized instead of the NOAEL/LOAEL methods, EPA's point of departure is the low end of the dose-response curve, not the high end.

¹¹ We excluded any waterborne-fluoride exposure studies that did not report the water fluoride levels in the endemic fluorosis area(s). We excluded Li et al. (2010) because it did not compare a high fluoride community against a low-fluoride community, but simply looked at whether children with dental fluorosis in the high-fluoride community (2.5 mg/L) had lower IQ than children without dental fluorosis in the same community. We treated the Wang et al. 2001 and Yang et al. 1994 papers as a single study because it is apparent from the IQ data in the two papers that they are based on the same underlying IQ study. For the 18 qualifying studies, we reviewed the manuscripts to determine the lowest average fluoride concentration in each of the studies that was associated with reduced IQ. In studies with multiple exposure groups (e.g., Yao et al. 1996; Yao et al. 1997), we selected the lowest exposure group that had a reduction in IQ. For studies that only provide a range of fluoride levels for a given exposure group, we selected the midway point in the range to represent the average fluoride concentration for the group.

¹² As set forth in the accompanying table, one of the two studies that failed to find a statistically significant difference in average IQ (Wang et al. 2001) found an “obvious” increase in the rate of children with IQ scores lower than 80 (36.7% vs. 16.7%).

TABLE 1: Water Fluoride Levels and Associated IQ Changes in Studies Reviewed by Choi, et al.		
Study	Water F Level	IQ Change
Zhang et al. 1998	0.8 mg/L	-2.1 ^g
Lin et al. 1991	0.9 mg/L ^Ω	-7.0 ^a
Xu et al. 1994	2.0 mg/L ^Ω	-5.6 ^d
Yao et al. 1996	2.0 mg/L	-3.6 ^d
Yao et al. 1997	2.0 mg/L	-5.1 ^d
Pourleslami et al. 2011	2.4 mg/L	-6.4 ^a
Xiang et al. 2003	2.5 mg/L	-8.2 ^d
Seraj et al. 2006	2.5 mg/L	-11.0 ^b
An et al. 1992	2.7 mg/L	-7.9 ^f
Hong et al. 2001	2.9 mg/L ^Ω	-7.2 ^d
Wang 2001/Yang 1994 [¶]	3.0 mg/L	-5.0 ^h
Lu et al. 2000	3.2 mg/L	-10.9 ^e
Fan et al. 2007	3.2 mg/L	-2.3 ^g
Zhao et al. 1996	4.1 mg/L	-7.5 ^c
Chen et al. 1991	4.6 mg/L	-3.8 ^d
Wang et al. 1996	4.8 mg/L	-5.6 ^a
Wang et al. 2006	5.5 mg/L	-4.1 ^d
Wang et al. 2007	8.3 mg/L	-6.0 ^a
^a p<0.05; ^b p=0.025; ^c p<0.02; ^d p<0.01; ^e p<0.005; ^f Statistical significance not reported; ^g Not statistically significant; ^h Not statistically significant when analyzed in terms of average IQ, but “obvious” difference seen when analyzed in terms of percentage with low IQ; ^Ω High-fluoride + low-iodine versus low-fluoride + low-iodine; [¶] These two papers appear to be the same study.		

Additional studies finding reduced IQ in communities with less than 4 mg/L have become available in the years since Choi’s review, including Sudhir et al. 2009 (**0.7 to 1.2 mg/L**); Zhang S. et al. 2015 (**1.4 mg/L**), Das & Mondal 2016 (**2.1 mg/L**), Choi et al. 2015 (**2.2 mg/L**), Sebastian & Sunitha 2012 (**2.2 mg/L**); Trivedi et al. 2012 (**2.3 mg/L**), Khan et al. 2015 (**2.4 mg/L**); Nagarajappa et al. 2013 (**2.4 to 3.5 mg/L**), Seraj et al. 2012 (**3.1 mg/L**), and Karimzade et al. 2014a,b (**3.94 mg/L**). Another study (Ding et al. 2011), which did not fit within Choi’s dichotomous exposure criteria, found reduced IQ in an area with fluoride levels ranging from **0.3 to 3 mg/L**. In total, there are now 23 studies reporting statistically significant reductions in IQ in areas with fluoride levels currently deemed safe by the EPA (less than 4 mg/L).¹³

B. Fluoride Linked to Cognitive Deficits at Levels of Individual Exposure Seen in Western Fluoridated Populations

Although the water fluoride levels associated with IQ reductions are modestly higher than the levels currently used in artificially water fluoridation programs, it is important to distinguish between the *concentration* of fluoride in a community’s water supply and the *dose* of fluoride that an individual ingests. For example, in rural China (where most of the IQ studies have been conducted), fluoridated toothpaste is rarely used, with less than 10% of children using any fluoride toothpaste at all.¹⁴ By contrast, in the United States, over 95% of toothpastes are fluoridated and research shows that toothpaste can contribute more fluoride to a child’s daily intake than fluoridated water. (CDC 2013c; Zohoori et al. 2013, Zohoori et al. 2012; Levy et al.

¹³ The 23 studies include the 10 studies listed in Table 1, the 11 studies listed in the paragraph above, and the studies by Eswar et al. 2011 and Shivaprakash et al. 2011.

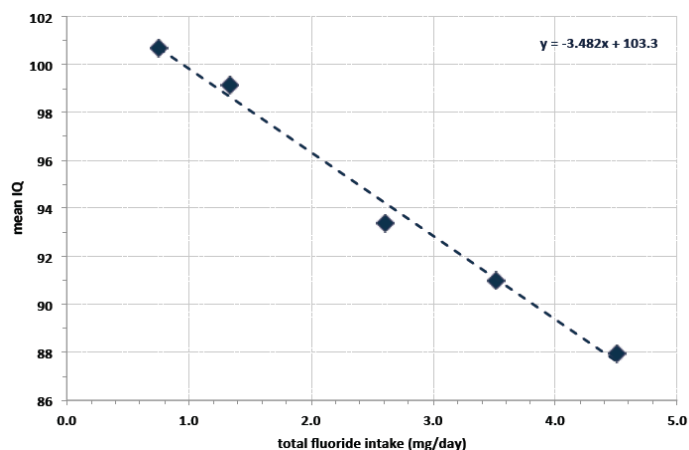
¹⁴ According to a 1996 national oral health survey in China, 75% of 12-year-old children use toothpaste, and of the children who use toothpaste, only 11% use fluoride-containing varieties. (Zhu et al. 2003, at 291, Tbl 1.)

1999). As noted by a review in the *Journal of Public Health Dentistry*, “Virtually all authors have noted that some children could ingest more fluoride from dentrifice alone than is recommended as a total daily fluoride ingestion.”¹⁵ (Levy and Guda-Chowdhury 1999, at 216-17). The abundance of fluoridated toothpaste in the U.S., versus its relative scarcity in rural China, will therefore lessen the difference in total daily fluoride intake between these populations. In fact, as set forth below, available evidence suggests that the (i) daily fluoride doses, (ii) urine fluoride levels, (iii) serum fluoride levels, and (iv) dental fluorosis levels associated with IQ reductions in the Chinese studies are seen in children and adults in western countries living in fluoridated areas. Each of these four metrics of fluoride exposure provide a more direct assessment of individual fluoride exposure than water fluoride concentration, and are thus more probative for risk assessment purposes.

(i) Daily Fluoride Intake

The overlap between the daily fluoride intake associated with significant IQ loss in China and the daily doses American children now receive is highlighted by the recent studies from Wang et al. (2012) and Das et al. (2016). In the study by Wang, researchers investigated the impact of total daily intake of fluoride on IQ among the same group of 512 rural Chinese 8-to-13 year old children studied by the Xiang team in 2003. (Xiang et al. 2003a,b). As the following table shows, the Wang study found a clear dose response relationship between daily fluoride dose and reduced IQ.

FIGURE 1: Relationship Between Daily Fluoride Dose and IQ
(SOURCE: Wang et al. 2012, Tbl. 4)



Wang found that a daily intake of just 2.61 mg F/day was associated with a large, statistically significant 7.28-point drop in *average* IQ. Assuming an average weight of 32 kg,¹⁶ a daily intake

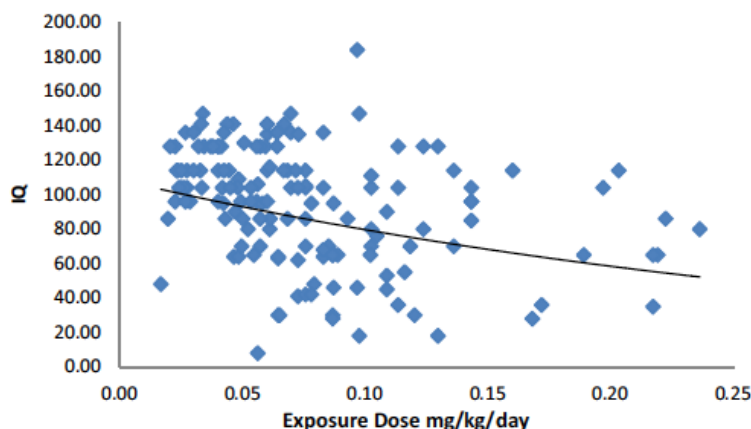
¹⁵ Petitioners recognize that the FDA has jurisdiction over fluoride toothpaste, but any assessment of the safe level of a contaminant in drinking water cannot be conducted in a vacuum, and must consider the additive effect of waterborne exposures with identifiable non-water sources of exposure. When considering the neurologic safety of fluoridated water, therefore, it is critical to consider the aggregate dose of fluoride in fluoridated communities from all sources, including toothpaste. EPA has recognized this principle in its “relative source contribution” analyses, which the EPA OW conducts when calculating the drinking water equivalent level (DWEL) of a reference dose. EPA (2016). TSCA also specifically contemplates consideration of aggregate and sentinel exposures in Section 6 risk evaluations. See 15 U.S.C. § 2605(b)(4)(F).

¹⁶ The authors did not provide data on the average weight of the children in the study, and we could not find data on the average weight of rural Chinese children between the ages of 8 and 13. We did, however, find published data on

of 2.61 mg would provide a dosage of approximately **0.08 mg/kg/day**,¹⁷ which is *lower* than the *average* daily intake (**0.087 mg/kg/day**) for non-nursing infants in the United States, as estimated by the NRC, and just two times greater than the *average* daily dose for 8-12 year old American children.¹⁸ (NRC 2006, at 65, Tbl. 2-13). Moreover, recent research has found that 10 to 15% of children under the age of 6 ingest over 0.05 mg/kg/day *from toothpaste alone*, with some children ingesting as much as **0.159 mg/kg/day** from this single source. (Strittholt et al. 2016 at 70 tbl. 2; Zohoori et al. 2012 at 418 tbl 2; Zohoori et al. 2013 at 460 tbl 1; Levy & Guha-Chowdhury 1999 at 217 tbl 3). In one study, published by Proctor & Gamble scientists (Strittholt et al. 2016), 5% of pre-schoolers were found to ingest at least 0.49 mg fluoride per brushing, which, at two brushings per day, will produce a daily dosage of 0.07 mg/kg/day from toothpaste alone for the average-weighting 2-year-old. (CDC 2000a,b). Other studies are consistent with these estimates. (Oliveria et al. 2007; Bentley et al. 1999; Levy 1993; Naccahe et al. 1992). For the many pre-school children ingesting these dosages from toothpaste, the consumption of fluoridated water will readily push them over the daily dosage (0.08 mg/kg/day) associated with sharp reductions in IQ among rural Chinese children.

Finally, as with other forms of fluoride toxicity, the potential for fluoride neurotoxicity is magnified among children with suboptimal nutrient intake. (Sun et al. 2016; Ge et al. 2011; Hong et al. 2008; Ge et al. 2005; Wang et al. 2004; Ekambaram & Paul 2002; Xu et al. 1994; Lin et al. 1991; Ren et al. 1989; Guan et al. 1988). This is highlighted by the recent study by Das and Mondal which assessed the relationship between fluoride intake and IQ among a population with a high prevalence of underweight children suggestive of an area with pervasive malnutrition. In this population, Das and Mondal confirmed a significant correlation between total fluoride intake and reduced IQ ($r = -0.343$, $p < 0.01$), as plotted in the following figure:

FIGURE 2: Relationship Between Total Daily Intake and IQ
(SOURCE: Das & Mondal 2016, Fig. 6)



the weight of rural Chinese children ages 0 to 7, as well as average weight data on U.S. children between the ages of 2 and 20. (Li et al. 2011; CDC 2000a,b) A comparison of these two datasets shows that rural Chinese children weigh approximately 4 kg less than U.S. children (18.7 kg vs. 23 kg) between the ages of 6 and 7. We thus determined the average weight of 8-to-13 year old rural Chinese children by calculating the average weight of 8-to-13 year old U.S. from the CDC growth charts (=36 kg) and subtracting 4 kg (=32 kg).

¹⁷ It bears noting that 0.08 mg/kg/day is EPA's new reference dose for fluoride, which the Agency established to protect solely against severe dental fluorosis (without the protection of a single uncertainty factor to account for potential neurotoxic risks). (EPA 2010)

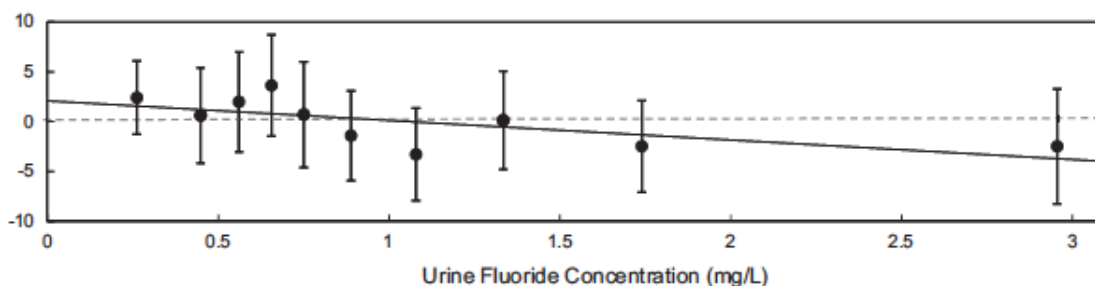
¹⁸ A recent national analysis of urinary fluoride levels in the United Kingdom UK concluded that over 65% of adults living in fluoridated areas consume more than 0.057 mg/kg/day. (Mansfield 2010)

Notably, Das and Mondal found a sharp 15-point drop in IQ among underweight children with *mild* dental fluorosis who were consuming average total daily fluoride exposures of just **0.06 mg/kg/day**. (Das & Mondal 2016, at 218, Tbl. 3). As discussed above, this is a dose that many infants and children in the U.S. are estimated to exceed.

(ii) Urine Fluoride Level

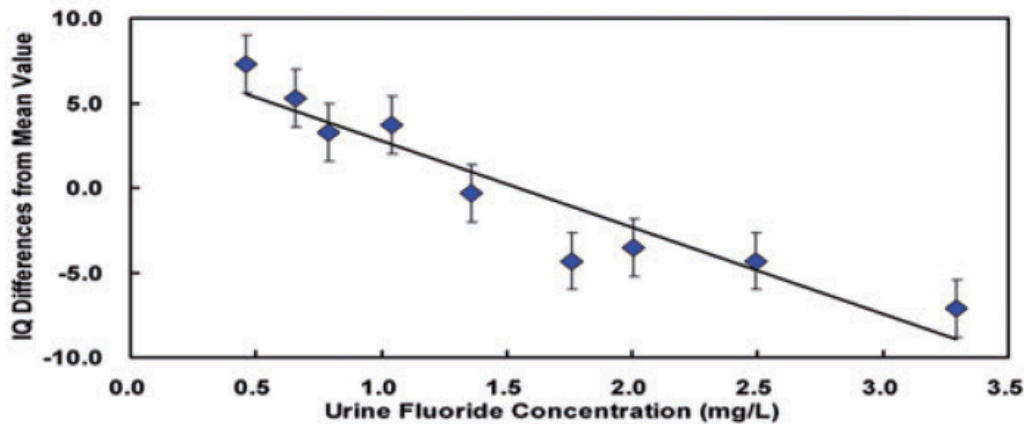
Many of the studies on fluoride and IQ have measured the concentration of fluoride in children's urine as a marker of individual fluoride exposure. As summarized in a 2011 review, these studies have repeatedly found significant, often large reductions in IQ when the average urinary fluoride level exceeds 2.5 mg/L, (Spittle 2011), and multiple regression analyses have repeatedly found that increased urinary fluoride correlates with reduced IQ, (Das et al. 2016; Zhang S. et al. 2015; Wang et al. 2007), even when controlling for other key risk factors. (Rocha Amador et al. 2009). While urinary fluoride levels exceeding 2.5 mg/L present a clear risk for neurotoxicity, recent studies have also found decrements in IQ at urinary fluoride concentrations well below this level. Most notable in this regard is the study by Ding et al., which examined the correlation between urinary fluoride and IQ among children with urinary fluoride levels ranging from just 0.25 mg/L to 3 mg/L. As shown in the following figure, a clear dose response trend was found within this urinary fluoride range ($p < 0.0001$), with the downward trend becoming apparent at roughly 1 mg/L. When adjusted for age, each 1 mg/L increment in urinary fluoride correlated with an average drop of 0.59 IQ points ($p < 0.0001$).

FIGURE 3: Relationship Between Urinary Fluoride and IQ
(SOURCE: Ding et al. 2011, Fig. 2)



The dose-response trend found by Ding is consistent with more recent data published by Zhang et al. 2015, which is displayed in the following figure. As can be seen, the Zhang study found a clear drop in IQ at urinary fluoride levels between 0.5 and 1.5 mg/L.

FIGURE 4: Relationship Between Urinary Fluoride and IQ
(SOURCE: Zhang S. et al. 2015, Fig. 1)



More recently, researchers have investigated the prevalence of cognitive impairment among elderly individuals living in an endemic fluorosis region of China. (Li et al. 2016). The researchers found a very high prevalence of cognitive impairment (81.2%) in the fluorosis region, and, in a case-control analysis, found a significantly elevated urinary fluoride level (2.5 mg/L vs. 1.5 mg/L, $p < 0.05$) in the cognitive impairment group.¹⁹ (Li et al. 2016, at 57, Tbl. 3). The data from this case-control analysis is presented in the following table:

TABLE 2: Urinary Fluoride & Cognitive Impairment in Elderly
(SOURCE: Li et al. 2016, Tbl 3)

Characteristics ^a	Normal group (n=38)	Cognitive impairment group (n= 38)	P value
Male/female	26/12	26/12	
Age (years)	64.95±4.60	65.05±4.40	0.920
MMSE score	27.79±0.96	21.50±4.37	0.000
Total daily water fluoride intake(mg ^b)	2.23±2.23	3.62±6.71	0.228
Urinary fluoride(mg/L ^b)	1.46±1.04	2.47±2.88	0.046
fluorosis score ^b	0.74±0.98	1.29±1.01	0.018
Serum Hcy(μmol/L ^b)	19.97±8.88	20.14±9.29	0.934

^a Values are n/n for gender and mean±SD for other indices.

^b The original values were log-transformed before comparison. The difference between two groups was tested using Student's t test.

Although there is a paucity of published data on urinary fluoride levels in the United States, a study from England found that the average urinary fluoride level among 88 adults living in a fluoridated area was 1.28 mg/L, with 16% of the tested individuals having over 2 mg/L, and 6%

¹⁹ A clear dose-response relationship between urinary fluoride and cognitive impairment was not detected in the non-case control component of Li et al.'s analysis, although urinary fluoride was found to be elevated in the population with severe cognitive impairment.

of individuals having over 3 mg/L.²⁰ (Mansfield 1999, at 28, Tbl. 1). These levels overlap those that have been associated in endemic fluorosis areas with both reduced IQ in children and cognitive impairment in the elderly. (Li et al. 2016; Zhang S. et al. 2015; Ding et al. 2011). A more recent study from Canada found that 5 percent of *children* had ≥ 1.3 mg/L fluoride in their urine, which is well within the range of urinary fluoride levels associated with reduced IQ in the Ding and Zhang studies. (Saravanabhavan et al. 2016). A separate Canadian study found that the *average* urinary fluoride concentration in fluoridated areas was 0.76 mg/L, which was almost twice the concentration (0.47 mg/L) found in non-fluoridated areas. (McLaren 2016).

(iii) Serum Fluoride Level

In 2011, Xiang et al. published a paper which assessed the relationship between IQ and serum fluoride levels in the same group of 512 children studied in Wang's daily dose analysis discussed above. As with the daily dose analysis, the authors found a significant dose-response relationship between serum fluoride level and reduced IQ. As shown in the following table, children with just 0.05 to 0.08 mg/L fluoride in their serum had a statistically significant 4.2-point drop in IQ when compared against children with less than 0.05 mg/L.²¹

TABLE 3: Association Between Serum Fluoride and Children's IQ
(SOURCE: Xiang et al. 2011, Tbl 2)

Serum fluoride level quartiles	N	Mean IQ	SD IQ	p ^b	IQ<80 (%)	p ^c	OR (95% CI) for IQ<80
Q1 and Q2 (<0.05 mg/L)	259	100.1	13.4	<0.001	7.0		1
Q3 (0.05–0.08 mg/L)	126	95.9	13.7		15.1	0.004	2.22 (1.42–3.47)
Q4 (>0.08 mg/L)	127	92.1	13.4		17.3		2.48 (1.85–3.32) p trend<0.001 ^d

^aAdjusted for age and gender using Logistic regression analysis. The data from two villages were combined.

^bNOVA.

^cChi-square test.

^dTests of linear trend were computed using ordinal scoring.

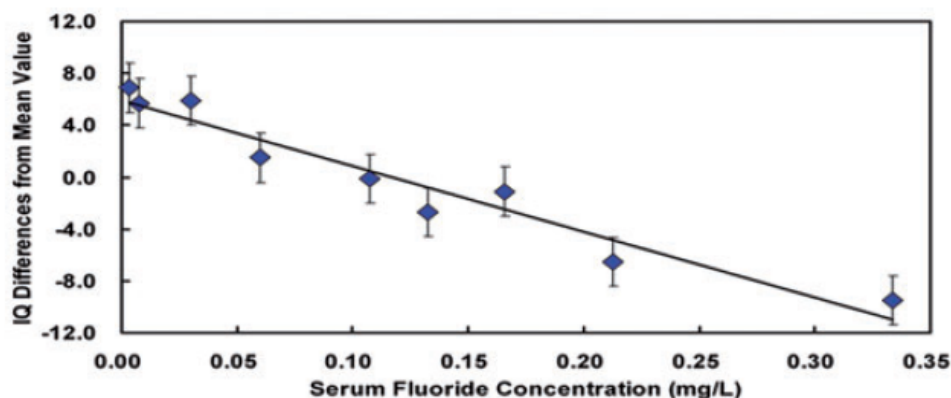
Abbreviations: CI Confidence Interval, IQ Intelligence Quotient, OR Odds Ratio, SD Standard Deviation.

The Xiang team's findings are consistent with the findings of other recent studies, including Guo Z. et al. (2008), which found impairment in neurobehavioral function among adult industrial workers with average serum fluoride levels of 0.066 mg/L, and Zhang S. et al. (2015), which found significant reductions in IQ among children with just over 0.05 mg/L fluoride in their blood when compared to children with the lowest levels. The Zhang study plotted the serum data in the following figure:

²⁰ These urinary fluoride levels exceeded those that were found among individuals (n = 165) living in non-fluoridated areas. The average urinary fluoride level in the non-fluoridated areas was 0.96 mg/L; with 8% having more than 2 mg/L; and 4% having more than 3 mg/L. (Mansfield 1999, at 28, Tbl. 1)

²¹ As the authors emphasize, their finding of a 4-point IQ drop in children with more than 0.05 mg/L fluoride in their serum does *not* mean that serum levels lower than 0.05 mg/L are safe.

FIGURE 5: Relationship Between Serum Fluoride and IQ
(SOURCE: Zhang S. et al. 2015, Fig. 1)



To put these serum fluoride levels in the context of U.S. exposures, typical serum fluoride levels for adults in the U.S. have been stated to range from about 0.01 to 0.076 mg/L (0.5 to 4 uM/L). (CDC 2014, at 2; see also Kissa 1987). In one study of infants, an average concentration of 0.08 mg/L was found among healthy 4-to-6 month old infants, while an average concentration of 0.10 to 0.18 mg/L was found among 4-to-18 month old infants receiving peritoneal dialysis. (Warady et al. 1989). A study by Ekstrand found that infants ingesting 0.25 mg in supplement form have spikes in their blood ranging as high as 0.092 mg/L, and averaging 0.063 mg/L. (Ekstrand 1994, at 159 tbl 3). Ekstrand's study did not measure the impact of ingesting fluoride in the form of infant formula reconstituted with fluoridated water, but the resulting daily peaks in serum fluoride levels may be comparable, since Ekstrand estimates that infants consuming fluoridated formula receive doses (up to five times a day) that are comparable to a supplement (i.e., 20-30 ug/kg of fluoride per formula feeding vs. 32 ug/kg per supplement). (Ekstrand 1994, at 162).

While there has long been a paucity of serum fluoride data available for children in the U.S., a recent NHANES survey found that roughly 1 in 200 American children between the ages of 3 to 19 have serum fluoride levels exceeding 0.04 mg/L. (NHANES 2016). Since there are approximately 70 million American children in this age range, (US Census Bureau 2011), the NHANES data indicates that approximately 350,000 American children have serum fluoride levels in the approximate range associated with overt neurotoxic effects.

(iv) Dental Fluorosis Level

EPA OW's 2010 risk assessment of the non-cancer effects of fluoride rests on the implicit assumption that *severe* dental fluorosis is the most sensitive adverse endpoint of fluoride exposure. This assumption, however, is at odds with a number of studies which have found significant associations between fluoride exposure and cognitive deficits among children with *non-severe* forms of fluorosis. Most notably, the study by Ding et al. (2011) found a dose-dependent relationship between reduced IQ and urinary fluoride concentration in a population where severe dental fluorosis was *completely absent*. The Ding study thus suggests that the doses of fluoride that impair cognitive ability are lower than the doses that cause severe fluorosis. Other recent studies have found impairment in cognitive abilities among children with *mild* fluorosis, *moderate* fluorosis, and *moderate/severe* fluorosis when compared with children with no fluorosis, thus suggesting that the doses of fluoride associated with the milder forms of

fluorosis are sufficient to impair brain development.²² (Das & Mondal 2016 at tbl 3; Choi et al. 2015; Li et al. 2009; Khan et al. 2015; Shivaprakash et al. 2011; Sudhir et al. 2009 at tbl 3).

Consistent with the above studies of human populations, studies of rodents have repeatedly found significant impairments in learning ability as well as other neurotoxic harms among rats with only mild forms of fluorosis.²³ (Liu et al. 2011; Pereira et al. 2011; Niu et al. 2008; Chioca et al. 2008). As noted by Niu et al., “these findings indicate that fluoride . . . can influence spontaneous behaviors and lower the learning ability of rats before the appearance of dental lesions.”²⁴ (Angmar-Mansson & Whitford 1982).

Taken together, the available human and animal studies suggest that fluoride can impair cognitive abilities prior to the development of severe fluorosis. This has obvious public health relevance in the United States, since recent studies show that the prevalence of dental fluorosis is now at historically unprecedented levels. In CDC’s 1999-2004 NHANES survey, for example, 41% of adolescents were diagnosed with dental fluorosis, including 8.6% with mild fluorosis, and 4% with moderate and severe. These rates are considerably higher than what was found in the 1986-87 national survey by the National Institute of Dental Research. (Beltran et al. 2010; Heller et al. 1997). Moreover, the rates appear to have increased yet further since the 1999-2004 NHANES survey. Specifically, the 2011-2012 NHANES survey found dental fluorosis in 58.3% of the surveyed adolescents, including an astonishing 21.2% with moderate fluorosis, and 2% with severe. (NHANES 2014). Since there are an estimated 42 million adolescents currently living in the U.S.,²⁵ the NHANES data suggests that up to 24 million adolescents now have some form of dental fluorosis, with over 8 million adolescents having moderate fluorosis, and 840,000 having severe fluorosis.

The NHANES surveys do not provide data on the respective rates of fluorosis in fluoridated vs. non-fluoridated communities, but research has repeatedly confirmed that both the prevalence and severity of dental fluorosis are greater in U.S. communities with fluoridated water than in communities without. (Heller et al. 1997; Jackson et al. 1995; Williams & Zwemer 1990). Ending fluoridation will thus reduce the number of children developing dental fluorosis, and the accompanying neurotoxic risks associated with the doses that produce fluorosis.²⁶

²² Some studies, however, including Ding, have not found a clear relationship between IQ and dental fluorosis status, thus suggesting that a person’s susceptibility to fluoride-induced neurotoxicity may be distinct from their susceptibility to dental fluorosis. (Asawa et al. 2014; Li et al. 2010)

²³ Consistent with this, Zhou Z. et al. (2016) recently reported that biochemical changes occur in rats at doses well below those that cause dental fluorosis.

²⁴ While rodent teeth undergo constant remodeling, thus distinguishing them from human teeth, research has found that rat teeth develop dental fluorosis at the same serum fluoride levels that produce fluorosis in humans. According to Angmar-Mansson & Whitford, “It is well known that, in fluoridated drinking water studies with rats, a water fluoride concentration of 10-25 ppm is necessary to produce minimal disturbances in enamel mineralization. Because of the high water concentrations required, the rat has been regarded as more resistant to this adverse effect of fluoride. However, when the associated plasma levels are considered, the rat and the human appear to develop enamel fluorosis at very nearly the same concentrations.” (Angmar-Mansson & Whitford 1982, at 339) Based on this finding, Angmar-Mansson & Whitford concluded that “the rat is a better model for the study of human enamel fluorosis than previously believed.” (*Id.* at 334)

²⁵ This estimate is based on the number of Americans between the ages of 10 and 19. It comes from the Office of Adolescent Health, which is part of the Department of Health & Human Services. (DHHS 2016).

²⁶ Decreases in dental fluorosis have been documented following temporary suspensions of fluoridation as short as 11 months. (Burt et al. 2000)

VI. NEUROTOXIC RISK OF LOW DOSE FLUORIDE IS FURTHER SUPPORTED BY ANIMAL AND CELL STUDIES

The studies linking fluoride exposure with neurotoxic effects in humans are consistent with research on both experimental animals and cell cultures. Studies on rodents, for example, have found neurotoxic effects, including learning impairments, at water fluoride levels less than 15 mg/L, with 8 studies published since the NRC review reporting neurotoxic effects at water fluoride levels less than 5 mg/L. These are notably low fluoride levels for rodents, since it is generally estimated that rats require approximately 5 times more fluoride in their water to achieve the same level of fluoride in their blood as humans, and over 10% of children living in fluoridated areas receive the same waterborne dosage of fluoride (mg/kg/day) as rats drinking water with up to 9 mg F/L. (NTP 2016, at 56-57)

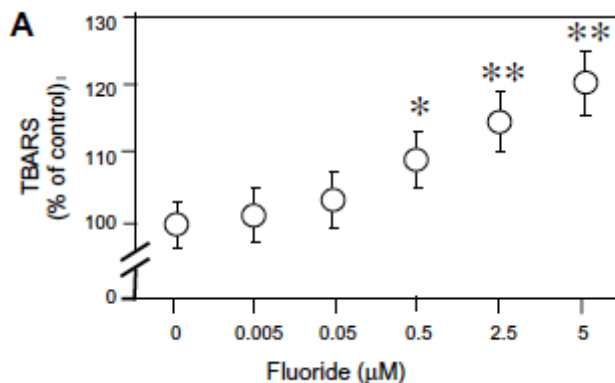
The following table lists the water fluoride concentrations associated with neurotoxic effects in rodents:

Study	F Concentration (F-)	Duration of Treatment	Effects
Chouhan (2010)	1 mg/L	4 months	Oxidative stress; alterations in neurotransmitters
Wu (2008)	1 mg/L	Gestation	Behavioral alterations
Gao (2009)	2.3 mg/L	6 months	Enzyme inhibition; impaired cognition; oxidative stress
Liu (2014)	2.3 mg/L	1 month	Impaired learning
Liu (2010)	2.3 mg/L	6 months	Impaired cognition; alterations in neurotransmitters
Sandeep (2013)	2.3 mg/L	3 months	Behavioral alterations; enzyme inhibition
Zhang (2015)	2.3 mg/L	6 months	Oxidative stress; activation of AGE/RAGE system
Zhang Z. (2008)	4.5 mg/L	10 weeks	Impaired learning; pathological changes in synaptic structure
Zhu (2011); Zhang (2011); Zhang J. (2013)	6.8 mg/L	9 months	Trend towards decreased synaptic membrane fluidity & PSD-95 expression level; altered expression of CaMKII α , c-fos, Bax, and Bcl-2 (statistically significant at 13.6 mg/L)
Bhatnagar (2011)	8 mg/L	1 month	Morphological changes in neurons
Banala (2015)	9 mg/L	Gestation + 30 days postnatal	Impaired learning; loss of motor control; & oxidative stress
Reddy (2014)	9 mg/L	3 months	Alterations in neurotransmitters; altered immunological parameters; oxidative stress
Lou (2014); Lou (2013)	10 mg/L	6 months	Increase in apoptotic neurons; altered expression of Bax and Bcl-2 at protein & mRNA levels; abnormal mitochondrial dynamics
Sun (2008)	10 mg/L	6 months	Impaired learning; increased ChE
Han (2014)	11 mg/L	6 months	Trend towards impaired learning (Fig 2a)
Zhou (2014)	11.3 mg/L	6 months	Altered expression levels of cytokines in hippocampus
Guner (2016)	13.6 mg/L	Gestation + Postnatal	Increased catalase immunoreactivity

Fluoride's ability to cause neurotoxic effects at low levels of exposure is further corroborated by in vitro cell studies conducted subsequent to the NRC review. While most of the in vitro studies

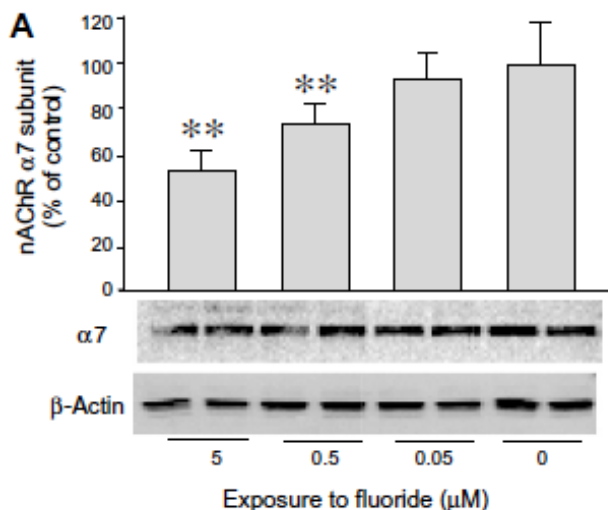
used high levels of fluoride (≥ 10 mg/L), two of the studies investigated the effects of concentrations that are found in the bloodstream of many Americans.²⁷ Both of these low-concentration studies detected adverse effects. As displayed in the following figure, Gao et al. (2008) found that just 0.5 μ M of fluoride (i.e., 0.009 mg/L) caused lipid peroxidation in SH-SY5Y cells after 48 hours of exposure. Most individuals living in fluoridated areas in the United States have fluoride levels in their blood that exceed this level. (CDC 2014; Kissa 1987).

FIGURE 6: Level of Lipid Oxidation in SH-SY5Y Cells Exposed to Fluoride
(SOURCE: Gao et al. 2008, Fig. 1)



The Gao study also found that 0.5 μ M had an effect on the level of $\alpha 7$ nAChR protein in the SH-SY5Y cells, as displayed in the following figure:

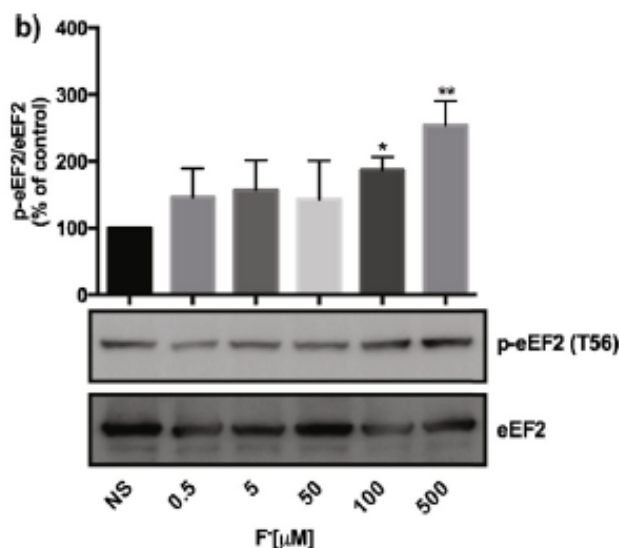
FIGURE 7: Level of $\alpha 7$ nAChR subunit protein in SH-SY5Y Cells Exposed to Fluoride
(SOURCE: Gao et al. 2008 Fig. 3)



²⁷ Consistent with the findings of these two brain cell studies, the in vitro studies by Gutowska have repeatedly found that concentrations of just 1 to 3 μ M (i.e., 0.019 to 0.057 mg/L) are sufficient to affect inflammatory responses. (Gutowska et al. 2015, 2012, 2010). The Gutowska team's findings underscore the biologically active nature of even micromolar concentrations of fluoride, and warrant consideration for their implications to neuroinflammation. (Louveau et al. 2011).

Flores-Mendez et al. (2014) also investigated the effect of 0.5 μM , and, per the following figure, found a suggestive trend towards an increase in eEF2 phosphorylation in cultured Bergmann glia cells (BGC) after 15 minutes of treatment.

FIGURE 8: eEF2 Phosphorylation in BGC Cultures Treated with Fluoride
W(SOURCE: Flores-Mendez et al. 2014., Fig. 4b)



Flores-Mendez also found a suggestive trend towards an increased influx of calcium into the cell after 3 minutes of treatment with 5 μM fluoride (i.e., 0.095 mg/L). (Flores-Mendez et al. 2014, at 130 Fig. 5c) This concentration can be found chronically in the blood of children with kidney disease living in fluoridated areas, (Warady et al. 1989), and is intermittently exceeded by children ingesting fluoride supplements, fluoridated toothpaste, and other dental products.²⁸

VII. RECENT EPIDEMIOLOGICAL STUDIES CORROBORATE NEUROTOXIC RISK FROM FLUORIDATED WATER IN WESTERN POPULATIONS

The overlap between the internal doses of fluoride experienced in western populations and the internal doses associated with neurotoxic effects in humans, animals, and cell cultures, is cause for public health concern. Although there has been a notable lack of epidemiological research into fluoride's neurotoxic effects in the U.S., a 2015 study by Malin and Till found a statistically significant correlation between the prevalence of water fluoridation at the state level and Attention-Deficit Hyperactivity Disorder (ADHD). Fluoridation prevalence significantly correlated with ADHD even after controlling for socioeconomic status (SES), and fluoridation "appeared to be the more robust predictor." As Malin and Till note, their findings "are consistent with prior epidemiological studies that have associated high and low fluoride concentration exposure with neurodevelopmental effects in children."

²⁸ While there is a paucity of research on the serum fluoride levels following use of fluoride tablets and toothpaste, Ekstrand found that, among a group of 5 preschool children, ingestion of 0.5 mg fluoride tablets caused serum fluoride levels to spike to 0.095 mg/L in 30 minutes, while ingestion of 0.6 mg fluoride in toothpaste caused serum fluoride levels to exceed 0.08 mg/L. (Ekstrand et al. 1983, Fig. 1). Since some preschool children swallow considerably more than 0.6 mg fluoride per brushing, the serum fluoride levels will likely be higher than 0.08 mg/L in those children. Levy & Guha-Chowdhury, for example, cite research showing that 10% of preschool children swallow in excess of 0.73 mg of fluoride per brushing. (Levy & Guha-Chowdhury 1999, Tbl. 3).

Another epidemiological study from 2015, by Peckham et al., provides further corroborative evidence that fluoridation can cause neurotoxic effects. Peckham's study examined the relationship between water fluoride levels and hypothyroidism in the United Kingdom, and found that fluoride levels ≥ 0.7 mg/L significantly correlated with higher rates of hypothyroidism. This correlation was strengthened, not weakened, when controlling for the covariates of age, gender, and index of deprivation.

The correlation between fluoridation and hypothyroidism reported by Peckham is (i) plausible and (ii) adds further support for the capacity of fluoridated water to cause neurotoxic effects. First, the correlation is plausible because, as summarized by the NRC, multiple lines of research indicate that fluoride can lower thyroid function, including the fact that fluoride was once used as a drug for this precise purpose, at doses as low as 2 to 5 mg/day. (NRC 2006; Galletti & Joyet 1958). Second, the correlation between fluoridation and hypothyroidism adds further support for fluoridation's neurotoxic potential because, as recognized in EPA's *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone." (EPA 1998, at 50). Since both clinical and subclinical hypothyroidism during pregnancy have been associated with reduced IQ in offspring, (Korevaar et al. 2016; Murphy et al. 2015; Klein et al. 2001), the relationship between fluoridation and hypothyroidism provides a mechanism by which fluoridation can reduce IQ, even absent a direct neurotoxic effect.

VIII. SUSCEPTIBLE SUBPOPULATIONS ARE AT HEIGHTENED RISK OF FLUORIDE NEUROTOXICITY AND NEED PROTECTION

EPA's *Guidelines* recognize that individual susceptibility to the neurotoxicity of environmental toxicants can vary by a factor of ten or more,²⁹ and is influenced by factors such as nutritional status, age, genetics, and disease. (EPA 1998, at 63-65, 78). Each of these factors—nutritional status, age, genetics,³⁰ and disease—are known to influence an individual's susceptibility to chronic fluoride toxicity.³¹ Any factor that can predispose an individual to chronic fluoride toxicity should be suspected as a factor that will predispose to fluoride neurotoxicity as well. In fact, recent research in both humans and animals has specifically demonstrated that nutrient deficiencies (i.e., iodine³² and calcium³³) amplify fluoride's neurotoxicity.³⁴ Further, Zhang S. et al. (2015) reported that certain COMT gene polymorphism

²⁹ "In general, it is assumed that an uncertainty factor of 10 for intrapopulation variability will be able to accommodate differences in sensitivity among various subpopulations, including children and the elderly. However, in cases where it can be demonstrated that a factor of 10 does not afford adequate protection, another uncertainty factor may be considered in conducting the risk assessment." (EPA 1998, at 65)

³⁰ Studies have repeatedly confirmed that genetic factors can significantly increase susceptibility to fluoride toxicity, (Everett 2011), including effects on bone (Kobayashi et al. 2014; Yan et al. 2007; Mousny et al. 2006); teeth (Buzalaf et al. 2014; Ba et al. 2011; Huang et al. 2008; Everett et al. 2002); and reproductive hormones (Zhou et al. 2016).

³¹ See, e.g., Irigoyen-Camacho ME et al. (2016); Simon et al. (2014); Ravula et al. (2012); Itai et al. (2010); Schiffli (2008); NRC (2006); Teotia et al. (1998); Torra et al. (1998); Warady et al. (1989); and Turner et al. (1995). For additional citations and discussion, see http://www.fluoridealert.org/studies/skeletal_fluorosis03.

³² See, e.g., Ge et al. (2011); Hong et al. (2008); Ge et al. (2005); Wang et al. (2004); Xu et al. (1994); Lin et al. (1991); Ren et al. (1989); Guan et al. (1988).

³³ Sun et al. (2016); Ekambaram & Paul (2002).

³⁴ As discussed earlier, the study by Das & Mondal (2016) examined the impact of fluoride on IQ in a population with a high prevalence of underweight children, suggestive of an area with chronic malnutrition. In this population, a daily fluoride dose of just 0.06 mg/kg/day was associated with a sharp 15-point drop in IQ among children with mild fluorosis. (Das & Mondal 2016, at 218, Tbl. 3).

greatly influences the extent of IQ loss resulting from fluoride exposure, which is consistent with research on other neurotoxins, including methyl mercury. (Julvez & Grandjean 2013).

While the full range of individual susceptibility to fluoride neurotoxicity in the U.S. cannot be precisely calculated, some subpopulations can be identified as being at elevated risk, including infants,³⁵ the elderly,³⁶ and individuals with (A) deficient nutrient intake (particularly iodine and calcium),³⁷ (B) certain COMT gene polymorphisms,³⁸ and (C) kidney disease.³⁹ Various factors suggest that African Americans may also suffer disproportionate risks as well, including elevated use of infant formula,⁴⁰ elevated exposure to lead,⁴¹ depressed calcium and anti-oxidant intake,⁴² and significantly higher rates of dental fluorosis, including in its moderate and severe forms.⁴³

³⁵ Although *breast fed* infants receive the lowest fluoride intake by bodyweight (<0.001 mg/kg/day) of all age-groups (Ekstrand et al. 1981), this situation is flipped on its head when infants are fed *formula reconstituted with fluoridated water*. As noted by the NRC, “On a per-body-weight basis, infants and young children have approximately three to four times greater exposure than do adults.” (NRC 2006, at 3). Not only do formula-fed infants receive an unnaturally high dose, they have an impaired ability to excrete the fluoride they ingest, retaining up to 87% of the absorbed dose. Ekstrand et al. (1994). Infants exposed to formula made with fluoridated water are at significantly higher risk for developing dental fluorosis on their permanent front teeth. Hong et al. (2006). In light of the research linking dental fluorosis and modest levels of fluoride exposure with reduced IQ, infants are a susceptible subpopulation of critical concern for fluoride neurotoxicity.

³⁶ As noted in the *Guidelines*, “[T]he aged population is considered to be at particular risk [of neurotoxicity] because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult.” (EPA 1998, at 65). This is of concern because the brain will be more exposed to fluoride in older age due to the (1) increased level of fluoride circulating in the serum from both age-related decreases in renal function and age-related increases in bone resorption (particularly in post-menopausal women), and (2) increased permeability of the blood-brain barrier. Rosenberg (2014); Ravula et al. (2012); Itai et al. (2010); Torra et al. (1998). This may help explain the very high prevalence of cognitive impairment (82%) found among elderly individuals in an endemic fluorosis area. Li et al. (2016); see also Shao et al. (2003).

³⁷ According to a consensus paper in the *Journal of the National Medical Association*, “Eighty-six percent of African Americans get just more than half of the daily recommended amount of calcium, and only half consume one or more servings of dairy a day. Of particular concern, 83% of African-American children 2-17 years of age are not getting enough calcium.” Wooten & Price (2004). Insufficient nutrient intakes in the United States are severe enough in some individuals to qualify as nutrient deficiencies. Recent NHANES data, for example, found that 6% of Americans have a vitamin C deficiency. CDC (2012). Vitamin C deficiency has been found to exacerbate fluoride’s toxicity in humans, while vitamin C supplementation has been found to ameliorate fluoride’s neurotoxic effects in animals. Nabavi et al. (2013); Basha & Madhusudhan (2010); Pandit et al. (1940). With respect to iodine, NHANES data shows that women of *child bearing* age (20 to 39 years old) have “median urine iodine concentrations bordering on insufficiency.” Pfeiffer et al. (2013). Children born to women with insufficient iodine levels should be considered a susceptible subpopulation for fluoride neurotoxicity due to fluoride’s ability to exacerbate the neurological effects of inadequate iodine.

³⁸ The study by Zhang S. et al. (2015) suggests that children with the COMT val/val genotype suffered a five-fold larger drop in IQ than children with the COMT val/met and met/met genotypes. As noted by Zhang, “In the subpopulation carrying the COMT reference genotype (Model 3), 1 unit increase in urinary fluoride (1 mg/l) was associated with a decrease of 9.67 points of IQ and was significant after controlling for covariates (P=0.003). Among children carrying variant genotypes, 1 unit increase in [urinary fluoride] resulted in a decrease of 1.85 IQ points, but this was not statistically significant in this stratum.”

³⁹ See, e.g., Schiffi (2008); Ibarra-Santana et al. (2007); Torra et al. (1998); Warady et al. (1989).

⁴⁰ In national surveys conducted between 2000 and 2008, “Black infants consistently had the lowest rates of breastfeeding initiation and duration across all study years.” CDC (2013b).

⁴¹ It is well established that non-Hispanic black children have higher levels of lead in their blood than non-Hispanic white children. CDC (2013a); Bernard & McGheein (2003). This has relevance to the risks of fluoride exposure, since animal studies have found that fluoride can exacerbate the toxicity of lead, and vice versa. Leite et al. (2011); Sawan et al. (2010); Mahaffey & Stone (1976).

⁴² Watters et al. (2007); Wooten & Price (2004). The reduced level of anti-oxidants found in the blood of African American adults, which may relate to low consumption of fresh fruits and vegetables (Zenk et al. 2005), has implications for fluoride toxicity, because oxidative stress is a key mechanism by which fluoride harms cells, (Barbier 2010), including in the brain. (E.g., Banala & Karnati 2015; Zhang K. et al. 2015; Basha et al. 2014; Nabavi et al.

Any risk assessment on the neurotoxicity of fluoride must thus be mindful of the need to protect susceptible subpopulations; anything less would be inconsistent with EPA's *Guidelines*. In fact, even where there is *no* specific information to indicate differential susceptibility to a neurotoxin, EPA's *Guidelines* state that a margin of safety (i.e., "uncertainty factor") should still be incorporated to account for "*potential* differences in susceptibility." (EPA 1998, at 78). In the case of fluoride, there is *uncontroverted* evidence indicating substantial differences in susceptibility, and thus the basis for applying an uncertainty factor is especially strong.

IX. A REFERENCE DOSE PROTECTIVE AGAINST FLUORIDE NEUROTOXICITY IS INCOMPATIBLE WITH WATER FLUORIDATION IF STANDARD RISK ASSESSMENT PROCEDURES ARE APPLIED

As recognized in EPA's *Guidelines*, it is standard risk assessment practice to apply "uncertainty factors" (UF) of 10 when converting a LOAEL, NOAEL, or BMD into a safe "reference dose" (RfD) or "reference concentration" (RfC). (Martin et al. 2013) This is significant because application of even a single UF of 10 to the daily doses/concentrations of fluoride associated with neurotoxic harm in humans and animals produces an RfD or RfC that is less than, and thereby *incompatible with*, the levels of fluoride added to water for fluoridation (0.7 to 1.2 mg/L). This point is illustrated in the following table, which shows what the RfD and RfC would be if *merely* one UF of 10 was applied to the various fluoride exposures that have been associated with neurotoxic harm.

TABLE 5: RfCs/RfDs for Fluoride If Just One Uncertainty Factor of 10 Is Applied				
Fluoride Dose/Concentration Producing Harm	Study	Effect	RfD/RfC After Application of one UF	Water Fluoridation Doses/Concentrations
0.06 mg/kg/day (Dose/Humans)	Das (2016)	Reduced IQ	0.006 mg/kg/day	0.03 to 0.09 mg/kg/day (Average Total Daily Dose in F areas) (NRC 2006, Tbl 2-13)
0.08 mg/kg/day (Dose/Humans)	Wang (2012)	Reduced IQ	0.008 mg/kg/day	0.03 to 0.09 mg/kg/day (Average Total Daily Dose in F areas) (NRC 2006, Tbl 2-13)
1 mg/L (Water/Rats)	Chouhan (2010); Wu (2008)	Behavioral alterations; Neurochemical changes	0.1 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.7 to 1.2 mg/L (Water/Humans)	Malin (2015); Peckham (2015)	Hypothyroidism; ADHD	0.07 to 0.12 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.7 to 1.2 mg/L (Water/Humans)	Sudhir (2009)	Reduced IQ	0.07 to 0.12 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)

2013; Nabavi et al. 2012a,b,c; Basha et al. 2011; Inkielewicz-Stepniak & Czarnowski 2011; Nabavi et al. 2011; Bharti & Srivastava 2009; Gao et al. 2009).

⁴³ Studies dating back to the 1960s have found that African Americans suffer higher rates of dental fluorosis than Caucasians. Martinez-Mier & Soto-Rojas 2010; Beltran-Aguilar et al. (2015, tbl. 23); Kumar (2000); Williams & Zerner (1990); Butler et al. (1985); Russell (1962). Consistent with this, documents obtained through the Freedom of Information Act show a stark racial disparity in adolescent fluorosis rates in CDC's 1999-2004 NHANES survey, with 58% of African American adolescents diagnosed as having the condition, versus 36% of white adolescents. FOIA (2011).

2.3 mg/L (Water/Rats)	Gao (2009); Liu (2014); Liu (2010); Sandeep (2013); Zhang K (2015)	Impaired learning; Behavioral alterations; Neurochemical changes	0.23 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
2.3 mg/L (Water/Humans)	The average water F concentration in the 13 studies reviewed by Choi (2012) which found effects at < 4 mg/L	Reduced IQ	0.23 mg/L	0.7 to 1.2 mg/L (Water F Levels in F areas)
0.05 mg/L (Serum/Humans)	Xiang (2011)	Reduced IQ	0.005 mg/L	0.019 to 0.076 mg/L (Typical range of Serum F in US) (CDC 2014)

The need to apply *at least* one UF to the doses/concentrations associated with fluoride neurotoxicity cannot seriously be disputed. After all, these are doses and concentrations associated with overt neurotoxic harm, and thus the safe reference dose will obviously need to be set at a lower level. Moreover, as discussed above, EPA's *Guidelines* recognize that there is often a large degree of intra-species variability in the way humans respond to neurotoxins and a default factor of 10 is generally considered necessary to protect against this variability.⁴⁴

Although we have only utilized one uncertainty factor in the analysis here, we do *not* mean to imply that only one UF is sufficient for converting these adverse effect levels into RfDs or RfCs. Indeed, it is clearly insufficient to apply only one UF when converting a LOAEL from an animal study into a safe dose for humans. We present the above Table, therefore, for the limited purpose of demonstrating that *even if* EPA were to apply an *insufficiently* protective UF, the resulting RfD or RfC would still be incompatible with water fluoridation; thus highlighting, once again, the overlap between the doses associated with a neurotoxic risk and the doses many Americans now receive.

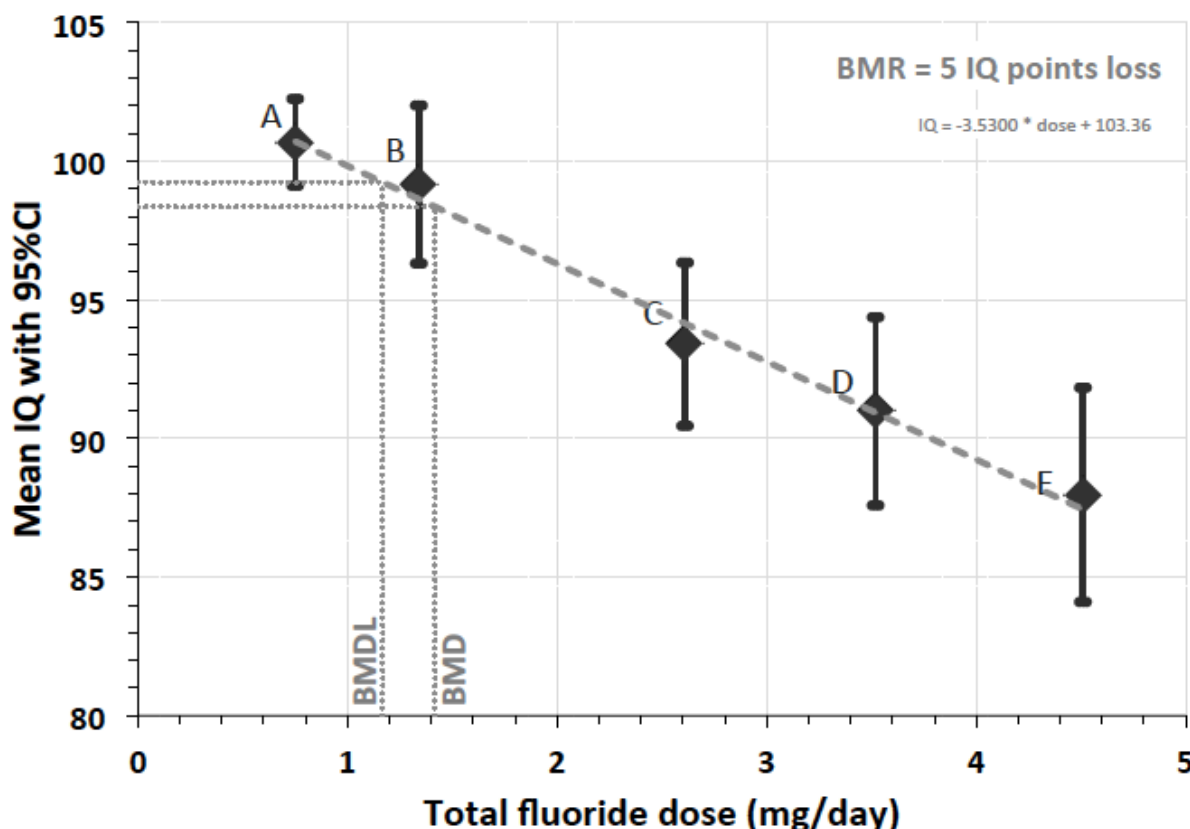
Finally, Petitioners recognize that EPA has a preference for utilizing Benchmark Dose (BMD) methodology for risk assessments where there is dose-response data that permits the analysis. In the case of fluoride neurotoxicity, the Xiang dataset is a suitable dataset for conducting a BMD analysis, as it shows a dose-related reduction in IQ spanning five dose groups ranging from 0.75 to 4.5 mg F/day without an apparent NOAEL. (Wang et al. 2012). EPA's *Guidelines* recognize the probative value (and rarity) of a human dataset covering more than three dose groups.⁴⁵ Further, the Xiang dataset benefits from the fact that the study controlled for most of the key confounding factors, including lead, arsenic, iodine, parental education, and socioeconomic status. (Xiang et al. 2003a,b; Xiang et al. 2013).

⁴⁴ According to the *Guidelines*, "In general, it is assumed that an uncertainty factor of 10 for intrapopulation variability will be able to accommodate differences in sensitivity among various subpopulations, including children and the elderly. However, in cases where it can be demonstrated that a factor of 10 does not afford adequate protection, another uncertainty factor may be considered in conducting the risk assessment." (EPA 1998, at 65). As demonstrated by Martin et al. (2013), the use of a default uncertainty factor of 10 to account for intra-species variability is amply justified by empirical data on differences in human sensitivity related to genetic polymorphisms, gender, disease, old age, and toxicokinetics.

⁴⁵ The *Guidelines* note that (1) "Human studies covering a range of exposures are rarely available" and (2) "Evidence for a dose-response relationship is an important criterion in establishing a neurotoxic effect, although this analysis may be limited when based on standard studies using three dose groups or fewer." (EPA 1998, at 50 & 106).

As with the LOAEL analyses discussed above, application of the BMD methodology to the Xiang dataset produces an RfD for fluoride that is incompatible with water fluoridation. Specifically, applying EPA's BMDS software to Xiang's dataset produces a BMD of just **1.4 mg F/day**, if the BenchMark Response (BMR) is set at 5 IQ points, as displayed in the following figure.⁴⁶ This result can be interpreted as predicting that children exposed to 1.4 mg fluoride per day will have, on average, 5 less IQ points than children exposed to no fluoride. The RfD would obviously need to be set at a lower level, since such a large loss in IQ is clearly an adverse effect, and because uncertainty factors would need to be added to account for variation in sensitivity within a population as large as the U.S.

FIGURE 9: BMD for Loss of 5 IQ Points from Fluoride
(Linear Model, BMR = 5 IQ Points)



X. THE BROADBENT STUDY DOES NOT ESTABLISH THE SAFETY OF FLUORIDATION

Some commentators have incorrectly claimed that the recent study by Broadbent et al. establishes the safety of water fluoridation for neurologic development. The Broadbent study found no difference in the IQs of children and adults who spent their first 3 to 5 years of life in fluoridated (0.7 to 1.0 mg/L) vs. non-fluoridated (0 to 0.3 mg/L) areas of Dunedin, New Zealand. A glaring limitation with the Broadbent study, however, is that a substantial portion of the “non-fluoridated” control population used 0.5 mg/day fluoride tablets and fluoridated toothpaste, resulting in only a marginal difference in average total fluoride exposure between the fluoridated

⁴⁶ If the BMR is set at 1 IQ point, the BMD is 0.28 mg/day of fluoride.

and non-fluoridated populations.⁴⁷ In fact, in response to criticism on this point, (Osmunson et al. 2016), the authors conceded that the average difference in total daily intake between the children in the fluoridated and non-fluoridated areas would be ≤ 0.3 milligrams per day, while the average intake for all subjects was 0.9 mg/day.⁴⁸ (Broadbent et al. 2016). At most, therefore, the Broadbent study established that ≤ 0.3 milligrams of fluoride was not a sufficiently large enough contrast in daily fluoride exposure to produce a demonstrable effect on *average IQ* in the study cohort. This does *not* mean, however, that the fluoride exposures in a fluoridated community are safe, since no truly low exposure comparison group existed in the Broadbent study, and the Broadbent team made no attempt to study vulnerable subsets of the population (e.g., those with suboptimal nutrition, genetic polymorphisms, etc).

The inherent limitation resulting from the Broadbent study's comparison of populations with marginal contrasts in fluoride intake highlights an important strength of the endemic fluorosis/IQ studies from China, India, Iran, and Mexico. Specifically, the endemic fluorosis studies have generally compared communities with clear and stable contrasts in fluoride exposure, thus increasing the power of these studies to detect fluoride's effect on IQ. Moreover, unlike Broadbent's study, many of the endemic fluorosis studies have analyzed the relationship between IQ and individual measures of exposure (e.g., individual urine fluoride levels), thus overcoming the limitation imposed by Broadbent's ecological (group level) estimates of fluoride intake. Although Broadbent and others have criticized the endemic fluorosis studies for failing to control for potential confounders, several of these studies did carefully control for confounders and the association between fluoride and cognitive impairment remained intact. (Choi et al. 2015; Rocha Amador et al. 2009; Xiang et al. 2003a,b; Xiang et al. 2013). Further, while it's undisputed that many of the IQ studies used relatively simple study designs, the consistency of these studies, and their repeated corroboration by research showing that fluoride impairs learning in rodents under carefully controlled laboratory conditions, gives confidence to the conclusion that fluoride is a neurotoxin that impairs cognition.

For the foregoing reasons, the reference dose for protecting against fluoride neurotoxicity cannot reasonably be based on a risk assessment that treats the Broadbent study as establishing 0.7 to 1.0 mg/L as a NOAEL without application of an uncertainty factor(s) to account for intra-human variability and other issues left unanswered by Broadbent's study. Indeed, as spelled out in the *Guidelines*, it is problematic to develop an NOAEL based on a single study of a single neurotoxic endpoint,⁴⁹ particularly a study with such limited "dose spacing" between the groups.⁵⁰

⁴⁷ There are several other significant problems with the Broadbent study as well. First, the study did not collect any data on individual water intake or internal biomarkers of fluoride exposure (e.g., urine fluoride, etc). Second, the study used a crude estimate of fluoride toothpaste usage ("always" vs "sometimes" vs "never") that fails to account for the frequency of brushings per day and actual amount of toothpaste used per brushing, thus obscuring the very large variations of daily exposure that occur among children using fluoride toothpaste. Zohoori et al. 2012; Levy & Guha-Chowdhury 1999, tbl 3. Third, it did not control for potential confounders including blood lead and maternal IQ, even though such information was available and there are plausible reasons for the non-fluoridated subjects to have elevated lead exposure from living in a more rural area known for its highly corrosive drinking water. (Osmunson et al. 2016).

⁴⁸ A previous study of total fluoride intake among 3-to-4 year olds in fluoridated and non-fluoridated areas of New Zealand found the daily intakes to be 0.68 ± 0.27 and 0.49 ± 0.25 mg F/day, respectively. (Guha-Chowdhury et al. 1996).

⁴⁹ According to the *Guidelines*, "Neurotoxic effects (and most kinds of toxicity) can be observed at many different levels, so only a single endpoint needs to be found to demonstrate a hazard, but many endpoints need to be examined to demonstrate no effect. For example, to judge that a hazard for neurotoxicity could exist for a given agent, the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study. In

XI. THE BENEFITS OF PREVENTING FLUORIDE NEUROTOXICITY DWARF THE COSTS OF RESTRICTING FLUORIDE CHEMICALS

EPA's authority to act under Section 6 of TSCA is premised on two distinct findings: (1) a *risk* exists and (2) the risk is *unreasonable*. Here, in evaluating the preliminary question of whether a neurotoxic risk exists from use of fluoridation chemicals, the EPA is duty bound to follow its *Guidelines*, as the Agency has stated it “will follow” the *Guidelines* when “evaluating data on *potential* neurotoxicity associated with exposure to environmental toxicants.” (EPA 1998, at 3). For the reasons set forth above, a good faith application of these *Guidelines* to the current research on fluoride will show that neurotoxicity is a hazard of fluoride exposure, and that the doses associated with this hazard overlap the doses—as reflected by (a) total daily intake, (b) urinary fluoride level, (c) serum fluoride level, and (d) severity of dental fluorosis—that U.S. children are exposed to in areas with fluoridated water. Neurotoxicity must thus be considered a risk from adding fluoridation chemicals to drinking water.

Petitioners now turn, therefore, to the second prong of the inquiry: whether the neurotoxic risk posed by fluoridation chemicals is an unreasonable one. As EPA has stated, the reasonableness inquiry considers the benefits of reducing the risk with the costs of doing so. EPA (1985); 15 U.S.C. § 2605(c)(A). In considering these respective benefits and costs of risk reduction, EPA has stated it will take into account “the extent and magnitude of risk posed; the societal consequences of removing or restricting use of products; availability and potential hazards of substitutes, and impacts on industry, employment, and international trade.” EPA (1985); see also 15 U.S.C. § 2605(c)(A). We turn now to a consideration of these factors

A. Extent and Magnitude of Neurotoxic Risk from Fluoridation Chemicals

There is little question that neurotoxicity is a serious insult to health. (Grandjean & Landrigan 2014). In a nation besieged by neurological disorders of poorly understood etiology, both in young children and the elderly, minimizing exposures to known neurotoxic substances should be a public health priority. (*Id.*)

The reduction in IQ associated with fluoride exposure has been found to be severe enough in some children to produce mental retardation. (*E.g.*, Lin et al. 1991). But even the loss of a single IQ point is associated with significant economic loss. As calculated by Spadaro et al. (2008), a loss of a single IQ point causes an average drop in lifetime earnings of \$18,000 in 2005 U.S. dollars, which, when adjusted for inflation, amounts to \$22,250 in current dollars.⁵¹ Since 200 million Americans now live in areas where water is fluoridated,⁵² and since virtually all Americans consume processed foods and beverages made with fluoridated water, any reduction in IQ from consumption of fluoride-treated water stands to have very large economic consequences.

contrast, to judge that an agent is unlikely to pose a hazard for neurotoxicity, the minimum evidence would include data from a host of endpoints that revealed no neurotoxic effects.” (EPA 1998, at 55).

⁵⁰ According to the *Guidelines*, “the NOAEL is also directly dependent on the dose spacing used in the study.” (EPA 1998, at 57)

⁵¹ We adjusted for inflation by using the U.S. Bureau of Labor Statistics’ CPI Inflation Calculator at <http://data.bls.gov/cgi-bin/cpicalc.pl>.

⁵² The CDC states that 211,393,167 Americans now drink fluoridated water; the vast majority of this population is consuming artificially fluoridated water, as CDC estimates that only 11,883,007 Americans have “naturally” fluoridated water. See: <http://www.cdc.gov/fluoridation/statistics/2014stats.htm>

While the precise extent to which fluoridation is reducing IQ in the U.S. cannot yet be calculated, the dose-response data from Wang et al. (2012) indicates that daily consumption of a liter of fluoridated water per day (=0.7 mg F/day) during childhood would cause IQ to drop by an average of 2.5 points when compared to children with no exposure to fluoride, while consumption of half a liter per day (=0.35 mg F/day) would cause IQ to drop by an average of 1.25 IQ points. (Wang's data is consistent with a linear, no threshold, dose-response relationship between fluoride and IQ, and we have applied Wang's data here with that assumption.)

In 2010, there were 74.2 million children under the age of 18 living in the U.S., of which we can estimate roughly 50 million were living in fluoridated areas.⁵³ US Census Bureau (2011). If we apply Wang's dose-response data and assume that these 50 million children consumed between 0.5 to 1 liters of fluoridated water per day during childhood, fluoridation would have caused a loss of between 62.5 to 125 million IQ points. Based on the earnings data from Spadaro et al. (2008), a loss in the range of 62.5 to 125 million IQ points represents a total loss in lifetime earnings of between \$13.9 to 27.8 *trillion* for this generation.

Due to the sheer number of people exposed to fluoridation chemicals, even if only sentinel or susceptible populations in fluoridated areas suffer IQ loss, the economic impacts will still be substantial. For example, even if we conservatively assume that only 1 to 5% of children in a fluoridated area suffer any IQ loss,⁵⁴ and even if this IQ loss averaged just 1 IQ point,⁵⁵ this would still amount to 500,000 to 2,500,000 lost IQ points, with a total loss in lifetime earnings ranging from \$11.1 billion to \$55.6 billion for this generation alone.

In short, because of the *massive* extent of exposure to fluoridation chemicals in the U.S., even small effects on IQ will have very substantial economic consequences.

B. Societal Consequences of Restricting Use of Fluoridation Chemicals

If EPA exercised its authority under TSCA to ban the waterborne use of fluoridation chemicals, the one and only potential societal consequence would be an increase in tooth decay. Current research, however, indicates that any increase in dental treatment costs would be small, inconsistent, and far less than the loss in earnings associated with even small drops in IQ.

First, Petitioners wish to call the Agency's attention to the fact that there are no randomized controlled trials on the effectiveness of fluoridation, and few of the available studies adequately account for potential confounders like socioeconomic status, sealants, and dietary habits. (Iheozor-Ejiofor et al. 2015; Cheng et al. 2007). The evidence has thus been characterized by the Cochrane Collaboration as having "high risk of bias" and limited applicability to modern lifestyles. (Iheozor-Ejiofor et al. 2015).

⁵³ According to the CDC, 66% of the U.S. population receives fluoridated tap water. See: <http://www.cdc.gov/fluoridation/statistics/fsgrowth.htm>.

⁵⁴ We base the 1 to 5% estimate on the approximate percentage of children with serum fluoride levels in the range (~0.05 mg/L) associated with a 4-point IQ drop (n = ~1%), and the approximate percentage of children with urinary fluoride levels (≥ 1.3 mg/L) associated with clear reductions in IQ (n = 5%). For discussion of this data, see pages 9 to 12 above. Since the serum and urinary fluoride data is for the *general population*, these estimates likely *understate* the percentage of children in *fluoridated* areas with serum and urinary fluoride levels in this range.

⁵⁵ This is a substantially lower loss in IQ than would be predicted by existing research. As noted in footnote 54 above, the serum fluoride level (~0.05 mg/L) upon which this estimate is based was associated with a 4-point drop in IQ by Xiang et al. (2011). Further, research on susceptible populations has found dramatic losses in IQ from fluoride exposure, including an average 15-point drop among malnourished children with mild fluorosis. Das & Mondal (2016).

Second, methodological limitations notwithstanding, modern studies of fluoridation and tooth decay have found that the difference in cavity rates between fluoridated and non-fluoridated areas is small, inconsistent, and often non-existent, particularly in the permanent teeth. (Chankanka et al. 2011a,b; Maupome et al. 2007; Warren et al. 2006; Shiboski et al. 2003; Colquhoun 1997; Heller et al. 1997; Diesendorf et al. 1997; Leroux et al. 1996; Brunelle & Carlos 1990; Yiamouyiannis 1990; Hildebolt et al. 1989).

Because of the small and inconsistent differences in cavities now seen between fluoridated and non-fluoridated areas, sensitive measurements of tooth decay must be utilized in order to detect *any* differences in decay.⁵⁶ But, even when sensitive measurements are utilized, the differences remain small in absolute terms, inconsistent, and overshadowed by the influence of other factors known to affect decay. (Chankanka et al. 2011a; Warren et al. 2006; Armfield & Spencer 2004). A large-scale study in Australia, for example, found that adolescents who consumed fluoridated water their entire life had just 0.08 less decayed tooth surfaces (1.35 vs. 1.43 DMFS) than adolescents who consumed non-fluoridated water their entire life. (Armfield & Spencer 2004, at 290 tbl.3). Consistent with these findings, studies from Canada, Cuba, Finland, Germany, and the United States did not detect *any* measurable increase in decay following the termination of water fluoridation programs.⁵⁷ (Maupome et al. 2001; Burt et al. 2000; Kunzel et al. 2000a,b; Seppa et al. 2000).

Third, one of the few *empirical* investigations of *actual* dental costs in fluoridated vs. non-fluoridated areas found little meaningful difference in frequency or costs of treatment. (Maupome et al. 2007). The study examined the frequency and costs (in 1995 U.S. dollars) of restorative dental procedures over a six-year time period in fluoridated and non-fluoridated areas of Oregon and Washington. Consistent with other recent research, the authors noted that the difference in frequency and costs of dental treatment was “generally small,” with several of the age groups in the fluoridated areas having a higher frequency of dental treatment procedures than their peers in the non-fluoridated areas. (Maupome et al. 2007, at 228, tbl. 3). In total, the dental treatment costs in the fluoridated areas over the six-year period averaged \$355 versus \$387 in the non-fluoridated areas.⁵⁸ (*Id.* at 228, tbl. 4). When adjusted to 2016 dollars, the average difference in dental costs was thus only \$51 over the 6-year period, *or just over \$8 per person per year*. With an average life expectancy of 78.8 years,⁵⁹ the Maupome study suggests that fluoridation saves an average of \$665 in lifetime dental costs in the U.S. This amounts to less than 3 percent of the reduction in lifetime earnings that results from the loss of a single IQ point (\$22,250).

Finally, the cost-effectiveness study (Griffin et al. 2001) that advocates of fluoridation generally rely upon, is based on theoretical estimates that have several major, demonstrable problems that inflate the purported savings. (Ko & Thiessen 2015). The Griffin paper provides estimates of the annual savings in dental costs from fluoridation (in 1995 U.S. dollars) based on a review of several studies of caries rates in fluoridated vs. non-fluoridated communities. The paper estimates that fluoridation provides a net savings of anywhere from \$0.85 to \$33.71 per year.

⁵⁶ As evident by the studies of Yiamouyiannis (1990) and Brunelle and Carlos (1990), the difference in tooth decay between fluoridated and non-fluoridated populations, while detectable when calculated in terms of Decayed, Missing & Filled Surfaces (DMFS), is not large enough to be detectable when calculated in terms of Decayed, Missing and Filled Teeth (DMFT).

⁵⁷ A recent Canadian study by McLaren et al. (2016) reported an increase in decay following cessation of fluoridation in Calgary. However, as explained by Connett (2016), the entirety of this purported increase disappears when survey data omitted from the paper is considered.

⁵⁸ The average costs estimate is for people who had at least one restorative procedure during this time.

⁵⁹ See: <http://www.cdc.gov/nchs/fastats/life-expectancy.htm>

(Griffin et al. 2001, at 82, tbl. 4). Over the course of the average lifespan, this amounts to a lifetime savings ranging from \$67 to \$2656 per person when expressed in 1995 U.S. dollars. Adjusting for inflation, this amounts to a lifetime savings of \$106 to \$4,207 in 2016 dollars, which, even at its zenith, amounts to less than 20% of the costs (\$22,500) incurred from loss of a single IQ point

As discussed by Ko and Thiessen (2015), Griffin's cost-savings estimates suffer from several important limitations. First, and foremost, Griffin did not make any attempt to include the costs of treating dental fluorosis in the costs side of the ledger, thereby inflating the net savings. This is a particularly significant omission since Griffin elsewhere estimated, in a separate paper, that fluoridating water causes 2 percent of children to develop aesthetically objectionable fluorosis on their front teeth. (Griffin et al. 2002). With approximately 50 million children now living in fluoridated areas, this amounts to roughly 1 million children developing aesthetically objectionable fluorosis on their front teeth as a direct result of water fluoridation. But even this is an under-estimate, since Griffin based this on the NIDR's 1986-87 national survey, and more recent national surveys show that both the rate and severity of dental fluorosis have increased considerably over the past 20 years. (NHANES 2014; Beltran 2010). In fact, as mentioned earlier, the 2011-2012 NHANES survey found that an astonishing 21% of adolescents now have *moderate* fluorosis, and an additional 2% have severe fluorosis. (NHANES 2014) Since many children who have fluorosis staining on their front teeth will have it cosmetically treated,⁶⁰ the aggregate costs of this treatment will be substantial, and any cost-effectiveness evaluations of fluoridation that fail to account for these treatment costs will artificially inflate the cost-savings of fluoridation. Griffin's cost-savings estimates should not, therefore, be taken at face value, but even if they are, they suggest a range of lifetime savings for the current population under 18 (i.e., \$5.3 to \$210 billion) that is still substantially less than the range of earnings losses associated with fluoridation-related drops in IQ (i.e., \$11.1 billion to \$27.8 trillion).

C. Availability and Potential Hazards of Substitutes to Fluoridation Chemicals

The addition of fluoridation chemicals to drinking water began in the U.S. prior to the advent of topical fluoride products in an era when public health authorities believed fluoride's predominant benefit to teeth comes from *ingestion*. Things have changed dramatically since that time.

Today, over 95% of toothpastes contain fluoride, as do many other dental products, (CDC 2013c), and dental researchers now universally acknowledge that fluoride's predominant benefit is topical, not systemic. (E.g., Fejerskov 2004; Featherstone 2000). As explained in the *Journal of the American Dental Association*, "fluoride incorporated during tooth development is insufficient to play a significant role in cavity protection." (Featherstone 2000, at 891). The Centers for Disease Control has confirmed the primacy of fluoride's topical mechanisms, declaring that "fluoride's predominant effect is *posteruptive* and *topical*." (CDC 2001, at 4). The NRC has confirmed this as well, stating that "the major anticaries benefit of fluoride is *topical* and *not systemic*." (NRC 2006, at 13).

Since fluoride's primary benefit comes from topical contact with the teeth, there is little benefit from swallowing fluoride, in water or any other product. In fact, a recent study of the relationship between tooth decay and total daily fluoride ingestion failed to find a detectable relationship

⁶⁰ Research has found that teeth with dental fluorosis, including in its "mild" forms, is perceived as an objectionable condition that warrants dental treatment. (E.g., Alkhatib et al. 2004; Riordan 1993). Consistent with this, studies have repeatedly found that staining of the front teeth, including the white splotches of fluorosis, can cause children significant anxiety and distress about the appearance of their teeth. (E.g., Tellez et al. 2012; Marshman et al. 2008).

between the two. (Levy et al. 2009). Other recent studies investigating the relationship between tooth decay and individual biomarkers of fluoride intake (e.g., toenail fluoride content and dental fluorosis) have reported similar results. (Charone et al. 2012; Komarek et al. 2005).

The widespread availability of topical fluoride products highlights the lack of necessity of adding fluoridation chemicals to water, particularly since the quality of evidence for fluoride toothpastes has been recognized as vastly superior to the quality of evidence for water fluoridation.⁶¹ (Cheng et al. 2007, at 701). Furthermore, it is well established that western countries that do not fluoridate their water have tooth decay rates that are just as low, and often lower, as western countries that do fluoridate their water.⁶² (Cheng et al. 2007; Pizzo et al. 2007; Neurath 2005; Colquhoun 1997; Diesendorf et al. 1997; Bratthall et al. 1996; Diesendorf 1986).

While fluoride toothpastes and other fluoridated dental products carry their own potential hazards *when ingested*, these products—unlike drinking water—are not *designed* to be ingested. Further, unlike the addition of fluoridation chemicals to drinking water, the use of topical fluoride products does not result in the contamination of processed foods and beverages, thus making it easier to regulate the amount of fluoride ingested when topical fluoride products are the vehicle for delivering fluoride to those who want it.

D. Impacts on Industry, Employment & International Trade from Restricting Fluoridation Chemicals

Prohibiting the addition of fluoridation chemicals to drinking water will have little, if any, impact on industry, employment and international trade. The chemicals used for fluoridation are waste by-products of the U.S. phosphate industry and various Chinese fertilizer and chemical companies. The sale of fluoridation chemicals represents a very small portion of the U.S. phosphate industry's overall sales, and thus removing this very limited market will have little impact on the profitability of the phosphate industry. Finally, while ending fluoridation will curb *imports* of fluoridation chemicals from China, it will not impact American exports, because—to the best of Petitioners' knowledge—U.S. companies do not export fluoridation chemicals abroad. Accordingly, ending fluoridation will not have any disadvantageous impact on America's balance of trade.

XII. IT IS IN THE PUBLIC INTEREST FOR EPA TO ACT UNDER TSCA

EPA has recognized that TSCA invests the Agency with the authority to regulate drinking water additives. (EPA/FDA 1979). Although EPA also has certain authorities to regulate fluoride in drinking water under the SDWA, it is in the public interest for EPA to act under TSCA because it allows EPA to enact a far less expensive regulation that targets fluoridation chemicals in a more narrowly crafted manner that is justified on both policy and scientific grounds.

Under SDWA, the EPA can limit the legally permissible levels of chemicals in public drinking water supplies by enacting "Maximum Contaminant Levels" (MCLs). The EPA can effectively ban fluoridation under SDWA, therefore, by enacting an MCL below the so-called "optimal"

⁶¹ This is evident when comparing the Cochrane Collaboration's systematic review of the effectiveness of fluoride toothpastes with its systematic review of water fluoridation. *Compare* Iheozor-Ejiofor et al. (2015) *with* Marinho et al. (2003).

⁶² For additional data demonstrating the lack of difference in tooth decay rates between countries with extensive water (and/or salt) fluoridation and those without, Petitioners refer EPA to the documentation available at: <http://fluoridealert.org/studies/caries01/>

concentration of fluoride used in fluoridation programs (0.7 mg/L). Since an MCL does not distinguish, however, between fluoride that is *added* to water and fluoride that occurs naturally therein, implementing an MCL below the level used in fluoridation would force communities with elevated levels of naturally occurring fluoride to implement filtration programs. Banning fluoridation *indirectly* by reducing the MCL under SDWA would thus be more expansive in scope, and far more expensive in implementation, than a *direct* ban on fluoridation additives under TSCA.

As with other naturally occurring toxicants, like arsenic, Petitioners recognize that natural fluoride contamination of some rural water supplies is a problem that needs to be addressed. However, there is a distinct policy difference between a risk *imposed* on a population through the *purposeful addition* of a chemical to water, versus a risk that arises from a naturally occurring phenomena beyond human control. The difference between these two scenarios is material under TSCA because it speaks to the ease by which the risk can be eliminated, and thereby the *reasonableness* of continuing to endure the risk. Differential treatment of the two scenarios is thus justified.

Differential treatment is further justified by laboratory and epidemiological research linking artificial fluoridation chemicals (i.e., fluorosilicic acid and sodium fluorosilicate) with pipe corrosion and elevated blood lead levels. (Coplan et al. 2007; Maas et al. 2007; Macek et al. 2006; Masters et al. 2000). This research includes the CDC's own study of the issue, which analyzed the blood lead levels of children from the 1988-1994 National Health and Nutrition Examination Survey. (Macek et al. 2006).

Although the CDC study is sometimes touted as refuting the link between fluoridation and lead hazards, a close look at its data reveals that it is actually *consistent* with the fluorosilicate/lead thesis. As can be seen in Table 4 of the study, fluorosilicic acid was associated with:

- a 20% increased risk (but not statistically significant) for high blood lead levels among children living in houses made prior to 1946;
- a 40% increased risk (but not statistically significant) for high blood lead levels among children living in houses made between 1946 and 1973;
- a 70% increased risk (but not statistically significant) for high blood lead levels among children living in houses made after 1974;
- a 530% increased risk (which was statistically significant) for high blood lead levels among children living in houses with unknown ages.

Since three of these four elevated risks were not statistically significant, the CDC dismissed them as essentially random aberrations. However, the consistency in the *direction* of the risk, coupled with the large and significant five-fold increased risk for children in homes of unknown age, raises a serious red flag.

Even the CDC acknowledged that this study does not refute the connection between fluoridation and lead, and that "it is possible that larger samples might have identified additional, significant differences." (Macek et al. 2006, at 133). Indeed, when Coplan et al. re-analyzed CDC's data by placing all children exposed to fluorosilicic acid and sodium fluorosilicate in one group ("silicofluorides"), and all other children in another, they found that the children exposed to "silicofluoridated" water had a significantly elevated risk of having high blood lead levels. (Coplan et al. 2007, at 1039-40). According to Coplan's re-analysis, children from the silicofluoridated communities had a 20% greater risk of having blood lead levels in excess of 5

ug/dl. Coplan's team estimated that the risk for exceeding the 10 ug/dl threshold would be even greater. (*Id.* at 1039 tbl.9).

The repeated association between fluoridation chemicals and elevated blood levels provides further reason why it is in public interest for EPA to prioritize a targeted ban on fluoridation additives under TSCA over broad-based regulatory action against all fluoride in drinking water under SDWA.

XIII. CONCLUSION

Petitioners request that EPA exercise its authority under Section 6 of TSCA, 15 U.S.C. § 2605(a)(2), to prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies. As set forth above, Petitioners make this request on the grounds that a large body of animal, cellular, and human research shows that fluoride is neurotoxic at doses within the range now seen in fluoridated communities. When considering the principles set forth in EPA's *Guidelines for Neurotoxicity Risk Assessment*, Petitioners submit that fluoridation is incompatible with a neurologically safe use of fluoride. Petitioners further make this request on the grounds that fluoride's predominant role in caries prevention comes from *topical* contact and thus there is no reasonable justification to expose hundreds of millions of Americans to the neurotoxic risks of *systemic* fluoride via water (and the many processed beverages and foods made therefrom) when topical fluoride products are now widely available for individual use. Most western nations, including the vast majority of western Europe, have already rejected water fluoridation. The EPA is the one federal agency with the authority to make this happen here in the U.S. We urge EPA to act accordingly.

Petitioners are represented by, and this Petition was prepared by:

Michael Connett, Esq
3454 Vinton Ave.
Los Angeles, CA 90034
(802) 355-0999
michael@fluoridealert.org

XIV. Bibliography

NOTE: For studies that were originally published in Chinese and later published in English, we use the date of English publication. For studies that were originally published in Chinese that have been translated into English but not yet republished, we use the date of the original study, not the date of translation.

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APPENDIX A:
Post-NRC Human Studies Investigating Fluoride's Impact on Cognition

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APPENDIX B:
Post-NRC Human Studies Investigating Fluoride's Impact on Fetal Brain

	Exhibit No.
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APPENDIX C:
Post-NRC Human Studies Investigating Fluoride's Impact on Other Parameters of Neurotoxicity

	Exhibit No.
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APPENDIX D:
Post-NRC Animal Studies Investigating Fluoride's
Neuroanatomical & Neurochemical Effects

	Exhibit No.
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APPENDIX E:
Post-NRC Animal Studies Investigating Fluoride's Effect on Learning/Memory

	Exhibit No.
1. Balaji B, Kumar EP, Kumar A. 2015. Evaluation of standardized Bacopa monniera extract in sodium fluoride induced behavioural, biochemical, and histopathological alterations in mice. <i>Toxicology and Industrial Health</i> 31(1):18-30.	14
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29. Zhang C, Ren C, Chen H, et al. 2013. The analog of ginkgo biloba extract 761 is a protective factor of cognitive impairment induced by chronic fluorosis. <i>Biological Trace Element Research</i> 153(1-3):229-36.	292
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31. Zheng X, Sun Y, Ke L, et al. 2016. Molecular mechanism of brain impairment caused by drinking-acquired fluorosis and selenium intervention. <i>Environmental Toxicology and Pharmacology</i> 43:134-139.	306

APPENDIX F:
Post-NRC Animal Studies Investigating Fluoride's Effect on Other Behavioral Parameters Beyond Learning/Memory

	Exhibit No.
1. Balaji B, Kumar EP, Kumar A. 2015. Evaluation of standardized Bacopa monniera extract in sodium fluoride induced behavioural, biochemical, and histopathological alterations in mice. <i>Toxicology and Industrial Health</i> 31(1):18-30.	14
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10. Kivrak Y. 2012. Effects of fluoride on anxiety and depression in mice. <i>Fluoride</i> 45(3 Pt 2):302–306.	130
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13. Niu R, Sun Z, Wang J, et al. 2008b. Effects of fluoride and lead on locomotor behavior and expression of nissl body in brain of adult rats. <i>Fluoride</i> 41(4):276-82.	191

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15. Reddy MM, Karnati PR. 2015. Protective effects of aqueous extract of fruit pulp of <i>Tamarindus indica</i> on motor activity and metabolism of the gastrocnemius muscle of rats treated with fluoride. <i>International Journal of Toxicological and Pharmacological Research</i> 7(5):241-246.	209
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APPENDIX G:
Post-NRC In Vitro Studies Investigating Fluoride's Effect on Brain Cells

	Exhibit No.
1. Flores-Méndez M, Ramírez D, Alamillo N. 2014. Fluoride exposure regulates the elongation phase of protein synthesis in cultured Bergmann glia cells. <i>Toxicology Letters</i> 229(1):126-133.	81
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4 **U.S. FEDERAL COURT**

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6 **ACTION NO. 17-CV-02162**

7 **FOOD AND WATER WATCH, *et al.* v. U.S. EPA**
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12 **EXPERT DECLARATION OF**
13 **PHILIPPE GRANDJEAN, MD, DMSc**

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17 **PREPARED ON BEHALF OF**
18 **PLAINTIFFS**

19 **20 May 2020**
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TABLE OF CONTENTS

I.	SUMMARY OF QUALIFICATIONS.....	1
II.	SUMMARY OF OPINIONS	4
III.	SUMMARY OF METHODOLOGY	4
A.	Weight of the Evidence.....	4
B.	Factors Considered When Assessing Epidemiological Literature.....	5
C.	Benchmark Dose Methodology	7
D.	Materials Relied Upon	7
IV.	GENERAL CONSIDERATIONS	7
A.	Emergence of Brain Development as Vulnerable Target	7
B.	Toxicokinetics During the Fetal Period	10
C.	Toxicological Findings	11
V.	EPIDEMIOLOGICAL STUDIES (CROSS-SECTIONAL).....	12
A.	Neurotoxicity from Occupational Fluoride Exposure.....	12
B.	Neurotoxicity in Endemic Fluorosis Areas.....	13
1.	Neurotoxic Endpoints in Fetuses and Neonates.....	15
2.	Neurotoxic Endpoints in Adults.....	16
3.	Childhood IQ.....	16
C.	Studies of Fluoride and ADHD in North America.....	20
VI.	EPIDEMIOLOGICAL STUDIES (PROSPECTIVE)	21
A.	Prospective Cohort Studies with Individual Assessment of Prenatal Exposure.....	21
B.	Prospective Cohort Studies without Prenatal Exposure Assessment.....	23
VII.	SYSTEMATIC REVIEW	24
A.	Dr. Chang's Systematic Review Confirms that I Considered All Significant Data.....	25
B.	Dr. Chang's Review Fails to Identify Any Systematic Biases that Explain Fluoride's Consistent Association with Neurodevelopmental Harm.....	27

C.	Bradford Hill Aspects Support, Rather than Detract from, the Causal Nature of Fluoride’s Association with Neurodevelopmental Harm.....	30
VIII.	BENCHMARK DOSE (BMD) ANALYSIS	35
A.	Selection of Source Data.....	35
B.	Selection of Benchmark Response (BMR)	37
C.	Analyses of ELEMENT and MIREC Data	38
IX.	ASSESSMENT OF RISK.....	41
A.	Comparing BMDLs with Current Exposures in Fluoridated Areas.....	41
B.	Comparing Fluoride’s Population-Level Effects with Other Causes of IQ Loss.....	46
X.	CONCLUSIONS.....	48

1 I, Philippe Grandjean, MD, DMSc, declare that:

2 1. I am a physician and environmental epidemiologist and serve as both an Adjunct Professor
3 at the Harvard T.H. Chan School of Public Health, and Professor and Chair of Environmental Medicine
4 at the University of Southern Denmark.

5 2. I was asked by Plaintiffs' counsel to provide an evaluation of the neurological health risks
6 associated with the exposure to fluoride in drinking water.

7
8 **I. SUMMARY OF QUALIFICATIONS**

9 3. A complete summary of my qualifications and publications can be found in my
10 Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 3 and attached herein.

11 4. Over the past 25 years, my research has focused on developmental exposures to
12 environmental chemicals and the association with adverse health effects in children, as described in my
13 book "Only One Chance" (2013) published by Oxford University Press.

14 5. My research has been entirely funded by public sources, mainly the National Institutes of
15 Health (NIH). In 2003-2007, my study of children's vulnerability to environmental immunotoxicants
16 was supported by the U.S. Environmental Protection Agency (EPA). My current funding as principal
17 investigator includes grants from the Superfund Research Program at the National Institute of
18 Environmental Health Sciences and the U.S. Agency for Toxic Substances and Disease Registry
19 (ATSDR).

20 6. I have published about 500 scientific papers, of which most are research articles in
21 international scientific journals with peer review. My h-index in the Web of Science data base is 70, and
22 my work is cited in scientific journals well over a thousand times every year. Seven of my articles
23 published in the last 10 years have earned the attribute "Highly Cited Paper," i.e., they received enough
24 citations to place them in the top 1% of published papers in the field.

25 7. My study on the neurodevelopmental effects of prenatal mercury exposure in a birth cohort
26 from Faroe Islands was relied upon by the EPA as the critical study for the Agency's derivation of a
27

1 Reference Dose for methylmercury (EPA 2001).

2 8. I have served as a technical advisor to the World Health Organization on environmental
3 health issues, including five occasions where I was elected Rapporteur. I have also served on, sometimes
4 chaired, or acted as rapporteur for, expert committees under the auspices of the EPA, ATSDR, Food &
5 Drug Administration (FDA); NIH; White House Office of Science and Technology Policy; International
6 Agency for Research on Cancer (IARC), European Commission, European Environmental Agency,
7 European Food Safety Authority, and other organizations. I have also served for over 30 years as
8 Consultant in Toxicology for the Danish Ministry of Health.

9 9. I am (Founding) Editor-in-Chief of the journal *Environmental Health* (since 2002), which
10 ranks among the most frequently cited journals in the field. I also serve or have served on editorial
11 boards of about a dozen journals within medicine, environmental science, and toxicology. As editor and
12 as reviewer for other major journals, I frequently evaluate manuscripts on environmental epidemiology
13 and toxicology.

14 10. I have received various awards and honors for my scientific work, including the John R.
15 Goldsmith Award from the International Society for Environmental Epidemiology, which is given to
16 investigators for “sustained and outstanding contributions to the knowledge and practice of
17 environmental epidemiology.”

18 11. I have been retained as an expert on the impact of environmental chemicals on human
19 health by government bodies, including the U.S. Department of Justice (on behalf of the EPA) and the
20 State of Minnesota.

21 12. I first began studying fluoride in 1980 at the suggestion of Dr. Irving J. Selikoff, who was
22 my mentor at the Mt. Sinai School of Medicine during my two-year Senior Fulbright Scholarship. Upon
23 returning to Denmark, I initiated a series of studies on a cohort of workers who had been occupationally
24 exposed to fluoride. I have remained involved in fluoride research since that time and have published 16
25 peer-reviewed reports on fluoride exposure and toxicity in humans.

26 13. In 1984, I drafted the Environmental Criteria Document on fluoride for the World Health
27

1 Organization (WHO). Ten years later, I drafted the Criteria Document for an occupational exposure
2 limit value for fluorine for the European Commission. In 2006, I served as a reviewer of the National
3 Research Council's report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*.

4 14. During the past 10 years, my research work on fluoride has focused on its developmental
5 effects on the brain. In 2012, I published a meta-analysis of the epidemiological studies on fluoride and
6 IQ (Choi et al. 2012); in 2015, I published an epidemiological study of fluoride and IQ in China (Choi et
7 al. 2015); and, in December of 2019, I published an updated review of fluoride neurotoxicity, which
8 relied in part on the work that I have performed in this case (Grandjean 2019).

9 15. In addition to my work on fluoride, I also have expertise in Benchmark Dose (BMD)
10 analysis. My experience doing BMD analysis started about 20 years ago in connection with my research
11 on the neurodevelopmental effects of methylmercury in the Faroe Islands that was selected as the critical
12 study for risk assessment by the EPA. Based on this research, the EPA provided me with a contract to
13 produce a BMD analysis of the data, which I carried out in collaboration with my biostatistician
14 colleagues, Dr. Esben Budtz-Jorgensen and Professor Niels Keiding. The EPA relied on this BMD
15 analysis to establish the safe level for methylmercury exposure in the U.S. (U.S. EPA 2001).

16 16. In 2009, I served on an expert panel that assisted the European Food Safety Authority
17 (EFSA) in developing a guidance document on BMD analysis titled "Use of the Benchmark Dose
18 (BMD) Approach in Risk Assessment."

19 17. In 2013, Dr. Budtz-Jorgensen and I extended our BMD methodology in collaboration with
20 the International Pooled Lead Study Investigators, which was peer-reviewed and published in the journal
21 *Risk Analysis* (Budtz-Jorgensen et al. 2013). As part of this analysis, we developed a BMD for lead and
22 IQ by analyzing pooled data from multiple different cohort studies. The paper was co-authored by
23 leading scholars on lead neurotoxicity, including Drs. David Bellinger and Bruce Lanphear.

24 18. More recently, Dr. Budtz-Jorgensen and I conducted an advanced BMD analysis on
25 perfluorinated chemicals, which was published in 2018 in the peer-reviewed journal *PLOS One* (Budtz-
26 Jorgensen and Grandjean 2018). In total, our achievements on BMD approaches and applications have
27

1 been published in seven articles so far in international biostatistical and biomedical journals.

2 19. In addition to my scientific training, I remain mindful, of the importance of translating the
3 results of epidemiological studies in a way that can facilitate public participation in making informed
4 decisions to protect their health, even prior to a “final proof” of causation being available; a final proof
5 that, all too often, has come too late to protect the public from harm, as reviewed most recently in the
6 monograph on *Late Lessons of Early Warnings*, published by the European Environment Agency (EEA
7 Report No 1/2013), for which I served as an editor. As Dr. Selikoff once impressed upon me, “Never
8 forget that the numbers in your tables are human destinies, although the tears have been wiped away.”

9 **II. SUMMARY OF OPINIONS**

10 20. The weight of epidemiological evidence leaves no reasonable doubt that developmental
11 neurotoxicity is a serious human health risk associated with elevated fluoride exposure, including those
12 occurring at the levels added to drinking water in fluoridated areas. The IQ losses associated with
13 community water fluoridation are substantial and of significant public health concern.

14 21. Application of the Benchmark Dose (BMD) methodology to the recent prospective birth
15 cohort data shows that the level of fluoride added to water in fluoridation programs greatly exceeds the
16 science-based limit needed to protect against developmental neurotoxicity.

17 22. The systematic review conducted by Dr. Ellen Chang, when corrected for its biases and
18 errors in judgment, further supports my opinions on the neurotoxic risks posed by elevated fluoride
19 exposure.

20 **III. SUMMARY OF METHODOLOGY**

21 **A. Weight of the Evidence**

22 23. I conducted a weight of the evidence assessment of available research on fluoride
23 neurotoxicity, with an emphasis on the epidemiology. While I place the greatest weight on the strong
24 epidemiological evidence, I also consider toxicokinetics, experimental toxicology data, and background
25
26
27

principles of brain development as part of my comprehensive analysis.

24. My review focuses on the evidence that carries the greatest weight which, as generally accepted, emphasizes the recent prospective cohort studies.

25. My methodology follows the general approach applied by the EPA, in the sense that I did a weight of the evidence analysis that focuses on the best available science (e.g., EPA 2017).

26. In light of my familiarity with the scientific literature on fluoride neurotoxicity, I did not conduct a formal systematic review on this occasion. Instead, my conclusions rely on a comprehensive and thorough review supplemented by a Benchmark Dose analysis of the recent prospective data.

27. I have read and considered the systematic review conducted by Dr. Ellen Chang, which mostly relies on the same evidence and which further confirms and supports my assessment of the literature. My opinions are thus fully informed by the insights offered by a formal systematic search of the literature.

B. Factors Considered When Assessing Epidemiological Literature

28. In evaluating the weight of the evidence, the question must be asked what each study could potentially reveal, given the design and choice of study parameters, including such factors as the precision of the exposure assessment. In the field of epidemiology, there is a well-known bias toward the null, e.g., from imprecise assessment of the exposure, of which epidemiologists (and readers of epidemiology reports) need to be careful, especially when human health is at stake (EPA 2005).

29. The following Table highlights common causes of bias toward the null in epidemiological studies, i.e., reasons that a study might not show the existence of a risk that indeed is present, though hidden due to the bias. While biases in the opposite direction also exist, they are usually of much less significance (Grandjean 2013).

*Table 1. Causes of bias toward the null in epidemiology studies
(Grandjean 2013a).*

Inadequate statistical power in small studies
Lost cases and inadequate follow-up for long-term effects
Exposed or otherwise inappropriate comparison (control) group
Exposure misclassification
Insensitive or imprecise outcome measures
Failure to adjust for confounders with effects in the opposite direction
Disregarding vulnerable subgroups
5% probability level to minimize risk of false positives (Type I error)
20% probability level to minimize risk of false negatives (Type II error)
Pressure to avoid false alarm

30. Studies that do not show a statistical significance are sometimes called “negative,” although this term is misleading. Joint analyses of several such studies may well show a significant difference or trend.

31. Observational studies will rarely if ever provide definitive proof of causation, and it is always possible for someone to raise doubts and uncertainties that require additional or improved data to resolve (Michaels 2008). It is important to recognize, however, that the presence of uncertainties often tends to cause underestimations of actual risks, not the opposite. This issue is of importance especially regarding substances that have not yet been studied in the detail desired or cannot be examined in randomized clinical trials. Many unfortunate past errors in regard to industrial chemicals have shown that initial assessments were often erroneous and led to an underestimation of the true risks (European Environment Agency 2001 & 2013).

32. In the context of developmental neurotoxicity, I place greatest weight on prospective studies of population-based birth cohorts followed over time (Grandjean et al. 2008; Grandjean & Landrigan 2014). Birth cohorts are crucial because it is not just the dose that can matter but also the timing of the dosing in regard to the developmental stage of the subjects (Grandjean et al. 2008; Grandjean et al. 2019). Follow-up studies of birth cohorts can thus reveal with greater certainty the

impacts of exposures incurred during early life stages.

C. Benchmark Dose Methodology

33. As part of my assessment in this case, I worked with my biostatistician colleague Dr. Budtz-Jørgensen on a BMD analysis of the prospective cohort data on fluoride and IQ using the same peer-reviewed method that we used for lead (Budtz-Jorgensen et al. 2013).

34. The statistical uncertainty in the BMD estimation is taken into account by calculating its lower one-sided 95% confidence limit, which is called the benchmark dose level (BMDL). The BMDL is then used as the point of departure for calculation of the exposure limit, by dividing the BMDL by an uncertainty factor (usually fixed at 10) to obtain a protective Reference Dose (RfD) or tolerable exposure (EFSA 2009; EPA 2012).

D. Materials Relied Upon

35. In my assessment, I relied upon my existing knowledge of the scientific literature (with citations to specific studies noted in my reports), my own meta-analysis of the epidemiological studies of fluoride and IQ (Choi et al. 2012), the more recent meta-analysis by Duan (2018), all available prospective studies, as well as the reviews by NRC (2006) and NTP (2016).

36. I also considered studies provided by counsel,¹ many of which I was already familiar with, and conducted supplemental searches on PubMed, including searches to see if there were any significant epidemiological studies published that I might have overlooked.

37. A complete list of the studies I relied upon is provided in my expert reports.

IV. GENERAL CONSIDERATIONS

A. Emergence of Brain Development as Vulnerable Target

38. Evidence has been accumulating over several decades that industrial chemicals can cause

¹ I understand that these studies were provided to EPA's experts as well, including Dr. Chang.

1 neurodevelopmental disorders that include learning disabilities, sensory deficits, developmental delays,
2 and cerebral palsy (NRC 2000), and current evidence also relates to other neurodevelopmental deficits,
3 such as attention deficit hyperactivity disorder (ADHD) (Bennett et al. 2016). Subclinical stages of these
4 conditions also appear to be common, and the suspicion of a link between neurotoxic chemical
5 exposures and widespread neurobehavioral damage has increased since it was first raised by research
6 demonstrating that lead is particularly toxic to the developing brain across a wide range of exposures
7 (Baghurst et al. 1987; Dietrich et al. 1987; Landrigan et al. 1975; Needleman et al. 1979).

8
9 39. The developing human brain is inherently much more susceptible to injury caused by toxic
10 agents than the brain of an adult. This susceptibility reflects the fact that in the nine months of prenatal
11 life the human brain must evolve from a strip of cells along the dorsal ectoderm into a complex organ
12 comprised of billions of precisely located, highly interconnected and specialized cells. Optimal brain
13 development requires that neurons move along precise pathways from their points of origin to their
14 assigned locations, that they establish connections with other cells near and distant, and that they
15 generate intercommunications in meaningful ways (Dobbing 1968; Rice and Barone 2000; Rodier
16 1995).

17
18 40. All of these processes must take place within a tightly controlled time frame, in which each
19 developmental stage must be reached on schedule and in the correct sequence. Due to the extraordinary
20 complexity of human brain development, windows of unique susceptibility to toxic interference occur
21 that have no counterpart in the mature brain, or in any other organ. Because of the unique structure of
22 the human brain and its advanced function, no other species shows similar degree of developmental
23 vulnerability. Thus, if a developmental process in the brain is halted or inhibited, there is little potential
24 for later repair, although plasticity will allow some compensation, and the consequences are therefore
25 likely to be permanent (Dobbing 1968; Rice and Barone 2000).

1 41. To test chemicals for developmental neurotoxicity, standardized protocols have been
2 developed using rodent models (OECD 2007). However, they may not necessarily be sufficiently
3 sensitive, as rodent brains are far less complex than human brains, and intrauterine brain development is
4 completed at a stage where the human fetal brain is still rapidly developing *in utero* for several more
5 weeks with possible continued impact from maternal transfer of neurotoxicants (Bal-Price et al. 2018).

6 42. During fetal development, the placenta can offer some protection against unwanted
7 chemical exposures, but it is not an effective barrier against most environmental neurotoxicants
8 (Andersen et al. 2000), including fluoride (NRC 2006). In addition, the blood-brain barrier, which
9 protects the adult brain from many toxic agents, is not completely formed until about 6 months after
10 birth (Adinolfi 1985).

12 43. Postnatally, the human brain continues to develop, and the period of heightened
13 vulnerability therefore extends over many months through infancy and into early childhood. While most
14 neurons have been formed by the time of birth, growth of glial cells and myelination of axons continue
15 for several years and is not complete until late teenage years (Rice and Barone 2000; Rodier 1995).

16 44. The susceptibility of infants and children to industrial chemicals is further amplified by
17 their relatively increased exposures in regard to body weight, their augmented absorption rates, and
18 diminished ability to detoxify many exogenous compounds as compared to adults (Ginsberg et al. 2004;
19 NRC 1993).

21 45. In 2005, when I evaluated the evidence of industrial chemicals regarding developmental
22 neurotoxicity, only five substances (arsenic, lead, methylmercury, polychlorinated biphenyls, and
23 toluene) fulfilled our criteria for causal relationship in humans (Grandjean and Landrigan 2006). Eight
24 years later, when we reassessed the evidence, we added six more substances, including fluoride
25 (Grandjean and Landrigan 2014), based on new evidence that had emerged.
26

1 46. Our 2014 assessment was focused on *hazard* (i.e., whether fluoride causes developmental
2 neurotoxicity in humans), not on *risk* (i.e., the exposure level at which this hazard may occur).
3 Substantial new evidence published since that time, particularly the prospective birth cohort studies,
4 now permit an assessment of risk.

5 **B. Toxicokinetics During the Fetal Period**

6 47. In my assessment, I considered the toxicokinetics of fluoride, with a particular focus on the
7 uptake, distribution and retention during the fetal period.

8 48. It is well accepted that fluoride crosses the placenta and reaches the fetus from the
9 mother's blood stream (NRC 2006; WHO 2006).

10 49. The first documentation of placental transfer in humans was the observation in 1974 (Shen
11 and Taves 1974) that fluoride concentrations in maternal and cord serum correlated well, with the cord
12 blood showing slightly lower concentrations. These findings were replicated in 1986 (Ron et al. 1986),
13 with results suggesting minor deviations depending on gestational age. A more recent study from an area
14 with water-fluoride levels of 0.4-0.8 mg/L showed that cord serum contained about 80% of the
15 concentrations occurring in maternal serum (Opydo-Szymaczek and Borysewicz-Lewicka 2007).
16 Consistent with this, French researchers measured fetal blood concentrations of fluoride after the
17 mothers were administered a small dose of sodium fluoride, and the elevations were statistically
18 significantly higher (2.6 $\mu\text{mol/l}$) than in a control group (less than 1 $\mu\text{mol/l}$) (Forestier et al. 1990).
19

20 50. A recent study from scientists at the University of California San Francisco (UCSF) further
21 confirms the placental transfer of fluoride (Uyghurturk et al. 2020). In this study, fluoride concentrations
22 were measured in the urine, blood, and amniotic fluid among pregnant women in fluoridated and non-
23 fluoridated areas of Northern California. Each additional 0.1 mg/L of fluoride in water was associated
24 with a significant increase in the fluoride levels in the amniotic fluid ($p < 0.001$), thus confirming the
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transplacental passage of fluoride.

51. As would be expected, given the undeveloped nature of the blood-brain barrier during the fetal period, laboratory studies of animals exposed to prenatal fluoride have found significant elevations of fluoride in the brain (McPherson et al. 2018; Mullenix et al. 1995). Similarly, in aborted human fetuses, fluoride concentrations in the brain have been shown to be higher in geographic areas with endemic fluorosis as compared to controls at lower exposures (Du et al. 2008; He et al. 2008).

C. Toxicological Findings

52. Neurotoxicity is a documented hazard of fluoride exposure in laboratory animals (NRC 2006), which supports the plausibility of fluoride causing neurotoxic effects in humans.

53. One of the first U.S. reports on experimental fluoride neurotoxicity emerged when a new method was developed for computerized surveillance of rat behavior. Fluoride was selected for a test of the new methodology and showed clear neurotoxicity (Mullenix et al. 1995). The authors noted that the behavioral effects they observed in the rats are indicative of fluoride's potential ability to cause IQ deficits in humans. This assessment, which was made prior to the publication of any studies of fluoride and IQ in western journals, proved prescient.

54. Since the Mullenix study was published in 1995, many additional animal studies have documented neurochemical and anatomic changes in the brains of fluoride-treated animals. By 2006, the NRC concluded that there was enough neurochemical and anatomic data to conclude that fluoride interferes with brain functions by both direct and indirect means.

55. Among prominent adverse outcome pathways, the NRC concluded that fluoride is an endocrine disrupter that can affect thyroid function at intake levels as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency (NRC 2006).² Thyroid toxicity supports the plausibility of fluoride

² Large epidemiological studies published since the NRC report suggest that thyroid dysfunction is a relevant risk at elevated fluoride exposures in fluoridated communities, especially in

1 neurotoxicity because availability of thyroid hormone is crucial for optimal brain development (Rovet
2 2014).

3 56. At the time of the NRC's review, there was little data yet available on fluoride's impact on
4 behavior and cognition in animals, but considerable data has since been published. In 2016, the National
5 Toxicology Program (NTP) conducted a systematic review of these behavioral/cognitive studies (NTP
6 2016). Although NTP did not consider any of the neurochemical/anatomical effects, it still concluded
7 that the evidence is "suggestive of an effect on learning and memory" (NTP 2016, p. vii). The NTP
8 characterized its confidence in the evidence as "moderate" for adult studies, and "low" for the few
9 available developmental studies.
10

11 57. Additional animal research on learning/memory has been published subsequent to the NTP
12 review, and most of it has reported adverse effects. As is often the case, the animal studies on
13 learning/memory have limitations or discrepancies but given the general consistency in their findings
14 they continue to be *at least* "suggestive" of fluoride being a neurocognitive hazard.
15

16 **V. EPIDEMIOLOGICAL STUDIES (CROSS-SECTIONAL)**

17 **A. Neurotoxicity from Occupational Fluoride Exposure**

18 58. The neurotoxicity of chemicals is often first discovered from workplace exposures
19 (Grandjean and Landrigan 2006), which are later followed by case reports that involve children or
20 pregnant women from the general population (Grandjean 2013). The same is true of fluoride.
21

22 59. Although largely overlooked or ignored, Roholm first reported evidence of nervous system
23 effects in his seminal study of cryolite workers in Copenhagen (Roholm 1937): "The marked frequency
24 of nervous disorders after employment has ceased might indicate that cryolite has a particularly harmful
25 effect on the central nervous system" (p. 178). The nervous system effects reported by Roholm included
26 tiredness, sleepiness, indisposition, headaches, and giddiness (p. 138).

27 adults with iodine deficiency (Malin et al. 2018; Peckham et al. 2015).

60. My own mortality study of the cryolite workers studied by Roholm showed an excess of violent deaths (Grandjean et al. 1985), but information on the causes of death did not allow any conclusions on deaths from nervous system disease.

61. One of the challenges with occupational studies of fluoride-exposed workers is that the fluoride exposure usually occurs as part of a mixture. In the 1940s, scientists at the Manhattan Project recorded CNS effects in workers exposed to uranium hexafluoride gas (UF₆). They observed a “rather marked central nervous system effect with mental confusion, drowsiness and lassitude as the conspicuous features” and attributed it to the fluoride rather than uranium (Ferry 1944; Mullenix 2005).

62. Consistent with the observations of the Manhattan Project scientists, published case reports have highlighted difficulties with concentration and memory accompanied by general malaise and fatigue following occupational fluoride exposures (Spittle 1994).

63. More recently, skeletal fluorosis in workers was found to be associated with gradually progressive effects on the normal function and metabolism of the brain and other aspects of the nervous system (Duan et al. 1995), and application of neuropsychological tests (i.e., WHO’s Neurobehavioural Core Test Battery) have reported significant associations between workplace fluoride exposures and cognitive problems (Guo et al. 2008; Yazdi et al. 2011).

64. The available evidence from occupationally exposed workers supports the neurotoxicity of fluoride but does not allow any detailed consideration of its dependence on dose, timing, and duration.

B. Neurotoxicity in Endemic Fluorosis Areas

65. Fluoride toxicity has received particular attention in China, where widespread dental fluorosis indicates pervasive high exposures (Wang et al. 2012). Areas with high prevalences of dental (and skeletal) fluorosis are known as “endemic fluorosis” areas.

66. Although microbiologically safe, water supplies from wells, small springs or mountain

1 sources have created pockets of increased fluoride exposures near or within areas of low exposures, thus
2 representing optimal settings for epidemiological research because only the fluoride exposure would
3 likely differ between nearby neighborhoods. In addition, rural families in China move much less
4 frequently than U.S. families, thus facilitating assessment of impacts from long-term exposures. Chinese
5 researchers took advantage of this fact and published their findings, though mainly in Chinese journals,
6 and according to the standards of science at the time. The early research dates to the 1980s but has not
7 been widely cited, in part because of limited access to Chinese journals, in part because the notion of
8 adverse effects from fluoride intake has often been considered unwelcome.

9
10 67. Most of the studies on fluoride neurotoxicity from China, and other countries (i.e., India,
11 Iran, and Mexico), have focused on IQ measures as the endpoint of concern, with the clear majority of
12 these studies reporting inverse associations (i.e., higher levels of fluoride exposure are associated with
13 lower IQ).

14 68. Many of the studies from China have significant limitations, including lack of information
15 on covariates, missing information on study details, assessment of exposures on a community basis, and
16 use of cross-sectional study designs. The reports have also tended to be relatively brief and simple in
17 design. These deficiencies, which in some cases are rather severe, limit the conclusions that can be
18 drawn, but are unlikely to explain the almost uniformly consistent inverse associations that have been
19 reported.

20
21 69. While most of the endemic fluorosis studies have rather simple designs and may have
22 failed to control for confounding factors of possible importance, they also have important strengths,
23 including: 1) Stable populations with stable water-fluoride concentrations; many of the studies
24 specifically limited the populations to those who had lived in the community their entire life. 2) Unlike
25 in the U.S., children in rural China have very little exposure to fluoridated dental products (Zhu et al.
26
27

2003), thus making water a more important and reliable metric of fluoride exposure. 3) The studies in endemic fluorosis areas that have controlled for or excluded key confounding factors (arsenic exposure, iodine deficiency, parental education) were still capable of identifying clear associations between elevated fluoride exposure and cognitive deficits (Choi et al. 2012).

70. I will discuss the Chinese research on IQ in fluoride-exposed communities in more detail, but I begin first with studies that have examined other neurotoxicity endpoints, including neuropathological outcomes in aborted fetuses, neurobehavioral effects during infancy, and cognitive deficits and other neurological problems in adults.

1. Neurotoxic Endpoints in Fetuses and Neonates

71. In brain tissue obtained from aborted fetuses in endemic fluorosis areas, electron microscopy showed retarded cell growth in the cerebral cortex, with substantial cytology changes (He et al. 2008). A similar study used stereology to examine nerve cell numbers and volumes in fetal brain tissue and found lower densities (Du et al. 2008). A third study focused on neurotransmitters and receptors and found deviations that suggested neural dysplasia (Yu et al. 2008). Another study of aborted fetal brain tissue showed similar neurotransmitter results (Dong et al. 1993). These studies are consistent with prenatal fluoride exposure causing anatomic and biochemical changes in the fetal brain, as concluded by the NRC. A limiting factor, however, is that the elevated fluoride exposure in these studies came primarily from coal burning, which may have contributed other contaminants besides fluoride that were not assessed.

72. The impact of elevated fluoride in drinking water on neurological behavior in 91 neonates was assessed by Li et al. (2008). The study found that neonates born in an endemic fluorosis area (water-fluoride concentrations of 1.7 - 6.0 mg/L) scored more poorly on the standard Neonatal Behavioral Assessment, and that visual and auditory responses were also deficient, as compared to controls from

1 areas with less than 1 mg/L (Li et al. 2008). These findings are again consistent with the notion that
2 fluoride can affect the brain during the prenatal period, although neonatal neurological assessments can
3 be somewhat imprecise and may be only weakly predictive of subsequent brain development.

4 73. In a separate study, infants from an endemic area were examined at ages 3, 6, 9 and 12
5 months and scored significantly lower in mental and psychomotor development indices than those of the
6 control group (Chang et al. 2017). The exposed group also showed lower birth weight, and it is unclear
7 whether this difference can lead to confounding or if a lower birth weight is a concomitant effect of the
8 fluoride exposure. As with the fetal neuropathology studies, the source of fluoride exposure in this study
9 was coal, not water, which limits the conclusions that can be drawn due to the potential for confounding.
10

11 2. Neurotoxic Endpoints in Adults

12 74. Studies in China using cross-sectional designs have also found cognitive problems and
13 neurological symptoms in adults with skeletal fluorosis living in endemic fluorosis areas. Using
14 neuropsychological tests, including the Wechsler scale, 49 adult fluorosis patients (it is not clear whether
15 the patients were from a coal- or waterborne fluorosis area) were compared with controls and showed
16 deficits in language fluency, recognition, similarities, associative learning, and working memory (Shao
17 et al. 2003). Likewise, cognitive impairment in elderly subjects was clearly elevated in a waterborne
18 fluorosis area, although within-group assessment of urine-fluoride concentrations failed to show a clear
19 gradient of effect (Li et al. 2016). Excess occurrence of neurological symptoms has also been recorded
20 in both adults and children from waterborne fluorosis areas, with headaches being the primary
21 manifestation (Sharma et al. 2009).
22

23 3. Childhood IQ

24 75. As noted above, most of the epidemiological studies on fluoride neurotoxicity have
25 focused on IQ scores in childhood. In 2012, my colleagues and I published a meta-analysis of the
26
27
28

1 available 27 studies, most of which were published in China³ (Choi et al. 2012). Because these
2 published studies were conducted independently, we used meta-analysis—a quantitative, formal,
3 statistical technique—to systematically review and assess these published research studies to derive
4 conclusions about the neurotoxicity of fluoride. The outcome of the meta-analysis includes a more
5 precise estimate of the association than any individual study that contributes to the pooled analysis. The
6 variability or heterogeneity in study results was also examined. We did not attempt to generate any
7 dose-response relationship, and the fluoride concentrations were used only for definitions of high and
8 low (reference) groups in each study.
9

10 76. Among the 27 studies we reviewed, two involved populations exposed to fluoride from
11 coal burning (Guo et al. 1991; Li et al. 2010); the rest of the studies involved exposure to fluoride
12 through drinking water containing fluoride from soil minerals. The Combined Raven's Test – The Rural
13 Edition in China (CRT-RC) was used to measure the children's intelligence in 16 studies. Other
14 intelligence measures included the Wechsler Intelligence scale (3 studies), Binet IQ test (2 studies),
15 Raven's test (2 studies), Japan IQ test (2 studies), Chinese comparative intelligence test (1 study), and
16 the mental work capacity index (1 study). As each of the intelligence tests used is designed to measure
17 general intelligence, we used data from all eligible studies to estimate the possible effects of fluoride
18 exposure on the children's intelligence. We conducted a sensitivity analysis restricted to studies that
19 used similar tests to measure the outcome (specifically, the CRT-RC, Wechsler Intelligence test, Binet
20 IQ test, or Raven's test), and an analysis restricted to studies that used the CRT-RC. We also performed
21 an analysis that excluded studies with possible concerns about co-exposures, such as iodine status and
22 arsenic exposure, or with non-drinking water fluoride exposure from coal burning, without finding
23 appreciable differences, as described below.
24
25

26
27 ³ Two of the 27 studies included in the analysis were conducted in Iran (Poureslami et al.
28 2011; Seraj et al. 2006), otherwise the study cohorts were populations from China.

77. The levels of fluoride exposure in the studies we examined, while higher than those associated with fluoridation programs (0.7 mg/L), are not as high as some have claimed. A surprising number of commentators, including the EPA, have only mentioned the *highest* concentration examined in the studies (11.5 mg/L) (Allukian et al. 2018; EPA 2018), although this high concentration occurred in only one of the 27 studies. The majority of studies that reported the water-fluoride level in the exposed group had between 1.5 and 4 mg/L, which is elevated, but only modestly.⁴ Similarly, Duan's more recent meta-analysis of waterborne fluoride exposures reported that 18 of 27 studies addressed water-fluoride concentrations below 4 mg/L, and IQ reductions were observed at elevated concentrations of 1 to 2 mg/L (Duan et al. 2018 Table 2).

78. Among the 27 studies, all but one showed random-effect standardized mean difference (SMD) estimates that indicated an inverse association, ranging from -0.95 to -0.10 (one study showed a slight, non-significant effect in the opposite direction). The overall random-effects SMD estimate (and the 95% confidence interval, CI) were -0.45 (-0.56, -0.34). Given that the standard deviation (SD) for the IQ scale is 15, an SMD of -0.45 corresponds to a loss of **6.75 IQ points**.⁵ I shall return to this result later. Among the restricted sets of intelligence tests, the SMD for the model with only CRT-RC tests and drinking-water exposure was lower than that for all studies combined, but the difference was not significant, and heterogeneity remained at a similar magnitude in the restricted analyses.

79. Several studies (Hong et al. 2001; Lin et al. 1991; Wang et al. 2001; Wang et al. 2007; Xiang et al. 2003; Zhao et al. 1996) reported other risk factors, such as iodine status, and exposure to arsenic or lead, both neurotoxicants, and our sensitivity analyses showed similar associations between

⁴ The fluoride levels in the control groups in the studies often approximated the concentrations (~0.7 mg/L) used in fluoridation programs. Some ill-informed commentators have mistakenly interpreted this to mean that these control levels are thereby safe. This is false. The control groups are not being compared to *lower* or zero fluoride groups, and, as such, provide no information about the safety, or lack thereof, of the control values.

⁵ The effect size we found is consistent with the prior meta-analysis of Tang (2008), who reported a mean difference of 5.03 IQ points between the high- and low-fluoride areas.

1 high fluoride exposure and the outcomes even after exclusion of these studies. Although large tracts of
2 China have superficial fluoride-rich minerals, there is little, if any, likelihood of contamination by other
3 neurotoxicants that would be consistently associated with fluoride concentrations in drinking water and
4 thereby systemically confound the results. For example, follow-up testing documented lower levels of
5 blood-lead concentrations and waterborne arsenic in the high-fluoride community than the control
6 (Xiang et al. 2003; Xiang et al. 2003; Xiang et al. 2013). In some instances, therefore, potential co-
7 exposure to other neurotoxicants may cause reverse confounding (i.e., may attenuate the real
8 relationship between fluoride and IQ), as we have documented for methylmercury exposure from
9 seafood (Choi et al. 2008).

11 80. Additional IQ studies in endemic fluorosis areas have been published since our 2012
12 review. As with the previous studies, these newer studies continue to replicate the consistent inverse
13 association between fluoride exposure and IQ, although many—but not all—suffer from similar
14 limitations. Two of the studies reported linear relationships between urinary fluoride excretion and IQ
15 (one study also included plasma-fluoride) among children living in areas with mean water-fluoride
16 contents of 1.4 mg/L and 1.5-2.5 mg/L (Cui et al. 2018; Zhang and Cheng 2015).⁶ Another study
17 published since our meta-analysis is the one I conducted with colleagues in China, which I will now
18 discuss.

20 81. To ascertain the validity of the Chinese reports on fluoride neurotoxicity, we carried out a
21 pilot study in Sichuan using methods commonly applied in neurobehavioral epidemiology (Choi et al.
22 2015). The children examined had lived in their respective communities since conception. Although we
23 examined only 51 children, our results are consistent with elevated fluoride exposure being a cause of
24 cognitive deficits. Interestingly, negative associations were found for cognitive function tests regarding

26 ⁶ These results are consistent with the findings of Ding et al. (2011), who reported a dose-
27 response relationship between urine-fluoride concentrations (range = 0.24-2.84 mg/L) and reduced IQ in
a population without any severe dental fluorosis (Ding et al. 2011).

all three measures of fluoride exposure. One was the known water-fluoride concentration at the residence where the child was born and had grown up, another was the child's morning urine-fluoride after having ingested fluoride-free water the night before (neither measure reached formal statistical significance as a predictor of cognitive deficits). The strongest and statistically significant association was seen with the degree of dental fluorosis that served as a marker of early-life fluoride exposure. While the milder forms of dental fluorosis have been considered a cosmetic effect (Aoba and Fejerskov 2002; WHO 2006), our study suggested that fluorosis can serve as a useful marker of early fluoride exposure in studies of neurodevelopmental toxicity.⁷

C. Studies of Fluoride and ADHD in North America

82. Four epidemiological studies have investigated the relationship between fluoride and ADHD behaviors in North America, the most important of which is the prospective cohort study by Bashash (2018). Two of the other three studies examined ADHD-related outcomes in the Canadian Health Measures Survey (CHMS) (Barberio et al. 2017; Riddell et al. 2019).⁸

83. In 2017, Barberio et al. examined two cycles of the CHMS to investigate the relationship between randomly measured urine-fluoride levels (in 3-to-12-year-old children) and parental reports or self-reported learning disabilities. When the two cycles of the CHMS were combined (both including at least 1,100 subjects), unadjusted urine-fluoride was significantly correlated with an increased incidence of learning disabilities. However, this effect lost its statistical significance after controlling for urine dilution by creatinine and specific gravity. The authors concluded that there was no robust association

⁷ A prior study that was co-authored by my colleague David Bellinger failed to observe a relationship between dental fluorosis and behavior, as determined from parental questionnaires (Morgan et al. 1998). Due to several weaknesses, the conclusions were cautious and, in the authors' wording, "cannot lay this issue to rest." The relationship between dental fluorosis and neurobehavioral deficits is an issue that thus requires further study, including the possibility that the relationship is only apparent for fluorosis of certain teeth that share windows of susceptibility that overlap the windows of susceptibility for developmental neurotoxicity.

⁸ The third study (Malin and Till 2015) was an ecological study that found an association between ADHD and water fluoridation in the U.S. This association was not robust, however, as it lost its significance after adjustment for altitude, although this adjustment is questionable.

between fluoride exposure and reported learning disability among Canadian children at the ages studied.

84. A more sophisticated study using the same CHMS data has now been completed and shows a significant association between fluoridated water and ADHD diagnoses/symptoms (Riddell et al. 2019). The latter study controlled for more potential covariates than Barberio and focused on an older subset of children (6 to 17 years old). Riddell's focus on an older group of children is an improvement because 90% of children with ADHD are diagnosed after age 6 (Riddell et al. 2019). Riddell also focused specifically on ADHD symptoms and diagnoses, rather than the broader category of "learning disabilities." The Riddell team also analyzed fluoride in water as well as in urine and conducted regression analyses to test the association with specific ADHD parameters: i.e., ADHD diagnosis and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

85. After adjustment for covariates, including lead exposure, Riddell and colleagues found that fluoridation of the home water supply significantly increased the risk of an ADHD diagnosis. An increase in water-fluoride by 1 mg/L was associated with a (statistically significant) 6-fold higher odds of an ADHD diagnosis in the 710 children known to rely on community water, although this association was not replicated using urine concentrations that may have been more variable. Similar tendencies were seen for the SDQ scores of hyperactivity/inattention, especially among the older youth (not covered by the Barberio study).

86. With its individual exposure data, more specific ADHD outcomes in adolescents, and large effect size, the Riddell study, along with Bashash et al. (2018) that I will discuss below, provide additional weight to the evidence of fluoride being a neurotoxicant at current levels of exposure in fluoridated areas.

VI. EPIDEMIOLOGICAL STUDIES (PROSPECTIVE)

A. Prospective Cohort Studies with Individual Assessment of Prenatal Exposure

1 87. The most reliable evidence of developmental neurotoxicity is obtained through prospective
2 studies that include real-time recording of information about exposure in early life followed by
3 subsequent clinical assessments of the child. (Grandjean & Landrigan 2014; Grandjean 2008). In our
4 meta-analysis we recommended that prospective studies be conducted to formally evaluate dose-
5 response relations based on individual-level measures over time, including more precise prenatal
6 measurements (Choi et al. 2012). Five such studies have now been conducted, and they have each found
7 significant adverse associations between prenatal fluoride exposure and neurodevelopmental harm
8 (Bashash 2017; Bashash 2018; Green 2019; Valdez-Jiminez 2017), with an additional study finding an
9 association between fluoride exposure during early infancy and IQ loss (Till 2020). The quality of these
10 studies, coupled with the consistency of their findings, also in regard to the cross-sectional studies, add
11 *substantial* weight to the evidence for developmental neurotoxicity from fluoride exposure.
12

13 88. I understand that Dr. Hu and Dr. Lanphear will be discussing the ELEMENT and MIREC
14 cohort studies in detail, so I will forego doing so here. As I explained in my initial expert report, these
15 are high-quality studies given their prospective birth cohort design, individual measurements of fluoride
16 exposure, and extensive control for potential confounders.
17

18 89. In addition to the ELEMENT and MIREC studies, a prospective birth cohort study has also
19 been published from a separate area of Mexico where there are elevated levels of fluoride in drinking
20 water (Valdez Jiminez 2017). In this study, maternal urine-fluoride (corrected for specific gravity) was
21 examined for its association with scores on the Bayley Scales among 65 children evaluated at age 3-15
22 months. The mothers in the study had average urine-fluoride concentrations at each of the three
23 trimesters of pregnancy of 1.9, 2.0, and 2.7 mg/L. These fluoride exposure indicators during the first and
24 second trimesters were associated with large and significant reductions in the Bayley Mental
25 Development Index (MDI) (cognitive) score after adjusting for covariates, including gestational age.
26
27

1 While this study is not as robust as the ELEMENT and MIREC studies due to the limited size, its
2 findings are consistent with and reinforce their findings, and add further weight to the neurotoxicity
3 assessment given its prospective cohort design.

4 **B. Prospective Cohort Studies without Prenatal Exposure Assessment**

5 90. Two additional prospective studies have been previously published on fluoride and
6 neurodevelopment (Shannon et al. 1986; Broadbent et al. 2015), both from New Zealand. They have
7 substantial limitations that make them much less informative than the North American studies, including
8 a failure to obtain individual measurements of fluoride exposure, and a failure to ascertain prenatal
9 fluoride exposure.
10

11 91. The first of the New Zealand studies was published in 1986 by Shannon. It found no
12 association between childhood behavior (as scored by mothers and teachers) and the duration of time the
13 child had lived in a fluoridated area during the first 7 years of life. The authors, however, made no
14 attempt to ascertain prenatal and early postnatal exposures. Postnatal exposures were measured by
15 simply tallying the number of years a child resided in a fluoridated area, with no distinctions made for
16 the *timing* of postnatal exposure. Under this exposure metric, a child who lived her first year of life in a
17 fluoridated area (a period of increased vulnerability) would be treated the same as a child who lived her
18 seventh year of life in a fluoridated area.
19

20 92. A second prospective study from New Zealand was based on a birth cohort established
21 from births in 1972-1973 (Broadbent et al. 2015). The 1,037 children were recruited at age 3 years, and
22 IQ tests were administered at ages 7, 9, 11 and 13 years, and again at age 38. Urine samples were again
23 not available for analysis, and the authors had no individual data on water intake. Instead, the authors
24 compared individuals who had lived for an undefined period of time in a fluoridated area during their
25 first five years of life, with individuals who had not lived in a fluoridated area during their first five
26 years of life.
27

years. No significant differences in IQ were noted using this exposure metric, and this finding was independent of potential confounding variables, including sex, socioeconomic status, breastfeeding, and birth weight.⁹

93. The Broadbent study also made no attempt to ascertain prenatal exposures, including maternal tea consumption, which is an important limitation given the high rate of tea consumption in New Zealand. Tea contains elevated levels of fluoride, and tea consumption can be a major source of fluoride intake among adults (Waugh 2017). During the time that the children in this study were born (1972-1973), New Zealanders consumed as much as 2.6 kg of tea per capita per year (corresponding to 3-4 teabags per day), as compared to the consumption of 0.5 kg in Canada in the approximate time the MIREC cohort was recruited (Grigg 2002). The failure of both New Zealand studies to consider maternal tea consumption may have introduced substantial imprecision into the exposure classification.

94. An additional concern is that the 10% of cohort subjects who had not lived in fluoridated areas very likely received fluoride supplements, which would eliminate much of the (postnatal) difference in exposure between the fluoridated and non-fluoridated areas. In a letter published subsequent to the study, the authors estimated that the average difference in exposure between children in fluoridated vs. non-fluoridated areas was only 0.3 mg/day (Broadbent et al. 2016).

95. Based on the absence of individual measurements of exposure; failure to control for the timing of exposure, including prenatal exposures; and the relatively small difference in postnatal exposures in the Broadbent study, the New Zealand studies provide virtually no information about the neurotoxic impact of early-life fluoride exposures. They carry little weight in my assessment.

VII. SYSTEMATIC REVIEW

96. Although I decided not to conduct a formal systematic review for my weight-of-the-

⁹ Despite the fact that lead exposure in this cohort was later reported to cause IQ deficits (Reuben et al. 2017), the authors of the fluoride study chose not to control for exposure to lead or other chemicals that can affect neurodevelopment.

evidence analysis, I had the opportunity to consider and analyze the review conducted by Dr. Ellen Chang of Exponent. As I described in my expert rebuttal report, Dr. Chang's systematic review provides no credible grounds for questioning my assessment of the literature; in fact, it further supports it.

A. Dr. Chang's Systematic Review Confirms that I Considered All Significant Data

97. Dr. Chang stated that her systematic review identified numerous studies that I did not address, with the apparent implication that these studies are somehow at odds with my opinion (p. 8). What Dr. Chang failed to reveal, however, is that the great majority of these studies reported significant associations between fluoride exposure and neurotoxic outcomes, further confirming my own assessment.

98. Of the 31 studies that Dr. Chang has identified and which I did not specifically address, 27 found associations of elevated fluoride exposure with adverse effects.¹⁰ These studies, which provide further *support* for my opinions, were not cited in my report because most are repetitions of the cross-sectional study design in endemic fluorosis areas that I have already discussed at length; some are only available in abstract form;¹¹ some are secondary analyses of primary studies that I already addressed;¹² and one was not available to me at the time of submitting my report (Till et al. 2020). As explained in my report, I do not consider it necessary to address and discuss each and every paper that reports on fluoride effects, especially when peer-reviewed systematic reviews are available, including our own (Choi et al. 2012). I consider it more informative to examine the various *types* of studies, including toxicokinetics (e.g., distribution of fluoride throughout the body, including transfer through the placenta and blood-brain barrier); toxicological findings from animals; and different endpoints relevant to

¹⁰ Aravind (2016); Asawa (2014), Calderon (2000), Das (2016), Khan (2015), Kundu (2015), Liu (2000); Lu (2019), Manju (2017), Mustafa (2018), Nagarajappa (2013); Qin (1990), Razdan (2017), Rocha-Amador (2007), Rocha-Amador (2008), Rocha-Amador (2009), Saxena (2012), Shivaprakash (2011), Singh (2013), Sudhir (2009), Thomas (2018), Till (2019), Trivedi (2007), Wang (2005), Xiang (2015), and Yu (2018).

¹¹ Calderon (2000); Thomas (2018).

¹² Xiang (2015); Wang (2012).

neurotoxicity (e.g., cognitive tests, thyroid function, histological assessments of fetal brain).

99. Conversely, many of the studies that I addressed in my report¹³ were not considered by Dr. Chang for unexplained or spurious reasons. Dr. Chang's review, for example, never addressed or considered fluoride's (i) passage through the placenta, (ii) uptake into fetal brain, and (iii) neurochemical and anatomical effects, and she spuriously dismisses the evidence of neurotoxicity in adults as irrelevant to developmental effects in humans (p. 31). In several important ways, therefore, Dr. Chang's review is not as systematic as my own.

100. Dr. Chang's systematic search of the literature identified four papers that reported no significant associations with neurodevelopmental effects and that I did not rely on, but upon inspection, they have no material effect on the conclusions that can be drawn, as I will now discuss.

101. One study highlighted by Dr. Chang is a publication by Spittle and colleagues (Spittle 1998) that Dr. Chang refers to repeatedly throughout her review. Although noted in a lengthy table at the end, Dr. Chang fails to acknowledge in the body of her review that this report is in the form of an abstract and relates to a previous (full) publication (Shannon et al. 1986) that I addressed in my report (and above). I did not cite the Spittle abstract in my report, just as I did not cite abstracts of studies reporting harm.¹⁴ It is standard practice for systematic reviews to omit abstracts, as practiced in systematic reviews conducted by the authoritative Cochrane group (Iheozor-Ejiofor et al. 2015). Dr. Chang provides no justification for including abstracts in her review, such as the one by Spittle (Spittle 1998). Dr. Chang's prominent references to the Spittle abstract is particularly surprising given that it does not describe *any* confounder adjustment,¹⁵ and uses an ecological metric for exposure (group water

¹³ *E.g.*, Dong (1993); Duan (1995); Ekstrand (1981); Li (2016); Spittle (1994); Guo (2001); Malin (2018); Opydo-Szymaczek (2005, 2007); Peckham (2015); Ron (1986); Salgarello (2016); Shao (2003); Shen & Taves (1974); Yazdi (2011); Yu (2008).

¹⁴ Calderon (2000); Thomas (2018).

¹⁵ On p. 132 of her Table, Dr. Chang "assume[s]" that the Spittle analysis controlled for the same confounders as the Shannon analysis. I understand that neither Dr. Chang, nor anyone else in her

1 F level) – features which Dr. Chang has used to dismiss many papers that support the neurotoxicity of
2 fluoride.

3 102. The other three “no-effect” studies that Dr. Chang cites and that I did not address are
4 similarly unavailing. Two are cross-sectional studies from China which fail to show statistically
5 significant associations between fluoride exposure and IQ,¹⁶ and one is an ecological analysis (Perrott
6 2018) of the Malin & Till (2015) study on ADHD which I addressed but placed little weight on. As I
7 explained in my report, there are many reasons why an ecological/cross-sectional study can fail to detect
8 an effect even when one is present. The failure of these three studies to find statistically significant
9 effects does nothing to contradict the robust literature that I rely upon, including the prospective birth
10 cohort studies that I placed the greatest weight on. Even Dr. Chang appears to recognize this, as she does
11 not include any of these three studies in her causal analysis, and correctly notes that the analysis by
12 Perrott (Perrott 2018) is a “relatively low quality” ecological study (p. 66).
13

14 103. In summary, despite asserting that my review failed to consider “numerous” papers, Dr.
15 Chang’s own review confirms that I addressed and considered the most relevant epidemiological studies
16 on cognitive outcomes. Dr. Chang’s literature search also confirms that the majority of studies that I did
17 not specifically address are consistent with and further support the association between fluoride and
18 cognitive impairment, in accordance with my conclusions.
19

20 **B. Dr. Chang’s Review Fails to Identify Any Systematic Biases that Explain Fluoride’s**
21 **Consistent Association with Neurodevelopmental Harm**

22 104. Dr. Chang’s systematic assessment of study quality provides a lengthy discussion of real or
23 perceived methodological limitations in the available studies. Importantly, however, Dr. Chang failed to
24 identify a likely explanation for how these limitations can explain the consistent adverse associations
25

26 office has contacted Dr. Spittle to confirm this statement (Personal email communication with Bruce
27 Spittle, August 13, 2019). According to Dr. Spittle, the abstract provided all important methodological
28 details.

¹⁶ He (2010); Kang (2011).

1 between fluoride and IQ across both cross-sectional and prospective studies. For example, Dr. Chang
2 referred to “high potential for selection bias” but did not consider how unlikely it is that dozens of
3 studies should all suffer from some particular exposure misclassification or selectivity that would all
4 cause bias *away* from the null, e.g., selection bias that would result in participation of intellectually
5 disabled children only in the high-fluoride group, or residual confounding resulting in bias only away
6 from the null in the many different study settings.

7
8 105. Dr. Chang claimed that “methodological uncertainties remain about the assessment of
9 fluoride exposure and neurodevelopmental outcomes; and the reported findings are plausibly explained
10 by confounding, bias, and chance” (p. 9). However, she did not provide any convincing evidence that
11 such issues could have resulted in erroneous conclusions, especially in the high-quality prospective
12 studies.

13
14 106. Throughout her analysis, Dr. Chang failed to grapple with the fact that random (i.e., non-
15 differential) error is unlikely to cause a bias away from the null, as is well-known in epidemiology, as I
16 have also discussed in past publications (Grandjean and Budtz-Jorgensen 2007, 2010). Dr. Chang thus
17 did not articulate a plausible basis for why the limitations she claimed to have identified can
18 *systematically* bias the results across the many study settings, including the North American birth
19 cohorts.

20
21 107. Dr. Chang described cross-sectional studies as if they are all equal and as if the exposure
22 parameter always represents a current and short-lasting exposure only. In so doing, Dr. Chang failed to
23 acknowledge in her causal analysis that exposure measures in many studies represent long-term
24 community conditions, in some studies also likely covering prenatal exposures, a critical detail.

25
26 108. Dr. Chang referred to exaggerated associations that can result from lack of blinding (p.
27 59), but failed to acknowledge that at least 11 of the studies reporting adverse neurocognitive effects

1 have clearly been blinded, including the recent birth cohort studies, where the exposure was determined
2 *after* the cognitive tests had been completed. Thus, while lack of blinding can create observation bias, it
3 cannot explain the inverse association between fluoride and IQ because similar associations have been
4 consistently found in studies known to be blinded. Despite producing a 56-page table to address “key
5 characteristics” of the studies, Dr. Chang failed to mention this methodological strength in her summary
6 of the studies (pp. 90-146).

7 109. Dr. Chang repeatedly highlighted the risk of publication bias, e.g., in the biomedical
8 journal *Fluoride*, which is not indexed by PubMed. However, she does not mention the bias *against*
9 publication, i.e., a bias that acts in the opposite direction. The examples that I mentioned in my report
10 illustrate that such bias exists.¹⁷ Further, Dr. Chang speculated that Chinese-language studies that did
11 not find adverse effects may not have been translated into English (p. 37). Instead of speculating about
12 this, Dr. Chang’s systematic review could have included a search of online databases of Chinese-
13 language research (e.g., CNKI) but, for unexplained reasons, did not do so.¹⁸

14 110. In summary, although Dr. Chang’s systematic assessment of study quality correctly
15 identified limitations in a number of studies, she failed to credibly explain how these limitations can
16 plausibly explain the significant inverse associations that have consistently been found across many
17 study settings and designs.¹⁹ Although I recognize the issues that Dr. Chang has raised and have fully
18

19
20
21 ¹⁷ The desire to use fluoride in caries prevention programs has sometimes made it difficult
22 for researchers, including myself, to present findings of potential toxic effects. In addition to my own
23 personal experiences, published case reports suggest that some studies reporting adverse results have
24 been suppressed, and, in at least one instance, a respected scientist at the Forsythe Dental Institute lost
25 her job after publishing evidence of neurotoxicity.

26 ¹⁸ A search of PubMed for “CNKI database” shows that many systematic reviews include
27 CNKI as one of the databases to retrieve studies, and the Institute of Medicine recommendations for
28 systematic review (which Chang relies on) calls for searching for foreign language studies when
appropriate (IOM 2011, p. 8). CNKI is publicly available online at:
<http://oversea.cnki.net/kns55/default.aspx>.

¹⁹ Unable to explain why so many studies have found significant associations between
fluoride and IQ, Dr. Chang claims that “most published scientific research findings are anticipated to be
false” (p. 38, citing Ioannidis (2005)). Although the original report by John Ioannidis (Ioannidis 2005)

considered them in my assessment, it remains extremely unlikely, if not impossible, that the overwhelming evidence of fluoride neurotoxicity is a mirage caused by bias, as Dr. Chang apparently believes. A far more likely and plausible explanation for the consistent findings in the epidemiological studies is that fluoride is a developmental neurotoxicant that reduces IQ and that this association is strong enough to be apparent also in studies with less-than-ideal designs.

C. Bradford Hill Aspects Support, Rather than Detract from, the Causal Nature of Fluoride's Association with Neurodevelopmental Harm

111. Dr. Chang used the Bradford Hill aspects to evaluate the causal relationship between fluoride and neurotoxicity. As I explained in my rebuttal report, her causal analysis is superficial and pays lip service only to Sir Austin's wise advice. An appropriate and systematic assessment of the Bradford Hill guidelines supports, rather than refutes, the causal relationship between elevated fluoride exposure and IQ loss. I will summarize here:

112. *Strength*: Dr. Chang dismissed the strength of the association between fluoride and IQ on the grounds that a loss of 3 to 5 IQ points is relatively small in comparison with normal, expected variation (p. 69). Under this arbitrarily high standard, other well-known neurotoxicants (e.g., lead, methylmercury, arsenic) would fail Dr. Chang's strength criterion. By failing to consider the strength of association of other well-known neurotoxicants, Dr. Chang subjectively analyzed the data on fluoride in a meaningless vacuum. Had Dr. Chang considered the strength of association for other neurotoxicants, she would have found that the effect size for fluoride actually is actually large, not small (i.e., it rivals the effects of lead), which *supports*, rather than detracts, from a causal relationship.

113. *Consistency*: One of the most compelling aspects about the epidemiological research on

did provide some stunning examples of how clinical medicine could be misled by single reports, it would be reckless and counterproductive if we were to ignore all published reports, as Dr. Chang seems to prefer. This nihilistic view was also not the intent of the author. In a more recent paper in the same journal, Dr. Ioannidis highlighted the need for balanced review of scientific evidence in the interest of inspiring responsible policy decisions (Ioannidis 2018).

1 fluoride is how consistent it has been in finding significant associations with IQ (Choi et al. 2012). Dr.
2 Chang obscured this by highlighting non-informative studies that made no attempt to measure or
3 investigate prenatal or early postnatal fluoride exposures (Barberio et al. 2017; Broadbent et al. 2015;
4 Morgan et al. 1998; Shannon et al. 1986; Spittle 1998) as being on the same level as, and contradicting,
5 the highly significant findings from the prospective ELEMENT (Bashash et al. 2017) and MIREC
6 (Green et al. 2019) prospective birth cohort studies (pp. 70-71). A particularly poor judgment by Dr.
7 Chang was to place the Spittle abstract on the same level as the ELEMENT and MIREC studies despite
8 the fact that Spittle's abstract does not describe *any* confounder adjustment. Dr. Chang cited the "mixed"
9 nature of the findings as a basis to conclude that the consistency factor has not been met, while failing to
10 acknowledge the inappropriate apples-to-oranges nature of comparing the prospective
11 ELEMENT/MIREC studies to much, much weaker studies.
12

13 114. In her assessment of consistency, Dr. Chang failed to mention the fact that every single
14 prospective birth cohort study with prenatal exposure measurements has found a significant adverse
15 effect of prenatal fluoride on neurodevelopment (Bashash et al. 2017; Bashash et al. 2018; Green et al.
16 2019; Valdez Jimenez et al. 2017). Dr. Chang also gave short shrift to the consistent association between
17 fluoride exposure and reduced IQ reported in the numerous cross-sectional studies (Choi et al. 2012;
18 Duan et al. 2018; Tang et al. 2008). This latter shortcoming may be a result of Dr. Chang's critical
19 misunderstanding of our meta-analysis (Choi et al. 2012), which I will now address.
20

21 115. Dr. Chang claimed that our meta-analysis found an average loss of 0.45 IQ points in the
22 high-fluoride areas and characterizes this as a 10-fold difference with the Tang meta-analysis (Tang et
23 al. 2008). This, however, is not what we reported (see paragraph 78). Because different intelligence
24 scales had been used in the studies considered, we expressed the outcome as a random-effect
25 standardized weighted mean difference estimate, as we clearly explained (Choi et al. 2012). In order to
26
27

1 translate this measure to a difference on the same IQ scale, the joint result must be multiplied by the
2 standard deviation of the IQ scale, i.e., 15. An SMD of -0.45 thus corresponds to a loss of 6.75 IQ
3 points. Contrary to Dr. Chang's mischaracterization, therefore, the results of our meta-analysis are
4 consistent with the Tang meta-analysis, a fact that we actually mention in our published paper (Choi et
5 al. 2012).

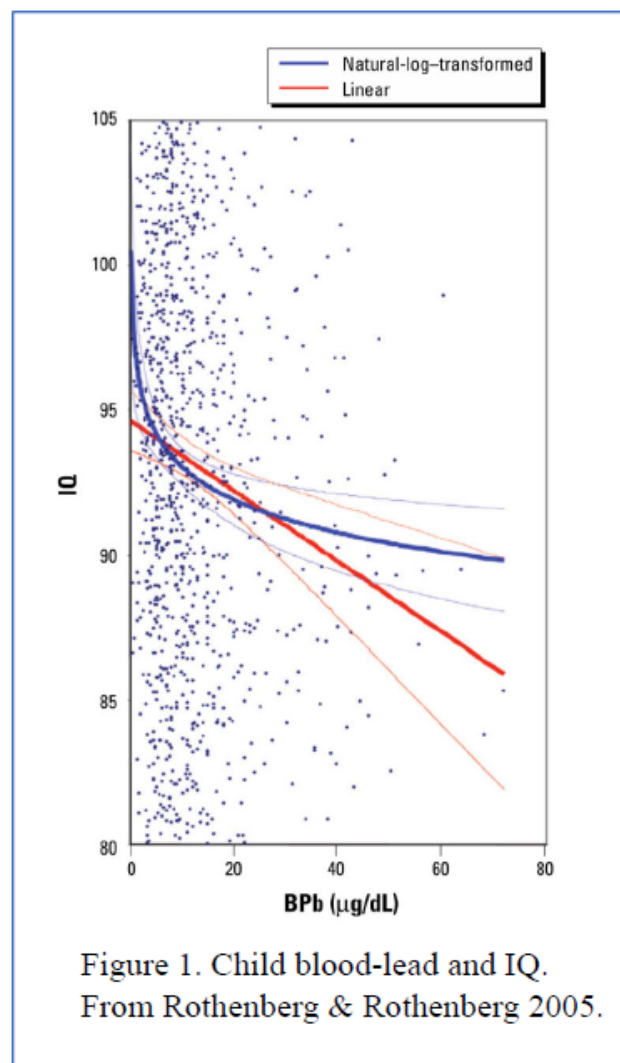
6 116. Dr. Chang's assessment of consistency also entirely ignored the findings from
7 occupational studies, as well as the neuropathology data from examinations of fetal brains in endemic
8 fluorosis areas. As I explained in my report, each of these types of studies is consistent with, and provide
9 support for, fluoride being a neurotoxic agent.
10

11 117. *Specificity*: As Kenneth Rothman (2012) and others (Neutra 2018) have emphasized, and
12 as Dr. Chang recognized, lack of specificity between an exposure and an outcome (e.g., asbestos and
13 mesothelioma) does not weigh against or in favor of a causal conclusion.

14 118. *Temporality*: Dr. Chang's assessment of temporality mirrored her assessment of
15 consistency in that she cited the two New Zealand studies as contradicting the findings from the
16 ELEMENT and MIREC cohorts. Once again, Dr. Chang fails to acknowledge the absence of prenatal or
17 early postnatal fluoride exposure assessments in the New Zealand studies, nor any of the other serious
18 shortcomings of these studies. Instead, Dr. Chang focused on non-differential measurement uncertainties
19 of the urine-fluoride data in the far superior ELEMENT and MIREC cohorts to cast doubt on the
20 findings of these studies. As already discussed in my report, however, the imprecision of the fluoride
21 exposure parameters would likely *bias the results toward the null*, not the reverse. The temporality
22 requirement is thus met with fluoride, as each of the prospective birth cohort studies has found a
23 significant association between early-life exposure to fluoride and the offspring's subsequent
24 performance on neurobehavioral testing. The exposure preceded the effect in these studies, which is
25
26
27
28

what the temporality factor is supposed to assess.

119. *Biological Gradient*: The ELEMENT and MIREC studies have reported monotonic dose-response relationships between elevated prenatal fluoride exposure and IQ deficits in the offspring (Bashash et al. 2017, Green et al. 2019), as well as ADHD behaviors (Bashash et al. 2018). Dr. Chang dismissed the biological gradient of these effects by showing scatterplots from the ELEMENT and MIREC cohorts without the trend lines. However, this approach proves little insight, other than illustrating the undisputed fact that there is substantial natural variation in IQ across the population and that an appropriate statistical analysis is needed to extract a reliable estimate of the average effect of the toxicant exposure. Similar scatterplots have been published showing the effects of lead and IQ, as can be seen in the figure to the right (Rothenberg & Rothenberg 2005, Figure 1). Lead would thus fail the biological gradient test that Dr. Chang has used for fluoride. Dr. Chang also argued that outliers may have distorted the effects seen in the ELEMENT and MIREC cohorts (p. 77-78), without acknowledging that statistical analyses on the impact of outliers have been conducted and that the results did not meaningfully change (Bashash et al. 2017).



120. *Plausibility*: Dr. Chang limited her assessment of biologic plausibility to NTP's assessment of learning and memory (NTP 2016) in animal models, and to Dr. Tsuji's expert report. In so doing, Dr.

1 Chang completely ignored the large body of animal literature showing adverse neuroanatomical and
2 neurochemical effects from fluoride exposure, as already reviewed by the National Research Council
3 (NRC 2006) and by Dr. Thiessen in her report. The NRC concluded that the neuroanatomical and
4 neurochemical effects are sufficient to determine that fluoride interferes with brain function (NRC
5 2006). Dr. Chang ignored this information in favor of the NTP's more narrow assessment on
6 learning/memory, but even the NTP assessment found suggestive evidence that fluoride impairs learning
7 and memory. In contrast to Dr. Chang's assessment, EPA's own experts on developmental
8 neurotoxicity, including internationally recognized scientists such as William R. Mundy and Kevin M.
9 Crofton (Mundy et al. 2015), have identified fluoride as a chemical with substantial evidence of
10 developmental neurotoxicity.
11

12 121. *Coherence*: Dr. Chang dismissed the coherence of fluoridated water reducing IQ on the
13 grounds that IQ scores in US children steadily improved throughout the 20th century (the so-called
14 "Flynn Effect"). Dr. Chang even went so far as to suggest that fluoridation may be responsible for the
15 increased scores, although more plausible explanations are known. Under Dr. Chang's simplistic
16 framework, leaded gasoline could not have reduced IQ and may have increased it, as it was introduced
17 in the early part of the 20th century and IQ scores continued to increase during the entire duration of its
18 use. It is well accepted, however, that low-level lead exposure reduces IQ, and thus the Flynn Effect
19 argument—while perhaps superficially appealing—does *not* demonstrate "incoherence."
20

21 122. In her assessment of coherence, Dr. Chang failed to consider other relevant considerations,
22 including the association between neonatal fluoride exposure mediated by infant formula feeding and
23 reduced IQ (Till et al. 2020), as further discussed below. While the studies prior to the recent Canadian
24 analysis did not evaluate the potential role of neonatal fluoride exposure, formula feeding is well
25 established to increase a baby's fluoride exposure, even in areas without fluoridated water (Harriehausen
26
27

et al. 2019; Zohoori et al. 2019). Although other factors are of likely importance, the relationship between formula-feeding and reduced IQ is coherent with maternal fluoride exposure during pregnancy being associated with a lowered IQ in the child and supports a causative relationship between early-life exposure to fluoride and IQ deficits.

123. *Experiment:* Dr. Chang ignored the NRC’s observation (NRC 2006) that case reports of fluoride toxicity constitute “experimental studies” of neurologic symptomatology following fluoride exposure (NRC, p. 208). The case reports involve “one or more individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under ‘blind’ conditions.” In most cases, the symptoms (which included lethargy, weakness, and impaired ability to concentrate) “disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated.” Although experimental support is not an obligatory criterion (Neutra 2018), the existence of such support should not be missed in what is dubbed a systematic assessment.

124. *Analogy:* I agree with Dr. Chang that “analogies can be drawn to other naturally occurring elements, especially certain metals” like lead (p. 85). As discussed above, many of the exaggerated criteria that she uses to reject a causal relationship between fluoride exposure and IQ could be equally used to erroneously dismiss the causal relationship between low-level lead exposure and IQ.

125. In summary, after correcting for Dr. Chang’s errors and biases in judgment, the Bradford-Hill aspects support, rather than detract from, a causal relationship between fluoride in water and neurotoxicity. After analyzing and considering Dr. Chang’s systematic review, I have more, not less, confidence that developmental neurotoxicity is a serious risk of elevated fluoride exposure.

VIII. BENCHMARK DOSE (BMD) ANALYSIS

A. Selection of Source Data

126. Regulatory agencies are in overall agreement in using Benchmark Dose (BMD) analyses to

1 calculate non-cancer health-based limits for dietary intakes of contaminants, such as those found in
2 drinking water (EFSA 2009; EPA 2012).

3 127. As with the Faroe Islands cohort that the EPA relied upon in its risk assessment for
4 methylmercury, the ELEMENT and MIREC studies are high-quality birth cohorts suitable for dose-
5 response analysis (Bashash et al. 2017; Green et al. 2019). Further, as the data refer to the critical effect
6 in a highly vulnerable population, they constitute appropriate data to use for identifying a safe exposure
7 limit for fluoride. I worked, therefore, with my colleague, Dr. Budtz-Jorgensen, on BMD analyses of
8 these studies, which I describe below.
9

10 128. Our selection of the ELEMENT and MIREC studies for BMD analysis is consistent with
11 an analogous assessment conducted by both Dr. Chang and her colleague, Dr. Joyce Tsuji (Tsuji et al.
12 2015) for another neurotoxicant. In their paper, Drs. Chang and Tsuji sought to determine if the existing
13 RfD for arsenic is adequately protective of neurotoxicity. To answer this question, they conducted a
14 systematic review of the literature to see if there were any studies that would permit a dose-response
15 analysis for quantitative risk assessment. After reviewing the literature, they found a study that, in their
16 judgment, was suitable for the purpose: a study from Bangladesh by Hamadani et al. (2011).
17

18 129. The ELEMENT and MIREC studies are at least equally suitable for dose-response analysis
19 as the one study Dr. Chang and Dr. Tsuji found sufficiently reliable to use for their risk assessment of
20 arsenic exposure. As with the Hamadani study, the ELEMENT and MIREC studies have a (i)
21 prospective birth cohort design; (ii) large sample size; (iii) control for potential confounders;²⁰ (iv) urine
22 measurements²¹ of the toxicant of interest during pregnancy; (v) and extended follow-up (up to 5 years
23

24 ²⁰ Drs. Chang and Tsuji considered studies to have sufficiently controlled for potential
25 confounders if they controlled for SES or HOME Score and parental education/IQ (Tsuji et al. 2015, p.
26 93).

27 ²¹ As with the ELEMENT and MIREC studies, the Bangladesh study measured prenatal
28 exposure through several samples of maternal urine (adjusted for specific gravity) (Hamadani 2011).
The Bangladesh study collected urine twice during the pregnancy (at gestational weeks 8 and 30), which

after birth). In fact, the ELEMENT and MIREC studies have an important advantage: the average arsenic exposure in Bangladesh substantially exceeded exposures in the U.S.,²² which is not the case with the North American fluoride cohort studies.

130. My calculations of benchmark values for fluoride from the ELEMENT and MIREC cohorts are therefore in accordance with the criteria that Drs. Chang and Tsuji have previously used when generating benchmark calculations for arsenic (where adverse effects were seen in girls, but not boys, at 5 years of age).

B. Selection of Benchmark Response (BMR)

131. The benchmark dose (BMD) is defined as the dose that leads to a specific loss (or degree of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be defined before the analysis (EPA 2012), and general guidelines been developed for the selection of a BMR (EFSA 2009).

132. According to the EPA Clean Air Scientific Advisory Committee, a 1-to-2 IQ point reduction at the population level is “highly significant from a public health standpoint,” and should be prevented in up to 99.5% of the population (EPA 2008). Consistent with this, previous BMD analyses of human neurotoxicity have selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-Jorgensen et al. 2013; EFSA 2010; Tsuji et al. 2015).

133. Economists have calculated the substantial losses in lifetime incomes from a decrease of 1 IQ point²³ (Gould 2009), as also practiced by economists at the EPA in regulatory impact analyses (EPA 2008).

134. Research on other neurotoxicants (Grandjean 2013) has shown that shifts to the left of IQ is a lower number of samples than the MIREC cohort, and roughly the same as the ELEMENT study.

²² The Bangladesh study addressed a population with mean urinary arsenic levels ranging from 35 to 80 ug/L, which is about 10-to-40 times the levels measured in the US population.

²³ In terms of 2006-dollars, the value of 1 IQ point was calculated to be about \$18,000 (Gould 2009; Spadaro and Rabl 2008).

distributions in a population (i.e., reductions in average IQ) can have substantial impacts, especially among those in the high and low ranges of the distribution (Bellinger 2007).

135. Consistent with prior analyses, including our own, we therefore selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-Jorgensen et al. 2013).

C. Analyses of ELEMENT and MIREC Data

136. For our BMD analysis, we used the same formula that we used in our prior assessment of lead (Budtz-Jorgensen et al. 2013). The formula is as follows:

The BMD is defined by

$$f(0) - f(\text{BMD}) = \text{BMR} \rightarrow \text{BMD} = f^{-1}(-\text{BMR})$$

In a linear model, $(Y = \alpha + \beta d + \epsilon)$, from which we get $\text{BMD} = -\text{BMR}/\beta$.

Likewise, the BMDL is defined as a lower one-sided 95% confidence limit of the BMD. In the linear model,

$$\text{BMDL} = -\text{BMR}/\beta_{\text{lower}}$$

where β_{lower} is the one-sided lower 95% confidence limit for β . Information on the (linear) regression coefficients and their standard deviations, from which the confidence intervals can be calculated, is available from the published articles on the two major prospective cohort studies.

137. For the ELEMENT study (Bashash et al. 2017), a linear dose-response model could be used for the effect of urine-fluoride concentrations on both measures of childhood IQ (i.e., the General Cognitive Index (GCI) results at age 4 and IQ results at ages 6-12). In this model, the BMD and BMDL can be calculated based only on the regression coefficient and its precision. In Table 4 of the publication (Bashash et al. 2017), this information is available both for a crude model and for a model A with confounder adjustment. The table below shows the benchmark results for these two models for both the age-4 GCI and school-age IQ.

Table 2. Benchmark dose results (mg/L urine adjusted for creatinine) obtained from the ELEMENT study results (Bashash et al. 2017).

Model	GCI		IQ	
	BMD	BMDL	BMD	BMDL
Crude	0.133	0.085	0.211	0.121
Adjusted	0.159	0.099	0.200	0.130
Read from plot	0.159	0.102	-	-

138. As these calculations are based on assumptions of Gaussian distributions, we checked the validity by scanning the numbers from the plot in the published article. We tentatively used the *WebPlotDigitizer* software to read the plot shown in the published paper (see Figure 1, page 22) (Bashash et al. 2017), to obtain the individual adjusted GCI results for more accurate BMD calculations. Of the original 287 observations, the software provided 286 observations, probably due to two overlapping observations. Thus, missing a single point only, our calculations based on the scanned data should be considered fairly reliable.

139. Using the standard benchmark approach to epidemiological data and a linear dependency, we find that the BMD for GCI is approximately 0.16 mg/L, and that the BMDL is 0.10 mg/L (bottom line of Table 2). These results are in excellent agreement with the results calculated only from the regression data presented in Table 4 of Bashash et al. (2017).

140. To assess the robustness of the calculation, we included a logarithmic conversion of the exposure parameter. We also used a split linear dose-response curve as in one of our previous studies (Budtz-Jorgensen et al., 2013). These sensitivity analyses showed BMD results that deviated only marginally from the calculation using the default linear association. In conclusion, Table 2 shows

reliable BMD results that have been calculated in accordance with standard EPA procedures.

141. We also conducted a BMD analysis of the MIREC data. As with the ELEMENT study, we calculated the BMD and BMDL from the reported regression coefficients and standard deviations, with the assumption of a Gaussian distribution (Green 2019, Table 2). In addition to calculating the BMD and BMDL from the urine-fluoride data (U-F), we also calculated a BMD and BMDL from the maternal fluoride intake data. Our results are shown in the table below:

Table 3. Benchmark dose results (mg/L urine adjusted for specific gravity, or mg estimated daily intake) obtained from MIREC study results on IQ (Green et al. 2019).

Study	Exposure	Sex	BMD	BMDL
MIREC	Maternal U-F	Both sexes	0.51	0.21
	Maternal U-F	Boys	0.22	0.13
	Maternal U-F	Girls	(–)	0.58
	Maternal F intake	Both sexes	0.27	0.15

142. As shown in the above table, the prenatal BMD for girls is not defined when relying on urine-fluoride, but the BMDL is still meaningful and is, as expected, higher than the other estimates obtained. No sex difference was found when relying on estimated fluoride intake.

143. Overall, the results derived from the two studies are comparable. In the ELEMENT study, the BMDL for maternal urine among ~4-year olds is approximately **0.1 mg/L** (both sexes), while in the MIREC study, it is **0.13 mg/L** (boys) and **0.21 mg/L** (both sexes).²⁴ The respective BMDL for the 6-to-12-year olds from the ELEMENT study is **0.13 mg/L**, thus overall approximately 0.15 mg/L. Consistent with these maternal urinary excretion values, the BMDL for maternal fluoride *intake* in the MIREC

²⁴ Based on how the authors reported the data, our BMDL values from the ELEMENT cohort are creatinine-adjusted, while our BMDL values from the MIREC cohort are specific gravity-adjusted.

study is **0.15 mg/day** (both sexes).

IX. ASSESSMENT OF RISK

A. Comparing BMDLs with Current Exposures in Fluoridated Areas

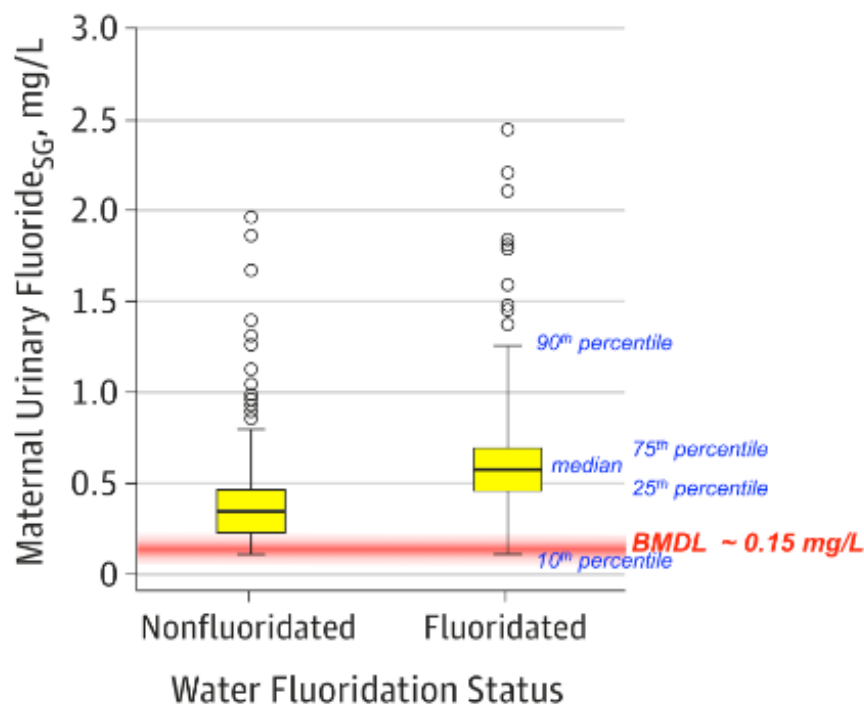
144. As benchmark dose calculations constitute a routine approach applied by the EPA for establishing safe limits on chemical exposure, the above calculations that rely on overall associations between fluoride exposure and cognitive deficits provide a basis for assessing the risk of cognitive deficits from current fluoride exposure levels.

145. Typically, the EPA uses the BMDL to calculate a Reference Dose (RfD) by dividing by an uncertainty factor for the purpose of accounting for variations in human susceptibility. The default value that EPA uses for the uncertainty factor is 10. Here, if we round up the overall BMDL to **0.2 mg/L**, or about 0.2 mg/day, the RfD would likely be 0.02, which is very much below current exposure levels, especially in communities with fluoridation programs (Till et al. 2018). But, *even if no uncertainty factor is applied, and even if relying on the BMD rather than the BMDL* (both of which would be unusual), the RfD would still be well below current exposure levels in fluoridated areas (Till et al. 2018).

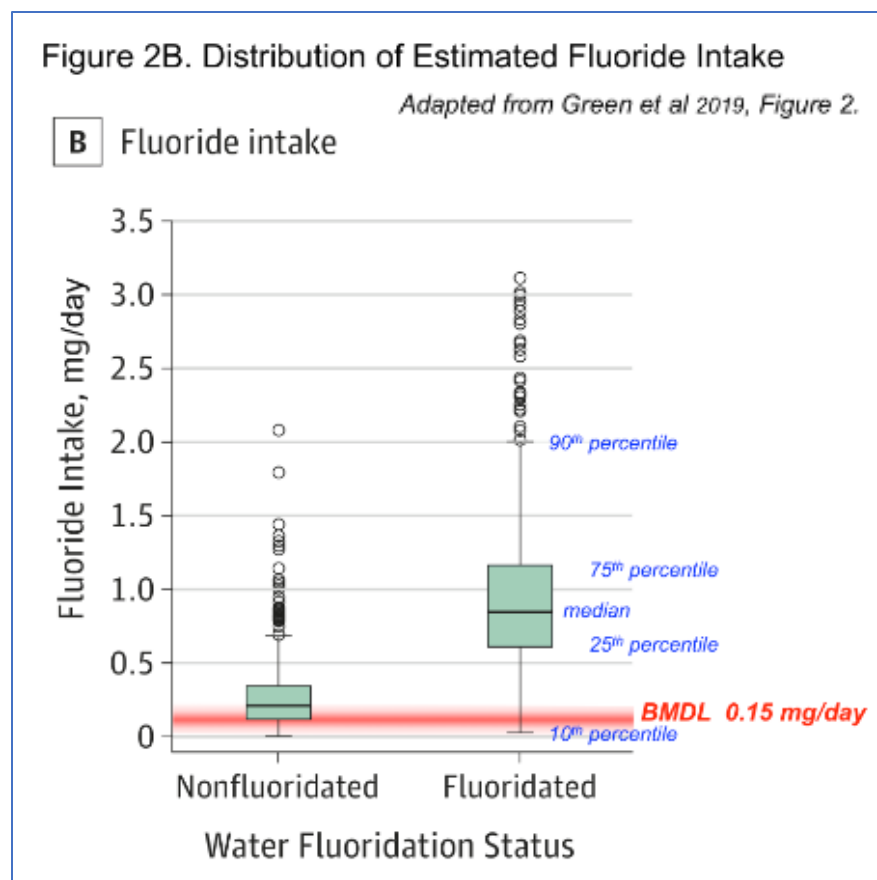
146. The serious risk that we are confronted with can be appreciated by visually comparing the BMDLs against documented exposure levels in fluoridated communities. The following Figure 2A, adapted from Green et al. (2019), compares an overall BMDL for maternal urine-fluoride (0.15 mg/L) with the maternal urine-fluoride concentrations reported in the study. As can be seen, the urine-fluoride levels far surpass the levels associated with IQ loss.

Figure 2A. Distribution of Maternal Urinary Fluoride

Adapted from Green et al 2019, Figure 2.

A Maternal urine

147. The below Figure 2B compares the approximate BMDL for maternal fluoride *intake* from beverages (0.15 mg/day) against the reported fluoride intakes in Green et al (2019). As can be seen, the estimated fluoride intakes in fluoridated areas far surpass the fluoride intake level associated with a clear IQ loss.



148. There are no contemporary large-scale studies of urine-fluoride concentrations in the United States, as the CDC has not yet reported urinary fluoride excretion levels as part of its ongoing National Health and Nutrition Examination Survey (NHANES) studies. One can reasonably infer, however, that urinary fluoride excretion levels in fluoridated areas of the U.S. are generally comparable to those in fluoridated areas of Canada. The reasonableness of this inference is supported by the following facts:

149. Canada and the U.S. add fluoride to water to reach the same target concentration (0.7 mg/L), although empirical data suggests Canadian cities only reach 0.6 mg/L which is slightly less than the U.S. (Till et al. 2018).

150. Fluoridated water is recognized as the largest source of fluoride exposure for adults, particularly when indirect sources are accounted for, such as beverages and foods prepared with the

water, including commercially prepared beverages such as soda and reconstituted juice (EPA 2010).

151. Urine-fluoride has been shown to be a good indicator of total daily fluoride intake, and has a close, linear correlation with the fluoride content in water (Villa et al. 2000; McClure 1944; Smith et al. 1950).

152. The largest study of urine-fluoride levels in the U.S. found that pooled urine samples from healthy young males generally mirrored the fluoride concentration in the drinking water (McClure 1944). Based on U.S. data, therefore, a person drinking water with 0.7 mg/L fluoride would be expected to have about 0.7 mg/L in their urine, which is similar to what was found in the MIREC cohort (Till et al. 2018). Although these U.S. data were published prior to widespread fluoridation, the levels today would, if anything, tend to be *higher* today, not lower because fluoride is now available from more sources than was the case in the 1940s (e.g., including commercial beverages made with fluoridated water, dental products, etc.).

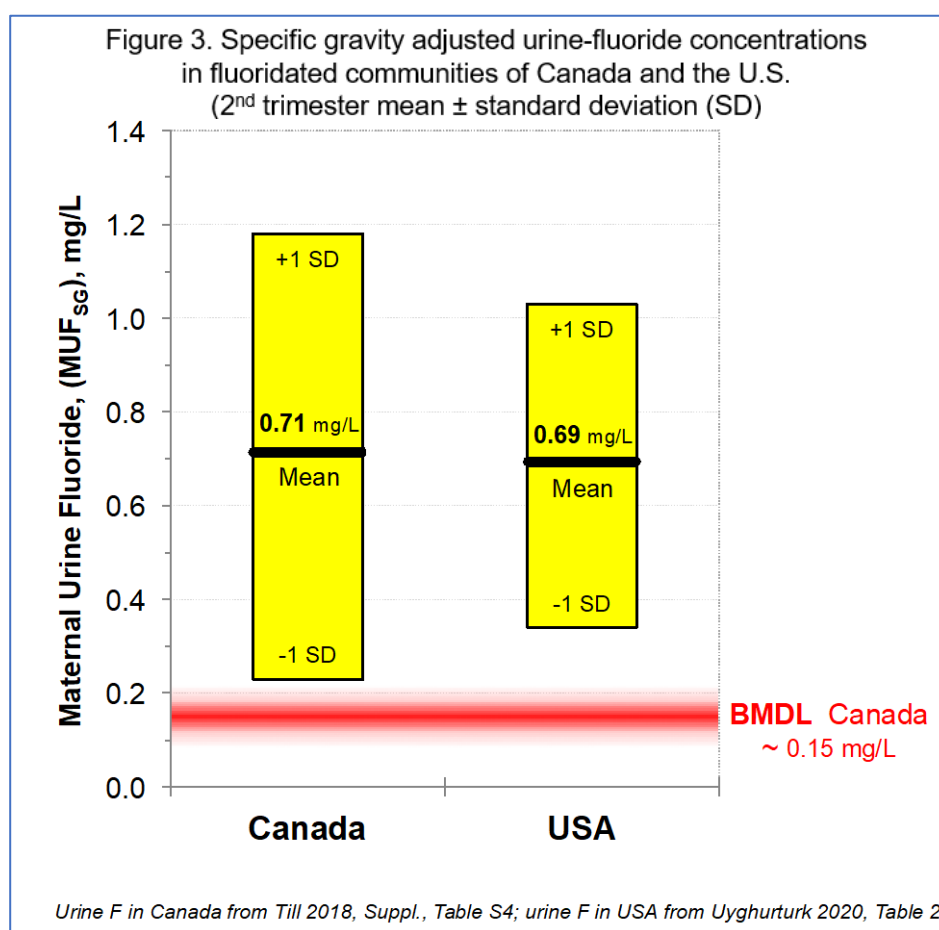
153. To address the lack of contemporary US data on fluoride exposures in pregnant women,²⁵ the recent UCSF study measured the concentrations of fluoride in urine (and blood²⁶) of 48 pregnant women living in fluoridated and non-fluoridated areas of California. As with the Canadian study, the UCSF team had the urine tested by Dr. Angeles Martinez-Mier at the University of Indiana and adjusted the fluoride measurements for specific gravity. The study found an average (specific gravity-adjusted) urine-fluoride concentration of **0.69 mg/L** among pregnant women in areas with at least 0.7 mg/L in the community water, which is clearly in the same range as the MIREC team found in Canada (Uyghurturk

²⁵ As noted by the UCSF team, there is only one prior published study of urine-fluoride levels among pregnant women in the US: this is the study by Shen & Taves (1974) that I discussed in my expert report. This study found an average of 1.02 mg/L in maternal urine among a group of 16 pregnant women, but the authors did not report the concentrations of fluoride in water.

²⁶ The study found an average of 0.021 mg/L fluoride in the blood (=1.1 µmol/L) of the women from fluoridated areas (~0.8 mg/L), which is higher than the predicted value (0.015 mg/L = 0.8 µmol/L). As discussed by the NRC, it has been historically estimated that adult populations will have 1 µmol/L in their blood for each 1 mg/L of fluoride in the water (NRC 2006).

2020, Table 2). While the small-scale nature of the study likely introduced some random scatter in the results of the UCSF study,²⁷ the study supports the general similarity in fluoride exposures in the Canadian and U.S. populations.

154. Finally, the relevance of the Canadian IQ data (Green et al., 2019) to the US can be appreciated by comparing the BMDL to the maternal urine-fluoride concentrations reported by the UCSF team (Uyghurturk 2020). As can be seen in the following Figure 3, maternal urine-fluoride concentrations found in pregnant women in the Californian cohort greatly exceed the BMDL for fluoride-associated IQ loss. This, ultimately, is the most important consideration.



²⁷ The study found some high levels of urine-fluoride in the mid-range fluoride communities (0.3-0.5 mg/L), which slightly skewed the distribution (Uyghurturk 2020, Fig. 2). As the authors note, this may be the result, in part, of the fact that the women had their urine tested while visiting a clinic in San Francisco, which is fluoridated (Uyghurturk 2020, p. 6-7). In the areas with >0.3 mg/L in water, the average (specific-gravity adjusted) fluoride level was 0.74 mg/L (Uyghurturk 2020, Table 5).

B. Comparing Fluoride's Population-Level Effects with Other Causes of IQ Loss

155. In order to compare fluoridation's population-level effects with other neurotoxicant exposures, some approximate estimates of fluoride-associated IQ losses can be made. The calculations rely on several assumptions that are necessary in the absence of actual data and are therefore meant only to identify relative orders of magnitude. On the conservative side, I shall assume that all children are equally vulnerable and that the dose-dependent IQ losses observed in the recent prospective studies can be used to assess the impact on the population at large (i.e., that genetic and other predisposition can be ignored).

156. My analysis focuses on the average difference in maternal urine-fluoride levels between fluoridated and non-fluoridated areas. The Canadian study (Till et al. 2018) showed that this difference is approximately 0.4 mg/L. It bears emphasizing that this difference likely understates the true contribution of fluoridated water because part of the exposure in "non-fluoridated" areas comes from the "halo" effect. The halo effect refers to the fact that many commercial beverages and foods made in fluoridated areas are shipped to and consumed in non-fluoridated areas and that residents from non-fluoridated communities may work or spend time in fluoridation areas.²⁸

157. Given the BMD results, an average increase of 0.4 mg/L in maternal fluoride concentrations is above the threshold for developmental neurotoxicity, even if assuming a zero background exposure. Using the dose-dependent losses observed in the recent prospective studies (Bashash et al. 2017; Green et al. 2019), this elevated exposure will correspond to an IQ loss of approximately 2 IQ points.

158. Because about two-thirds of the U.S. population receives fluoridated drinking water, one can assume that a similar proportion of the 4 million annual U.S. births (i.e., more than 2.5 million

²⁸ This widespread dispersal of fluoridated water in commercial products helps to explain the relatively high urine-fluoride levels now seen in non-fluoridated communities versus the situation back in the 1940s (Till et al. 2018).

1 births) are affected by fluoridation-associated exposure increases. With the 2-point average IQ loss
2 associated with fluoridation, the 2.5 million births will lose a total estimated number of 5 million IQ
3 points annually.

4 159. This approximate estimate can be compared with calculations made by Professor David
5 Bellinger on IQ losses due to major pediatric diagnoses affecting 0-to-5-year-old children (Bellinger
6 2012). According to CDC data and Bellinger's calculations, the top pediatric etiologies for IQ loss are
7 preterm birth at 34 million IQ points lost and lead exposure representing 23 million IQ points lost. For
8 fluoridation, the estimate for children aged 0 to 5 years is approximately 25 million IQ points. Even if
9 this estimate is somewhat imprecise, and unevenly distributed, the order of magnitude is likely to be
10 correct and is very considerable.

12 160. Finally, even if we assume that a threshold exists at approximately 0.8 mg/L in maternal
13 urine (as suggested by mere inspection of the IQ plots in the ELEMENT study for the 6-to-12-year-old
14 cohort members), water fluoridation would still result in substantial IQ losses. As documented in the
15 MIREC study, the 75th percentile maternal urine-fluoride levels (adjusted for creatinine) are 1.04 mg/L
16 in the fluoridated areas versus 0.52 mg/L in the non-fluoridated areas (Till et al. 2018, Table S4). In
17 fluoridated areas, pregnant women above the 75th percentile are already at least 0.29 mg/L above the
18 hypothetical threshold, and thus 25% of the children would then experience an average IQ loss of at
19 least 1.5 points. This would amount to over 4.5 million lost IQ points among 0-to-5-year-olds. Even this
20 smaller amount of IQ losses exceeds the IQ losses attributed to methylmercury exposure in the U.S.
21 (Grandjean et al. 2012).

23 161. I have made these calculations only to illustrate the significance and impact of
24 neurotoxicity outcomes from fluoridation exposures, and I offer these crude estimates to emphasize my
25 concern that developmental neurotoxicity due to early-life exposure to fluoride is a serious public health
26

1 hazard with substantial societal impacts that must be controlled.

2
3 **X. CONCLUSIONS**

4 162. Recent research has shown that the most vulnerable life stage for many toxicants,
5 particularly those that adversely affect the brain, is during intrauterine and early postnatal development.
6 Fluoride fits into this paradigm, and efforts to control human fluoride exposures must therefore focus on
7 pregnant women and small children.

8 163. Research on fluoride-exposed workers and laboratory animals suggest that elevated
9 fluoride exposure is toxic to the brain and nerve cells. Epidemiological studies have identified links to
10 learning, memory, and intelligence deficits, though most of the past studies focused on populations with
11 fluoride exposures higher than those typically provided by U.S. water supplies.

12 164. Epidemiology studies of birth cohorts from the most recent years document that adverse
13 effects on brain development happen at elevated exposure levels that occur widely in North America, in
14 particular in communities with fluoridated drinking water. These new prospective studies are of very
15 high quality and show very similar results, thus leaving little doubt that developmental neurotoxicity is a
16 serious risk associated with elevated fluoride exposure. This evidence shows that community water
17 fluoridation is associated with IQ losses that are substantial and of economic and societal concern.

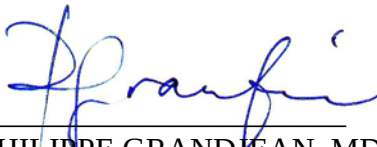
18 165. Applying methods for standards setting routinely used by the EPA (i.e., Benchmark Dose
19 analysis), the recent studies on IQ deficits in children allow the estimation of a recommended limit that
20 would protect against neurotoxicity. Such calculations show that current allowable limits for fluoride in
21 drinking water and the levels of fluoride added in community water fluoridation programs both greatly
22 exceed a science-based limit that would protect against developmental neurotoxicity.

23 166. The evidence on fluoride neurotoxicity in the general population is fairly recent and
24
25
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27

1 unlikely to represent the full toxicological perspective, including adverse effects that may occur at
2 longer delays. As has been seen on numerous occasions, the evidence available today may well
3 underestimate the true extent of the fluoride toxicity. With a reasonable degree of scientific certainty, I
4 therefore consider the elevated levels of fluoride exposure in the U.S. population as a serious public
5 health concern.

6
7 I declare under penalty of perjury, under the laws of the United States, that the foregoing is true
8 and correct to the best of my knowledge and belief.
9

10 Executed on May 20, 2020, in Copenhagen, Denmark.

11 
12
13 PHILIPPE GRANDJEAN, MD, DMSc

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Nalgonda District, Andhra Pradesh. *J Indian Assoc Publ Hlth Dent* 13:88-94.
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19 of Water, U.S. EPA.
- 20 United States Protection Agency (U.S. EPA). 2012. Benchmark dose technical guidance.
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- 22 United States Environmental Protection Agency (U.S. EPA): Six-Year Review 3 - Health Effects
23 Assessment for Existing Chemical and Radionuclide National Primary Drinking Water
24 Regulations - Summary Report. Office of Science and Technology, Office of Water, U.S. EPA.
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- 26 United States Environmental Protection Agency (U.S. EPA). 2017. Procedures for Chemical
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fetal exposures to fluoride during mid-gestation among pregnant women in northern California.
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Hernandez J, Alcaraz Contreras Y, et al. 2017. In utero exposure to fluoride and cognitive
development delay in infants. *Neurotoxicology* 59:65-70.

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- Wang QJ, Gao MX, Zhang MF, et al. 2012. Study on the correlation between daily total fluoride intake and children's intelligence quotient. *J Southeast Univ (Med Sci Edi)* 31(6):743-746
- Wang S, Wang L, Hu P, Guo S, Law S. 2001. Effects of high iodine and high fluorine on children's intelligence and thyroid function (in chinese). *Chin J Endemiol* 20:288-290.
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- Xiang Q, Wang Y, Yang M, Zhang M, Xu Y. 2013. Level of fluoride and arsenic in household shallow well water in Wamiao and Xinhuai villages in Jiangsu Province, China. *Fluoride* 46:192-197.
- Xiang Q. 2015. Correspondence. *Fluoride* 48:78-89.
- Yazdi SM, Sharifian A, Dehghani-Beshne M, Momeni VR, Aminian O. 2011. Effects of fluoride on psychomotor performance and memory of aluminum potroom workers. *Fluoride* 44:158-162.

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2 changes in the brains of fetuses from areas of endemic fluorosis. *Fluoride* 41:134-138.
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4 children's health: A potential association between dental fluorosis and loss of excellent
5 intelligence. *Environ Int* 118:116-124.
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7 intelligence. *Fluoride* 29:190-192.
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9 exposure on cognitive ability and the underlying mechanisms: Role of autophagy and its
10 association with apoptosis. *Toxicol Appl Pharmacol* 378:114608.
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12 behaviour of children and adolescents in China. *Int Dent J* 53:289-298.
- 13 Zohoori FV, Omid N, Sanderson RA, Valentine RA, Maguire A. 2019. Fluoride retention in
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**CURRICULUM VITAE OF
PHILIPPE GRANDJEAN, MD, DMSc**

PHILIPPE GRANDJEAN, M.D.

Office address

Institute of Public Health
University of Southern Denmark
Winsløwparken 17
DK-5000 Odense C, Denmark
Tel. (+45) 6550.3769
Fax (+45) 6591.1458
Email: pgrand@health.sdu.dk
<http://www.sdu.dk/staff/PGrandjean.aspx>

Harvard School of Public Health
Department of Environmental Health
665 Huntington Avenue
Building 1, room 1312
P.O. Box 15697
Boston, MA 02115
Tel: 617-384-8907
Fax: 617-384-8994
Email: Pgrand@hsph.harvard.edu
<http://www.hsph.harvard.edu/faculty/philippe-grandjean/>

Academic degrees

1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

Chronology of employment

1974-1975	Postgraduate training fellowship, University of Copenhagen
1975-1978	Research fellow, Institute of Hygiene, Univ. Copenhagen
1978-1980	Senior research fellow, University of Copenhagen Visiting fellow, Department of Community Medicine, Mount Sinai School of Medicine, New York
1980-1982	Director, Department of Occupational Medicine, Danish National Institute of Occupational Health
1982-	Professor of Environmental Medicine, Odense University
1983-2017	Consultant in Toxicology, Danish Health Authority
1994-2002	Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston
2003-	Adjunct Professor of Environmental Health, Harvard T.H. Chan School Public Health, Boston

Awards and honors

Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA
(1985)

Fellow, Collegium Ramazzini (1987)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)
Irish Congress Lecturer, Royal College of Physicians of Ireland and
Irish Society of Toxicology (1996)
Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark
(2003)
'Mercury madness award' for excellence in science in the public
interest from eight US environmental organizations (2004)
Emeritus Fellow, International Union of Pure and Applied Chemistry,
IUPAC (2009)
Honorary Research Award, International Order of Odd Fellows (2010)
Science Communication Award, University of Southern Denmark (2012)
Bernardino Ramazzini Award (2015)
Basic & Clinical Pharmacology & Toxicology Nordic Award (2015)
Margrethegaarden honorary prize (2016)
John R. Goldsmith Award, International Society for Environmental
Epidemiology (2016)

Editorial boards

American Journal of Industrial Medicine (1987-2017)
Applied Organometal Chemistry (1985-1991)
Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)
Archives of Environmental Health (European Editor, 1986-1992)
Archives of Toxicology (1987-)
Biomarkers (1996-2001)
Central European Journal of Occupational and Environmental Medicine
(2015-)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (Editor-in-Chief, 2002-)
Environmental Health Perspectives (2003-)
Environmental Research (1981-1994 and 2014-2017, Associate Editor,
1995-2014)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001-)
International Journal of Occupational and Environmental Health (1994-
2011)
International Journal of Occupational Medicine & Environ Health (1991-
Journal of Clean Technology, Environmental Toxicology, and
Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Læger (Danish Medical Journal, in Danish) (1991-2007)

Scientific societies

American Association for the Advancement of Science (Fellow, 1994)
American Public Health Association
Collegium Ramazzini (Fellow, 1987; Member of the Council, 2005-2013)
Danish Medical Association

Danish Societies of Clinical Chemistry, Epidemiology, Occupational and Environmental Medicine, and Public Health
Faroese Society of Science and Letters
International Society for Environmental Epidemiology

Teaching experience

Professor of Environmental Medicine, Odense University (University of Southern Denmark) (1982-). Member of curriculum committee.

Coordinator, Global Health class.

Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston (1994-2002)

Adjunct Professor of Environmental Health, Harvard T.H.Chan School of Public Health, Boston (2003-)

Invited teacher, École des hautes études en santé publique (EHESP, French school of public health) (2009-)

International: Numerous teaching assignments, including guest lectures at universities and related tasks, e.g. as external examiner, National University of Singapore (1995). External evaluator of PhD theses from other universities, including University of Sydney and University of South Pacific (Fiji).

Research support as Principal Investigator since 2000

2000-2006 NIEHS

Mercury associated neurobehavioral deficit in children

2001-2003 Nordic Arctic Research Programme (NARP)

Changing patterns of biomagnified pollutants in the northern marine environment

2001-2004 Danish Medical Research Council

Exposure assessment for endocrine disruptors

2002-2004 Danish Medical Research Council

Environmental epidemiology research

2003-2004 European Commission

Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)

2003-2005 Danish Medical Research Council

Research in hormone related substances

2003-2006 NIEHS ES11687

Effects of perinatal disruptors in children

2003-2007 EPA STAR RD-83075801-0

Children's vulnerability to environmental immunotoxicant

2004-2011 NIEHS ES12199

Epidemiology of immunotoxicant exposure in children

2006-2011 NIEHS ES13692

Health effects of lifetime exposure to food contaminants

2006-2012 NIEHS ES14460

Three-generation human study of reproductive effects of marine food contaminants

2008-2012 Danish Council for Strategic Research

Environmental pollutant impact on antibody production against current and new childhood vaccines

2007-2013 NIEHS ES009797

Mercury associated neurobehavioral deficit in children

2011-2017 NIEHS ES012199

Epidemiology of immunotoxicant exposure in children

2012-2020 NIEHS ES021993 and NSF OCE-1321612

Immunotoxicity in Humans with Lifetime Exposure to Ocean Pollutants

2013-2019 NIEHS ES021477

Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants

2013-2018 NIEHS ES021372

Pollutant-related diabetes in the Nurses' Health Study II

2014-2020 NIEHS ES023376

Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals

Major Current Funding as Principal Investigator

2017-2020 NIEHS ES026596

Inflammation and metabolic abnormalities in pollutant-exposed children

2017-2022 NIEHS P42ES027706

Sources, Transport, Exposure and Effects of PFASs (STEEP)

2019-2024 ATSDR TS000313

Assessment of PFAS exposures and health effects in two Massachusetts communities with PFAS drinking water contamination

2019-2023 NIEHS ES030394

Vulnerability During Infancy to Immunotoxic Contaminant Exposures

Major committees, boards and elective offices

Danish:

Danish Medical Association: Member, Prevention Council (2011-2014)

Danish Medical Research Council: Consultant on environmental medicine (1985-1990); Member, Joint Research Council Committee on Environmental Research (1986-1991); Member of DMRC (1992-1998)

Danish Society of Community Medicine: Secretary (1977-1978)

Danish Society of Industrial Medicine: Board Member (1974-1983)

Ministry of Education: Member, Committee on Toxicology (1984-1986); Member, Committee on Environmental Education (1986-1987)

Ministry of the Environment: Member, Council on Environmental Chemicals (1983-1989); Member, Environmental Appeal Board (1986-2010); Member, Environmental Research Council (1990-1992); Member, Advisory Committee on Pesticide Research (1995-2004 and 2018-2020); Member, Advisory Committee on Arctic Research (1996-2004)

Ministry of Health: numerous committee appointments; Chair, Committee on Risk Perception (2000-2001)

Ministry of Labour: Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993); Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)

Ministry of Research: Chair, Committee on Research at the Faroe Islands (1995-1996); Member, Committee on Scientific Dishonesty (2004-2006); Chair, Program Committee on Non-Ionizing Radiation (2004-2009)

Odense University (from 2000 University of Southern Denmark), elected

offices: Chairman, Institute of Community Health (1982-1985; 1996-1999); Member of Executive Committee, Institute of Community Health (from 2000 Institute of Public Health) (1986-1995; 2000-2005); Member, Faculty Research Committee (1983-1985); Member, Curriculum Committee (1984-1986); Member, Faculty Council (1985-1993); Vice-Dean (1991-1993); Member, Scientific Integrity Committee (2003-2022)

United States and international:

Academy of Finland: member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)

Agency for Toxic Substances and Disease Registry: Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992); Member, Expert Panel of Mercury (1998)

Association of Schools of Public Health in the European Region: Treasurer (1975-1977)

BioMedCentral: Member, Editors Advisory Group (2011-2013)

Boston Environmental Hazards Center: Consultant (1994-1999)

Collegium Ramazzini: President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002); Member, Executive Council (2005-2013)

Commission of the European Communities: National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); ad hoc Consultant for evaluation of research applications; ad hoc Scientific Advisor on Risk Assessment (2009-); Member, Scientific Committee on Emerging and Newly Identified Health Risks; - Working group on Dental Amalgam (Human Health)(2012-2013)

European Environment Agency: Member, Scientific Committee (2012-2020)

European Food Safety Authority: Member, Panel on Contaminants in the Food Chain responsible for 85 opinions (2003-2009); Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose

Food Advisory Committee, U.S.FDA, Methylmercury: invited expert (2002)

INMA (Infancia y Medio Ambiente), Spain: Member, Project Steering Committee (2010-)

Institut de Recherche Santé, Environnement et Travail, France: Member, Board of Advisers (2015-)

International Agency for Research on Cancer: Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), Vol. 49 (1989), as chairman, Vol. 58 (1993), and as Subgroup chair, Vol. 100C (2009)

International Commission on Occupational Health: Danish Delegation Secretary (1982-90); Member, Scientific Committee on the Toxicology of Metals (1987-); Member of the Board (1990-1996)

International Programme on Chemical Safety: Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)

International Society for Environmental Epidemiology: Councillor (1991-1994)

International Union of Pure and Applied Chemistry: Member, Subcommittee on the Toxicology of Nickel (1979-1989); Titular

Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology; Chairman, Subcommittee on Risk Assessment (1985-1989)
Instituto de Saude Ambiental, Lisboa, Portugal: Member, External Advisory Committee (2018-2020)
Karolinska Institute (Stockholm, Sweden): Member of international evaluation panel on environmental medicine (1993)
Ministry for Scientific Policy (Belgium): Consultant on national research program on health hazards (1990 and 1994)
National Institutes of Health (USA): Member of Special emphasis panels (2009-)
NATO Priority Area Panel on Environmental Security: Member (1996-1997)
Norwegian Research Council: ad hoc reviewer (2001-2008); Chairman of Environment and Health Review Group (2009-2010); member of steering committee (2011-2015)
Prenatal Programming and Toxicity (PPTOX) conferences: Organizer/Chair/Co-chair, Torshavn (2007), Miami (2009), Paris (2012), Boston (2014), Kita-Kyushu (2016), Torshavn (2018)
Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)
Swedish Council for Work Life Research: Member, Priority Committee on Chemical Health Risks (1997-1998)
U.N.Environment Programme: Member, Global Mercury Assessment Working Group (2002)
U.S. Environmental Protection Agency: Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999); Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-2003)
White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)
World Health Organization: Temporary Adviser or Consultant on several occasions, five times elected Rapporteur; Member, European Advisory Committee on Health Research (2011-2017)

Books

1. Grandjean P, ed. Standards setting. Copenhagen: Occupational Health Foundation, 1977, 210 pp.
2. Grandjean P, Nielsen T. Organiske blyforbindelser, forurening og toksikologi (Organolead compounds, pollution and toxicology, in Danish). Report No. SNV PM 879. Stockholm: Naturvårdsverket, 1977, 78 pp.
3. Grandjean P. Occupational health aspects of construction work. EURO Reports and Studies 86. Copenhagen: World Health Organization, Regional Office for Europe, 1983, 28 pp. (also published in German, French and Russian)
4. Grandjean P, ed. Biological effects of organolead compounds. Boca Raton, FL: CRC Press, 1984, 278 pp.
5. Grandjean P, Tarkowski S, eds. Toxic oil syndrome: mass food poisoning in Spain. Copenhagen: World Health Organization, Regional Office for Europe, 1984, 92 pp. (also published in Spanish)
6. Grandjean P. Miljø og forebyggelse. (Environment and prevention, student's guide in Danish). Copenhagen: F.a.d.L.'s Forlag, 1984, 109 pp.
7. Gilioli R, Grandjean P, Johnson B, Seppäläinen AM, Tarkowski S, eds. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 3. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 209 pp.
8. Grandjean P, ed. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 6. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 72 pp.
9. Grandjean P, ed. Miljømedicin (Environmental medicine, textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1986, 257 pp.
10. Grandjean P, ed. Trace elements in human health and disease: extended abstracts. Environmental Health No. 20. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 230 pp.
11. Grandjean P, ed. Trace elements in human health and disease: symposium report. Environmental Health No. 26. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 134 pp.
12. Grandjean P, Kimbrough RD, Rantanen J, Tarkowski S, Yrjänheikki E. Assessment of health risks in infants associated with exposure to PCBs, PCDDs and PCDFs in breast milk. Environmental Health No. 29. Copenhagen: World Health Organization, Regional Office for Europe, 1988, 116 pp.
13. Grandjean P, ed. Miljømedicin, 2. udg. (Environmental medicine, 2nd ed., textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1988, 311 pp.
14. Kimbrough RD, Mahaffey KR, Grandjean P, Sandø SH, Ruttstein DD. Clinical Effects of Environmental Chemicals: A Software Approach to Etiologic Diagnosis. New York: Hemisphere, 1989, 110 pp. and one floppy disk.
15. Grandjean P. Skin Penetration: Hazardous Chemicals at Work. (Published on behalf of the Commission of the European Communities.) London: Taylor and Francis, 1990, 187 pp.
16. Grandjean P, ed. Ecogenetics: Genetic Predisposition to Toxic

Effects of Chemicals. London: Chapman & Hall, 1991, 288 pp.

17. Grandjean P, ed. Miljø, sundhed og samfund (Environment, health and society, in Danish). Copenhagen: Nyt Nordisk Forlag, 1991, 453 pp.
18. Grandjean P, Brown SS, Reavey P, Young DS, Rej R (eds). Biomarkers of Chemical Exposure. Proceedings of the Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1994; 40 (issue 7B).
19. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajper-DeMeyts E, Scheike T, Sumpter J, Skakkebaek N. Male reproductive health and environmental chemicals with estrogenic effects. Copenhagen: Danish Environmental Protection Agency, 1995, 166 pp.
20. Grandjean P, Brown SS, Reavey P, Young DS, Sampson E (eds). Biomarkers. Proceedings of the Second Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1995; 41 (issue 12B).
21. Grandjean P. Farlig forurening (Dangerous pollution, in Danish). Copenhagen: Nyt Nordisk Forlag and National Board of Health, 1998, 174 pp.
22. Grandjean P ed. Human health effects of environmental mercury exposure (special issue). Environ Res 1998; 77 (67-177).
23. Grandjean P, Sofritti M, Minardi F, Brazier J (eds). The Precautionary Principle. Implications for research and prevention in environmental and occupational health. Eur J Oncol Library 2003; 2: 1-245. Also published in Int J Occup Med Environ Health 2004; 17: 3-201.
24. Grandjean P (ed). Prenatal programming and toxicity. Basic Clin Pharmacol Toxicol. 2008; 102(2): 71-273.
25. Gee D, Grandjean P, Hansen SF, van den Hove S, MacGarvin M, Martin J, Nielsen G, Quist D, Stanners D, eds. Late Lessons from Early Warnings, volume II (EEA Report No 1/2013). Copenhagen, European Environment Agency, 2013, 746 pp.
26. Grandjean P. Only one chance. How Environmental Pollution Impairs Brain Development – and How to Protect the Brains of the Next Generation. New York: Oxford University Press, 2013 (232 pp.).
27. Grandjean P, Hermann P. Kemi på hjernen – går ud over enhver forstand. København: Gyldendal, 2015 (334 sider).
28. Grandjean P. Cerveaux en danger (Brains in danger, in French). Translated by Odile Demange. Paris: Buchet Chastel, 2016 (336 pp.).
29. Kishi R, Grandjean P, eds. Health Impacts of Developmental Exposure to Environmental Chemicals. Singapore: Springer, 2020 (555 pp.)

Publications in international peer-reviewed journals

1. Grandjean P, Holma B. A history of lead retention in the Danish population. *Environ Biochem Physiol* 1973; 3: 268-73.
2. Grandjean P. Lead in Danes, historical and toxicological studies. *Environ Qual Saf* 1975; Suppl. Vol. 2: 6-75.
3. Grandjean P. Possible effect of lead on egg-shell thickness in kestrels 1874-1974. *Bull Environ Contam Toxicol* 1976; 16: 101-6.
4. Grandjean P. Regional distribution of lead in human brains. *Toxicol Lett* 1978; 2: 65-9.
5. Nielsen T, Jensen KA, Grandjean P. Organic lead in normal human brains. *Nature (Lond.)* 1978; 274: 602-3.
6. Grandjean P. Lead concentration in single hairs as a monitor of occupational lead exposure. *Int Arch Occup Environ Health* 1978; 42: 69-81.
7. Grandjean P, Lintrup J. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. *Scand J Clin Lab Invest* 1978; 38: 669-75.
8. Grandjean P, Arnvig E, Beckmann J. Psychological dysfunctions of lead-exposed workers: Relation to biological parameters of exposure. *Scand J Work Environ Health* 1978; 4: 295-303.
9. Grandjean P. Widening perspectives of lead toxicity, a review of health effects of lead exposure in adults. *Environ Res* 1978; 17: 303-21. (Also published as a special report to the U.S. National Institute of Environmental Health Sciences)
10. Grandjean P. Occupational lead exposure in Denmark: Screening with the haematofluorometer. *Br J Ind Med* 1979; 36: 52-8.
11. Grandjean P, Nielsen OV, Shapiro IM. Lead retention in ancient Nubian and contemporary populations. *J Environ Path Toxicol* 1979; 2: 781-7.
12. Grandjean P, Nielsen T. Organolead compounds, environmental health aspects. *Residue Rev* 1979; 72: 97-148.
13. Arnvig E, Grandjean P, Beckmann J. Neuropsychological effect of heavy lead exposure determined with psychological tests. *Toxicol Lett* 1980; 5: 399-404.
14. Hertz MM, Bolwig TG, Grandjean P, Westergaard E. Lead poisoning and the blood-brain barrier. *Acta Neurol Scand* 1981; 63: 286-96.
15. Grandjean P, Selikoff IJ, Shen SK, Sundermann FW Jr. Nickel concentrations in plasma and urine of shipyard workers. *Am J Ind Med* 1981; 1: 181-9.
16. Olsen NB, Hollnagel H, Grandjean P. Indicators of lead exposure in an adult Danish suburban population. *Dan Med Bull* 1981; 28: 168-76.
17. Grandjean P, Olsen NB, Hollnagel H. Influence of smoking and alcohol consumption on blood lead levels. *Int Arch Occup Environ Health* 1981; 48: 391-7.
18. Grandjean P, Kon SH. Lead exposure of welders and bystanders in a ship repair yard. *Am J Ind Med* 1981; 2: 65-70.
19. Grandjean P, Lintrup J. Sources of variation in fluorometry of zinc-protoporphyrin in blood. *Scand J Work Environ Health* 1981; 7: 311-2.
20. Grandjean P, Olsen NB, Hollnagel H. Occupationally related lead exposure in the general population. *Scand J Work Environ Health* 1981;

7: 298-301.

21. Grandjean P. Occupational fluorosis through 50 years: clinical and epidemiological experiences. *Am J Ind Med* 1982; 3: 227-36.
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C. ANDREW WATERS, ESQ., CA Bar No. 147259
MICHAEL CONNETT, ESQ., CA Bar No. 300314
WATERS, KRAUS & PAUL
222 N. Pacific Coast Hwy, Suite 1900
El Segundo, CA 90245
310-414-8146 Telephone
310-414-8156 Facsimile

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al.,

Plaintiffs,

vs.

U.S. ENVIRONMENTAL PROTECTION
AGENCY, et al.

Defendants.

Civ. No. 17-CV-02162-EMC

**DECLARATION OF
HOWARD HU, MD, MPH, ScD**

TABLE OF CONTENTS

I. SUMMARY OF QUALIFICATIONS1

II. SUMMARY OF OPINIONS3

III. BASIS FOR OPINIONS.....3

 A. The Methodological Strengths of the ELEMENT Studies3

 B. Prenatal Fluoride Exposure Is Associated with Substantial and
Significant Adverse Effects on IQ and ADHD-Behaviors in the
ELEMENT Cohort.....7

 C. The Limitations of Our Studies Do Not Provide Plausible
Alternative Explanations for the Results12

 D. Implications of Our Findings to the General Population in Water-
Fluoridated Areas.....15

IV. REFERENCES18

I, Howard Hu, MD, MPH, ScD, declare that:

1. I am a physician-scientist trained in internal medicine, occupational/environmental medicine, epidemiology and general public health who has held leadership positions in science and academia for over 2 decades.

2. I am also the Principal Investigator of ongoing research that is examining the impact of early-life exposures to fluoride on neurobehavioral development in the offspring participating in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project.

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 5 and attached herein.

4. As relevant to my testimony here, I am an epidemiologist with decades of research experience investigating the impact of environmental toxicants on human health. In 1990, I received a Doctor of Science degree in Epidemiology from the Harvard School of Public Health, and since that time have taught epidemiology at Harvard, University of Michigan, and University of Toronto, where I served as Dean of the School of Public Health.

5. I hold editorial positions on leading environmental and occupational health journals, including the *American Journal of Industrial Medicine*, *Current Environmental Health Reports* and *Environmental Health Perspectives*, and serve as a peer reviewer for the *American Journal of Epidemiology*, *Epidemiology*, *Journal of the American Medical Association*, *Lancet*, *New England Journal of Medicine*, and *Pediatrics*, amongst others.

6. My own epidemiological research has resulted in hundreds of peer-reviewed publications in leading scientific journals. For the past 29 years, this research has been continuously funded by the National Institutes of Health (NIH) through a number of competitive R01 grants.

1 7. The Environmental Protection Agency (EPA) has funded several of my epidemiological
2 studies, including a \$7.8 million research grant to study the effects of metals mixtures on children's
3 health. I have also served as an expert advisor to the EPA, including as a member of EPA's Science
4 Advisory Board on Relative Risk Reduction Strategies and as an expert reviewer of EPA's recent draft
5 report on the concentration-response functions between lead exposure and cardiovascular disease.

6 8. In 1993, I co-founded the ELEMENT research project, a pregnancy and birth cohort that
7 has been funded by both the EPA and NIH. Since its inception, ELEMENT has evolved into a highly
8 successful, award-winning project involving collaborators at the University of Michigan, Harvard, and
9 other academic institutions in the U.S., Canada, and Mexico.

10 9. Through the ELEMENT cohort, we have studied how prenatal exposure to environmental
11 toxicants—including lead, mercury, and fluoride—affect children's health, including their
12 neurodevelopment. Thus far, the ELEMENT cohort has generated over 80 high-impact publications and
13 provided evidence contributing towards environmental health policies around the world, including the
14 EPA's national air standard for lead and the CDC's "Guidelines for the Identification and Management
15 of Lead Exposure in Pregnant and Lactating Women."

16 10. In 2012, following the National Research Council's (NRC) call for more research to
17 investigate the neurobehavioral risks of fluoride exposure, the team I lead successfully competed for a
18 peer-reviewed NIH RO1 grant to study the neurodevelopmental effects of pre- and post-natal fluoride
19 exposures. This research was funded with an understanding that it would provide a major contribution to
20 fluoride risk assessment and policy decision-making on the neurotoxicity concerns identified by the
21 NRC.

22 11. To date, my team has published five peer-reviewed studies on fluoride, including two
23 prospective studies on fluoride and neurodevelopment that were published in the world's two most
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1 prominent environmental health journals: *Environmental Health Perspectives* and *Environment*
2 *International* (Bashash 2017, Bashash 2018, Cantoral 2019, Liu 2019, Thomas 2016). As with our own
3 research, the journal *Environmental Health Perspectives* is funded by the NIH.

4 **II. SUMMARY OF OPINIONS**

5 12. The ELEMENT prospective cohort studies of fluoride's neurodevelopmental effects are
6 methodologically rigorous studies that provide scientifically reliable and robust results.

7 13. The results of the ELEMENT prospective cohort studies are consistent with and support
8 the conclusion that fluoride is a developmental neurotoxicant at levels of exposure seen in the general
9 population in water-fluoridated communities.
10

11 **III. BASIS FOR OPINIONS**

12 **A. The Methodological Strengths of the ELEMENT Studies**

13 14. ***Prospective Birth Cohort Study Design:*** One of the key strengths of our ELEMENT
14 research is that it has utilized a prospective birth cohort design. Prospective studies (aka longitudinal
15 cohort studies designed at the outset to enable research on the topics of interest and that follow a defined
16 group of individuals) are recognized by epidemiologists as the ideal study design for investigating the
17 impact of environmental toxicants on human health, in part, because the measurement of exposure
18 precedes the development of disease/dysfunction. This is important because it permits greater
19 confidence in the causal relationship of an association since the requirement of temporality is satisfied
20 i.e., the exposure precedes the effect, which, in turn, is one of the components of the Bradford Hill
21 criteria. Where there is suspicion that a chemical may exert a toxic effect *in utero*, a birth cohort study
22 design is critical because it allows an assessment of exposure during the prenatal period.
23

24 15. ***Effective Control for Other Factors that Influence IQ:*** Our ELEMENT studies have
25 considered and controlled for a large number of factors known to affect neurodevelopment, which
26
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increases the rigor of the results. First, we excluded women from the study who had characteristics known to affect neurodevelopment, including gestational diabetes, renal disease, hypertension, circulatory diseases, use of illicit drugs, and alcohol consumption. Second, our analyses of fluoride and neurodevelopment controlled for a large number of potential confounders, including maternal age, maternal education, maternal IQ, birth weight, gestational age at time of delivery, sex of child, birth order, maternal smoking, and marital status. Third, we performed sensitivity analyses which controlled for the quality of the child's home environment (i.e., HOME),¹ as well as prenatal lead and mercury exposures.

16. ***Blinded Assessments:*** Our studies employed a "blinded" study design where neither the examiners nor the subjects were aware of the subject's fluoride exposure status at the time of the neurodevelopmental exams. A blinded study design is superior to a non-blinded study because it helps protect against bias, including unconscious bias, in the assessment.

17. ***Individual Biomarkers of Both Prenatal and Postnatal Exposure:*** As cohort studies, our investigations have collected and utilized individual measurements of fluoride exposure, covariates, and the outcomes of interest. Cohort studies with individual measurements of exposure, covariates and outcomes are considered much more robust than studies with group-level metrics (otherwise known as "ecological studies") because the accuracy and precision of individual-level measures are far superior to the estimates of these parameters that are associated with ecological studies. In our studies, we measured prenatal fluoride exposure by testing archived samples of the mother's urine that were collected during pregnancy. Urine fluoride is a well-accepted biomarker of total fluoride exposure. As the EPA has

¹ The HOME Score is a rating that is performed by a research observer who gains permission to enter the home and observe the interactions between the offspring and other family members, as well as other characteristics of the home environment. It is intended to try to capture the ability of the home to enrich a child's educational development and skill development. It is often highly correlated with socio-economic status, but it also has some independent value of its own in determining a child's neurodevelopmental trajectory.

1 recognized, “archives of biological samples from birth cohort studies . . . provide critical information on
2 the prenatal and childhood determinants of adult disease” (EPA-NIEHS 2017, p. 9). The archived urine
3 samples in our studies were tested under the oversight and direction of Dr. Angeles Martinez-Mier, a
4 leading authority on the measurement of fluoride in urine and plasma.

5 18. As I acknowledge and discuss further below, there are some limitations with our urine-
6 based exposure estimates. These limitations, however, do not provide a plausible explanation for the
7 results we have observed as they create *non-differential* imprecision in the exposure variable (in this
8 case, the non-differential exposure misclassification is sometimes referred to as “random” or “classical”
9 measurement error associated with exposure). It is a basic epidemiologic axiom that non-differential
10 errors, such as non-differential exposure misclassification, bias the results towards the null (i.e., no
11 association exists), rather than create spurious associations where none otherwise exist. I discuss this
12 further below.
13

14 19. ***Large Cohort Sizes:*** Our studies have involved a sufficiently large number of mother-
15 offspring pairs to permit statistical analyses that are stable and robust. In our 2017 study (“Bashash
16 2017”), we investigated fluoride’s relationship with intelligence among 299 mother-offspring pairs. This
17 included 287 mother-offspring pairs for the analysis of intelligence at age 4, and 211 mother-offspring
18 pairs for an analysis of intelligence at ages 6-12. In our 2018 study (“Bashash 2018”), we investigated
19 the relationship between fluoride and symptoms of Attention-Deficit Hyperactivity Disorder (ADHD)
20 among a total of 213 mother-offspring pairs, with the ADHD assessment conducted between the ages of
21 6 and 12.
22

23 20. ***Reliable Neurocognitive Tests:*** Our 2017 study on intelligence used validated,
24 standardized neurocognitive tests that were administered by a team of psychologists. For the 4-year old
25 children, we used the McCarthy Scales of Children’s Abilities (MSCA), and focused on the General
26
27

Cognitive Index (GCI) score. For the 6-12 year old children, we used the Spanish version of the Wechsler Abbreviated Scale of Intelligence (WASI)² to assess Full-Scale IQ. All raw scores were standardized for age and sex. The examining psychologists were trained and supervised by an experienced developmental psychologist, and independent testing confirmed a very high correlation (0.99) in the scoring, thus confirming a high degree of inter-examiner reliability.

21. **Reliable Neurobehavioral Tests:** Behaviors associated with ADHD were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R)³ and Conners' Continuous Performance Test (CPT-II, 2nd Edition).⁴ All measures of ADHD-behaviors were standardized for age- and sex. Higher T-scores (mean of 50, SD of 10) indicate poorer performance. All psychometric tests were applied under the supervision of an experienced psychologist.

22. **Appropriate Statistical Analyses that Did Not Assume Linearity:** We used the same standard statistical analyses for our fluoride studies as we have used for our other ELEMENT studies. These included regression analyses that appropriately adjusted for potential confounders, as well as Generalized Additive Models (GAM) that visualized adjusted associations between fluoride and neurodevelopment for purposes of assessing the linearity of the relationship. We did *not* assume

² The WASI shows strong criterion validity with the full-length Wechsler Intelligence Scale for Children (WISC-III; ages 6-16 yrs), and the Wechsler Adult Intelligence Scale (WAIS; ages 16+ yrs). The correlation coefficient between the Full Scale IQ of the WASI and WISC-III is 0.81 (Wechsler, 1991), and 0.92 between the WASI and the WAIS-III (Wechsler, 1999), indicating a high covariance between the abbreviated and full-length measures of intellectual ability. The WASI is also correlated with another abbreviated IQ test, the Kaufman Brief Intelligence Test ($r = 0.89$), providing evidence for convergent validity (Hays et al., 2002). Finally, the WASI demonstrates excellent internal consistency (reliability=0.976) (based on data from Tables 5.1 and 5.8 of the WASI manual).

³ The CRS-R contains three ADHD scales that correspond with the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) criteria for ADHD: 1) DSM-IV Inattention Index, 2) DSM-IV Hyperactive-Impulsive Index, and 3) DSM-IV Total Index (inattentive and hyperactive-impulsive behaviors combined). It also examines seven types of behavior problems that were derived through factor analysis, including: Oppositional, Anxious-Shy, Cognitive Problem/Inattention, Hyperactivity, Perfectionism, Psychosomatic, and Social Problems. For our study, we examined the three DSM-IV ADHD scales as our primary outcomes because these scales are intended to screen for ADHD, and are commonly used to study the association between diverse environmental contaminants and ADHD- behavior problems.

⁴ The CPT-II is a computer-administered signal detection paradigm. Using the CPT-II, we measured errors of omission and commission, and hit reaction time (response latency).

linearity in the dose-response relationship. Additionally, we took appropriate steps to eliminate the influence of outliers and influential points.

B. Prenatal Fluoride Exposure Is Associated with Substantial and Significant Adverse Effects on IQ and ADHD-Behaviors in the ELEMENT Cohort

23. In the ELEMENT cohort, we found that prenatal fluoride exposure has a linear, dose-response relationship with reduced IQ among both 4-year old and 6-12 year old children (Bashash 2017).⁵ In our main model that adjusted for potential confounders, we found that each 0.5 mg/L increase in maternal urinary fluoride (which approximates the interquartile range, i.e., the difference between the 25th v. 75th percentile) was significantly associated with a loss of 3.15 GCI points among the 4-year-olds, and a loss of 2.5 IQ points among the 6-to-12 year olds. These are substantial reductions in intelligence that rival the effect sizes associated with lead exposure. As one measure of practical impact developed and published in 2009 by an expert from the Economics Policy Institute, each IQ point lost due to lead exposure was estimated to represent a loss of \$17,815 in present discounted value of lifetime earnings (in 2006 USD) (Gould 2009).

24. Visual assessment of the adjusted associations between fluoride and intelligence confirmed the monotonic, mostly linear nature of the relationships (see Figures A and B). Notably, there was no evidence of a threshold among the 4-year olds, although there was some suggestion of a threshold at approximately 0.8 mg/L among the 6-12 year olds.

⁵ We have subsequently reported an analysis, in abstract form, of neurocognitive outcomes at ages 1 to 3, as measured through the Mental Development Index (Thomas 2018). These results are consistent with the age 4 and age 6-12 analyses in that they show significant adverse associations with maternal urinary fluoride. I do not rely on these results here, however, since they have not yet been published in full

Figure A: Visual Association Between Maternal Urinary Fluoride and Intelligence at Age 4

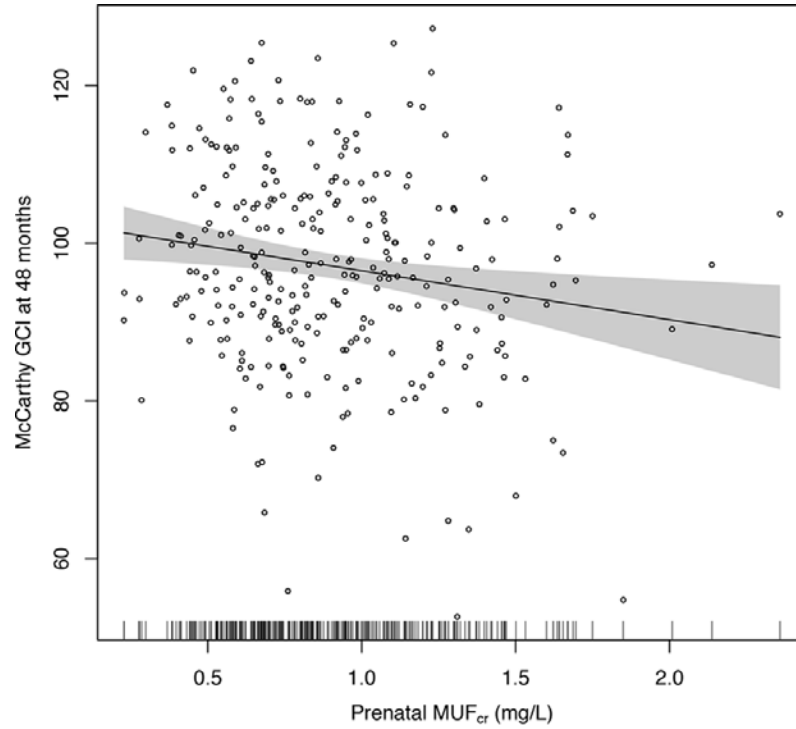
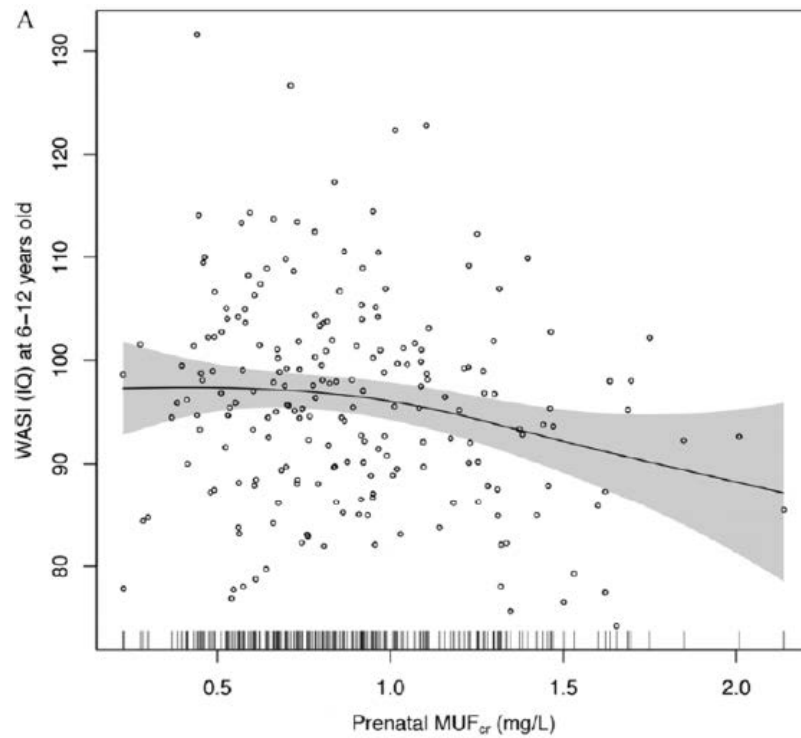


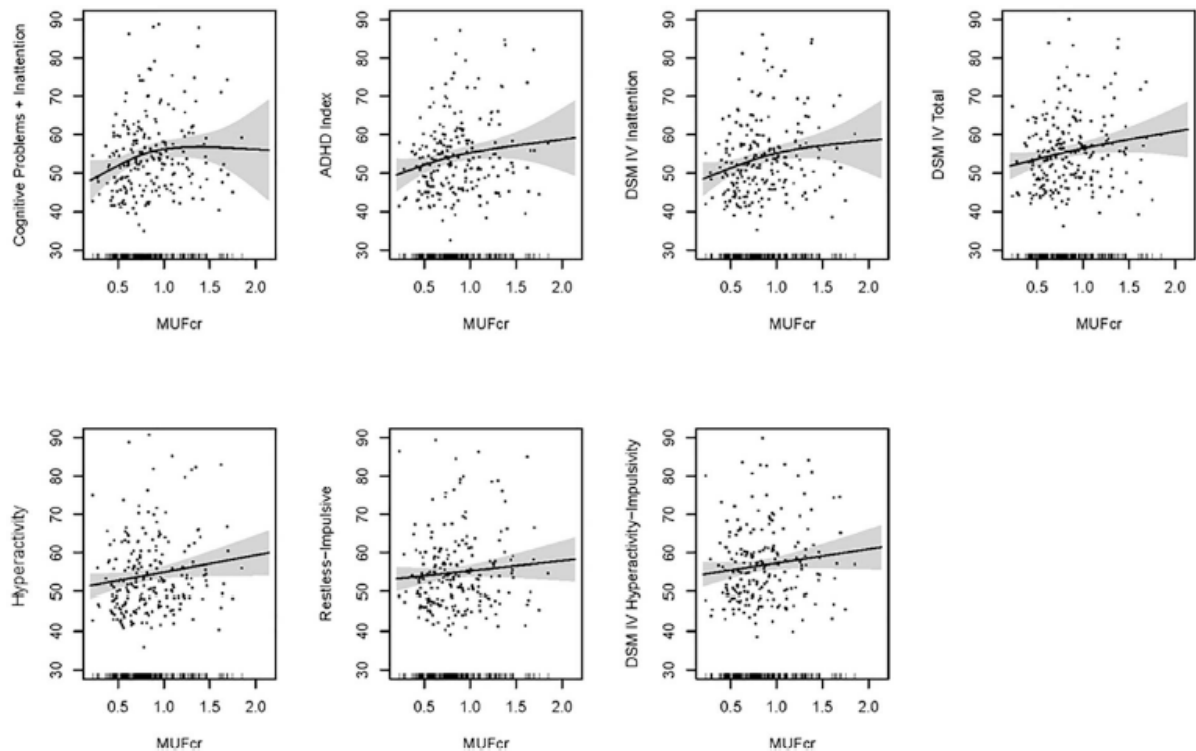
Figure B: Visual Association Between Maternal Urinary Fluoride and Intelligence at Ages 6-12



1 25. In contrast with prenatal exposures, we did not find statistically significant associations
2 between IQ and childhood urinary fluoride levels at ages 6 to 12, although there was some suggestion of
3 an adverse effect. This suggests that the timing of fluoride exposure is an important determinant of
4 fluoride's neurodevelopmental effects, and is consistent with exposures occurring prenatally being more
5 detrimental than those occurring during school-aged years. This is plausible given fluoride's passage
6 through the placental barrier, and the known enhanced vulnerability of the developing brain to
7 neurotoxins during the *in utero* period.

8
9 26. In addition to IQ, we have also found a significant association between prenatal fluoride
10 exposure and some attention deficit hyperactivity disorder (ADHD)-like behaviors on the CRS-R test,
11 including cognitive problems and inattention (Bashash 2018). As with our IQ analyses, the associations
12 were linear, although—as we have found for lead (Huang 2016)—there was some indication in some of
13 the analyses of a ceiling effect at higher doses (i.e., the dose-response curve for cognitive problems and
14 inattention began to flatten above 1 mg/L).

15
16 27. The effect sizes between prenatal fluoride and ADHD behaviors in our cohort were
17 substantial. For those effects which reached statistical significance, increases of 0.5 mg/L in maternal
18 urinary fluoride were associated with 2.4 to 2.8-point higher scores (higher scores reflect indicate poorer
19 performance). Whereas IQ is standardized to a mean of 100, the ADHD behavior scales are standardized
20 to a scale of 50. The effect sizes that we found for prenatal fluoride are similar to what we have found
21 for childhood blood lead levels (Huang 2016).

Figure C: Association Between Maternal Urinary Fluoride & ADHD Behaviors

28. We did not find statistically significant associations between fluoride and ADHD-behaviors on the CPT-II test. Other studies of environmental chemicals have reported similar discrepancies between the two tests, suggesting that they are assessing different constructs. The stronger association that we found between fluoride and ADHD behaviors on the CRS-R scale may be explained by the CRS-R's focus on constructs that rely on attention (e.g., new learning, ability to hold information and complete tasks, organizational skills, etc).

29. The relationship we observed between fluoride and inattention is consistent with some animal research that has reported a relationship between prenatal fluoride exposure and hypoactive behavioral patterns (Mullenix 1995), as well as prior epidemiological research associating fluoride with impaired working memory (Choi 2015). Working memory is linked with the ability to control attention and it is common for youth with ADHD to have weaknesses in working memory (Kasper 2012).

Fluoride's effect on working memory may relate to an effect on the dopamine system, which fluoride has been found to alter in animal studies (Pal & Sarkar 2014). Dopamine is an important modulatory neurotransmitter in planning and initiation of motor responses, activation, switching, reaction to novelty and processing of reward (Fararone 2015).

30. Some have suggested that the “scatter” in the above scatterplots is a basis to doubt the relation between fluoride and the neurodevelopmental outcomes. Such scatter, however, is typical in epidemiological studies of neurotoxicants, as can be seen in the following figure from our study on lead and neurocognitive effects which the EPA relied upon as evidence of low-level lead neurotoxicity when the Agency set the national air standard for lead (Tellez-Rojos 2006, Fig 1, reproduced as Figure D below). We also found similar scatter in our analysis of blood lead and ADHD behaviors, as measured by CRS-R (Huang 2016, Fig. 1, reproduced as Figure E below). The scatter relates to the fact that there are multiple factors that impact on intelligence and behavior; however, unless they are confounders (which we controlled for), they do not preclude the ability to focus on the specific effect of fluoride.

Figure D: Association Between Childhood Blood Lead Levels and Mental Development Index

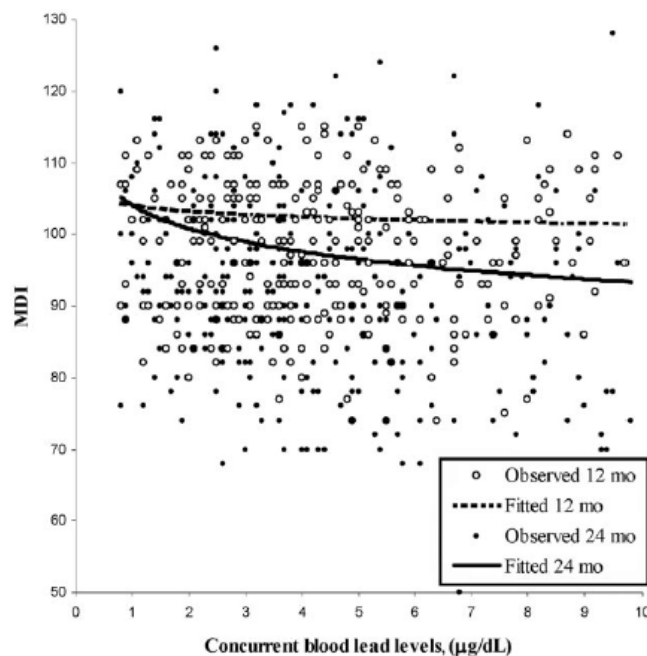
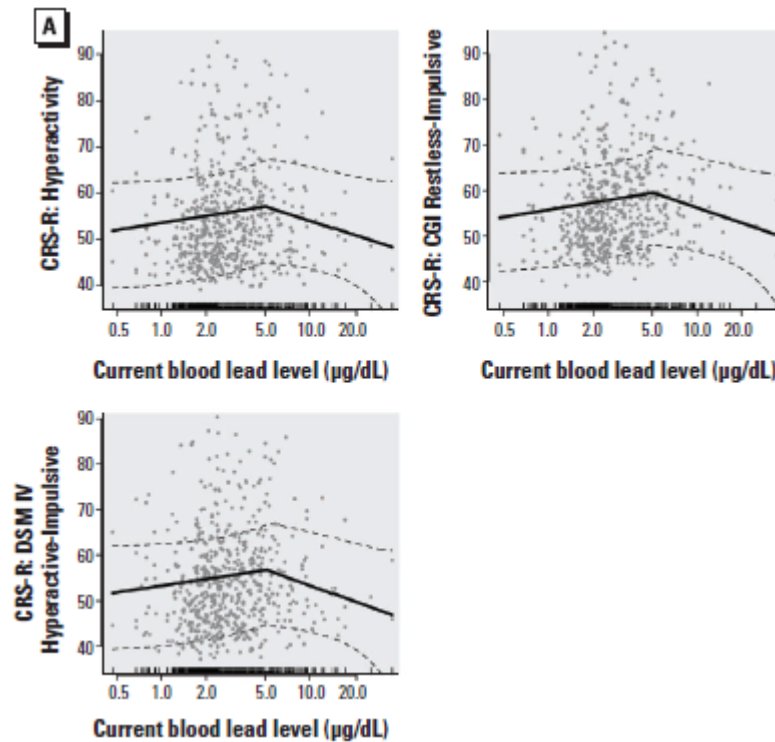


Figure E: Association Between Childhood Blood Lead Levels and ADHD Behaviors



C. The Limitations of Our Studies Do Not Provide Plausible Alternative Explanations for the Results

31. Every epidemiological study, including our studies on fluoride and neurodevelopment, has its limitations. Some of these limitations could theoretically be avoided through the use of human experiments where the toxicant is delivered to the study participants in a controlled and randomized manner. Human experimentation on neurotoxicants, however, is strictly prohibited for obvious ethical reasons. We are thus left with “observational” studies to investigate the impact of environmental toxicants on human health, with prospective cohort studies being the study design best suited for this purpose.

32. As is often the case with epidemiological studies of environmental toxicants, there are limitations in the exposure measurements that we have used in the ELEMENT studies. Our use of spot samples to collect the urine introduces some imprecision into the exposure measurement because urinary

1 fluoride concentrations can fluctuate somewhat throughout the day. This imprecision would have been
2 reduced through the use of 24-hour urine collection samples, and, to a lesser extent, fasting first-morning
3 voids, which are both considered more rigorous measures of fluoride exposure. We compensated for this
4 limitation by using “timed” samples (i.e., second void in the morning) and adjusting for urinary
5 creatinine. Urinary fluoride concentrations fluctuate during the day in large part because fluctuations in
6 an individual’s hydration during the day result in fluctuations in urinary dilution (and therefore, urinary
7 concentrations). Adjusting for urinary creatinine is particularly important because the resulting measure
8 adjusts for urinary dilution. As a result, measures of fluoride in spot urine samples adjusted for
9 creatinine have been found to have excellent agreement with 24-hour samples (Zohouri 2006). Timed
10 spot samples also have an important advantage over 24-hour samples in that they are less imposing on
11 study participants. This is an important consideration when designing cohort studies because the
12 imposition of difficult tasks like collecting 24-hour urines serve to reduce participation, which, in turn,
13 reduces the study’s sample size and statistical power.⁶
14

15 33. Another limitation in our exposure measurements is that, for most of the mothers, we did
16 not have urine samples for every trimester. In our age 4 IQ analysis, 49%, 42%, and 9% of the mother-
17 offspring pairs had urine samples for one, two, and all three trimesters, respectively. In the age 6-12
18 analysis, the respective percentages were 56%, 39%, and 5%; while in the ADHD study, the respective
19 numbers were 57%, 36.4%, and 6.5%. It is common for prospective cohort studies to only have one or
20 two exposure measurements during the prenatal period, but this does not introduce undue imprecision in
21 the exposure estimate, as exposures to a toxicant have limited variation during pregnancy.
22

23 34. Importantly, the imprecision in our exposure measurements does not explain the large
24 and significant associations we observed between maternal urinary fluoride and neurodevelopmental
25

26 ⁶ To put it in simple terms, less people will volunteer to participate in a study if it requires them to
27 collect all of their urine throughout the entire day, including while they are in public spaces, such as
28 their work environment and restaurants, etc.

1 effects. Imprecision in exposure measurements (of the classical or random type, as noted above) is a
2 type of non-differential error that introduces scatter into the analysis which has a generally expected
3 effect of biasing the results towards the null hypothesis. To put it another way, imprecisions in exposure
4 measurements make it *harder*, not easier, to detect an association between an exposure and outcome,
5 much like background noise makes it harder to hear a sound or signal of interest. Imprecision in the
6 exposure measurement is thus anticipated to *obscure* an association, rather than create spurious
7 associations where none otherwise exist. Because of this, improvement in the measurement of a
8 particular exposure tends to reveal and strengthen associations associated with that exposure, not
9 eliminate them.
10

11 35. Another limitation with our studies is, as with most observational studies, we could not
12 rule out the potential for uncontrolled confounding from factors that we did not measure. For example,
13 we did not have data on arsenic which is a neurotoxicant that has been associated with fluoride in certain
14 rural drinking water supplies. While it is always preferable to have more data than less, it is unlikely that
15 arsenic is a meaningful confounder in our cohort. To be a confounder, a covariate must be associated
16 with *both* the outcome *and* exposure. In our cohort, the main source of fluoride is from *salt*, not water.⁷
17 Accordingly, even if arsenic is correlated with fluoride in rural water supplies in Mexico, this
18 association is unlikely to be materially associated with fluoride exposures in our cohort.
19

20 36. Finally, an additional limitation in our studies is that we did not have information on the
21 iodine status of our cohort. Iodine has been theorized to be a potential effect-modifier for fluoride's
22 nervous system effects, i.e., deficiencies of iodine may magnify fluoride's effects, and vice versa (NRC
23 2006). However, failure to control for an effect modifier is unlikely to produce an association between
24 exposure and outcome that does not otherwise exist. Moreover, in Mexico, salt is required by law to be
25

26 ⁷ The water in Mexico City has low levels of fluoride (i.e., 0.16 mg/L) and thus does not present a
27 meaningful exposure in our cohort (Cantoral et al. 2019).

1 iodized. Fluoride levels in our cohort are thus likely correlated with *increased* iodine. To the extent that
2 iodine modifies the effect of fluoride in our population, it is more likely to be in the direction of
3 *reducing* toxicity rather than magnifying it.

4 **D. Implications of Our Findings to the General Population in Water-Fluoridated**
5 **Areas**

6 37. In 2016, we published the largest characterization to date of urinary and plasma fluoride
7 levels throughout pregnancy (Thomas, et al. 2016). At the time we published this study, there had yet to
8 be a population-based study of fluoride exposures among pregnant women in North America, although
9 there were two small-scale studies available from Israel and Poland. The lack of data from North
10 America prevented us, at that time, from comparing the urinary fluoride levels in our cohort with
11 populations from Canada or the United States.

12 38. Urine and plasma fluoride are metrics of the total absorbed dose of fluoride, sometimes
13 referred to as the “internalized” or “bioavailable” dose. These internalized doses do not currently permit
14 one to directly estimate the amount of fluoride that is ingested (i.e., the “external” exposure), nor do they
15 permit the determination of source apportionment of the fluoride exposures. Internalized doses,
16 however, are more relevant than external intake in predicting toxic effects, since they reflect the
17 concentration of toxics that are being delivered to target organs in the body.

18 39. Our 2016 study presented the urinary and plasma fluoride levels from 825 and 330
19 pregnant women from our cohort, respectively. The urine samples were collected and measured using
20 the procedures discussed above for our neurodevelopmental papers (i.e., early morning 2nd voids that
21 were adjusted for creatinine), and both the urine and plasma samples were tested under the direction of
22 Dr. Angeles Martinez-Mier from Indiana University, a world leader in the measurement of fluoride in
23 biological samples.

24 40. The average creatinine-adjusted urinary fluoride level across all three trimesters in the
25
26
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28

1 ELEMENT cohort was 0.91 mg/L, with a standard deviation of 0.4 mg/L.⁸ The average plasma fluoride
2 level across all three trimesters was 0.0221 mg/L, with a standard deviation of 0.0164 mg/L.⁹

3 41. By the time we published our 2018 study on ADHD behaviors, general population data
4 had become available on maternal urinary fluoride levels in pregnancy (Till 2018). As we noted in our
5 2018 study, the maternal fluoride levels in the Canadian study are similar to the levels in our cohort
6 (Bashash 2018). The mean (creatinine-adjusted) maternal urinary fluoride level among pregnant women
7 living in the water-fluoridated areas of Canada was 0.87 mg/L, with a standard deviation of 0.50 mg/L,
8 which is clearly in the same range as our cohort (i.e., mean = 0.91 mg/L, SD = 0.4 mg/L). The urine
9 samples in the Canadian study were tested by Dr. Martinez-Mier using the same creatinine-adjustment
10 method, which increases the comparability of the data.
11

12 42. The similarity in maternal urinary fluoride levels between pregnant women in the
13 ELEMENT cohort and water-fluoridated areas of the Canadian cohort is consistent with the fact that
14 both populations are receiving so-called “optimal” levels of fluoride through fluoridation programs (i.e.,
15 salt fluoridation in Mexico, and water fluoridation in Canada). Since salt fluoridation programs are
16 designed to replicate the doses provided by fluoridated water, it is a reasonable, first-order expectation
17 that populations living in salt-fluoridated and water-fluoridated areas will receive similar doses of
18 fluoride.
19

20 43. The maternal urinary fluoride data from the ELEMENT cohort and water-fluoridated
21 areas of Canada support the conclusions that the two populations have essentially the same *internalized*
22 doses of fluoride. The internalized doses in water-fluoridated areas are thus in the range that we have
23

24 ⁸ The 75th and 90th percentile values were 1.09 mg/L and 1.37 mg/L, respectively.

25 ⁹ We tested for and found no correlation between creatinine-adjusted urinary fluoride and
26 sociodemographic variables, including maternal age, maternal education, child sex, smoking status, birth
27 order, and cohort. Although we found a trend towards increasing urinary fluoride levels through the first
28 22-23 weeks of pregnancy, and a reduction thereafter, these trends were not statistically significant
(Thomas 2016).

1 found to be associated with substantial and significant neurodevelopmental harms in the ELEMENT
2 cohort.

3 44. Although direct comparisons of *external* fluoride intake cannot yet be made, such
4 information is not necessary to generalize the neurodevelopmental results from the ELEMENT cohort to
5 water-fluoridated areas.

6 45. There is no identified reason to believe that the neurodevelopmental effects of fluoride
7 will differ by the source of exposure, be it fluoridated salt or fluoridated water; once inside the body the
8 source of fluoride is immaterial.

9 46. For the reasons stated, it is my opinion to a reasonable degree of scientific certainty that
10 the results of the ELEMENT studies support the conclusion that fluoride is a developmental
11 neurotoxicant at levels of internalized exposure seen in water-fluoridated communities.
12

13
14 I declare under penalty of perjury, under the laws of the United States, that the foregoing
15 is true and correct to the best of my knowledge and belief.
16

17 Executed on May 20, 2020, in Seattle Washington.

18
19 

20 HOWARD HU, MD, MPH, ScD
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**CURRICULUM VITAE OF
HOWARD HU, MD, MPH, ScD**

CURRICULUM VITAE

Date Prepared: May, 2019

NAME: Howard Hu

PRIMARY AFFILIATION: School of Public Health, University of Washington

SECONDARY AFFILIATION: School of Public Health, University of Michigan

CONTACT: Howard Hu, M.D, M.P.H., Sc.D.

Email: hhu5@uw.eduLINKS: https://deohs.washington.edu/faculty/hu_howard
<https://www.linkedin.com/in/howard-hu-059703a/?trk=public-profile-join-page>

TABLE OF CONTENTS

SUBJECT	PAGE
EDUCATION	2
POSTDOCTORAL TRAINING	2
CERTIFICATION AND LICENSURE	2
ACADEMIC APPOINTMENTS	2
ADMINISTRATIVE APPOINTMENTS	3
CLINICAL APPOINTMENTS	4
OTHER ACADEMIC POSITION/VISITING APPOINTMENTS	4
MAJOR RESEARCH INTERESTS	5
GRANTS	5
HONORS AND AWARDS	9
MEMBERSHIPS	10
EDITORIAL POSITIONS AND BOARDS	10
PEER REVIEW SERVICE	11
TEACHING	11
COMMITTEE, ORGANIZATIONAL, VOLUNTEER SERVICE	17
OTHER PUBLIC SERVICE	22
CONSULTING POSITIONS	22
VISITING PROFESSORSHIPS	23
SEMINARS AND EXTRAMURAL INVITED PRESENTATIONS	23
BIBLIOGRAPHY	31

EDUCATION:

9/1973-6/1976	Biology	B.Sc.	Brown University
9/1977-6/1982	Medicine	M.D.	Albert Einstein College of Medicine
9/1979-6/1980 (degree in 6/1982*)		M.P.H. (Occ Hlth)	Harvard School of Public Health
9/1985-6/1986	Epidemiology	M.S.	Harvard School of Public Health
7/1986-6/1990	Epidemiology	Sc.D.	Harvard School of Public Health

* Awarding of the Harvard M.P.H. to medical students is delayed until the M.D. degree is conferred

POSTDOCTORAL TRAINING:

Research Fellowships

7/1987-6/1988 Occupational Health Research Fellow, Dept. of Environmental Health
Harvard School of Public Health

Internship and Residencies

7/1982-6/1983	Intern in Medicine	Boston City Hospital
7/1983-6/1984	Junior Assistant Resident, Internal Medicine	Boston City Hospital
7/1984-6/1985	Senior Assistant Resident, Internal Medicine	Boston City Hospital
7/1985-6/1987	Resident, Occupational Medicine	Harvard School of Public Health

CERTIFICATION AND LICENSURE:

1984	Massachusetts Medical License Registration
1985	American Board of Internal Medicine, Diplomate
1987	American Board of Preventive Medicine, Diplomate (Occupational Medicine)
2006	Michigan Medical License Registration
2013	College of Physicians & Surgeons of Ontario
2018	Washington State Medical License Registration

ACADEMIC APPOINTMENTS:

9/1988-6/1992	Instructor in Medicine Department of Medicine, Harvard Medical School
9/1988-6/2006	Associate Physician (Clinical and Research), Channing Laboratory, Department of Medicine, Brigham & Women's Hospital
9/1990-6/1994	Assistant Professor of Occupational Medicine Department of Environmental Health, Harvard School of Public Health

CV: Howard Hu, M.D., M.P.H., Sc.D.

7/1992-6/1997 Assistant Professor of Medicine
Department of Medicine, Harvard Medical School

7/1994-6/2002 Associate Professor of Occupational Medicine
Department of Environmental Health, Harvard School of Public Health

7/1997-8/2006 Associate Professor of Medicine
Department of Medicine, Harvard Medical School

7/2002-8/2006 Professor of Occupational and Environmental Medicine (tenured)
Department of Environmental Health, Harvard School of Public Health

9/2006-6/2012 Chair and Professor of Environmental Health Sciences (tenured), Department of
Environmental Health Sciences, University of Michigan School of Public Health

9/2006-8/2009 Adjunct Professor of Occupational and Environmental Medicine
Department of Environmental Health, Harvard School of Public Health

9/2006-6/2012 Research Associate Physician, Channing Laboratory, Department of
Medicine, Brigham & Women's Hospital

5/2007-2012 Professor of Epidemiology, University of Michigan School of Public Health

5/2007-2012 Professor of Internal Medicine, University of Michigan Medical School

1/2009-2012 NSF International Endowed Department Chair, University of Michigan School of
Public Health, Department of Environmental Health Sciences

7/2012-2018 Professor of Environmental Health, Epidemiology and Global Health (tenured)
Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario,
Canada (on sabbatical/administrative leave, 2017-2018)

7/2012-2018 Professor, School of Medicine, University of Toronto, Toronto, Ontario, Canada

7/2012- Adjunct Professor, Department of Environmental Health Sciences, University of
Michigan School of Public Health

7/2012-2013 Director, Dalla Lana School of Public Health, University of Toronto, Toronto,
Ontario, Canada

7/2013-6/2017 Founding Dean, Dalla Lana School of Public Health, a Faculty of the University
of Toronto, Toronto, Ontario, Canada

7/2017- Affiliate Professor (started as Visiting Scholar until December, 2017),
Department of Occupational and Environmental Health Sciences, University of
Washington School of Public Health, Seattle, WA

ADMINISTRATIVE APPOINTMENTS:

7/1991-6/2006 (Founding) Director, Metals Epidemiology Research Group, Channing Laboratory,
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and
Department of Environmental Health, Harvard School of Public Health

7/1992-6/1995 Director, Commission to Investigate the Health and Environmental Effects of Nuclear
Weapons Production, International Physicians for the Prevention of Nuclear War

7/1996-6/2006 Director, Residency Program in Occupational and Environmental Medicine, Harvard
School of Public Health

7/1996-8/2006 Director, Occupational and Environmental Medicine Core, National Institute for
Occupational Safety and Health Educational Resource Center at the Harvard School of

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Public Health

- 7/1998-6/2004 (Founding) Medical Editor, Environmental Health Perspectives (official journal of NIEHS)
- 7/2000-8/2006 Associate Director, the Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health
- 7/2004-6/2009 (Founding) Principal Investigator and Director, Harvard Center for Children's Environmental Health and Disease Prevention Research (co-PI and co-Director after 9/1/08)
- 9/2006-6/2012 Chair, Department of Environmental Health Sciences, University of Michigan School of Public Health
- 9/2006-2012 Director, Occupational Epidemiology Core, NIOSH Education and Research Center, University of Michigan
- 9/2006-2012 Co-Director, Michigan-Harvard/Harvard-Michigan Metals Epidemiology Research Group
- 7/2009-2011 Director, NIA T32 Training Grant in Aging and Public Health, University of Michigan School of Public Health
- 1/2010-2012 Chair, Faculty Steering Committee on Global Health, University of Michigan School of Public Health
- 4/2011-2012 (Founding PI) and Director, University of Michigan NIEHS P30 Core Center.
- 7/2012-2013 Director, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
- 7/2013-6/2017 Founding Dean, Dalla Lana School of Public Health, a Faculty of the University of Toronto, Toronto, Ontario, Canada

CLINICAL APPOINTMENTS:

- 7/1985-6/1987 Attending Physician, Emergency Department, Whidden Memorial Hospital
- 7/1985-6/1988 Assistant Visiting Physician, Department of Medicine, Boston City Hospital
- 1/1985-6/2006 Consultant in Occupational and Environmental Medicine, Center for Occupational and Environmental Medicine, Northeast Specialty Hospital (formerly known as the Olympus Specialty Hospital, the Massachusetts Respiratory Hospital, and Norfolk County Hospital).
- 3/1987-9/1987 Attending Physician, Occupational Health Program, University Hospital/Boston University Medical Center
- 7/1988-9/2006 Associate Physician, Brigham and Women's Hospital
- 7/1990-6/1995 Occupational/Environmental Medicine Consultant, Brigham and Women's Hospital Employee Health Services
- 7/2007-2012 Associate Physician, Division of General Medicine, Department of Medicine, University of Michigan Health System
- 1/2019-present Staff Physician, RotaClinic-Lake City, Seattle, WA

OTHER ACADEMIC POSITIONS and MAJOR VISITING APPOINTMENTS:

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7/1987-6/1990 Visiting Physician, South Cove Health Center, Boston (Chinatown)
 7/1996-8/2006 Associate, Center for Health and the Global Environment, Harvard Medical School
 2/1997 Alice Hamilton Visiting Professor, Division of Occupational and Environmental
 Medicine, Department of Medicine, University of California at San Francisco
 11/2000- Visiting Scientist, Sri Ramachandra Medical College and Research Institute
 7/2010- Senior Consultant, Tianjin Centers for Disease Control and Prevention, Tianjin,
 China
 10/2012- Visiting Professor, Shanghai Key Laboratory of Children's Environmental Health,
 Xinhua Hospital, Shanghai Jiao-Tung University, China
 7/2013-6/2016 Visiting Professor, Shanghai Jiao Tong School of Medicine, China
 5/2015- Affiliate Scientist to the Li Ka Shing Knowledge Institute, St. Michael's Hospital,
 Toronto, Canada

MAJOR RESEARCH INTERESTS:

1. Environmental and molecular epidemiologic research related to heavy metals, potential endocrine disruptors, other neurotoxicants, carcinogens, etc.
2. Gene-environment interactions; epigenetic dysregulation
3. Fetal/early life exposures and long-term effects
4. Aging-environment interactions
5. Environmental health, health inequities and health disparities, human rights
6. Health and the global environment
7. "Big Data" for population health
8. Environmental sensitivities/Multiple chemical sensitivities

GRANTS (as PI, Co-PI, or primary mentor only):

Past Funding:

1980 (summer) Montefiore Hospital, Bronx NY, PI; \$2,000 (approx)
 A study of rural and occupational health in Tulua, Colombia, South America
 1982 (summer) Albert Einstein College of Medicine, PI; \$3,000 (approx)
 A study of occupational/environmental health in Shanghai, China
 7/1987-6/1989 NIEHS Center Grant ES00002 Pilot Project, PI; \$12,000
 The Long-term Renal and Neurologic Effects of Childhood Plumbism
 7/1989-6/1990 NIEHS subcontract 7083-1, PI; \$50,000 (approx)
 The Use of X-Ray Fluorescence to Measure Lead Burden and Childhood Lead
 Exposure
 7/1990-6/1992 Agency for Toxic Substances and Disease Registry, PI; \$150,000 (approx)
 "Clinical Environmental/ Occupational Medicine Research Fellowship Award",
 7/1990-6/1991 NIEHS Center Grant ES00002 Pilot Project, PI; \$12,000
 The Metabolic Effects of Pregnancy and Lactation on Lead Burden

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7/1990-6/1991 Harvard School of Public Health Basic, PI
Research Support Grant; \$10,000
K-X-Ray Fluorescence Measured Lead Burden

10/1991-11/1991 NIOSH Special Grants, PI; \$50,000 (approx)
The Carpenters Lead Project

4/1991-3/1996 NIEHS/R01, PI; \$2,200,000 (approx)
The Epidemiology of Lead, Diet and Blood Pressure

7/1991-6/1996 NIEHS/R01 supplement, PI; \$240,000 (approx)
The Epidemiology of Lead, Diet and Blood
Pressure--Research Supplement for Minority Investigator

7/1992-6/1995 NIEHS/R01 (Office of Research on Women), PI; \$200,000 (approx)
Lead and Hypertension in Women

7/1993-6/1996 NIEHS/subcontract, PI; \$150,000 (approx)
Exposure to Neurotoxins as Risk Factors for Amyotrophic Lateral Sclerosis

7/1995-6/1998 State of Washington, Department of Labor, PI; \$350,000 (approx)
SPECT Imaging of the Brain in Patients with Multiple Chemical Sensitivity
Syndrome and Controls

7/1996-6/1997 NIEHS Center Grant ES00002 Pilot Project, PI; \$15,000
Electrocardiographic abnormalities in association with low-level lead exposure
among middle-aged to elderly men: the Normative Aging Study

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); \$1,800,000 (approx)
Lead Exposure, Accumulation in Bone, and Reproductive Toxicity Among Men and
Women In Mexico

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); \$1,900,000 (approx)
Lead Exposure, Accumulation in Bone, and Cognitive Toxicity Among Elderly Men
and Women

6/1997-5/2002 NIEHS/R01 ES05257 PI; \$2,312,274
Lead Biomarkers, Aging, and Chronic Disease

7/1997-6/1999 NIEHS Center Grant ES00002 Pilot Project, PI; \$10,000
The effect of genetic polymorphisms of metallothionein-IIA on mRNA levels in
middle-aged to elderly men: the Normative Aging Study

7/1998-6/2003 NIEHS/R01 PI (with no-cost extension; 5R01ES007821); \$2,291,833
Lead Dose Biomarkers, Reproduction, and Infant Outcomes

7/1999-6/2000 NIEHS Center Grant ES00002 Pilot Project, co-PI; \$14,000
Magnetic Resonance Spectroscopy in the Evaluation of Lead Neurotoxicity: the
Normative Aging Study

7/2000-6/2001 MAVERIC (Massachusetts Area Veterans Epidemiology Resource and Institute
Center) Pilot Project PI (with Dr. Robert Wright, co-PI); \$10,000
The Use of Magnetic Resonance Spectroscopy in Lead Poisoning

7/2000-6/2001 NIOSH Center Grant Pilot Project, PI (with Dr. Robert Wright, co-PI); \$12,000
Interaction between ApoE Genotype and Lead Exposure in the Development of
Cognitive Impairment

7/2002-6/2004 The Rasmussen Foundation/Health Care Without Harm; \$50,000

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7

- Medical Use of Phthalate Containing Products in the Neonatal Intensive Care Unit and Biomarkers of Neonatal Phthalate Metabolites
7/2002-6/2003 NIEHS Center Grant Pilot Project, PI; \$8,000
Vitamin D Receptor Gene and Bone Lead in Reproduction
- 3/2004-2/2005 The Critelli Family Foundation; \$10,000
Review of Environmental Cadmium Exposure and Toxicity
- 4/2000-3/2007 NIEHS Project Leader (Program Project PI: Richard Monson; 5P01ES05947); \$2,472,677; Controlled Trial in Pregnancy of Dietary Supplements for the Suppression of Bone Resorption and Mobilization of Lead into Plasma (no cost extension)
- 4/2000-3/2007 NIEHS Project co-Leader (Program Project PI: Richard Monson; 5P01ES05947); \$1,210,000 (approx); A Community-Based Study of Lead Exposure Pathways, Biomarkers of Dose, Health Effects, and Phytoremediation Strategies at the Tar Creek Superfund Site (no cost extension)
- 4/2002-9/2007 NIEHS/R01 PI (5R01ES010798); \$3,011,295
Gene-Metal Interactions and Parkinson's Disease
- 10/2003-9/2007 NCMHI/P20 Project Leader (MD000501-01; Hughes Harris, PI); \$828,781 (Project)
"FAMU and Harvard Center for Health and Health Care Disparities"
- 8/2003-7/2008 NIEHS/R01 PI (2R01ES05257-11A2); \$3,357,424 (became co-PI in 2007 after move to University of Michigan)
Lead-Gene Interactions and Cognition
- 6/2004-3/2009 NIEHS/P01 PI (5 P01ES012874-01); \$6,662,670 (became co-PI in 2006 after move to University of Michigan)
Metals Mixtures and Children's Health (Center for Children's Environmental Health and Disease Prevention Research)
- 7/2002-12/2009 NIH/R03 PI (1R03TW005914; no cost ext through 2008); \$192,000 (approx)
Lead, Genes, and Cognition in Children in Chennai, India
- 9/2006-7/2011 NIEHS/R01 PI (R01ES0007821); \$3,116,831
Fetal Origins of Neurobehavior: Lead and Cholesterol Metabolism Interactions
- 7/2006-6/2011 NIEHS/R01 co-PI (R01ES013744; PI Wright), \$3,200,000
Stress, Lead, Iron Deficiency and Neurodevelopment
- 7/2006-6/2011 NIEHS/R01 co-PI (R01ES014930; PI Wright), \$2,800,000
Metal Mixtures and Neurodevelopment
- 2/2008-2/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; \$26,000 (no cost extension)
Epigenetics of Early Life Events and Environmental Toxicants
- 4/2009-4/2010 Michigan Alzheimer's Disease Research Center Pilot Project PI, \$25,000
Environment, Epigenetics and Alzheimer's Disease (no cost extension)
- 12/2009-12/2010 University of Michigan Center for Global Health Pilot Project PI, \$25,000
Climate Variability and Impacts on Mortality and Morbidity in Chennai, India: A Pilot Project Stemming from the 2009 U.S.-India Workshop on Climate Change and Public Health, Goa India (no cost extension)

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8

9/2009-9/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; \$26,000 (no cost extension)
Epigenetics and Epigenomics in the Etiology of Alzheimer Disease

7/2008-6/2011 NIA/T32 PI (T32AG027708); \$450,000
Interdisciplinary Training Program in Aging and Public Health

4/2010-3/2015 NIEHS P42 Superfund Co-Inv, Project 2, Co-investigator (P42ES017198; PI: Alshawabkeh, Project 2 Leader: Meeker) Puerto Rico Testsite For Exploring Contaminant Threats, \$12,000,000

4/1/2011-6/2015 NIEHS Core Environmental Health Sciences Center, Founding PI and Director (until 2012; now consultant; P30 ES017885), \$ 4,620,100;
“Lifestage Exposures and Adult Disease”

4/2010-3/2014 NIEHS/EPA P20 Co-PI and Clin Health Specialist (P20 ES018171; PI Peterson) Formative Children’s Environmental Health and Disease Prevention Center, \$1,959,960; “Perinatal Exposures, Epigenetics, Child Obesity & Sexual Maturation”

7/1/2013-6/30/2014 CIHR, Canadian Institute for Health Services and Policy Research; Planning Grants-Priority Announcement:Partnerships for Health System Improvement; PI, \$24,992
“The Surviving Opioid Overdose with Naloxone (SOON) Project and Roundtable”

07/1/11-06/30/16 NIEHS K01 ES019909 (co-mentor; PI: Somers)
“Immune dysfunction associated with early life heavy metal exposure”

4/1/12-3/30/17 NIEHS R01ES013744 (consultant; PI: Wright; Mt Sinai School of Medicine)
“Stress-Lead Interactions and Child Development”

7/1/2012-7/1/2017 European Commission (EC), Funded under FP7-Health, Project 304925, co-Investigator; PI, epidemiologic studies, \$6,000,000 E
“A novel micronutrient-based strategy to prevent hearing impairments: test and road to market for age-related hearing loss and preservation of residual hearing”

Current Funding

6/1/2012-7/1/2019 1R01ES021446-01, PI, \$4,140,000 (parent + supplement awards);
“Prenatal and Childhood Exposure to Fluoride and Neurodevelopment”

5/15/2015-5/15/2019 Health Canada; PI, \$200,000 (Phase 1); \$1,400,000 (proposed Phase 2)
“A Community-based First Nation Study of Cancer and the Environment in Northern Ontario”

4/1/13-3/31/23NIEHS/EPA P01ES022844 (co-inv; PI: Peterson at the University of Michigan)
“Lifecourse Exposures & Diet: Epigenetics, Maturation & Metabolic Syndrome.”

7/1/16-6/30/21 CIHR (co-PI; Director; PI: Jeffrey Brook at the Dalla Lana School of Public Health) \$4,700,000 CDN
“CANadian Urban Environmental (CANUE) Health Research Consortium”

9/1/16-8/31/21 NIH 5R01ES026033-02, (consultant; PI: Arora at Mt. Sinai School of Medicine) \$648,000 “Novel Biomarker to Identify Critical Windows of Susceptibility to Metal Mixture”

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9

Applications Under Review

Wellcome Trust, co-investigator (PI: P Landrigan)

“Quantifying the Cognitive and Economic Benefits of Reducing Air Pollution to Achieve Climate Change Mitigation”

Competitive Renewal Application In Progress

R01ES021446-01, PI, \$4,140,000

A Prospective Study of Early Life Exposure to Fluoride, Thyroid Function, and Neurobehavioral Outcomes

Amended Application In Progress

R01ES007821-11, PI, \$4,800,000;

Early Life Toxicants and Cardiovascular Outcomes” (priority score 27 by CASE Study section; 25th percentile)New Application in Progress

Wellcome Trust, xxx, multiple-PI

Addressing Two Critical Gaps in Understanding the Impacts of Lead Exposure on the Global Burden of Disease: (a) Impacts on Cardiovascular Disease; (b) Exposures and Sources in Low and Middle-Income Countries

HONORS AND AWARDS:

1978-1982 National Health Service Corps Scholarship

1985-1988 National Research Service Award

1990-1992 Agency for Toxic Substances and Disease Registry Clinical Environmental Medicine Award

1994 Will Solimene Award of Excellence, American Medical Writers Association, for: Chivian E, McCally M, Hu H, Haines H, eds. *Critical Condition: Human Health and the Environment*. Cambridge: The MIT Press, 1993.

1997 Alice Hamilton Lecturer, University of California at San Francisco

1998 First Prize for Best Infant Nutrition Research, Instituto Danone, Mexico (for González-Cossío T, Peterson KE, Sanín L, Fishbein SE, Palazuelos E, Aro A, Hernández-Avila M, Hu H. “Decrease in birth weight in relation to maternal bone lead burden.” Published in *Pediatrics*)

1999 National Institute for Environmental Health Sciences “Progress and Achievement of the

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10

- Year Award", 1998-1999
- 1999 True Memorial Lecturer, Maine Medical Center, Portland ME.
- 2000-2001 Faculty Sabbatical Award, Harvard School of Public Health
- 2000-2001 Senior Fulbright Scholar in India
- 2001 Hoopes Prize, Faculty Mentorship (for Senior Thesis of Charles Lin, "More than Black and White: Lead Poisoning as an Environmental Justice Issue in Boston")
- 2003 Best Paper in Preventive Medicine by a Medical Student (for Senior Thesis of Vanitha Janakiraman; Janakiraman V, Hu H, Mercado-Garcia A, Hernandez-Avila M. A randomized crossover trial of nocturnal calcium supplements to suppress bone resorption during pregnancy. *Am J Prev Med* 2003;24:260-4.). American College of Preventive Medicine, Ulrich and Ruth Frank Foundation for International Health.
- 2004 Das Travel Grant Award, The South Asia Initiative, Harvard University (for Travel in India)
- 2005 Adolph G. Kammer Merit in Authorship Award, the American College of Occupational and Environmental Medicine (for Rhodes D, Spiro A, Aro A, Hu H "Relationship of Bone and Blood Lead Levels to Psychiatric Symptoms: The Normative Aging Study", Published in the *Journal of Occupational and Environmental Medicine*)
- 2006 Teacher of the Year Award, Occupational/Environmental Medicine Residents, Harvard School of Public Health
- 2006 Harriett Hardy Award, the New England College of Occupational and Environmental Medicine
- 2009 Linus Pauling Award for Lifetime Achievements, American College for the Advancement of Medicine
- 2011 Award for Excellence, American Public Health Association
- 2015 John R. Goldsmith Award for Outstanding Contributions to Environmental Epidemiology, International Society for Environmental Epidemiology
- 2016 Election to Fellowship, Canadian Academy of Health Sciences

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

Memberships

- 1981- American Public Health Association (APHA)
- 1982-2006 Massachusetts Coalition for Occupational Safety and Health
- 1983-1989 American College of Physicians
- 1985- Physicians for Social Responsibility
- 1987- Physicians for Human Rights
- 1990- International Society for Environmental Epidemiology (ISEE)
- 1990-2000 American Association for the Advancement of Science
- 1990-2006 Association of Occupational and Environmental Clinics (AOEC)
- 1991- International Physicians for the Prevention of Nuclear War (IPPNW)

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11

1994-1996 Society for Occupational and Environmental Health (SOEH)
2000-2012 American College of Occupational and Environmental Medicine (ACOEM)
2009-2012 Society of Toxicology
2012- Canadian Public Health Association (CPHA)

Committee Assignments

1981-1982 Program Committee, Occupational Safety and Health Section, APHA
1987-1988 Program Committee, Asian-American Caucus, APHA
1992-1998 Membership Committee, ISEE
1995-1998 Quality Assurance Committee, AOEC
1997-1998 Program Committee, 1998 Superfund Basic Research Program, Annual National Meeting
2001-2006 Program Committee, New England College of Occupational and Environmental Medicine
Annual Meetings

EDITORIAL POSITIONS AND BOARDS:

1977-1982 Einstein Community Health Newsletter
1988-1992 Bookreview Co-Editor, Section on Occupational Safety and Health, Am Public Health
Assoc.
1993- Journal of Health and Human Rights
1998- Environmental Health Perspectives (Founding Medical Editor, 1998-2004; Associated
Editor, 2004-)
2004- American Journal of Industrial Medicine
2007-2009 Faculty of 1000 Medicine
2017- Current Environmental Health Reports
2017- Faculty of 1000 Medicine

PEER REVIEW SERVICE

American Journal of Epidemiology
American Journal of Industrial Medicine
Archives of Environmental and Occupational Health
Biomed Central
Circulation
Environmental Health
Environmental Health Perspectives
Environment International
Environmental Research
Epidemiology

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12

Indian Journal of Medical Research
 Journal of Health and Human Rights
 Journal of the American Medical Association
 Kidney International
 Lancet
 New England Journal of Medicine
 Pediatrics
 PLOS One
 Science of the Total Environment

TEACHING:

1. LOCAL CONTRIBUTIONS (at the Harvard School of Public Health, 1985-2006)

1985-	“Toxicology of the Kidney and Urinary Tract” Guest Lecturer for TOX204a,b
1988-	“Occupational Health” Guest Lecturer for EH201a,b
1989-1992	“Lead Toxicology” Guest Lecturer for TOX204a,b
1990-	<u>Grand Rounds in Occupational/Environmental Medicine</u> Director
1990-2000	<u>Introduction to Occupational and Environmental Medicine (EH232c,d)</u> Course director, lecturer
1990-	“The Epidemiology of Lead Exposure, Dose, and Toxicity” Guest Lecturer for EPE215c,d and EPE215t
1990-	“Solvent toxicity” Fundamentals of Industrial Hygiene, Continuing Education Department
1992	"Current Research on Lead", Metals Epidemiology Research Group Seminar Presenter
1992	"Lead Poisoning Without a Known Source in a Hyperthyroid Patient" Case discussant, Grand Rounds in Occupational and Environmental Medicine
1992-	“Biological Markers of Lead Dose” Guest Lecturer, EHE280c,d
1994-	“Screening for Lead Toxicity” Guest lecturer, EPI227d
1994-	“Lead Exposure and Biological Monitoring” Guest Lecturer, ID263b
1994-	“Case Study: Lead” Guest Lecturer and Case Discussant, EH202d
1996-	<u>Introduction to Environmental Health (EH201b)</u>

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13

- 1997- Course director and lecturer
Human Health and Global Environment Change (EH278a,b)
 Course Co-developer, Co-director, and lecturer

Hospital courses and Invited Teaching Presentations (Harvard-affiliated Hospitals)

- 1990 Guest Lecturer on Occupational Medicine
 Residency Program, Department of Medicine, Brigham and Women's Hospital
- 1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
 Department of Obstetrics and Gynecology, Brigham and Women's Hospital
- 1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
 Department of Medicine, Brockton V.A. Hospital
- 1994 Speaker, Symposium on Preventive Medicine and Clinical Epidemiology,; "Is Lead a Ticking Time Bomb"; Brigham and Women's Hospital
- 1995 Discussant, "Multiple Chemical Sensitivity", Occupational/Environmental Medicine
 Grand Rounds, Occupational Health Program, Harvard School of Public Health
- 1996 Guest lecturer, "Lead Toxicity as a Paradigm for a Regional and Global Health Hazard", Environmental Health Student Group, Holmes Society, Harvard Medical School
- 1997 Speaker, "Mobilization of maternal bone lead as a hazard to the fetus", Grand Rounds, Dept. of Neonatology, Beth Israel Hospital, Boston, MA
- 2000 Guest lecturer, "Update on Lead Toxicity Research", Program in Pediatric Toxicology, Children's Hospital
- 2000 Discussant, "Adult Lead Toxicity", Weekly Case Round, Department of Medicine, Brigham and Women's Hospital, Boston.
- 2000 Lecturer, "Update on Lead Toxicity, Hypertension, and Chronic Renal Failure", Renal Rounds, Division of Nephrology, Department of Medicine, Brigham and Women's Hospital, Boston.
- 2002 Lecturer, "Maternal Bone Lead as a Threat to Fetal Development", Program in Neonatology, Beth Israel-Deaconness Hospital, Boston, MA

Doctoral student committees

Chair and member:

- | | |
|-----------------------|---|
| Dr. Rokho Kim | Dr.P.H. Occupational Health and Epidemiology, '96 |
| Dr. Yawen Cheng | Sc.D. Epidemiology, '98 |
| Dr. Sharon Tsaih | Sc.D. Epidemiology, '99 |
| Dr. Hung Yi Chuang | Sc.D. Occupational Health, '99 |
| Dr. Adrienne Ettinger | Sc.D. Environmental Health, '03 |
| Dr. Florence Wang | Sc.D. Environmental Health, '05 |
| Dr. Sung K. Park | Sc.D. Environmental Health, '05 |
| Dr. Pradeep Rajan, | Sc.D. Occupational Health, '06 |

Member/Advisor:

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14

Dr. How Ran Guo	Sc.D. Occupational Health, '94
Dr. Joshua Cohen	Sc.D. Health Policy and Management, '94
Dr. Jane Hoppin	Sc.D. Environmental Health, '95
Dr. Salma Elreedy	Sc.D. Environmental Health, '97
Dr. Mary Jean Brown	Sc.D. Maternal and Child Health, '00
Dr. Brisa Sanchez	Sc.D. Biostatistics, '06
Dr. Ami Zota	Sc.D. Environmental Health, '07
Dr. Ananya Roy	Sc.D. Environmental Health, '08
Dr. Elissa Wilker	Sc.D. Environmental Health, '09

Post-doctoral fellow mentor:

Dr. Marinelle Payton (Channing Lab), Dr. Susan Korrick (Channing Lab), Dr. Rokho Kim (Channing Lab), Dr. Viji Potula (HSPH Research Fellow), Dr. Barbara Nowak (Visiting Scientist from Silesian University School of Medicine, Poland), Dr. Robert Wright (Channing Lab), Dr. Ming Tsuang Wu (HSPH Research Fellow), Dr. Yawen Cheng (Channing Lab), Dr. Geeta Mathur (neonatology fellow at the Brigham and Women's Hospital), Dr. Sri Hari Bojja (HSPH Research Fellow), Dr. Hae-Kwan Cheong (Visiting Scientist from Dongguk University School of Medicine, S. Korea), Dr. Sahar Elmarsafawy (HSPH Research Fellow), Dr. Jing Lu (Visiting Scientist from the Chinese Academy of Preventive Medicine), Dr. Dieter Affeln (Occ/Env Med Fellow), Dr. Ahmed Gomaa (Occ/Env Med Fellow), Dr. Chris Leffler (Occ/Env Med Fellow), Dr. Ronald Dykeman (Occ/Env Med Fellow), Dr. Uma Dhanabalan (Occ/Env Med Fellow), Dr. Hsien-Wen Hsu (Occ/Env Med Fellow), Dr. Betty Ann Cohen (Occ/Env Med Fellow), Dr. Arvin Chin (Occ/Env Med Fellow), Dr. Daniel Rhodes (Occ/Env Med Fellow), Dr. Richard Wittman (Occ/Env Med Fellow), Dr. Sun-Dong Lee (Visiting Scientist from Sangji University, Korea), Dr. Ronald Green (Occ/Env Med Fellow), Dr. Erma Lawson (Environmental Health Fellow), Dr. Marc Weisskopf (Environmental Health Fellow), Dr. Bridget Bagert (Occ/Env Med Fellow), Dr. John Jarrell (Visiting Scientist from University of Calgary), Dr. Jennifer Weuve (Environmental Health Fellow), Dr. Karen Chou (Visiting Scientist from Michigan State), Dr. Nitin Jain (Channing Laboratory Fellow), Dr. Adrienne Ettinger (Children's Center Scientist), Dr. Sam Myers (Fellow in Alternative and Complementary Medicine), Dr. Marcelo Targino (Occ/Env Med Fellow), Dr. Manish Arora (Post-doctoral fellow from University of Sydney), Dr. Huiling Nie (Post-doctoral fellow from McMaster University).

Other faculty mentorship:

Elizabeth Rubinstein (HMS Summer research), Alicia Marier (HMS Summer research), Vanitha Janakiraman (HMS Summer research), Young-Sook Lim (Harvard College Summer research), Charles Lin (Harvard College Senior thesis research), Ed Hsieh (Harvard College Summer research), Naveen Thomas (Emory University Medical School Senior thesis research), Shreekrishna Akilesh (Harvard Dental School summer research), Christine Pace (HMS Summer research)

Advisory and supervisory responsibilities

1985-1987 Attending Physician, outpatient general medicine clinic, Boston City Hospital; weekly precepting for housestaff and medical students

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15

- 1990-2006 Preceptor, Residency in Occupational and Environmental Medicine, Harvard School of Public Health at the Mass Respiratory Hospital
- 1990-2006 Advisor to general M.P.H. students, Harvard School of Public Health.

2. LOCAL CONTRIBUTIONS (at the University of Michigan, 2006-2012)

- 2006- Principles of Environmental Health (EHS-500)
Course director and lecturer
- 2006- Environmental Epidemiology (EHS-608)
Guest lecturer on birth cohorts and environmental epidemiology
- 2006- Occupational and Environmental Disease (EHS-501)
Guest lecturer on metals exposure and health effects; Course Director (2009-)
- 2007- Metals Exposure, Biomarkers and Toxicity: A Multi-disciplinary Environmental Epidemiology Approach (EHS-698 reading course)
Course director and lecturer
- 2008-2009, Topics in Environmental Health Sciences (EHS-688)
2010-2011 Course director and lecturer
- 2009 Occupational and Environmental Disease (EHS-501)
Course director and lecturer
- 2009- On-line (Long-distance Foundations in Public Health Certificate Program): Principles of Environmental Health (EHS-500-801)
Course director and lecturer
- 2009 Introduction to Public Health (HMP-200)
Guest lecturer on environmental health
- 2009- Seminars in Aging and Public Health (EPID 813)
Course director and lecturer
- 2011 Seminar on Public Health in China (HMP-xxx)
Guest lecturer on "Environmental Health in China"

Post-doctoral fellow mentor:

Dr. Sung Kyun Park (Environmental Health Sciences Fellow, now Research Assistant Professor), Dr. Brisa Sanchez (Biostatistics Research Assistant Professor, now Assistant Professor), Dr. Richard Pilsner (Robert Wood Johnson Health & Society Fellow), Dr. Aimin Zhang (Environmental Health Sciences Fellow, Toxicology Training Grant), Dr. Ananya Roy (Environmental Health Sciences Fellow), Dr. David Cantonwine (Reproductive Sciences Fellow).

Doctoral Student Advisor (principal)

- | | |
|------------------|---|
| David Cantonwine | Ph.D. Environmental Health Sciences (2009) |
| Myriam Afeiche | Ph.D. Environmental Health Sciences (co-mentor with Karen Peterson; 2010) |
| Yoon-Hyeong Choi | Ph.D. Environmental Health Sciences (co-mentor with Sung Kyun Park; 2011) |

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16

Katie F. Bush	Ph.D. Environmental Health Sciences (co-mentor with Marie O'Neill; 2011)
Kelly Bakulski	Ph.D. Environmental Health Sciences (2012)
Gamola Fortenberry	Ph.D. Environmental Health Sciences (co-mentor with John Meeker; 2013)
Siyang Huang	Ph.D. Environmental Health Sciences (2013)
Deena Thomas	Ph.D. Environmental Health Sciences (2014)
Rebecca Tutino	Ph.D. Environmental Health Sciences (2015)
Zishaan Farooqui	Ph.D. MD-PhD Medical Scientist Training Program (2015)

Masters Student Thesis Advisor

Bradley Lampe (OEE), Troy Meissner (OEE), Pheba Alexander (OEE), Brian Davis (OEE & HBHE), Aaron Leftwich (OJOC program), Suengwon Lee (Nutrition), Allen Zhong (OEE), Graham Newman (OEE), Jacqueline Barkoski (OEE)

Undergraduate Thesis Advisor

Lauren Schwartz (Neuroscience, LSA)

3. LOCAL CONTRIBUTIONS (at the University of Toronto, 2012-present)

2012	Determinants of Community Health (Faculty of Medicine) Guest lecturer on 'The Future of Medicine & Public Health in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World'.
2012-	CHL5004H Introduction to Public Health Guest lecturer on "The Future of Public Health (and Your Role !) in a Hot, Flat, Crowded...and Diverse, Aging, Stratified, Urbanized, Polluted, Thirsty, Hungry, Debt-Ridden World". "What is Public Health?", "Climate Change and Health"
2012-	CHL 5912F Industrial Toxicology. Guest lecturer on the "Toxicology of Metals".
2013-2014	Department of Family & Community Medicine "Building Blocks" (short course for International post-graduate primary care trainees); Guest lecturer on "Public Health & Primary Care"
2013-	CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health Guest lecturer on "The Challenges of Environmental Health in a Rapidly-Changing World, from the Molecular to the Global".
2014	JCR1000 "Interdisciplinary Approach to Global Challenges" Guest lecturer on "Global Environmental Health"
2014-	PHS100H1 "Grand Opportunities in Global Health"; Guest lecturer on "Urban Environments"
2015	Public Health & Preventive Medicine Residency Rounds "Physicians, Climate, and other Global Environmental Changes: Our Role"
2016	<u>CHL5004H Introduction to Public Health, Course Co-Director (with Professor Erica</u>

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17

- 2016 DiRuggiero)
CHL 7001H F6 Environmental-Molecular Epidemiology, Course Co-Moderator (with Professor Morteza Bashash)
- 2016 CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health, Course Co-Director (with Professors Erica DiRuggiero and Abdallah Daar)
- 2016 Joint Seminar, “The Impact on Intelligence, Behaviour, and Society of Lead Exposure: A Case Study of a Global Pollutant and On-going Research”; Collaborative Program in Neurosciences and Collaborative Global Health Doctoral Program, University of Toronto
- 2016 CHL5420H “Global Health Research Methods”
 Guest lecturer on “The Early Life Exposures in Mexico to Environmental Toxicants Project (ELEMENT): A Global Health Collaboration Case Study”

Masters student research advisor

Maele Marchand

Doctoral student advisor

Adele Carty

Doctoral student thesis committee member

Laura Bogaert

Doctoral student thesis examination committee member

Claudie CY Wong (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)

Zilong Zhang (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)

Post-doctoral fellow mentor:

Siyang Huang, Ph.D.; Morteza Bashash, Ph.D.; Roman Pabayo, Sc.D. (Harvard School of Public Health); Tripler Pell, M.D., M.P.H.

4. LOCAL CONTRIBUTIONS (at the University of Washington, 2017-present)

Doctoral student thesis research mentor

Megan Suter

Doctoral student special projects advisor

Rachel Shaffer

Joey Frostad

Rebecca De Buen

5. NIH K-grant mentorship:

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18

Robert Wright, M.D., M.P.H. (K-23 ES000381, “*Neurochemical and Genetic Markers of Lead Toxicity*”), 2000-2005; Dr. Wright is now Prof of Pediatrics, Mt. Sinai School of Medicine
 Marc Weisskopf, Ph.D. (K-01 ES012653, “*New Biomarkers of Neurotoxicity*”), 2004-2009; Dr. Weisskopf is now Associate Prof of Occup Health, Harvard Sch Public Health
 Sung Kyun Park, Sc.D. (K-01 ES016587; “*Environment, Novel Aging Outcomes, and Genetics*”), 2009-2014; Dr. Park is now Assistant Prof, Department of Epidemiology, University of Michigan Sch Public Health
 Emily Somers, Ph.D. (K-01 ES019909; “*Immune Dysfunction Associated with Early Life Heavy Metals Exposure*”), 2011-2016; Dr. Somers is now Associate Prof, Division of Rheumatology, Department of Internal Medicine, University of Michigan Medical School

COMMITTEE, ORGANIZATIONAL, AND VOLUNTEER SERVICE

National/International

1978-1982 Taskforce on Occupational and Environmental Health, Co-coordinator, Am Med Stu Assoc
 1989 Ad Hoc Study Committee, National Institute for Environmental Health Sciences Council
 1989-2006 Association of Occupational and Environmental Medicine Clinics (AOEC)-- (through the Northeast Specialty Hospital Center for Occupational and Environmental Medicine)
 1989-1990 Member, Relative Risk Reduction Strategies Committee, Science Advisory Board, U.S. Environmental Protection Agency
 1989-1992 Member, Board of Directors, Physicians for Human Rights, Boston, MA
 1991 National Institutes of Health, General Clinical Research Center Program, Site Visit Team
 1992- Member, National Advisory Committee, Physicians for Human Rights, Boston, MA
 1992 Special Study Section member (R3/S1/B3), National Institutes of Health
 1994 Ad Hoc Reviewer, National Institutes of Health, General Dental Research Center Program
 1994- Advisory Board, Institute for Energy and Environmental Research
 1994-1996 Associate, Project on Global Environmental Change and Health, Physicians for Social Responsibility
 1995 Ad Hoc Reviewer, National Institutes of Health, Diagnostic Radiology Study Section
 1996- Membor, Editorial Board, Health and Human Rights—an International Journal
 1995-1998 Advisory Committee, Consortium for Environmental Education in Medicine, Cambridge, MA.
 1996-1997 Reviewer, Agency for Toxic Substances and Disease Registry
 1997-1998 Program Committee, Annual Mtg, NIEHS Superfund Basic Research Group Centers
 1998-2013 (Founding) Medical Editor (1998-2004); Associated Medical Editor (2004-), Environmental Health Perspectives (official journal of NIEHS)
 2001 Ad Hoc Reviewer, National Institutes of Health, R-13 applications

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19

- 2002-2006 External Advisory Committee, Program Project on Lead and Osteoporosis, University of Rochester
- 2003-2005 Member, Ad-Hoc Expert Panel to Form Medical Management Guidelines for Lead-Exposed Adults, (supported by NIOSH and AOEC)
- 2003-2009 Member, Working Group on Lead and Pregnancy, Advisory Committee on Childhood Lead Poisoning Prevention, U.S. Centers for Disease Control and Prevention
- 2004 Ad Hoc Reviewer, National Institutes of Health, K-23 applications
- 2004 Ad Hoc Reviewer, Draft of "Immunization Safety Review: Vaccines and Autism" Immunization Safety Review Committee, Institute of Medicine, National Academies of Science
- 2004 Finalist (one of 8), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
- 2005 Member, Strategic Planning Conference, National Institute for Environmental Health Sciences, Research Triangle Park, NC
- 2006 Ad Hoc Reviewer, Draft of "Preterm Birth: Causes, Consequence, and Prevention" Committee on Understanding Premature Birth and Assuring Health Outcomes, Institute of Medicine, National Academies of Science
- 2006 Member, External Advisory Committee, NIEHS Center, University of Rochester
- 2007 Member, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2007/05 ZES1 JAB-C (DI) (NIEHS Discover Centers)
- 2007-2010 Member, Board on Population Health and Public Health Practice, Institute of Medicine, National Academies, Washington DC.
- 2007 Member, Ad Hoc Review Panel, Centers of Excellence Program, Swedish Council for Working Life and Social Research.
- 2007-2008 Member, Search Committee for Director of Extramural Research, NIEHS
- 2007 Special Consultant, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2008/01 ZAR1 CHW-G (NIAMS Arthritis Centers)
- 2008 Report Reviewer, Draft National Research Council Report, "The National Children's Study Research Plan: A Review", National Academies
- 2008 Report Reviewer, Draft National Research Council Report, "Gulf War and Health: Updated Literature Review of Depleted Uranium", Institute of Medicine, National Academies
- 2008-2009 Data Safety Monitoring Board, "d-Penicillamine Chelation in lead-poisoned Children—A Phase II/III Trial" (R01FD003361; PI: Michael Shannon)
- 2008 Subcommittee to review Draft Report on Bisphenol A, Science Board, Food and Drug Administration
- 2008 Planning Committee, International Symposium on the Environmental and Health Consequences of Metal Mining and Smelting
- 2008-2009 Co-Chair, Planning Committee, "Climate Change Impacts on Public Health in India", Workshop that took place in Goa, India in Aug-Sept 2009 co-sponsored by UM Center for Global Health, the US Centers for Disease Control and Prevention and the Indian Council for Medical Research

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20

- 2008 Finalist (one of 2), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
- 2009-2012 Member, Board on Environmental Studies and Toxicology, National Research Council
- 2009 Reviewer, NIH Challenge Grants, Special Emphasis Panel/Scientific Review Group
2009/10 ZRG1 GGG-F
- 2009-2010 External Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health
- 2010-2012 Member, External Advisory Committee, University of Rochester NIEHS P30 Core Center
- 2010 Member, Ad-hoc review committee, National Health Research Institutes of Taiwan, Special Emphasis Panel—NHRI-Kaoshiung Medical College Program Project on “: “Gene Environment Interaction in the Genesis of Asthma and Allergic Diseases”
- 2010-2012 Member, Advisory Board, Institute of Public Health, Florida Agricultural & Mechanical University, Tallahassee, FL
- 2011 Reviewer, NIEHS Career Development Awards, Special Emphasis Panel/Scientific Review Group 2011/05 ZES1 LKB-J (K9)
- 2011-2016 Member, NIEHS National Advisory Environmental Health Sciences Council
- 2012 Member, Editorial Board, Journal of Alzheimer’s Disease
- 2015 Member and External Reviewer, School of Population and Public Health Review Committee, University of British Columbia, Vancouver, B.C.
- 2016- Chair, Board of Directors, Canadian Urban Environmental Health Research Consortium, (National Consortium based out of the Dalla Lana School of Public Health)
- 2017- Member, Energy Research Committee, Health Effects Institute, Boston, MA
- 2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative, March 1-2, 2018, Institute for Health Metrics and Evaluation, Seattle, WA
- 2017- Executive Co-Leader, Global Burden of Disease-Pollution and Health Initiative
- 2019- Member, Research Advisory Committee, Centre of Environmental Health, The Public Health Foundation of India and the Tata Institute of Social Sciences, New Delhi, India
- 2019- Reviewer, draft report on trace metals levels in pregnancy women, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta

Regional

- 1988-1990 Health Facilities Appeals Board, Member, Dept. Public Health, Comm. Of Mass.
- 1988-2006 Advisory Board, Massachusetts Department of Public Health, Sentinel Event Notification System for Occupational Risks (SENSOR) Project
- 1989-1995 Advisory Board, Massachusetts Division of Occupational Hygiene, Lead Registry Project
- 1990-1992 Board of Directors, Member, Health Care for All, Boston, Massachusetts
- 1993-1995 Faculty Council, Member, Harvard School of Public Health
- 1995-2006 Faculty Advisory Committee, Public Health Practice Program, Harvard School of Public Health

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21

1996-2006 Advisory Board, Boston VA Environmental Hazards Center, Boston

1997-2001 Faculty Steering Committee, Center for Children's Health, Harvard School of Public Health

1996-2006 Senior Epidemiology Consultant, Massachusetts Veterans Epidemiology Research and Information Center, Boston.

1996-2006 Associate, Center for Health and the Global Environment, Harvard Medical School

1997-2002 Faculty Advisory Committee on Continuing Professional Education, Harvard School of Public Health

1998-2006 Faculty Steering Committee, Masters of Public Health program, Harvard School of Public Health

2001-2003 Board of Directors, New England College of Occupational and Environmental Medicine

2001-2006 Associate Director, Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health

2001-2006 Senior Advisory Council Member, Lowell Center for Sustainable Production, University of Massachusetts, Lowell, MA

2003-2006 Member, Human Subjects Committee, Harvard School of Public Health

2003-2006 Advisory Committee, Occupational Health Services Research Program, Harvard School of Public Health

2006 Study Section Review Committee, Pilot Project Program, Graham Environmental Sustainability Institute, School of Natural Resources and Environment, University of Michigan

2006-2007 Chair, Planning Committee, Health Sector, May 8-10, 2007 National Summit on Coping with Climate Change, University of Michigan

2007-2009 Member, Advisory Committee, SPH Practice Committee, University of Michigan School of Public Health

2007-2012 Member, Residency Advisory Committee, General Preventive Medicine Residency, University of Michigan School of Public Health

2008-2009 Member, Steering Committee, NIA T32 Training Grant on Aging Research (PI: Mary Haan), University of Michigan School of Public Health

2008-2013 Member, Advisory Committee, Outstanding New Environmental Scientist Awardee (Marie O'Neill), NIEHS

2008-2009 Member, Search Committee for Director of the Risk Science Center, University of Michigan School of Public Health

2009 Co-Chair, Planning Committee, Workshop on Predicting and Preventing Climate Change Impacts on Public Health, Goa, India (Collaboration with the UM Center for Global Health, the US Centers for Disease Control and Prevention, and the Indian Council for Medical Research)

2009-2011 Director and PI, NIA T32 Training Grant on Aging Research, University of Michigan School of Public Health

2009-2010 Member, Planning Committee, University Research Corridor (U of M, Michigan State, Wayne State) symposium on environmental health sciences in January 2010

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22

2009-2012 Faculty Associate, Center for Global Health, University of Michigan
 2009-2012 Member, Internal Advisory Board, Cancer Epidemiology Education in Special Populations Program, University of Michigan School of Public Health
 2009-2011 Chair, Steering Committee on Global Health, University of Michigan School of Public Health
 2010-2012 Member, Executive Committee, Graham Environmental Sustainability Institute, University Of Michigan
 2010-2012 Member, Committee on Diversity, University of Michigan School of Public Health
 2012-2017 Chair, Executive Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Tenure Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Decanal Promotions Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Executive Advisory Committee, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
 2013-2015 Interim Director, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
 2013-2014 Co-Chair, Research Committee, Dalla Lana School of Public Health, University of Toronto
 2014-2017 Chair, Executive Advisory Committee, Institute for Health Policy Management and Evaluation, University of Toronto
 2014 Chair, Ad-hoc Committee to create an Institute for Indigenous Health (based on a \$10 million endowment gift made to DLSPH), Dalla Lana School of Public Health, University of Toronto; Chair, Executive Advisory Committee beginning 2015
 2015-2017 Chair, Executive Advisory Committee, Joint Centre for Bioethics, University of Toronto
 2015- Chair (2015-2017); Member (2017-present), Taskforce on Environmental Health, Ministry of Health and Longterm Care, Province of Ontario
 2016-2017 Chair, Executive Advisory Committee, Centre for Critical Qualitative Health Research, University of Toronto
 2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative (a collaboration between the Global Alliance on Health and Pollution and the Institute for Health Metrics), Seattle, WA

Hospital

1982-1985 Occupational Safety and Health Committee, Member, Boston City Hospital, Boston
 1983-1984 House Officers Association, Treasurer, Boston City Hospital
 1984-1985 House Officers Association, Co-President, Boston City Hospital

OTHER PUBLIC SERVICE

1987 Member, Fact-finding tour on "The Health Effects of Massive Exposure to Tear Gas",

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23

- Seoul, South Korea, July 11-18 (Sponsored by Physicians for Human Rights, American College of Physicians)
- 1988 Member, Fact-finding tour on "Chemical Weapons and the Iraqi Kurdish refugees", Turkey Oct 6-16 (Sponsored by Physician for Human Rights and the MacArthur Foundation)
- 1990 Leader, Fact-finding tour on "Health and Human Rights in Burma (Myanmar)", Thailand-Burma Dec. 26-Jan 6 (Sponsored by Physician for Human Rights and the MacArthur Foundation)
- 2009 Consultant and senior advisor, Fact-finding tour on "Mining and Potential Exposures and Health Effects in Guatemala", August 2009 (Sponsored by Physicians for Human Rights)

CONSULTING POSITIONS

- 1987-1989 Consultant, "In-Vivo Total Body Lead Analysis by X-Ray Fluorescence", NIH/SBIR Grant 2R44ES03918-02
- 1988-1989 Consultant, "Boston Area Health Coalition Demonstration Project", DHHS/MP000003-A1
- 1993-1995 Consultant, Employee Health Services, Brigham and Women's Hospital
- 1994 Consultant, Public Welfare Foundation, Washington, DC (review of Environmental Programs)
- 1997-2006 Consultant, Pediatric Environmental Health Center, Children's Hospital, Boston, MA
- 2000 Consultant, Doris Duke Foundation, New York, NY (review of potential Environment and Medicine programs)
- 2009-2010 Consultant and Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health, Seattle, WA
- 2011 Consultant, JPB Foundation, New York, NY (review of Environmental Health programs)
- 2014- Advisor, Hearing Health Sciences, Ann Arbor MI and Amsterdam, Netherlands

VISITING PROFESSORSHIPS

- 1997 Alice Hamilton Visiting Professor, University of California at San Francisco
- 2000-2001 Visiting Professor, Sri Ramachandra Medical College & Research Institute, Chennai, India
- 2004 Visiting Professor, Department of Environmental Medicine, University of Rochester
- 2013 Visiting Professor, Shanghai Key Laboratory, Shanghai Jiao-Tung University

SEMINARS AND EXTRAMURAL INVITED PRESENTATIONS (last 15 years, since 2003; prior presentations upon request)

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24

- 2003 Guest lecturer, "Lead as a trans-generational toxin", Seminar series, Department of OB/GYN, Brigham and Women's Hospital
- 2003 Plenary speaker, "Clinical opportunities in environmental health", Annual Leadership Retreat, National Institute for Environmental Health Sciences, Greensboro, NC.
- 2003 Discussant, "Uncontrolled Hypertension in a Painter", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2003 Discussant, "A 53-Year Old Teacher with Chemical Sensitivities", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2003 Lecturer, "Pestilence and Progress: The Future of Public Health through the Lens of Blood", Center for Blood Research Symposium, Museum of Science, Boston, MA.
- 2003 Speaker, "Bones, Genes, Plasma, and Lead: New Frontiers in Understanding the Toxicity of an Old Hazard", Distinguished Lecture Series. National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta GA.
- 2003 Plenary speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Superfund Basic Research Program Annual Meeting, Dartmouth University, Hanover, NH.
- 2003 Special Lecturer, "Lead Exposure and Chronic Disease: Recent Research on Susceptible Sub-populations", Florida Agricultural and Mechanical University, Tallahassee, FL.
- 2004 Speaker, "New Frontiers in Understanding the Toxicity of Lead", Department of Environmental Medicine, University of Rochester, Rochester, NY.
- 2004 Presenter, "Lead Exposure During Pregnancy: Mobilization of Maternal Bone Lead Stores and Their Threat to the Fetus", Semi-annual meeting of the Childhood Lead Poisoning Prevention Branch, Centers for Disease Control and Prevention, Baltimore, MD
- 2004 Presenter, "Environmental Medicine", Annual meeting of the Editorial Board, *Environmental Health Perspectives*, Baltimore MD
- 2004 Plenary speaker, "Metals, Genes, and Neurodegeneration: the Approach of the Metals Epidemiology Research Group at the Harvard School of Public Health", National Institute for Environmental Health Sciences Conference on Neurodegeneration.
- 2004 Discussant, "Suspected Lead Toxicity" Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2004 Discussant, "Mercury Exposure in a Metal Worker", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2004 Presenter, "Effects of Our Environment on Intellect, Behavior, Life and Death," Leadership Council meeting, Harvard School of Public Health
- 2004 Guest Speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Department of Environmental Health, University of Michigan School of Public Health
- 2004 Guest Speaker, "Medicine, Public Health, and the Great American Melting Pot: A Second-Generation Chinese-American Reflects on His Personal Odyssey", Sponsored by the Asian Student Association, Harvard School of Public Health
- 2004 Speaker, "Aging, the Environment and Genetics: Recent Insights from

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25

- Epidemiologic Studies of Environmental Lead Exposure”, Annual Leadership Retreat, National Institute for Environmental Health Sciences, Pinehurst, NC.
- 2004 Plenary Speaker, “Guidelines for the Management of Lead-Exposed Adults: Recommendations by a National Expert Panel Based on Recent Research”, New England College of Occupational and Environmental Medicine Annual Meeting
- 2005 Lecturer, “Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard”, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India
- 2005 Lecturer, “Your Child's IQ, Behavior and Neuropathology: Genes or Environment?”, the Harvard Club of Boston, Boston, MA
- 2005 Guest Speaker, “Metals, Neurodevelopment, and Neurodegeneration: The Work of the Metals Epidemiology Research Group at HSPH”, Neurostatistics Working Group, Harvard School of Public Health, Boston, MA.
- 2005 Plenary Speaker, “Aging, the Environment and Genetics: Recent Insights from Epidemiologic Cohort Studies of Environmental Lead Exposure”, NIEHS Symposium on Aging and the Environment, Duke University, Durham, NC.
- 2005 Plenary Speaker, “SPECT Imaging and Chemical Intolerance”, NIEHS/NIAA symposium on “Chemical Intolerance and Addiction: a Shared Etiology?”, Research Triangle Park, NC
- 2005 Workshop Presenter, “Social and Environmental Threats: the Unnecessary Epidemics”, Harvard School of Public Health Leadership Council Annual Conference, Boston, MA
- 2005 Keynote Speaker, “Our Food, Our Water, Our Homes: Toxic Metals”, The Boston Foundation, Boston, MA.
- 2006 Invited Speaker (invited by David Schwartz, NIEHS Director), “Goal IV: Improve and Expand Community-Linked Research”, Roundtable on Environmental Health Sciences, Research, and Medicine; Institute of Medicine, National Academy of Sciences, Wash DC.
- 2006 Speaker, “The Future of Environmental Health Sciences at the University of Michigan”, Dean’s Advisory Board, University of Michigan School of Public Health, Ann Arbor, MI
- 2006 Keynote Speaker and Harriett Hardy Annual Lecturer, “The ‘E’ in Occupational/Environmental Medicine: the Present and the Future”, New England College of Occupational Medicine Annual Meeting, New Bedford, MA
- 2007 Speaker, “The Future of Environmental Health Sciences at the University of Michigan”, Meetings of the UMSPH Alumni Council and the EHS Emeritus Faculty, Ann Arbor, MI
- 2007 Moderator and Speaker, “The Normative Aging Study: Health Effects of Lead”, Symposium on the Health Effects of Lead, 2007 Annual Meeting of the International Society for Environmental Epidemiology, Mexico City, Sept 8, 2007
- 2007 Guest Lecture, “Uncovering the Impact of the Environment on Disease: Big Opportunities for Physician-Scientists”, Medical Scientist Training Program, University of Michigan Medical School
- 2007 Guest Lecture, “Industrialization, Pollution and Public Health in India: Can India Survive Modernization?”, Osher Institute, Ann Arbor, MI
- 2007 Plenary Speaker, “Environmental Equity: Local and Global Challenges and the Balance Between Research and Advocacy”, Michigan’s Premier Public Health Conference,

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26

- October 16, 2007, Dearborn, MI
- 2007 Board Member Lecture, "Metals, Genes, Health and Human Rights: from the Molecular to the Global", Fall Meeting of the Board of Population Health and Public Health Practice, Institute of Medicine, National Academies of Science, Washington DC, Dec 13, 2007.
- 2008 Speaker, "MDs as Leaders for Change in Environmentalism", 2008 Annual Regional Political Leadership Institute, American Medical Student Association, University of Michigan Medical School, February 16, 2008
- 2008 Speaker, Grand Rounds, "The Impact of Environmental Pollutants on Disease: New Insights and Implications for Research and Medical Practice" Department of Medicine, University of Michigan Health System.
- 2008 Guest Lecture, "Emerging Insights into the Pervasive Influence of Environment Toxicants on Reproductive Outcomes and Offspring Development: Lead as a Case Study", Reproductive Sciences Program, University of Michigan
- 2008 Panelist, "Environmental Health in China", Public Health Grand Rounds, Division of Health Practice, University of Michigan School of Public Health
- 2008 Keynote Speaker, "Human Health and the Role of Water", Symposium on Water, Health & The Environment, Graham Environmental Sustainability Institute, University of Michigan
- 2008 Guest Speaker, "Lead Exposure and Toxicity: New Insights Using Molecular Epidemiology" Wadsworth Laboratories and SUNY-Albany
- 2008 Speaker: "Impact of Climate Change on Human Health: Vulnerability" 5th AKKA World Kannada Conference, Chicago IL
- 2008 Speaker, "The 'E' in Occupational/Environmental Medicine: the Present and the Future", Michigan Occupational/Environmental Medicine Annual Meeting, Mackinac Island, MI
- 2008 Speaker, "Impact of Climate Change on Human Health", University of Michigan Chapter of the American Medical Student Association, Ann Arbor, MI
- 2008 Speaker, "Early Life Origins of Adult Chronic Disease: Environmental Health and Toxicology at a Crossroads" Michigan Chapter of the Society for Toxicology, Ann Arbor, MI
- 2009 Speaker, "Evidence for Lead as an Environmental Stressor of Alzheimer's Disease and the Role of Epigenetics", Symposium Panel, Annual Meeting of the Society for Toxicology, Baltimore, MD
- 2009 Keynote Speaker, "Lead, Late-Life and Early Life Effects, and the Emerging Field of Environmental Epigenetics: Looking Ahead", Annual Meeting of the American College for the Advancement of Medicine, San Diego, CA
- 2009 Speaker, "Lead Toxicity and Mechanistically-Oriented Molecular Epidemiology: Targeting the Epigenetics of Alzheimer's Disease", Seminar Series, Institute for Environmental Health Sciences, Wayne State University, Detroit, MI
- 2009 Speaker, "Climate Change Impacts on Health in the Developing World", Research Discussion Series, University of Michigan Center for Global Health
- 2009 Speaker, "Autism, Aggressive Behavior, Anxiety, and Alzheimer's: are Environmental Toxicants Playing a Major Etiologic Role?", Department of Psychology, University of Michigan
- 2009 Speaker, "Early Life Exposures and Endocrine Disruption: Evidence from Molecular

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27

- Epidemiology”, Pediatric Endocrine Seminar, University of Michigan Medical School
- 2009 Distinguished Speaker, “Lead Toxicity: Twenty Years of Research On The Poison That Keeps on Poisoning” 10th Anniversary of the Department of Microbiology and Environmental Toxicology, University of California at Santa Cruz
- 2010 Speaker, “The Centers for Disease Control and Prevention & the Environmental Protection Agency: Potential Funding Opportunities for Regional Collaboration in Michigan”, University Research Corridor Symposium on Environmental Health, Detroit, MI.
- 2010 Speaker, “The Future of Public Health”, University of Washington School of Public Health
- 2010 Speaker, “The Environment Meets the Epigenome: Is This Where Autoimmunity Begins?” Symposium on Autoimmunity and Epigenetics, University of Michigan
- 2010 Keynote Speaker, “A New Twist to an Old Story: The Evidence for Early Life Lead Exposure as a Risk Factor for Alzheimer's Disease through Epigenetic Programming”, NIEHS Environmental Health Sciences Center and Toxicology Training Program Retreat, University of Rochester, NY
- 2010 Speaker, “Lead Toxicity: Twenty Years of Research on The Poison That Keeps on Poisoning” and “Environmental Health Sciences at the University of Michigan”, Tianjin Centers for Disease Control, Tianjin, China
- 2010 Speaker, “Pediatric Lead Toxicity”, Xinhua Hospital and the Shanghai Jiao-Tung Medical University Department of Pediatrics, Shanghai, China
- 2010 Speaker, “Environmental Health Sciences at the University of Michigan”, Fudan University, Shanghai, China
- 2010 Speaker, “Alzheimer’s Disease, Epigenetics and the Environment”, Symposium Update, Alzheimer’s Disease Association, Ann Arbor, MI
- 2010 Speaker, “Environmental Justice, Progress (and the Lack Thereof) and the Role of Research”, Roundtable on Environmental Health Sciences, Research and Medicine, Institute of Medicine, National Academies, Washington DC.
- 2010 Speaker, “White Coats, Population Science and Poison Gas: A Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights”, Robert Wood Johnson Clinical Fellows Program, University of Michigan Medical School, Ann Arbor, MI
- 2011 Speaker, “The Three Most Difficult Challenges to Molecular Epidemiologic Research on Gene-Environment Interactions: Lead Toxicity as a Case Study.” Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI
- 2011 Speaker, “The Integration of Data on Environmental Carcinogens with Population and Genetic Resources”, “Opportunities & Challenges for Translational Research on Cancer Prevention”, Translational Cancer Prevention & Biomarkers Workshop, Mazamdur-Shaw Cancer Center, Bangalore, India.
- 2011 Speaker, “Success in the Academy”, Faculty Panel, Students of Color of Rackham, Rackham Graduate School, University of Michigan
- 2011 Speaker, “White Coats, Population Science and Poison Gas: Fact-Finding Missions by Health Professionals for Human Rights”, Sujal Parikh Memorial Symposium, University of Michigan Medical School.
- 2011 Speaker, “The Analysis of Biomarker Data to Ascertain the Contribution of Environmental

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28

- Exposures to the Etiology of Disease: Lead Exposure and Toxicity as a Case Study”, Department of Computational Medicine and Bioinformatics, University of Michigan Medical School.
- 2012 Speaker, “Research and Analysis Linking Upstream and Downstream Disparities Work”, Webinar hosted by the Health & Environmental Funders Network, Bethesda, MD, with 52 Foundations related Health.
- 2012 Keynote Speaker, “The Future of Public Health & Medicine in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World”. E.J. Van Liere Memorial Convocation and Health Sciences Center Research Day, West Virginia University, Morgantown, West Virginia
- 2012 Plenary Speaker, “Transgenerational Impacts of Pollutants on Offspring: Recent Insights and Case Studies”, Connaught Global Challenge International Symposium, University of Toronto.
- 2012 Speaker, “Environmental Impacts on Aging (+ an update on the Dalla Lana School of Public Health)”, Community Medicine Rounds, University of Toronto
- 2012 Speaker, “The Environment & Public Health in a Research-Intensive University: Opportunities for Scholarship in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World”, School for the Environment, University of Toronto
- 2012 Speaker, “Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, External Advisory Meeting, Public Health Ontario, Toronto
- 2012 Speaker, “Canadian Public Health Schools (in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World): The View from Toronto, External Advisory Board Meeting, Institute for Population and Public Health, Canadian Institutes for Health Research, Toronto
- 2012 Speaker, “Sustainable Development and Health: The Global Mining Industry”, Canadian Society for International Health Annual Meeting, Ottawa
- 2012 Speaker, “Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Xinhua Hospital/Shanghai Jiao-Tung University, Shanghai, China.
- 2012 Speaker, “The Impact of Population-Wide Lead Exposure and Gene-Lead Interactions on Chronic Disease”, Genetic Grand Rounds, Sick Kids Hospital, Toronto.
- 2012 Speaker, “Looking behind the curtain: Lead Toxicity as a Case Study of Methodologic Challenges in Gene-Environment Interactions Research”, Strategic Training in Advanced Genetic Epidemiology (STAGE), Dalla Lana School of Public Health, University of Toronto.
- 2012 Keynote speaker: “Public Health—the Next Frontier in Health Professions Education”. Council of Health Sciences annual retreat, University of Toronto.
- 2013 Speaker, “White Coats, Population Science and Poison Gas: Lessons from a Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights”, Joint Center for Bioethics, University of Toronto
- 2013 Speaker, “Gauging environmental impact on the development of chronic inflammation”,

CV: Howard Hu, M.D., M.P.H., Sc.D.

CV: Howard Hu

29

- Connaught Global Challenge Workshop, University of Toronto.
- 2013 Speaker, “The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Grand Rounds, Department of Medicine, University of Toronto.
- 2013 Speaker, “Metals, Mega-trends, and Me: Reflections on Research and the Vision for the Dalla Lana SPH”, Occupational and Environmental Medicine Grand Rounds, St. Michael’s Hospital, Toronto, ON.
- 2013 Speaker, “Air pollution and Cardiovascular Disease: Health Impacts, Mechanisms, and Research Opportunities”, University of Toronto & FMUSP-InCor Symposium on Cardiology, Sao Paulo, Brazil.
- 2013 Speaker: “Lead Exposure’s Impact on Health and Policy: A History of Neglect and Missed Opportunities”, Public Health Policy Rounds, CIHR Strategic Training Program in Public Health Policy, University of Toronto.
- 2013 Speaker: “Lead Toxicity: The Long Tail of Health Impacts (and On-going Research Opportunities!) From an Historical Environmental Air Pollutant”, Southern Ontario Centre for Air Pollution and Aerosol Research, University of Toronto.
- 2013 Speaker: “Water and Sanitation”, Water, Sanitation and Hygiene (WASH) Canada, Toronto, Ontario, Canada
- 2014 Speaker: “Conflict and Public Health”, Ontario Medical Association, Toronto, Canada
- 2014 Panelist: “Judging Evidence: Finding a Place for Variation in an Evidence-Based World”, Health Quality Ontario, Toronto, Canada
- 2014 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, Special meeting of the Canadian Chamber of Commerce in Shanghai
- 2014 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China
- 2015 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, School of Public Health and the ASEAN Institute, Mahidol University, Bangkok, Thailand
- 2015 Speaker: “Gene-environment Interactions and the Role of Big Data in Environmental Health” Seminar series, School of the Environment, University of Toronto, Toronto, Canada
- 2015 Speaker: “Global Health Security”, Ill with Illness—Economic, Social & Security Barriers to the Provision of Global Health, Munk School of Global Affairs, University of Toronto, Toronto, Canada
- 2015 Speaker: “The Dalla Lana School of Public Health: Big Ideas and Initiatives for Creating Health in a Globalized World”, Speaker Series, University of Toronto Alumni of Toronto.
- 2015 Speaker: “Unique Scientific Opportunities for the Precision Medicine Initiative National Research Cohort: Exposomics, Data Linkage, and Global Collaborations”. Working group on President Obama’s Precision Medicine Initiative (Chaired by Francis Collins, Director, NIH)
- 2015 Speaker: “What is the Role of Schools of Public Health in the 21st Century?” 50th Anniversary Celebration of the Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec.
- 2015 Welcoming Address: “Global Public Health and Mental Health”, Going Global for Mental Health conference, Centre for Addictions and Mental Health/Department of Psychiatry/Dalla

CV: Howard Hu, M.D., M.P.H., Sc.D.

CV: Howard Hu

30

- Lana School of Public Health, Toronto, ON
- 2015 John Goldsmith Memorial Lecture: “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Opening Plenary Session, International Society for Environmental Epidemiology Annual Meeting, Sao Paulo, Brazil
- 2015 Inaugural Speaker: “The Future of Public Health and Medicine in a Crowded and Complex World”, Global Health Leadership Series, PSG Medical School & the Shanti Ashram Foundation, Coimbatore, Tamil Nadu, India
- 2016 Speaker “The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Indian Institutes of Public Health—Hyderabad, Hyderabad, India
- 2016 Speaker: “Integration of Public Health & Health Care: The Unmet Agenda for a Truly Sustainable Health System”, Board of Directors Retreat, Toronto East General Hospital, Toronto
- 2016 Plenary speaker: “Health Promotion, Prevention and Health Protection: Innovative Initiatives”, 6th Asia-Pacific Conference on Public Health | 1st ASEAN Health Promotion Conference Bangkok, August
- 2016 Speaker: “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Mount Sinai School of Medicine, New York, NY
- 2016 Plenary Speaker: “The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances”, International College of Integrative Medicine Annual Meeting, Toronto, ON
- 2016 Plenary Speaker: “Big Data and Implications for Environmental Health”, 15th Anniversary Conference, Jockey Club School of Public Health & Primary Care, Chinese University of Hong Kong, Hong Kong
- 2016 Plenary Speaker: “Innovations in Assessing Lead Poisoning and Child Health: Policy & Clinical Implications”, Chinese University of Hong Kong-Fudan-Oxford International Symposium on Health Impacts of Environmental Exposures”, Hong Kong
- 2016 Speaker: “Addressing a Changing Environment (and Impacts on Health, AKA Can India Survive Modernization?)”, Indian Institutes of Technology Alumni, Canada, International Conference 2016, Toronto.
- 2016 Plenary Speaker, “Hidradenitis Suppurativa: Research Directions from a Population Health Perspective”, Symposium on Hidradenitis Suppurativa Advances, Toronto.
- 2016 Plenary Speaker, “Children’s Environmental Health”, The 2016 Annual National Conference on Children’s Healthcare, Shanghai, China
- 2016 Special Guest Speaker, “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Shanghai Municipal Center for Disease Control, Shanghai, China
- 2016 Lecturer, “Lead and Human Health: Recent Research and Associated Lessons for Science & Policy”, Fudan University School of Public Health, Shanghai, China
- 2017 Lecturer, “The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances”, Saw Swee Hock School of Public Health, National University of Singapore, Singapore
- 2017 Lecturer, “The Future of Academic Public Health”, Saw Swee Hock School of Public Health,

CV: Howard Hu, M.D., M.P.H., Sc.D.

CV: Howard Hu

31

- National University of Singapore, Singapore
- 2017 Lecturer, “Recent Advances in Understanding, Preventing, and Reversing the Impact of Environmental Factors on Health”, Society of Chinese Bioscientists in America, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, ON
- 2017 Lecturer, “Environmental Epidemiology in the Era of Exposomics, Lifecourse Epidemiology, Big Data and Big Science”, Department of Environmental Health, Harvard School of Public Health, Boston, MA
- 2017 Speaker, “The Role of a Re-emergent Canadian School of Public Health in a Hot, Hungry, Polluted, Aging, Polarized World Prone to Pandemics, Chronic Disease, and Unsustainable Health Systems”, Royal Canadian Institute for Science, Toronto, ON
- 2017 Speaker, “The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment”, Seminar Series in Environmental Epidemiology, University of Washington School of Public Health, Seattle, WA
- 2017 Plenary Speaker: “New realities arising from the extractive industries and agri-business: the Pollution and health perspective,” Hong Kong Summit of Global Health Leaders. University of Hong Kong, Hong Kong
- 2018 Plenary Speaker: “The GBD-Pollution and Health Initiative: Challenges & Opportunities”, Workshop on the Global Burden of Disease-Pollution and Health Initiative, Institute for Health Metrics, University of Washington, Seattle, WA
- 2018 Guest Lecturer: “Partnerships, Local Responsiveness, National and Global Impacts”, University of Iowa College of Public Health, Iowa City, IA
- 2018 Plenary Speaker: “Current Research on Fluoride and Neurodevelopment: The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study”, Annual meeting of the International Academy of Oral Medicine and Toxicology, Denver, CO
- 2018 Speaker, “Recent Epidemiologic Research on Lead Toxicity: New Surprises regarding an Old Global Pollutant”, Department of Environmental and Occupational Health Sciences Seminar Series, University of Washington School of Public Health, Seattle, WA
- 2018 Speaker: “The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment”, Symposium on Fluoride research, Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON
- 2018 Panelist, “The Fluoridation Decision: Considering the Evidence for Benefits, Possible Risks as well as Ethical World Views”, Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON
- 2018 Speaker: “Grand Opportunities”, The UC-Irvine School of Population Health and the Samueli College of Health Sciences, Irvine, CA
- 2018 Speaker, “The Global Burden of Disease-Pollution and Health Initiative”, Office of the Director and the Global Environmental Health Program, U.S. National Institute for Environmental Health Sciences, Research Triangle Park, NC
- 2019 Speaker, “Evaluating, treating and managing disabilities of patients with chemical intolerance”, Symposium on Chemical Intolerance—A Way Forward, Marilyn Brachman

CV: Howard Hu, M.D., M.P.H., Sc.D.

CV: Howard Hu

32

Hoffman Foundation and the Hoffman Program on Chemicals and Health at the Harvard T.H. Chan School of Public Health, Dallas, TX

2019 Guest Lecturer: “The Global Burden of Disease-Pollution and Health Initiative”, Center for Population Health Sciences, Stanford University, Palo Alto, CA

INVENTIONS/PATENTS: n/a

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Peer-reviewed journals

1. Hu H, Markowitz SB. A case-study of industrial bladder cancer. *Einstein Quarterly Review of Biology and Medicine* 1982;1:29-35.
2. Hu H. Benzene and myelofibrosis. *Annals of Internal Medicine* 1987;106:171-172
3. Hu H, Milder FL, Burger DE. X-Ray Fluorescence: Issues surrounding the application of a new tool for measuring burden of lead. *Environmental Research* 1989;49:295-317.
4. Hu H, Fine J, Epstein P, Kelsey K, Reynolds P, Walker B. Tear Gas: Harrassing agent or toxic chemical weapon? *JAMA* 1989;262:660-663.
5. Hu H, Cook-Deegan R, Shukri A. The use of chemical weapons: Conducting an investigation using survey epidemiology. *JAMA* 1989;262:640-643.
6. Hu H, Tosteson T, Aufderheide AC, Wittmers L, Burger DE, Milder FL, Schidlovsky G, Jones KW. Distribution of lead in human bone: I. Atomic absorption measurements. *Basic Life Sci* 1990;55:267-274.
7. Burger DE, Milder FL, Morsillo PR, Adams BB, Hu H. Automated bone lead analysis by k-x-ray fluorescence for the clinical environment. *Basic Life Sci* 1990;55:287-292.
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9. Jones KW, Schidlovsky G, Burger DE, Milder FL, Hu H. Distribution of lead in human bone: III. Synchrotron x-ray microscope measurements. *Basic Life Sci* 1990;55:281-286.
10. Hu H, Milder FL, Burger DE. X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposure. *Arch Environ Health* 1990;45:335-341.

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CV: Howard Hu

33

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12. Hu H. A 50-year follow-up of childhood plumbism: hypertension, renal function, and hemoglobin levels among survivors. *Am J Dis Child* 1991;145:681-687.
13. Hu H. Knowledge of diagnosis and reproductive history among survivors of childhood plumbism. *Am J Publ Health* 1991;81:1070-1072.
14. Hu H, Milder FL, Burger DE. The use of K-X-Ray Fluorescence for measuring lead burden in epidemiological studies: high and low lead burdens and measurement uncertainty. *Environ Health Perspect* 1991;94:107-110.
15. Hu H, Pepper L, Goldman R. Effect of repeated occupational exposure to lead, cessation of exposure, and chelation on levels of lead in bone. *Am J Ind Med* 1991;20:723-735.
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21. Hu H, Beckett L, Kelsey K, Christiani D. The left-sided predominance of asbestos-related pleural disease. *Am Rev Resp Dis* 1993;148:981-984.
22. Payton M, Hu H, Sparrow D, Young JB, Landsberg L, Weiss ST. Relation between blood lead and urinary biogenic amines in community-exposed men. *Am J Epidemiol* 1993;138:815-825.
23. Hu H, Kotha S. Ethics and epidemiology: International Guidelines. *Polit Life Sci* 1993;February:29-30.
24. Goldman RH, White R, Kales SN, Hu H. Lead poisoning from mobilization of bone stores during thyrotoxicosis. *Am J Industr Med* 1994;25:417-424.

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CV: Howard Hu

34

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CV: Howard Hu

35

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36

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CV: Howard Hu

37

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CV: Howard Hu

38

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CV: Howard Hu

39

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47

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49

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CV: Howard Hu, M.D., M.P.H., Sc.D.

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58

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CV: Howard Hu, M.D., M.P.H., Sc.D.

C. ANDREW WATERS, ESQ., CA Bar No. 147259
MICHAEL CONNETT, ESQ., CA Bar No. 300314
WATERS, KRAUS & PAUL
222 N. Pacific Coast Hwy, Suite 1900
El Segundo, CA 90245
310-414-8146 Telephone
310-414-8156 Facsimile

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al.,

Plaintiffs,

vs.

U.S. ENVIRONMENTAL PROTECTION
AGENCY, et al.

Defendants.

Civ. No. 17-CV-02162-EMC

**DECLARATION OF
BRUCE LANPHEAR, MD, MPH**

DECLARATION OF BRUCE LANPHEAR, MD, MPH

TABLE OF CONTENTS

I. SUMMARY OF QUALIFICATIONS1

II. SUMMARY OF OPINIONS3

III. BASIS FOR OPINIONS.....4

 A. The Growing Problem with Brain-Based Disorders4

 B. The MIREC Cohort Is a Comprehensively Characterized Birth Cohort5

 C. Urinary Fluoride Study (Till 2018).....6

 1. Methodological Strengths6

 2. Fluoridated Water Has a Large and Significant Effect on Urinary Fluoride.....7

 3. Pregnant Women in Water-Fluoridated Areas of the MIREC Cohort Have Similar Urinary Fluoride Levels as the ELEMENT Cohort.....8

 D. Prenatal Fluoride/IQ Study (Green 2019).....8

 1. Methodological Strengths8

 2. Prenatal Fluoride Exposure Is Associated with Large and Significant Reductions in IQ in the MIREC Cohort.....11

 3. Convergent Findings of ELEMENT and MIREC Cohorts.....13

 E. Infant Fluoride/IQ Study (Till 2020)13

 1. Methodological Strengths14

 2. Fluoride Exposure During Infancy Is Associated with Significant Reductions in Non-Verbal IQ in the MIREC Cohort15

 F. The Limitations of Our Studies Do Not Provide a Likely Explanation for the Results.....16

IV. CONCLUSION.....18

REFERENCES19

I, Bruce Lanphear, MD, MPH, declare that:

1. I am a Clinical Investigator at the BC Children's Hospital Research Institute, BC Children's Hospital, and Professor in the Faculty of Health Sciences at Simon Fraser University in Vancouver, British Columbia.

2. I am also the Co-Principal Investigator of an ongoing study to examine the impact of early-life fluoride exposures on intellectual abilities in a cohort of mothers and offspring from Canada known as the MIREC Study. Our study of fluoride and IQ in the MIREC cohort was funded by a grant from the U.S. National Institutes of Health (NIH).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 6 and attached herein.

4. I have studied the impact of toxic chemicals, including lead and pesticides, on children's brain development for over 20 years. My research has been almost exclusively funded by federal agencies, including the Environmental Protection Agency (EPA), Centers for Disease Control and Prevention, the Department of Housing and Urban Development, Health Canada, National Institute of Allergy and Infectious Diseases, National Institute for Child Health and Human Development, National Institute of Environmental Health Sciences, National Institute of Neurologic Diseases, and the National Heart, Lung and Blood Institute.

5. My research has been published in leading medical and scientific journals, including *Journal of the American Medical Association*, *New England Journal of Medicine*, and *Pediatrics*, and has been extensively relied upon by environmental and public health agencies, including the EPA. My pooled analysis of blood lead and IQ (Lanphear 2005) was cited by the EPA as the critical study upon which the Agency based the current national air standard for lead.

1 6. I have served on the editorial boards of seven academic journals, including *Public Health*
2 *Reports* (the official journal of the U.S. Surgeon General), *PLoS Medicine* (a peer-reviewed medical
3 journal published by the Public Library of Science), and *Environmental Health Perspectives* (a journal
4 funded by the National Institutes of Environmental Health Sciences).

5 7. I have served on numerous scientific committees on environmental health issues impacting
6 children, including multiple scientific advisory boards for the EPA and the Executive Council on
7 Environmental Health for the American Academy of Pediatrics. My work with the EPA has included
8 invited expert advisory roles on EPA's (i) Science and Research Work Group of the Children's Health
9 Protection Advisory Committee (1998-2001); (ii) Workshop on Assessing Environmental Exposures to
10 Children (2000-2002); (iii) Clean Air Scientific Advisory Committee (2006-2008); (iv) Science Advisory
11 Board for Evaluating Dust Lead Standards (2010-2012); and (v) Science Advisory Board for Evaluating
12 Hazards of Partial Water Line Replacement (2011-2012).

13
14 8. My research has earned various awards and honors, including the Research Integrity Award
15 from the International Society for Environmental Epidemiology in 2012, the Public Policy and Advocacy
16 Award from the Academic Pediatric Association in 2013, and the Research Award from the Academic
17 Pediatric Association in 2015.

18
19 9. I have been involved with the MIREC Study for over 10 years. I was a Co-Principal
20 Investigator for the neurobehavioral assessments conducted when the children were 3 to 4 years old and I
21 oversaw the neurodevelopmental assessments in Vancouver. I have been a coauthor of twelve publications
22 from the MIREC Study, including three publications on fluoride described below.

23
24 10. In light of the consistent association between elevated fluoride and IQ reported in cross-
25 sectional studies (Choi, et al. 2012), we received a grant from the NIH to study the association between
26 prenatal and early-life measures of fluoride and IQ in children in the MIREC cohort. To date, we have
27

1 published three peer-reviewed studies, including the most extensive assessment of fluoride exposure
2 during pregnancy ever conducted and prospective studies on early life fluoride exposure on IQ. These
3 studies have been published in *Environmental Health Perspectives*, *JAMA Pediatrics*, and *Environment*
4 *International* (Till 2018, Green 2019, Till 2020). Our study on prenatal fluoride and IQ was the highest
5 scoring study in *JAMA Pediatrics* in 2019 (Christakis 2020).

6 11. I agreed to participate as a non-retained expert in this case because I believe it is a public
7 duty to present the results of studies that suggest substantial risk to public health. I have asked *not* to be
8 compensated for this work.
9

10 II. SUMMARY OF OPINIONS

11 12. Our study of prenatal fluoride and IQ in the MIREC cohort (Green 2019) further enhances
12 the quality of data related to the neurotoxicity of fluoride. As with the ELEMENT cohort, we employed a
13 prospective cohort design, had extensive control for potential confounders, and had multiple measures of
14 fluoride exposure during pregnancy, including three types of urinary fluoride measurements for each
15 trimester of pregnancy.
16

17 13. The maternal urinary fluoride levels in the MIREC cohort were significantly associated
18 with lower intellectual abilities in 3-4-year-old children. These associations remain large and significant
19 when controlling for relevant covariates.

20 14. Converging results from the MIREC and ELEMENT cohorts indicate that exposure to
21 “optimal” levels of fluoride during fetal development is associated with diminished intelligence in
22 childhood.
23

24 15. In the MIREC cohort, exposure to fluoridated water in infancy, particularly among
25 formula-fed infants, was also associated with diminished intelligence (Till 2020). This association remains
26 significant after controlling for fetal fluoride exposure and other relevant covariates, suggesting that
27

1 susceptibility to fluoride's adverse neurological effects may extend into infancy.

2 **III. BASIS FOR OPINIONS**

3 **A. The Growing Problem with Brain-Based Disorders**

4 16. As I have discussed elsewhere, the causes of death and disability in children have shifted
5 over the past century (Lanphear 2015). Concerted public health efforts to control tuberculosis, cholera,
6 typhoid, and other infectious agents in the early twentieth century led to a dramatic reduction in child
7 mortality, followed by a rise in life expectancy. By the end of the twentieth century, the 'new morbidities
8 of childhood' had emerged: attention deficit hyperactivity disorder (ADHD), autism, asthma, obesity, and
9 preterm birth. Learning disabilities and neurodevelopmental disorders are now two of the most prevalent
10 morbidities in children. About 7.6% of US children are estimated to have a learning disability, and 13%
11 are estimated to have a neurodevelopmental disorder, including anxiety, autism, conduct disorder,
12 depression, or ADHD (Lanphear 2015). These data indicate that we are in the midst of an epidemic of
13 brain-based disorders.
14

15 17. Neurotoxicants can have a lifelong impact on brain function. Children who have higher
16 blood lead concentrations, for example, may never meet the same peak cognitive ability in adulthood as
17 that in less exposed children. At the other end of the age spectrum, cognitive decline is accelerated in
18 adults who have higher bone lead concentrations and some evidence has shown that lead exposure is a
19 risk factor for the development of late-onset Alzheimer's disease. Few birth cohorts have been studied
20 into adulthood; however, it would be surprising if the effects of other neurotoxicants observed in school-
21 aged children do not persist into adulthood (Lanphear 2015). The cumulative impact of exposures to
22 various toxins that only modestly impact intellectual abilities can be substantial (Lanphear 2015).
23

24 18. The high reported prevalence of learning disabilities and neurodevelopmental disorders has
25 fueled research to better understand the role of environmental chemicals, including the use of prospective
26
27

1 cohort studies that collect individualized biomarkers of exposure to environmental toxins. Biologic
2 markers, or biomarkers, of exposure, which can enhance our ability to quantify an individual's internal
3 dose of a contaminant, are revolutionizing the study of environmental toxins in the same way genetic tests
4 are revolutionizing the study of heritability (Lanphear 2015).

5 **B. The MIREC Cohort Is a Comprehensively Characterized Birth Cohort**

6 19. The MIREC¹ cohort in Canada was developed to obtain biomonitoring data for pregnant
7 women and their infants to examine potential adverse health effects of early-life exposure to
8 environmental chemicals.

9 20. The MIREC cohort is a geographically diverse and comprehensively characterized birth
10 cohort. Women were recruited during the first trimester of pregnancy from 10 cities across Canada,
11 including cities that add fluoride to water for caries prevention purposes (e.g., Toronto), and cities that do
12 not (e.g., Vancouver). Women were followed through delivery and their offspring have undergone
13 periodic neurodevelopmental tests, including IQ testing.

14 21. We administered questionnaires during pregnancy and early childhood to collect
15 information on demographics, occupation, lifestyle, medical history, environmental exposures and diet.
16 Dietary questions included whether the mother drank tap water during pregnancy, how many glasses of
17 water and other beverages she consumed, and duration of breastfeeding.

18 22. Information on the pregnancy and the infant was abstracted from medical charts. Maternal
19 urine was collected at multiple points throughout pregnancy, as was blood, urine, hair, breast milk, cord
20 blood and infant meconium. These samples have been archived in a biobank.

21 23. Study staff from each participating study site completed a 3-day training session that was
22

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¹ MIREC stands for Maternal-Infant Research on Environmental Chemicals. It is an
26 interdisciplinary collaboration between Health Canada scientists and clinical and academic researchers,
27 and was funded by Health Canada, the Ontario Ministry of the Environment, and a grant from the
28 Canadian Institutes of Health Research.

led by a PhD-level psychologist and focused on specialized training of the neurodevelopmental tests. The training emphasized the importance of providing an ideal and standardized environment in the home by ensuring that the test area was well-lit, quiet, and free from distractions and interruptions.

C. Urinary Fluoride Study (Till 2018)

24. In 2018, we published the most comprehensive study of urinary fluoride during pregnancy that has ever been conducted (Till 2018). Our study included 1,566 pregnant women from the MIREC cohort who had urine samples for each trimester of pregnancy. It was the first study of its kind in water-fluoridated areas of North America. A similar study has recently been published of a smaller pregnancy cohort in California (Uyghurturk 2020), but our study remains the largest and most thorough.

1. Methodological Strengths

25. Our study of urinary fluoride was conducted in accordance with sound and objective science practices. Important strengths of the study include: (1) a large study size, with over 1,500 women and over 5,000 urine samples; (2) collection of urine samples from each trimester for each mother; (3) empirical data on the actual measured water fluoride levels for each mother's water treatment plant boundary (WTP) during the course of the pregnancy; (4) control for other factors that have potential to influence urinary fluoride excretion, including tea consumption, alcohol use, pre-pregnancy BMI, maternal age, maternal education, annual household income, and race; (5) control for fluctuations that can occur in urine fluoride during the day by adjusting for dilution using two methods (specific gravity and creatinine) and controlling for time of void and time since last void; and (6) measurement of fluoride in urine using the same scientist (Dr. Martinez-Mier), method (microdiffusion), and laboratory (University of Indiana) as the ELEMENT cohort, thereby enhancing the comparability of the data.

26. Dr. Martinez-Mier's lab at the University of Indiana is considered a gold-standard lab for the testing of fluoride in urine and blood. EPA appears to recognize Dr. Martinez-Mier's expertise as she

was approached by EPA to serve as an expert in this case.

2. Fluoridated Water Has a Large and Significant Effect on Urinary Fluoride

27. In our study, fluoride in water had the strongest correlation with urine fluoride of all the factors that we measured, thus confirming that fluoridated water remains a major source of fluoride intake (Till, 2018).

28. The average urinary fluoride level among pregnant women in fluoridated areas is almost two times higher than the average levels in nonfluoridated areas (Till 2018).

29. The average creatinine-adjusted² maternal urinary fluoride level in the fluoridated areas is 0.87 mg/L, versus 0.46 mg/L in the non-fluoridated areas.³

30. Our data suggests that, for every 0.5 mg/L increase in water fluoride level, urinary fluoride levels will increase by 74-82%.

31. Our findings are consistent with prior studies showing that, among adults, fluoride levels in urine are closely correlated with the concentration of fluoride in water.

32. As part of our study, we attached a table showing the full distribution of urinary fluoride levels, including the 75th and 95th percentile exposures for each trimester (Till et al. 2018, Table S4). At the second trimester, 95th percentile values in the fluoridated areas were 2 mg/L (adjusted for creatinine), and 1.63 mg/L (adjusted for specific gravity).

² Creatinine-adjustment of spot urine samples adjusts for dilution and has been found to have good agreement with 24-hour fluoride values (WHO 2014, Zohouri 2006). We used the same method for creatinine adjustment as Bashash (2017). We also adjusted for dilution by correcting for specific gravity. Our adjustments for creatinine and specific gravity produced results that were highly correlated ($r = 0.91$) and interchangeable in our analyses of the factors that increase urinary fluoride.

³ The average specific gravity-adjusted concentration in the fluoridated areas was 0.71 mg/L (SD 0.38 mg/L), with a range of 0.10 to 3.12 mg/L.

3. Pregnant Women in Water-Fluoridated Areas of the MIREC Cohort Have Similar Urinary Fluoride Levels as the ELEMENT Cohort

33. One of the key findings from our 2018 study is that pregnant women who live in water-fluoridated areas of Canada have urinary fluoride levels that are essentially the same as the urinary fluoride levels documented in the ELEMENT cohort.

34. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts can be appreciated when comparing the respective mean values (0.87 vs. 0.91 mg/L), standard deviations (0.50 vs. 0.40 mg/L), and ranges (0.14-3.80 vs. 0.02-3.67 mg/L) of the study participants in the water fluoridated areas of the MIREC cohort vs. the ELEMENT cohort.

35. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts is of scientific and public health relevance given the findings of Bashash (2017) showing an inverse association between maternal urinary fluoride and offspring IQ.

D. Prenatal Fluoride/IQ Study (Green 2019)

36. In 2019, we published our findings on the relationship between prenatal fluoride exposure and IQ in the MIREC cohort. The study, which was published in *JAMA Pediatrics*, provides reliable and unbiased results and was conducted in accordance with sound and objective science practices.

1. Methodological Strengths

37. ***Prospective Birth Cohort Study Design:*** A key strength with our study is that we used a prospective cohort study design, also known as a longitudinal study. Prospective studies are the best available method for investigating the impact of environmental chemicals and, as noted earlier, have helped to revolutionize our understanding of how chemicals impact childhood health.

38. ***Extensive Control for Potential Confounders:*** The MIREC cohort is one of the most comprehensively characterized birth cohorts, with abundant individualized data on factors that may influence neurodevelopment. We took full advantage of this data. We excluded study participants if there

was a known fetal abnormality, if they had any medical complications (i.e., cancer, renal disease, cardiovascular disease), or if there was known maternal alcohol or drug abuse during pregnancy. For analyses using water fluoride, we excluded women if they did not drink tap water during their pregnancy. For those not excluded, we controlled for the following factors: maternal education; maternal age; quality of the child's home environment (HOME); child sex; mother's race; city of residence; secondhand smoke; maternal blood or urinary concentrations of other neurotoxicants, such as lead, arsenic, mercury, manganese, and PFOA. Additionally, we controlled for the diurnal fluctuations that may occur in urinary fluoride levels by including time of day that the urine sample was collected and time since last void.

39. ***Individualized Measures of Fluoride Exposure:*** Another important strength of our study is that we had multiple individualized measures of prenatal fluoride exposure, including: (1) urinary fluoride samples averaged across each trimester of pregnancy and corrected for urinary dilution; (2) measured water fluoride levels from within each participant's water treatment plant boundary during the course of their pregnancy;⁴ and (3) questionnaire data about how much water each woman drank from tap water and water-based beverages.

40. ***Large, Multi-Center Cohort:*** Our study included 512 mother-offspring pairs which is a robust sample size for statistical analyses. Further, the mother-offspring pairs came from 6 cities across Canada, some of which fluoridate their water (average F = 0.59 mg/L), and some of which do not (average F = 0.13 mg/L).⁵ Our study thus permitted us to examine the impact of fluoride exposures on IQ in communities with water fluoridation, thus addressing what some have perceived to be a limitation of prior

⁴ Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water. We matched participants' postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) during the duration of pregnancy.

⁵ Pregnant women in the fluoridated areas tended to have higher incomes and more education, which may help explain the lack of difference in average *unadjusted* IQs between fluoridated and non-fluoridated areas (Green 2019, Table 1).

studies of fluoride neurotoxicity.

41. ***Reliable and Objective IQ Test:*** We assessed children’s intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). This is a validated IQ test with excellent internal reliability ($r = 0.96$), and good test-retest reliability ($r = 0.86$). We used Full Scale IQ (FSIQ), which is a measure of global intellectual functioning, as the primary outcome. The FSIQ score is comprised of two composite scores: Verbal IQ (VIQ)—representing verbal reasoning and comprehension—and Performance IQ (PIQ)—representing nonverbal reasoning, spatial processing, and visual-motor skills.

42. ***Blinded Assessments:*** As with the ELEMENT cohort, our study was “blinded,” meaning the examiners were not aware of the mother’s fluoride exposure status at the time of the examination. This eliminates the potential for examiner bias.

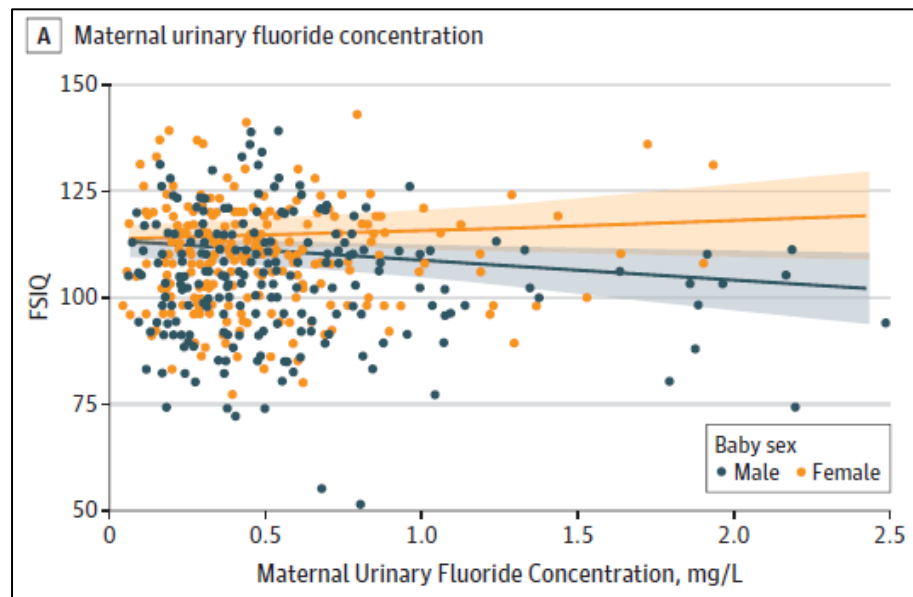
43. ***Statistical Analyses that Did Not Assume Linearity:*** We conducted sound, objective, and rigorous statistical analyses that: (i) controlled for the impact of the large number of measured covariates; (ii) examined the data for collinearity, outliers, and influential points; and (iii) scrutinized the shape of the relationship between fluoride and IQ. With respect to linearity and possible threshold effects, we conducted sensitivity analyses that used quadratic and natural log effect models as well as ran spline analyses that examined the relationship below 0.5 mg/L, 0.8 mg/L, and 1.0 mg/L in urine (and below 0.4 mg/day and 0.8 mg/day in fluoride intake). We did *not* assume that statistical associations between fluoride and IQ were linear and without threshold.

44. Short of intentionally dosing pregnant mothers with fluoride, we maximized the power of environmental epidemiology to investigate whether prenatal fluoride exposure is associated with neurocognitive deficits in a prospective, observational cohort study.

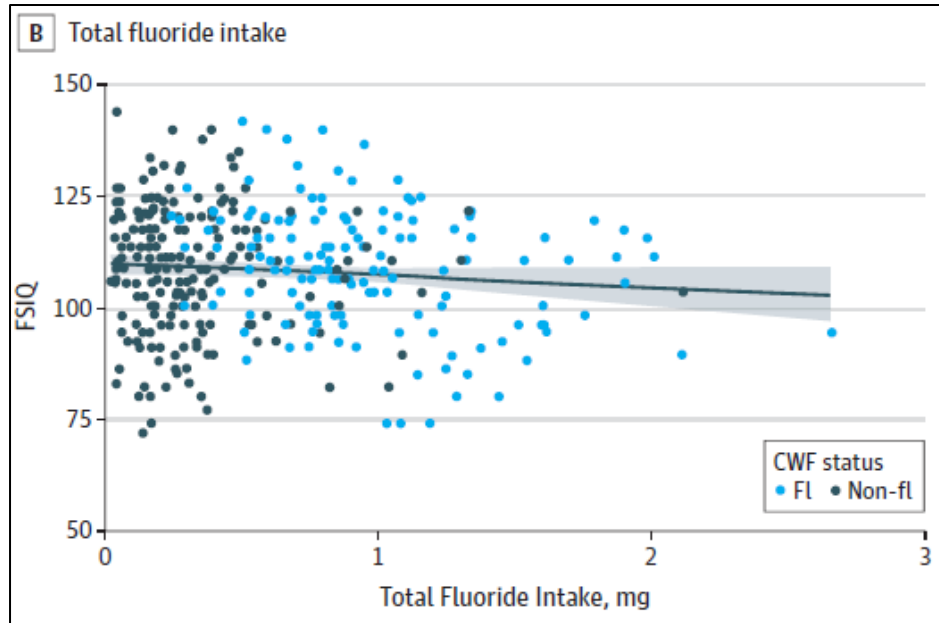
2. Prenatal Fluoride Exposure Is Associated with Large and Significant Reductions in IQ in the MIREC Cohort

45. All three measures of prenatal fluoride exposure—(i) maternal urinary fluoride, (ii) maternal fluoride intake from beverages, and (iii) water fluoride concentration during pregnancy—were associated with large, statistically significant decreases in IQ among the 3 to 4-year old children in the MIREC cohort.

46. After controlling for covariates, a 1-mg/L increase in maternal urinary fluoride⁶ was associated with a **4.49 lower IQ** score (in boys); a 1-mg higher daily intake of fluoride from beverages was associated with a **3.66 lower IQ** score (in boys and girls); and a 1 mg/L higher water fluoride concentration was associated with a **5.29 lower IQ** score (in boys and girls). These fluoride-associated reductions in IQ that we found showed a linear, dose-response relationship with no apparent indication of a threshold (see figures below).



⁶ We used specific gravity (SG) as the primary adjustment method for this study. The average SG-adjusted concentration among women from the fluoridated areas was 0.69 mg/L (SD = 0.42), which is consistent with the concentration in fluoridated areas from the larger cohort (0.71 mg/L, SD = 0.38) (Till 2018). Sensitivity analyses using the creatinine-adjusted urinary fluoride values did not change the results between fluoride and IQ (Green 2019, eTable 2).



47. The effect sizes that we found are large and rival the impact of a population blood lead concentration of 5 $\mu\text{g}/\text{dL}$.⁷ Fourteen percent of the women had urinary fluoride concentrations exceeding 1.0 mg/L, and thus the impact for some children may exceed the ranges identified above.

48. Although maternal urinary fluoride was associated with significant reduction in full-scale IQ in boys, it was not associated with diminished full-scale IQ in girls. As is often the case, the reason for this discrepancy is not currently known. It is known, however, that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities than girls. It is also known that boys and girls may respond differently to some neurotoxicants. In our studies of the MIREC cohort, for example, we found that low levels of blood lead correlate with a loss of IQ in boys, but not girls (Desrochers-Couture 2018).

49. The possibility that boys are more sensitive to prenatal fluoride exposure than girls is

⁷ My pooled analysis of blood lead and IQ found that an increase in childhood blood lead from <1 to 10 $\mu\text{g}/\text{dL}$ was associated with a 6.9 IQ point decrement (Lanphear 2015, p. 814). General population exposures to lead today are now on the low-to-mid range of this spectrum, with relatively few children having blood lead levels as high as 10 $\mu\text{g}/\text{dL}$.

supported by at least one animal study, in which males had greater deficits from prenatal exposure and females had greater deficits from postnatal exposure (Mullenix et al 1995). While we did not find sex-specific differences with our other two exposure measures (water F concentration and water F intake), these other measures may better correlate with chronic or postnatal exposure and thereby reflect distinct risks.

3. Convergent Findings of ELEMENT and MIREC Cohorts.

50. The significant associations we observed between prenatal fluoride and IQ in the MIREC cohort are consistent with the findings from the ELEMENT cohort (Bashash, 2017).

51. In the ELEMENT study, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 6.3 IQ points among 4-year olds, as measured by General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities. In our analysis, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 4.96 IQ points among 3- to 4-year old boys, as measured by the WPPSI-III test (Green 2019, eTable 2). These effect sizes are generally consistent with each other.

52. The consistency of results in both population cohorts adds further confidence that the association is real, particularly when viewed in the context of other studies that have reported inverse associations between fluoride and IQ in many different locations in other countries, as well as general knowledge about the vulnerability of the developing brain.

E. Infant Fluoride/IQ Study (Till 2020)

53. We recently completed and published a study that examined whether fluoride exposures during infancy have an influence on IQ at 3-4 years (Till 2020).

54. Concerns have been raised about the use of fluoridated water in baby formula due to the high intake of water by bodyweight during infancy. These high intakes have been associated with

significant increases in dental fluorosis, including in the permanent teeth.

55. In our study, we obtained information about fluoride intake of infants through questionnaires that the mothers completed when the children were 30 to 48 months of age.⁸ The questionnaire included the question, “How old was your baby when you ceased breastfeeding exclusively?” Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

56. As a separate measure of infant fluoride exposure, we estimated fluoride intake by obtaining the measured water fluoride levels within the water treatment plant boundary during infancy. We took the average of these levels, multiplied by the amount of time that the infant was not exclusively breast-fed during the first year,⁹ and divided it by the estimated average water intake among Canadian formula-fed infants (0.8 L). We excluded any mother-offspring pair if the mother reported not drinking tap water.

1. Methodological Strengths

57. Our study of infants shares many of the same methodological strengths as our prenatal study, including: (i) prospective cohort design; (2) extensive control for potential confounders (discussed below); (3) blinded assessment; (4) relatively large cohort (398 mother-offspring pairs) from both fluoridated and non-fluoridated areas; (5) the same validated and standardized IQ test that we used for the prenatal study (i.e., Wechsler Primary and Preschool Scale of Intelligence-III); and (6) rigorous statistical

⁸ The answers to these questions correlated well with the contemporaneous infant feeding practices that were reported among 11% of the cohort. Among women with breastfeeding questionnaire data and infant feeding observation data, the median difference for when breast-feeding ceased was 0 months, with two-thirds being within 1.5 months of each other.

⁹ The mean duration of exclusive breastfeeding was 4.98 months; 13.6% of women reported never breastfeeding, 8% reported discontinuing breastfeeding after the first three months, and 50.2% reported continuing to breastfeed at six months or longer. Average water fluoride concentration did not significantly differ between the BF (mean=0.32 mg/L) and FF groups (mean=0.29 mg/L; p=.18).

analyses that tested for sex-specific effects and scrutinized the impact of outliers and influential points.

58. We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates¹⁰ included child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME)). We also controlled for fetal fluoride exposure, using the previously measured maternal urinary fluoride concentrations averaged across each trimester of pregnancy.

2. Fluoride Exposure During Infancy Is Associated with Significant Reductions in Non-Verbal IQ in the MIREC Cohort

59. We found that fluoride exposure during infancy is associated with significant reductions in non-verbal IQ in the MIREC cohort.

60. For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 Full-Scale IQ (FSIQ) points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among children who were exclusively breastfed in the first 6 months.

61. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became nonsignificant when two outliers were removed.

62. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in non-verbal IQ in both

¹⁰ For each analysis, a covariate was retained in the final model if its p-value was <0.20 or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10%.

1 the formula-fed (**9.3-points**) and the breastfed groups (**6.2-points**). Adjusting for fetal exposure or
2 removing two extreme scores did not appreciably alter these results.

3 63. We observed converging results using fluoride intake from formula feeding, which is a
4 continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an **8.8-**
5 **point** decrement in non-verbal IQ; adjusting for fetal exposure attenuated the association only slightly
6 (**7.6-point** decrement).

7 64. The time-weighted fluoride intake estimate may reflect a more refined measure of exposure
8 in infancy because it captures differences in both water fluoride level and the proportion of time each child
9 was given formula over the first year of life. Yet, our binary classification of whether a child was
10 exclusively breastfed for the first 6 months may distinguish infants who are exposed to higher amounts of
11 fluoride during the early infancy period when the brain undergoes significant development because breast
12 milk contains minutes amounts of fluoride.

13 65. Taken together, these findings suggest that using “optimally” fluoridated water (0.7 mg/L)
14 to reconstitute infant formula may diminish the development of intellectual abilities in young children,
15 particularly non-verbal abilities. The findings also suggest that both prenatal and early childhood fluoride
16 exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence.
17 Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern.
18

19
20 **F. The Limitations of Our Studies Do Not Provide a Likely Explanation for the**
21 **Results**

22 66. As with all epidemiological studies, our fluoride studies have limitations. These
23 limitations, however, are unlikely to explain the large and significant associations that we have found
24 between early-life exposures and IQ.

25 67. Most of the limitations in our studies involve fluoride measurement. These limitations
26
27

1 include: (1) use of spot urine samples instead of 24-hour samples;¹¹ (2) lack of water fluoride
2 measurements from the participant's home; (3) reliance on questionnaire data as to water consumption
3 and breast-feeding; (4) lack of information on the fluoride content of the infant formula concentrate and
4 other sources of fluoride exposure; and (5) use of non-validated methods¹² for estimating total beverage-
5 based intake of fluoride by mothers and water fluoride intake by infants.

6 68. The limitations in our exposure estimates are non-differential, meaning they apply equally
7 to study participants with low fluoride exposure and high fluoride exposure. Non-differential errors in
8 exposure measurement will generally bias the results towards the null (i.e., attenuate, rather than inflate,
9 an association between exposure and outcome). Because of this, the limitations in our exposure estimates
10 do not provide a likely explanation for the significant IQ decrements we observed with fluoride exposures.
11 If anything, these limitations likely attenuated the relationship.
12

13 69. Another limitation of our studies is that the MIREC cohort tends to be more affluent, more
14 educated, and less ethnically diverse than the general population. Our results may thus not be
15 representative of how fluoride may affect IQ in more disadvantaged populations. On the other hand,
16 affluent populations tend to have less confounders (e.g., less exposure to other stressors and toxicants that
17 can negatively affect neurodevelopment) (Lanphear 2015). We thus worry less about the role of
18 confounders in the MIREC cohort than we would in other cohorts.
19

20 70. Finally, despite our comprehensive array of covariates included, our studies could not
21 address the possibility of unmeasured residual confounding. This is a limitation in all observational
22

23 ¹¹ A 24-hour sample of urine is considered the optimal dosimeter for measuring chronic fluoride
24 exposure (WHO 2014). While we did not have 24-hour samples available to test, we partially controlled
25 for this by adjusting samples by creatinine. Creatine-adjusted urine fluoride measurements have been
26 found to have a strong correlation with 24-hour samples (Villa 2010; Zohouri 2006).

27 ¹² These methods were not validated in the sense that they have not yet been replicated by other
28 authors in other studies. Our method for assessing fluoride intake from beverages did show internal
validity, however, by predicting maternal urinary fluoride levels. This can be seen in the highly significant
correlations that we found ($p < 0.0001$) between maternal urinary fluoride and number of glasses of water
consumed per day and black tea consumption (see Till 2018).

1 studies, and thus inherent to the field. One of the potential confounders for which we lacked data was
2 maternal IQ. We did, however, control for maternal education which is highly correlated with maternal
3 IQ. Moreover, a greater proportion of women living in fluoridated communities (76%) had a university-
4 level degree compared with women living in nonfluoridated communities (66%), and thus it seems
5 unlikely that controlling for maternal IQ would affect our results, particularly since there is no reason to
6 believe that maternal IQ would be correlated with maternal urinary fluoride.

7
8 71. I understand that the EPA has suggested that the location of our study in Canada somehow
9 reduces the relevance of our findings to populations in the US. I disagree. From a biologic standpoint,
10 there is no credible basis to believe that people in the U.S. will respond differently to fluoride than people
11 in Canada. Nor am I aware of any credible reason to conclude, let alone suspect, that people in water-
12 fluoridated areas of the U.S. are exposed to materially less fluoride than people in water-fluoridated cities
13 of Canada.

14 IV. CONCLUSION

15 72. The collective evidence from prospective cohort studies supports the conclusion that
16 fluoride exposure during early brain development diminishes the intellectual abilities in young children,
17 including at the purportedly “optimal” levels of exposure for caries prevention.
18

19
20 I declare under penalty of perjury, under the laws of the United States, that the foregoing is true
21 and correct to the best of my knowledge and belief.

22 Executed on May 20, 2020, in Vancouver, British Columbia, Canada.
23

24
25 

26 BRUCE LANPHEAR, MD, MPH
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**CURRICULUM VITAE OF
BRUCE LANPHEAR, MD, MPH**

CURRICULUM VITAE

Bruce Perrin Lanphear, MD, MPH

Office Address

Blusson Hall
8888 University Drive
Burnaby, BC V5A 1S6
Canada
e-mail: blanchephear@sfu.ca

Marital status: Married to Nancy Ebbesmeyer Lanphear, M.D., a developmental pediatrician

Citizenship: United States of America and Canada (dual citizenship)

Specialty: Board Certified in General Preventive Medicine & Public Health

Employment

1984-1986	Paramedic, Jackson County Jail, Kansas City, Missouri
1988-1989	Physician, International Travel Clinic, University of Cincinnati, Cincinnati, Ohio
1988-1989	Staff Physician, Sexually Transmitted Disease Clinic, Cincinnati Public Health Department, Cincinnati, Ohio
1989-1992	Assistant Professor of Environmental Health, Associate Director, Medical Center Health Services, University of Cincinnati
1992-1997	Senior Instructor, Departments of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1992-1994	National Research Scholar Award in General Pediatric Research, University of Rochester School of Medicine and Dentistry.
1992-1997	Assistant Professor, Department of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1997-2002	Associate Professor, Department of Pediatrics, Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, Ohio.
1997-2008	Director, General Pediatric Research Fellowship Training Program, Children's Hospital Medical Center and the University of Cincinnati.
1997-2008	Director, Children's Environmental Health Center, Children's Hospital Medical Center and the University of Cincinnati.
1997-2006	Associate Professor (Adjunct), Departments of Pediatrics and of Environmental Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY.
1998-2003	Associate Director for Research, Division of General & Community Pediatrics, Children's Hospital Medical Center.
2001-2002	Associate Professor (tenured), Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
2001-2004	Associate Professor (Adjunct), Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan.
2002-2008	Sloan Professor of Children's Environmental Health, Departments of Pediatrics and Environmental Health, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

2008-2012 Adjunct Professor of Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati.
 2008- Professor of Children's Environmental Health, Faculty of Health Sciences, Simon Fraser University
 2008- Clinician Scientist, Child & Family Research Institute, BC Children's Hospital, University of British Columbia

Education

1980-1985 Bachelor of Arts in Biology
 1980-1986 University of Missouri at Kansas City, Medical Degree (1986)
 1986-1987 Internship, University of Arkansas for Medical Sciences, Little Rock, Arkansas
 1987-1988 Tulane School of Public Health & Tropical Medicine
 Masters in Public Health & Tropical Medicine
 1987-1989 General Preventive Medicine and Public Health Residency
 Tulane School of Public Health & Tropical Medicine
 1992-1995 Postdoctoral Fellowship in General Academic Pediatric Research
 University of Rochester School of Medicine, Rochester, NY

Awards and Honors

2011 Sterling Prize in Controversy, Simon Fraser University
 2012 Research Integrity Award, International Society for Environmental Epidemiology
 2013 Public Policy and Advocacy Award, Academic Pediatric Association
 2015 Research Award, Academic Pediatric Association
 2015 Confederation of Union Faculty Associations of British Columbia (CUFA-BC) Academic of the Year Award
 2018 Lumina Award from the Women for Healthy Environmental Health, Pittsburgh, PA

Teaching Experience

1992-1997 Course Instructor, "Public Health & the Environment", Department of Community & Preventive Medicine, The University of Rochester School of Medicine and Dentistry. A required course for MPH students taught annually.
 1997-2008 Founding Director, NIH-funded, General Academic and Community Pediatric Research Fellowship Training Program, Cincinnati Children's Hospital Medical Center. This interdisciplinary, research training program, which included pediatricians, psychologists and epidemiologists, was the first training program in Children's Environmental Health.
 1998-2008 Course Co-Instructor, "Children's Health & the Environment", Department of Environmental Health, The University of Cincinnati School of Medicine. A course taught every other year to MPH, PhD and postdoctoral trainees in medical subspecialties.
 2008- Course Instructor, "Children's Health and the Environment". A 2-week intensive course taught annually to 4th year undergraduate students at Simon Fraser University.
 2011- Course Instructor, "Plagues, Pollutants and Poverty: The Origins and Evolution of Public Health". An undergraduate course at Simon Fraser University.

Committee and Community Involvement

1993-1997	Lead Poisoning Prevention Task Force, Monroe County Health Department.
1994-1997	Investigational Review Board, Rochester General Hospital
1995-	Scientific Consultant, National Center for Healthy Housing, Columbia, Maryland.
1996-1997	Member, New York State Task Force on Environmental Neurotoxins, University of Rochester School of Medicine
1996-2001	Member, National Institute for Environmental Health Sciences Grant Review Committee for Community-Based Interventions (FG)
1996-1998	Chairman, U.S. Department of Housing and Urban Development Committee on Lead-Contaminated House Dust
1998	Member, Review Group for National Research Service Awards, Health Resources and Services Administration
1998-2000	Member, Cincinnati Board of Health, Cincinnati, Ohio.
1998-2001	Member, Science and Research Work Group, Office of Children's Health Protection Advisory Committee, U.S. EPA
1998-2000	Member, Cincinnati Lead Poisoning Prevention Advisory Task Force, Cincinnati, Ohio.
1999	Member, K23 Grant Review Committee, National Institute for Environmental Health Sciences, August 1999
1999	Member, Expert Panel on Soil Pica Behavior, Agency for Toxic Substance Disease Registry, June 7 th -8 th , Atlanta, Georgia
2000	Member, Panel on Health Disparities: Linking Biological and Behavioral Mechanisms with Social and Physical Environments, National Institute for Environmental Health Sciences, July 14-15 th
2000-2002	Member, Workshop on Assessing Environmental Exposures to Children, U.S. Environmental Protection Agency, July 26-27 th
2000-2004	Member, Children's Environmental Health Project, AAP's Child Health Research Center, Rochester, NY.
2001	Senate Testimony, "Ensuring that Children with Dangerous Levels of Lead in their Blood Receive Care as Early as Possible". Subcommittee on Housing and Transportation of the Committee on Banking, Housing and Urban Affairs, 107 th U.S. Congress, November 13 th , 2001.
2001	Reviewer, National Research Council, National Academy of Science Update of the 1999 Arsenic in Drinking Water Report
2001-2003	Member, Expert Panel on Children's Health and the Environment, North American Commission for Environmental Cooperation
2002-	Member, Scientific Advisory Board, Scientist Communication Network.
2003	Member, "Herculaneum Health Study Workshop" Agency for Toxic Substance Diseases Registry, May 22 nd to 23 rd , 2003
2003-2004	Panel Member, "Lead Poisoning in Pregnant Women", Mt. Sinai for Children's Health and the Environment, New York, NY
2003	Member, "Invitational Workshop on a proposed American Family Study" National Human Genome Research Institute, December 1 st to 3 rd , 2003.

2004-2006 Member, Committee on “Ethical Consideration for Research on Housing-Related Health-Hazards involving Children”, National Research Council and the Institute of Medicine, The National Academies

2004 Congressional Testimony, “Tapped Out? Lead in the District of Columbia and the Providing of Safe Drinking Water”, Subcommittee on Environment and Hazardous Materials of the Committee on Energy and Commerce, U.S. House of Representatives, 108th Congress, July 22nd, 2004

2005 Reviewer, “Superfund and Mining Megasites – Lessons from the Couer d’ Alene River Basin”, National Research Council, The National Academies.

2005 Ad Hoc Member, NIEHS Board of Scientific Counselors Review of the Epidemiology Branch, April 3rd to April 5th, 2005

2005 Senate Briefing, “The Connection of Environmental Chemicals and Learning Disabilities”, U.S. Senate, May 10th, 2005

2006 Invited Participant, NIEHS Strategic Planning Forum, National Institute for Environmental Health Sciences, Chapel Hill, North Carolina, October 17-18th, 2006.

2006-2008 Member, U.S. EPA’s Clean Air Scientific Advisory Committee Lead Review Panel.

2006-2008 Member, National Children’s Study Steering Committee, NICHD

2006 Invited Participant, “How Does Housing Affect Health Outcomes of Children?”, MacArthur Foundation, Chicago, Illinois, June 21st-22nd, 2006.

2006- 2010 Member, External Scientific Advisory Committee, Richmond Center for Excellence in Tobacco Research, American Academy of Pediatrics.

2007 Testimony, Vermont State Legislature, “The Lingering Legacy of Lead Toxicity”, Montpelier, Vermont, February 1st, 2007

2007 Testimony, Connecticut State Legislature, “The Legacy of Lead Toxicity”, Hartford, Connecticut, March 14th, 2007. (PG)

2007 Invited Testimony, United States Senate Hearing, “Lead and Children’s Health”. Committee on Environmental and Public Works, October 18th, 2007

2007-2008 Member, Committee on “Committee on Contaminated Drinking Water at Camp Lejeune”, National Research Council, The National Academies.

2008 Member, Expert Panel on Health and the Environment, Statistics Canada, Ottawa,

2008- Member, Alliance for the Global Elimination of Lead Paint, Intergovernmental Forum on Chemical Safety (IFCS), World Health Organization

2008-2009 Reviewer, Toxicological Review and Recommended Toxicological Reference Values for Environmental Lead Exposure in Canada, Health Canada

2009-2013 Scientific Advisor, Canada Lead Study funded by Health Canada (Patrick Levallois, Principal Investigator).

2009-2014 Board Member, Barro Sin Plomo

2009-2010 Member, Health and Environment Experts Advisory Group of the Canadian Longitudinal Study on Aging, Canadian Institutes of Health Research

2010-2012 Member, US Environmental Protection Agency Science Advisory Board for Evaluating Dust Lead Standards

2010-2013 Advisor, Canada Environmental Health Law and Canadian Partnership for Children’s Health and Environment Retrofit Project

2010-2012 Member, Physicians Advisory Panel, Canada Health Measures Survey

2010 Invited Testimony, United States Senate Hearing, “Research on Environmental Health Factors with Autism and Neurodevelopmental Disorders”, August 3rd, 2010

2010 Member, Joint FAO/WHO Expert Panel for Toxicological and Health Review of Bisphenol A

2010-2015 Board Member, Global Community Monitoring, Oakland, California

2010- Chairman, Scientific Advisory Committee for Dartmouth University’s Program in Children’s Health and the Environment

2011-2016	Member, American Academy of Pediatrics Executive Council on Environmental Health
2011-2012	Member, US Environmental Protection Agency Science Advisory Board for Evaluating Hazards of Partial Water Line Replacement
2011	Invited Testimony, Special Committee on Cosmetic Pesticides, Legislative Assembly, Province of British Columbia, October 7 th , 2011
2011-2012	Member, Panel on Health Effects of Low-level Lead, Office of Health Effects, National Toxicology Program of the National Institutes of Environmental Health Sciences,
2012-	Member, Expert Advisory Committee, Canada Health Measures Survey
2012-	Member, Environmental Defence Fund Science Advisory Committee on Toxics
2015	Reviewer, Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejeune Legislation, Institute of Medicine, The National Academies
2016-	Member, The Lancet Commission on Pollution, Health & Development
2016-	Member, Targeting Environmental Neuro-Developmental Risks (TENDR)
2016	Member, Steering Committee, The National Lead Summit, United States
2017	Rockefeller Foundation Academic Writing Retreat, Bellagio, Italy
2017-	Member, Advisory Committee for the Flint (MI) Cohort Study
2017-	Pure Earth Leadership Council
2018-	Member Project TENDR Advisory Board
2018-	Member, Mercury Disability Board Committee, Health Canada

Editorial Boards

2000-2015	Assistant Editor, <i>Environmental Research</i>
2000-2008	Deputy Editor, <i>Public Health Reports</i>
2004	Associate Editor, <i>Pediatrics</i> supplement on Children's Environmental Health
2004-2017	Editorial Board Member, <i>PLoS Medicine</i>
2005-2014	Editorial Board Member, <i>Breastfeeding Medicine</i>
2007-	Editorial Board Member, <i>Environmental Health</i>
2008-2012	Editorial Review Board Member, <i>Environmental Health Perspectives</i>
2012-2015	Associate Editor, <i>Environmental Health Perspectives</i>
2016-	Advisor, <i>Environmental Health Perspectives</i> News Section

Societies and Organizations

1989-2008	American Public Health Association
1996-2015	Academic Pediatric Association
1997-2012	American Association for the Advancement of Science
2000-2008	Society for Pediatric Research
2001-2008	American Pediatric Society
2001-2016	Specialty Fellow, American Academy of Pediatrics
2006-	Fellow, Collegium Ramazzini
2006-	Member, International Society for Environmental Epidemiology
2008-	Founding Member, International Society for Children's Health & the Environment
2011-2017	Secretary and Treasurer, International Society for Children's Health & the Environment
2012-	Member, International Society for Exposure Science
2017-2018	Vice-President, International Society for Children's Health & the Environment
2019-2020	President, International Society for Children's Health & the Environment

Video and Website Production – www.littlethingsmatter.ca

1. Canadian Environmental Health Atlas: A Portal to Discover the Promise of Environmental Health.
2. Shifting the Curve: The Impact of Toxins on ADHD in U.S. Children (video)
3. Little Things Matter: The Impact of Toxins on the Developing Brain (video)
4. Little Things Matter: The Impact of Toxins on Preterm Birth (video)
5. Prevention Paradox: Why We are Failing to Prevent Disease (video)
6. Little Things Matter: The Deadly Impact of Airborne Particles (video)
7. Cause or Cure: A Plea for Prevention (video)
8. Crime of the Century: The Failure to Prevent the Lead Pandemic (video)

Original Research

1. Lanphear BP. Deaths in Custody. American Journal Forensic Medicine & Pathology 1987;8:299-301.
2. Lanphear BP, Snider DE. Myths of Tuberculosis. J Occ Med 1991;33:501-504.
3. Linnemann CC Jr, Cannon C, DeRonde M, Lanphear BP. Effect of educational programs, rigid sharps containers, and universal precautions on reported needle-stick injuries in healthcare workers. Infection Control Hospital Epidemiology 1991;12:214-20.
4. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. Journal Occupational Med 1992;34:718-721.
5. Lanphear BP, Linnemann CC Jr, Cannon CG, DeRonde MM. Decline of clinical hepatitis B in workers at a general hospital. Clinical Infectious Disease 1993;11:10-14.
6. Lanphear BP, Linnemann CC Jr, Cannon C, DeRonde MM, Pender L, Kerly L. Hepatitis C virus infection in health care workers. Infection Control Hospital Epidemiology 1994;15:745-750.
7. Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.
8. Lanphear BP, Winter NL, Apetz L, Eberly S, Weitzman M. A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 1996;98:35-40.
9. Christy C, Pulcino M, Lanphear BP, McConnochie K. Screening for tuberculosis infection in urban children. Arch Pediatrics Adolescent Med 1996;150:722-726.
10. Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.
11. Lanphear BP, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S, Emond M, Matte TD. Lead-contaminated house dust and urban children's blood lead levels. American Journal of Public Health 1996;86:1416-1421.

12. Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. *Pediatrics* 1997.
<http://www.pediatrics.org/cgi/contents/full99/3/e1>.
13. Emond MJ, Lanphear BP, Watts A, Eberly S for the Rochester Lead-in-Dust Study Group. Measurement error and its impact on the estimated relationship between dust lead and children's blood lead. *Environmental Research* 1997;72:82-92.
14. Lanphear BP, le Cessie S, Atkinson WL, Watelet L. Association of live births and the resurgence of measles. *International Journal Epidemiology* 1997;26:204-211.
15. Rust SW, Burgoon DA, Lanphear BP, Eberly S. Log-additive versus log-linear analysis of lead-contaminated house dust and children's blood lead levels: Implications for residential dust-lead standard. *Environmental Research* 1997;72:173-184.
16. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. *Environmental Research* 1997;74:67-73.
17. Lanphear BP, Byrd RS, Auinger P, Schaffer S. Community characteristics associated with elevated blood lead levels in children. *Pediatrics* 1998;101:264-271.
18. Lanphear BP, Rust SW, Burgoon DA, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. *Environmental Research* 1998;76:120-130.
19. Lanphear BP. The paradox of lead poisoning prevention. *Science* 1998;281:1617-1618.
20. Lanphear BP, Hall CB, Black J, Auinger P. Risk factors for the early acquisition of HHV-6 and HHV-7 infection in children. *Pediatric Infectious Disease Journal* 1998;17:792-795.
21. Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. *Environmental Research* 1998;79:51-68.
22. Marron R, Lanphear BP, Kouides R, Dudman L, Manchester R, Christy C. Efficacy of informational letters on Hepatitis B immunization rates in university students. *J Am College Health* 1998;47:123-127.
23. Howard CR, Howard FM, Lanphear BP, deBlieck EA, Eberly S, Lawrence RA. Effect of early pacifier use on breastfeeding duration. *Pediatrics* 1999;103.
<http://www.pediatrics.org/cgi/contents/full103/3/e33>.
24. Lanphear BP, Howard CR, Eberly S, Auinger P, Kolassa J, Weitzman M, Alexander K, Schaffer S. Primary prevention of childhood lead exposure: A randomized trial of dust control. *Pediatrics* 1999;103:772-777.

25. Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels among the U.S. population. *JAMA* 1999;281:2294-2298.
26. Howard CR, de Blieck EA, ten Hoopen C, Howard F, Lanphear BP, Lawrence RA. Physiologic stability of newborns during cup and bottle-feeding. *Pediatrics* 1999;104:1204-1207.
27. Steiner JF, Curtis P, Lanphear BP, Vu KO, Reid A. Federally-funded fellowship training in primary care research: perspectives of program directors. *Academic Medicine* 2000;75:74-80.
28. Stone KE, Lanphear BP, Pomerantz WJ, Khoury J. Injuries and deaths in children due to window-falls. *Journal of Urban Health* 2000;77:26-33.
29. Mansour M, Lanphear BP, DeWitt TG. Barriers to asthma care among underserved, urban children. *Pediatrics* 2000;106:512-519.
30. Lanphear BP, Eberly S, Howard CR. Long-term effect of dust control on children's blood lead levels. *Pediatrics* 2000 <http://www.pediatrics.org/cgi/contents/full106/4/e48>.
31. Lanphear BP, Dietrich KN, Auinger P, Cox C. Cognitive deficits associated with blood lead levels <10 µg/dl in U.S. children and adolescents. *Public Health Reports* 2000;115:521-529.
32. Lanphear BP, Aligne C, Auinger P, Byrd R, Weitzman M. Residential exposures associated with asthma in U.S. children. *Pediatrics* 2001;107:505-511.
33. Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick S, Naahas R. Contribution of residential exposures to asthma in US children and adolescents. *Pediatrics* 2001. <http://www.pediatrics.org/cgi/content/full/107/6/e98>.
34. Phelan KJ, Kalkwarf H, Khoury J, Lanphear BP. Trends and patterns of playground injuries in U.S. children and adolescents. *Ambulatory Pediatrics* 2001;1:227-233.
35. Mansour M, Lanphear BP, Hornung R, Khoury J, Bernstein DI, Menrath W, Decolongon J. A side-by-side comparison of sampling methods for settled indoor allergens. *Environ Res* 2001;87:37-46.
36. Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of dust control on children's blood lead concentrations: A systematic review. *Env Health Perspect* 2002;110:103-107.
37. Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. *Journal of Pediatrics* 2002;140:40-47.
38. Steiner JF, Lanphear BP, Curtis P, Vu KO. The training and career paths of fellows in the National Research Service Award (NRSA) program for research in primary medical care. *Acad Med* 2002;77:712-718.
39. Steiner JF, Lanphear BP, Curtis P, Vu KO. Indicators of early research productivity among primary care fellows. *J Gen Intern Med* 2002;17:845-851.

40. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake in childhood and adolescence, adult bone density and osteoporotic fractures in U.S. women. *Am J Clin Nut* 2003;77:257-265.
41. Howard CR, Howard FM, Lanphear BP, Eberly S, deBlieck EA, Oakes D, Lawrence RA. A randomized trial of pacifier use and bottle-feeding and their effect on breastfeeding. *Pediatrics* 2003;111:511-518.
42. Curtis P, Dickinson P, Steiner J, Lanphear BP, Vu K. Building capacity for research in family medicine: Is the blueprint faulty? *Family Medicine* 2003;35:124-130.
43. Lanphear BP, Succop P, Roda S, Henningsen G. The effect of soil abatement on blood lead levels in children living near a former smelting and milling operation. *Public Health Reports* 2003;118:83-90.
44. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. *N Engl J Med* 2003;348:1517-1526.
45. Kahn RS, Khoury JC, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactivity-impulsivity, inattentive and oppositional behaviors. *Journal of Pediatrics* 2003;143: 104-110.
46. Auinger P, Kalkwarf HJ, Mansour M, Lanphear BP. Trends in otitis media in US children. *Pediatrics* 2003;112:514-520.
47. Haynes E, Kalkwarf H, Hornung R, Wenstrup R, Dietrich K, Lanphear B. Vitamin D Fok1 polymorphism and blood lead levels in children. *Environ Health Persp* 2003;111:1665-1669.
48. Steiner JF, Curtis P, Lanphear BP, Vu KO, Main DS. Assessing the role of influential mentors in the research development of primary care fellows. *Academic Medicine* 2004;79:865-872.
49. Yolton K, Auinger P, Dietrich KN, Lanphear BP, Hornung R. Exposure to environmental tobacco smoke and cognitive abilities among US children and adolescents. *Environ Health Persp* 2005;113:98-103.
50. Phelan KJ, Khoury J, Kalkwarf H, Lanphear BP. Residential injuries in US children and adolescents. *Public Health Reports* 2005;120:63-70.
51. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in exposure to environmental tobacco smoke among children. *Environ Health Perspect* 2005;113:362-367.
52. Lanphear BP, Hornung R, Ho M. Screening housing to prevent lead toxicity in children. *Pub Health Rep* 2005;120:305-310.
53. Rosner D, Markowitz G, Lanphear BP. J. Lockhart Gibson and the discovery of the impact of lead pigments on children's health: A review of a century of knowledge. *Pub Health Rep* 2005;120:296-300.

54. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environ Health Perspect* 2005;113:894-899.
55. Nagaraja J, Menkedick J, Phelan KJ, Ashley PJ, Zhang J, Lanphear BP. Deaths from residential injuries in US children and adolescents, 1985 to 1997. *Pediatrics* 2005;116:454-61.
56. Eskenazi B, Gladstone EA, Berkowitz GS, Drew CH, Faustman EM, Holland NT, Lanphear BP, Meisel SJ, Perera FP, Rauh VA, Sweeney A, Whyatt RM, Yolton K. Methodologic and logistic issues in conducting longitudinal birth cohort studies: Lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Persp* 2005;113:1419-1429.
57. Eggleston PA, Diette G, Lipsett M, Lewis T, Tager I, McConnell R, Chrischilles E, Lanphear BP, Miller R, Krishnan J. Lessons learned for the study of childhood asthma from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Persp* 2005;113:1430-1436.
58. Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. *J Pediatrics* 2006;149:220-226.
59. Yuan W, Holland S, Cecil K, Dietrich K, Wessel SD, Altaye M, Hornung R, Ris M, Egelhoff J, Lanphear B. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. *Pediatrics* 2006;118:971-977.
60. Howard CR, Lanphear N, Lanphear BP, Eberly S, Lawrence RA. Parental responses to infant crying and colic: the effect on breastfeeding duration. *Breastfeeding Med* 2006;1:146-155.
61. Brinkman W, Geraghty S, Lanphear B, Khoury J, Gonzalez-Del-Rey J, DeWitt T, Britto M. Evaluation of resident communication skills and professionalism: A matter of perspective? *Pediatrics* 2006;118:1371-1379.
62. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect* 2006;114:1904-1909.
63. Brinkman WB, Geraghty SR, Lanphear BP, Khoury JC, Gonzalez-Del-Rey JA, DeWitt TG, Britto MT. Effect of multisource feedback on resident communication skills and professionalism: a randomized controlled trial. *Arch Pediatr Adolesc Med* 2007;161:44-49.
64. Wilson SE, Kahn RS, Khoury J, Lanphear BP. The role of air nicotine in explaining racial differences in cotinine among tobacco-exposed children. *Chest* 2007;131:856-862.

65. Froehlich T, Lanphear BP, Dietrich KN, Cory-Slechta D, Wang N, Kahn RS. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. *Biol Psychiatry* 2007;62:243-249.
66. Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Arch Pediatr Adolesc Med* 2007;161:857-864.
67. Landrigan PJ, Woolf AD, Gitterman B, Lanphear B, Forman J, Karr C, Moshier EL, Godbold J, Crain E. The Ambulatory Pediatric Association Fellowship in Pediatric Environmental Health: A five-year assessment. *EHP* 2007;115:1383-1387.
68. Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, Canfield RL. Blood lead concentrations < 10 µg/dL and child intelligence at 6 years of age. *Environ Health Perspect* 2008;116:243-248.
69. Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. Decreased brain volume in adults with childhood lead exposure. *PLoS Med* 2008;5:e112.
70. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, Lanphear BP, Ho M, Rae MN. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 2008;5:e101.
71. Spanier AJ, Hornung RW, Kahn RS, Lierl MB, Lanphear BP. Seasonal variation and environmental predictors of exhaled nitric oxide in children with asthma. *Pediatr Pulmonol* 2008;43:576-583.
72. Braun JM, Froehlich TE, Daniels JL, Dietrich KN, Hornung R, Auinger P, Lanphear BP. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. *Environ Health Perspect* 2008;116:956-962.
73. Yolton K, Khoury J, Hornung R, Dietrich KN, Succop P, Lanphear BP. Environmental tobacco smoke exposure and child behaviors. *J Dev Behav Pediatr* 2008;29:456-463.
74. Yeoh B, Woolfenden S, Wheeler D, Alperstein G, Lanphear B. Household interventions for prevention of domestic lead exposure in children. *Cochrane Database Syst Rev*. 2008;2:CD006047.
75. Geraghty SR, Khoury JC, Morrow AL, Lanphear BP. Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning. *Breastfeed Med*. 2008;3:207-213.

76. Spanier AJ, Kahn RS, Hornung RW, Wang N, Sun G, Lierl MB, Lanphear BP. Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children. *Pediatr Pulmonol*. 2009;44:812-819.
77. Hornung RW, Lanphear BP, Dietrich KN. Age of greatest susceptibility to childhood lead exposure: A new statistical approach. *Environ Health Persp* 2009;117:1309-1312.
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7. "Relation of Lead-Contaminated House Dust and Blood Lead Levels in Urban Children" Environmental Protection Agency, Washington, D.C., February, 1994.
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9. "EPA Health-Based Standards for Soil and Dust". Alliance to End Childhood Lead Poisoning, Washington, D.C., May 17, 1994.
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14. "Transmission and Control of Infections in Health Care Workers". (Moderator & Speaker) American College of Occupational Environmental Medicine, Las Vegas, Nevada, May 4, 1995.
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26. "Lead Hazard Control Research" Conference on Linking Health, Housing & Environment, Centers for Disease Control, Department of Housing and Urban Development, National Institutes of Health, Phoenix, Arizona, June 21-24, 1998.
27. "A Randomized Trial of Dust Control to Prevent Childhood Lead Exposure." Presenter and Co-chairman, Section on Heavy Metals, 1st International Conference on Children's Environmental Health, Amsterdam, The Netherlands, August 11-13th, 1998.
28. "Prevention of Childhood Lead Exposure: A Critique of the EPA's Proposed Residential Lead Standard". Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, D.C., November 5, 1998.
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30. "Behaviors in Early Childhood and Exposure to Environmental Toxins". (invited) Pediatric Environmental Health Conference, San Francisco, CA May 4, 1999.
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32. "Adverse Effects of Blood Lead Concentrations <10 µg/dL" (Invited), 17th International Conference Neurotoxicology Conference, Little Rock, Arkansas, October 17-20, 1999.
33. "Emerging Research and Implications for Prevention of Childhood Lead Exposure" (Invited), 2nd Annual Syracuse Lead Conference, Syracuse, New York October 27th, 1999.
34. "Prevention of Lead Poisoning in Children" Sierra Club, Omaha, NE, November 16th, 1999.
35. "Children's Environmental Health: A Focus on Residential Hazards" Department of Pediatrics, University of Nebraska Hospital, November 17th, 1999.
36. "Effectiveness of Lead Hazard Controls", New England Lead Conference, New Hampshire, Tufts University School of Medicine, April 25, 2000.

37. "Subclinical Lead Toxicity in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 15, 2000.
38. "Contribution of Residential Exposures to Asthma in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 16, 2000.
39. "The Effect of Soil Abatement on Blood Lead Concentration in Children living near a former Smelter and Milling Operation" (invited). Coeur d'Alene, Idaho, May 24, 2000.
40. "The Paradox of Lead Poisoning Prevention" (invited). National Institute of Justice, Washington, D.C., July 18th, 2000.
41. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Children's Hospital Medical Center, Cincinnati, Ohio, August 22, 2000.
42. "Children's Environmental Health: A Focus on Residential Hazards" Pediatric Grand Rounds, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY, September 20th, 2000.
43. "Prevention of Lead Poisoning in Childhood" 7th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, NY, September 29, 2000.
44. "Excavating the Enigmas of Childhood Lead Exposure". Department of Environmental and Occupational Medicine, Harvard University School of Public Health, Boston, MA, October 16th, 2000.
45. "Contribution of Residential Exposures to Asthma". Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 11th, 2000.
46. "Setting Research Priorities for the Decade". (Moderator & Speaker) Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 13th, 2000.
47. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation) Look Out for Lead Conference, Madison, WI, April 12, 2001.
48. "Environmental Lead Exposure and Children's Intelligence at Blood Lead Concentrations below 10 µg/dl." APA Presidential Plenary Session, Pediatric Academic Society Meeting, Baltimore, MD, April 30, 2001.
49. "Elimination of Childhood Lead Exposure: Obstacles & Opportunities" (Plenary). National Housing Conference and Exposition, New Orleans, LA, May 16th, 2001.
50. "Prevention of Childhood Lead Exposure: A Public Health Perspective" (Keynote Presentation). Philadelphia Health Department, Philadelphia, PA, May 23rd, 2001.

51. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation), Charles Drew University, Los Angeles, California, October 22nd, 2001.
52. "Primary Prevention of Childhood Lead Exposure" (Keynote Presentation), Midwest Regional Lead Conference, Pittsburgh PA, October 29th, 2001.
53. "Prevention of Childhood Lead Exposure: Shifting to Primary Prevention" (Keynote Presentation), Indiana Department of Health, Lead-Safe Conference, November 7th, 2001.
54. "A Strategy for Primary Prevention of Childhood Lead Exposure" A testimony to Housing and Transportation Subcommittee, U.S. Senate, Washington, D.C., November 13, 2001.
55. "Ethical issues of Environmental Research involving Children" (moderator and speaker). Panelists were Jeffrey Kahn, Ph.D., and Leonard Glantz, J.D., Raleigh-Durham, North Carolina, NIEHS Conference of Children's Environmental Health Centers, January 23, 2001.
56. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Omaha Children's Hospital, Omaha, Nebraska, March 1, 2002.
57. "Racial Disparities in Children due to Environmental Hazards" Ohio Commission on Minority Health, Columbus, Ohio March 27, 2002.
58. "Prevention of Childhood Lead Exposure in a Former Mining Community" Tar Creek, Oklahoma, April 4, 2002.
59. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Hasbro Children's Hospital, Brown University, Providence Rhode Island, May 17, 2002.
60. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Dayton Children's Hospital, Wright University, Dayton, Ohio May 22, 2002.
61. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." International Lead Congress, Washington, DC, June 3rd, 2002.
62. "Residential Hazards: A Neglected Health Problem" Agency for Toxic Substances Disease Registry, Centers for Disease Control and Prevention, Atlanta, Georgia, August 19th, 2002.
63. "Control of Residential Exposures to Environmental Neurotoxins" National Center for Healthy Homes (Moderator and Speaker), Annapolis, VA, November 7th, 2003.
64. "The Promises and Potential Pitfalls of Primary Lead Poisoning Prevention" Purchase College, 9th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, New York,, October 4th, 2002.
65. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Syracuse, NY, October 9th, 2002.
66. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." University of Texas at El Paso, El Paso, Texas January 29th, 2003.

67. "Childhood Lead Poisoning" Introduction to Children's Environmental Health, Seattle, Washington, Pediatric Academic Society, May 3rd, 2003.
68. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Chicago Lead Summit, Chicago, Illinois, May 28th, 2003.
69. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Case Western Reserve University, Cleveland, Ohio, June 3rd, 2003.
70. "Housing and Children's Health", Sprawl: The impact on vulnerable populations, University of Cincinnati College of Medicine, Cincinnati, Ohio, July 8th, 2003.
71. "Trials and Tribulations of Protecting Children from Environmental Toxins". Duke University, Nicholas School of the Environment, Durham, NC, November 6th, 2003.
72. "Adverse Effects of Fetal and Childhood Exposures to Prevalent Toxins" Midwest Critical Regional Neonatology Conference, Covington, KY, November 14th, 2003.
73. "Control of Residential Hazards in Children" American Public Health Association, San Francisco, CA, November 18th, 2003.
74. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis". 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 11th, 2004.
75. "Trials and Tribulations of Protecting Children from Environmental Hazards" Workshop on Ethical Issues on Children's Environmental Health, Children's Environmental Health Network, Washington, D.C. March 5, 2004.
76. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis", Pediatric Academic Societies Annual Meeting. Pediatric Research 2004;55:163A.
77. "The Impact of the Environment on Children's Health" Bob Smith Endowed Lecture, Department of Pediatrics, First Gulf Coast Children's Environmental Health Symposium, Baylor University, Houston, Texas.
78. "The Search for Environmental Causes of Learning Disabilities, Learning Disabilities Initiative, Baltimore, MD, May 18th, 2004.
79. "Residential Hazards in Children: A Neglected Public Health Problem", Pediatric Grand Rounds, Boston Medical Center, Department of Pediatrics, Boston University Medical Center, Boston, MA, May 20th, 2004.
80. "Residential Hazards in Children" "Healthier Homes, Stronger Families: Public Policy Approaches to Healthy Housing", National Center for Healthy Housing, Washington, D.C., June 2nd, 2004.

81. "Fetal and Early Childhood Exposures to Prevalent Toxins" Pediatric Grand Rounds, Ste. Justine Children's Hospital, University of Montréal, Montreal, Canada, June 16th, 2004.
82. "Childhood Exposure to Lead-Contaminated Soil: A Problem of the Past or a Problem from the Past?" National Academy of Science Committee on Superfund Site Assessment and Remediation in Coeur d'Alene River Basin", June 17th, 2004, Coeur d'Alene, Idaho.
83. "The Legacy of Lead" (Keynote Speaker). Chicago Lead Summit, Region V EPA Headquarters, September 15th, 2004.
84. "A Tale of Two Toxins: Children's Exposure to Tobacco and Lead" (with Michael Weitzman), The American Academy of Pediatrics, San Francisco, CA, October 10th, 2004.
85. "A Legacy of Childhood Lead Poisoning" University of Washington, Seattle, Washington, October 30, 2004.
86. "Protecting Children from Environmental Toxins", Pediatric Grand Rounds, Seattle Children's Hospital, Seattle Washington, March 10th, 2005.
87. "The Science and Politics of Childhood Lead Poisoning", Northwest Pediatric Environmental Health Conference, University of Washington, Seattle, Washington, March 11th, 2005.
88. "The Effects of Low-level Exposure to Environmental Toxins during Fetal Development and Early Childhood", Children's' Hospital of Fudan University, Shanghai International Pediatric Forum, Shanghai, China, June 16th to 18th, 2005.
89. "The Role of Biomarkers in Revealing Genetic and Environmental Influences of Disease and Disability" Psychiatry Grand Rounds, University of Cincinnati, February 8th, 2006.
90. "Trials and Tribulations of Protecting Children from Environmental Hazards: Ethical Issues", Johns Hopkins University of Medicine, March 17th, 2006.
91. "Key Elements of a Primary Prevention Strategy for Lead Poisoning", Albany Law School, Union University, Albany, New York, March 16th, 2006.
92. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", Case Western Reserve University, City Club of Cleveland, Cleveland, OH March 4th, 2006.
93. Integrating Genetic and Environmental Influences in Pediatric Research" (Moderator and Speaker), Pediatric Academic Societies, San Francisco, CA, April 30th 2006.

94. "Ethical Issues in Housing Health Hazard Research Involving Children" (Topic Symposia) Pediatric Academic Societies, San Francisco, CA, May 2nd 2006.
95. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", International Workshop on Neurotoxic metals: from Research to Prevention, University of Brescia, Italy, June 17th, 2006.
96. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", International Society for Environmental Epidemiology, Paris France, September 6th, 2006.
97. "Protecting Children from Environmental Toxins", Region VIII Children's Environmental Health Summit, Vail, Colorado September 20th, 2006.
98. "Integrating Genetic and Environmental Biomarkers in Pediatric Epidemiology", Visiting Professor, Simon Fraser University and University of British Columbia, Vancouver, British Columbia, October 19th-20th, 2006.
99. "The Legacy of Lead", Indiana Lead Conference, Indianapolis, Indiana, October 24, 2006.
100. "Ethical dilemmas in Children's Environmental Health", Seminar Series in Ethics of Toxicology, University of Champagne-Urbana, Champagne, Illinois, November 19th, 2006.
101. "Low-Level Lead Toxicity: Implications for Prevention", WHO Informal Workshop on Lead, University of Munich, Germany, November 30th, 2006.
102. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", National Environmental Public Health Conference, National Centers for Disease Control, Atlanta, Georgia, December 4th, 2006.
103. "The Epidemiologic Conquest of Childhood Lead Toxicity: A Pyrrhic Victory". NIEHS Workshop on Children's Environmental Health Research: Past, Present and Future. January 22nd, 2007.
104. "Linking Low-level Exposures to Environmental Toxicants with ADHD". Duke Integrated Toxicology and Environmental Health Program Symposium on Developmental Neurobehavioral Disabilities and Toxic Exposures, March 23, 2007, Durham, North Carolina.
105. "Using Biomarkers to Link Environmental Influences with Disease and Disability", The Channing Laboratory, Harvard University, Boston, Massachusetts, April 4th, 2007.
106. "The Lingering Legacy of Lead Toxicity". Grand Rounds, Department of Pediatrics, St. Louis Children's Hospital, St. Louis University, St. Louis, Missouri, April 11th, 2007.
107. "Protecting Children from Environmental Toxicants", United States Council of Catholic Bishops, Washington, D.C., April 30th, 2007.
108. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", Pediatric Academic Societies, APA Presidential Platform Plenary Session, Toronto, Canada, May 7th, 2007.

109. "The Lingering Legacy of Lead Toxicity" Grand Rounds, Department of Pediatrics, Omaha Children's Hospital, University of Nebraska, Omaha, Nebraska, April 11th, 2007.
110. "Linking Low-level Neurotoxicant Exposures of the Developing Brain to Learning and Behavioral Problems." International Conference on Developmental Programming and Effects of Environmental Toxicants in Human Health and Disease, Faroe Islands, May 20th, 2007.
111. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson", National Policy Consultation Series on Children's Health and Environment, Moncton, New Brunswick, Canada, May 31, 2007.
112. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" Occupational and Environmental Health Seminar Series, Health Canada, Ottawa, Canada, June 6th, 2007.
113. "Linking Low-Level Lead Exposure with Child and Adolescent Psychopathology", 13th Annual International Society for Research in Child and Adolescent Psychopathology, London, England, June 19th, 2007.
114. "The Legacy of Lead Toxicity". Pediatric Grand Rounds, New York Presbyterian Hospital-Weill Cornell Medical Center, September 18th, 2007.
115. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Pediatric Grand Rounds, Children's Hospital at Dartmouth, Dartmouth Medical School, September 19th, 2007.
116. "The Legacy of Lead Toxicity: Effects of Childhood Lead Exposure in Children, Adolescents and Adults". Mid-America Conference, Philadelphia, Pennsylvania, October 4th, 2007.
117. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" International Society for Exposure Analysis (invited plenary session), Raleigh-Durham, North Carolina, October 17th, 2007.
118. The Global Elimination of Lead Toxicity: A Focus on Housing." National Institute of Public Health, Rennes, France, October 22nd, 2007.
119. Linkage of Environmental Lead Exposure with Psychopathology in Children and Adolescents" Ramazzini Collegium, Carpi, Italy, October 25th, 2007.
120. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology", Symposium on Environmental Toxicity and the Brain, University of Toronto, Toronto, Canada, December 7th, 2007.
121. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology." Pediatric Grand Rounds, Rochester General Hospital and Strong Memorial Hospital, Rochester, New York, April 1&2, 2008.

122. "Rochester's Role in the Ongoing Elimination of Childhood Lead Toxicity." Beaven Lecture, Rochester Academy of Medicine, Rochester, New York, April 1, 2008.
123. "The Lingering Legacy of Lead Toxicity: Lansing Legacy." Michigan's Conference for Lead Safe & Healthy Homes, East Lansing, MI, April 22, 2008.
124. First Annual Controversies in Pediatric Environmental Health, "Should the Centers for Disease Control Lower the Blood Lead Level of Concern". A debate by Bruce Lanphear and George G. Rhoads (James Sargent, Moderator). Pediatric Academic Societies Meeting, Honolulu, Hawaii, May 2nd, 2008.
125. "Linking Exposure to Environmental Toxicants with Psychopathology in Children and Youth". Visiting Professor, Alberta Child and Youth Network, Calgary Children's Hospital, Calgary, Alberta. May 13th-15th, 2008.
126. "Lead Toxicity and the Teenage Brain", Youth Exploring Science Program, St. Louis Science Center, St. Louis, Missouri, June 30th, 2008.
127. "The Legacy of Childhood Lead Toxicity". Health Canada, Ottawa, Canada, October 6th, 2008.
128. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". The 2008 Rachel Carson Legacy Conference: Green Chemistry – Solutions for a Healthy Economy, Duquesne University, Pittsburgh, Pennsylvania, September 20th, 2008.
129. "Trials and Tribulations of Protecting Children from Environmental Hazards", Ethics in Toxicology Seminar Series, University of Champagne-Urbana, Champagne, Illinois, September 22nd, 2008.
130. "Industry's Influence on the Prevention of Childhood Lead Poisoning." In: Symposia on Insulating Environmental Health Research from Conflicting Interests. International Society for Environmental Epidemiology Annual Meeting, Pasadena, California, October 14th, 2008.
131. "The Lingering Legacy of Lead Toxicity: Implications for Research and Policy on Other Environmental Toxicants". (Keynote Presentation) BC Environmental and Occupational Health Research Network, Vancouver, BC, November 7th, 2008.
132. "Effects of Environmental Toxicants on Children's Development". DB-PREP Course, American Academy of Pediatrics, Atlanta, Georgia, December 5th, 2008.
133. "Linking Low-level Environmental Toxicants with New Morbidities of Childhood". BC Children's Grand Rounds, British Columbia, Vancouver, February 6th, 2009.
134. "Using Biomarkers to Link Exposures with Disease and Disability in Children". Workshop on Physical and Chemical Exposures in Canadian Cohort Studies, Canadian Institute of Health Research and Health Canada, February 8th-9th, 2009.

135. "How Dangerous Is Lead In Drinking Water?" An interview on "Around The Water Cooler" with Werner Troesken and Bruce Lanphear. February 18th, 2009.
136. "Linking Environmental Toxicants with ADHD in Children" (invited), Learning Disabilities Association Annual Meeting, February 25th, Salt Lake City, Utah.
137. "The Lingering Legacy of Lead Toxicity", Norfolk Children's Hospital, April 30th, 2009, Norfolk Virginia.
138. Second Annual Controversies in Pediatric Environmental Health Debate, "Should Pediatricians Advise Parents to Feed their Children Organic Foods?" A debate by Joel Forman and Janet Silverstein (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Baltimore, MD, May 4th, 2009.
139. "A Pattern of Pathology: The Population Impact of Environmental Toxicants on Health". Workshop on Endocrine Disruptors, Endocrine Society, Washington, DC, June 9th, 2009.
140. "The Quandary of Environmental Contaminants in Human Milk", 25th Anniversary of US Surgeon General's Report on Breastfeeding, Washington, DC, June 13th, 2009.
141. "Linking Exposures to Environmental Toxicants with Learning Problems and Psychopathology in Children." Northwest Conference on Children's Health and Environment, Tukwila, Washington, October 1st, 2009.
142. "The Second Coming of the Sanitarians", Pediatric Grand Rounds, University of California at Davis Children's Hospital, Sacramento, California, October 9th, 2009.
143. "The Second Coming of the Sanitarians", National Institute of Public Health, Rennes, France, November 4th, 2009.
144. "Linking Exposure to Environmental Toxicants with ADHD in Children." Symposium on ADHD. Riyadh, Saudi Arabia, November 7th, 2009.
145. "The Interplay of Genetic and Environmental Influences in Common Conditions of Children." Macquarie University, Department of Geology, Sydney, Australia, November 18th, 2009.
146. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure." Pacific Basin Consortium Symposium on Environment and Health, Perth, Australia, November 13th, 2009.
147. "The Second Coming of the Sanitarians", SFU President's Lecture, Simon Fraser University, Burnaby, BC, March 4th, 2010.
148. Third Annual Controversies in Pediatric Environmental Health Debate, "Should the American Academy of Pediatrics Sponsor a Ratings Board to Provide Evidence-based Ratings for Media?" A debate by James Sargent and Donald Shifrin (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Vancouver, BC, May 2nd, 2010.

149. "Efficacy of Reducing Lead Hazards in Housing on Lead-Contaminated House Dust, Blood Lead Concentration and Intellectual Abilities in Children." Pediatric Academic Societies Meeting, Vancouver, BC May 1st, 2010.
150. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Pediatric Grand Rounds, Cornell Weill Medical College, New York, New York. May 25th, 2010.
151. "Excavating the Enigmas of Childhood Lead Toxicity", Guest Lecturer, "Introduction to Toxicology, Harvard School of Public Health, Boston, Massachusetts, October 27th, 2010.
152. "The Conquest of Lead Poisoning: A Pyrrhic Victory", Lead Action Collaborative, New England Carpenters Center, Boston, Massachusetts, October 28th, 2010.
153. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Academy of Breastfeeding Medicine, San Francisco, California, October 29th, 2010.
154. "Bisphenol A and Behavior Problems in Children". Eastern Perinatal Conference, Kingston, Ontario, November 10th, 2010.
155. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" UBC Statistics Department Seminar, November 18th, 2010.
156. "Protecting Children from Environmental Toxicants." Children's Hospital of Quebec, University of Laval, Quebec City, Quebec, December 17th, 2010.
157. "Low-level Toxicity: Implications for Research and Policy", Joint Talks by C. Arden Pope and Bruce Lanphear, SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 7th, 2011.
158. "Crime of the Century: Lead Toxicity in the 20th Century", Panel Presentation and Discussion, UC Davis, Sacramento, California April 7th, 2011.
159. Fourth Annual Controversies in Pediatric Environmental Health Debate, "Should Parent Slather their Children with Sunscreen?" A debate with Russell Chesney, MD and Sophie Balk, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Denver, Colorado, May 1st, 2011.
160. "The Conquest of Lead Toxicity: A Pyrrhic Victory", Canadian Water Network, Ecole Polytechnique de Montreal, Montreal, Canada, June 9th, 2011.
161. "The Contribution of Environmental Influences on Chronic Disease, Canadian Partnership for Health and Environment, Toronto, Canada, June 16th, 2011.
162. "The Second Coming of the Sanitarians", Environmental and Occupational Health Seminar, University of Washington School of Public Health, Seattle, WA, May 12th, 2011.
163. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Sterling Prize in Controversy, Wosk Centre, Simon Fraser University, Vancouver, BC, October 19th, 2011.

164. "Measuring Exposure: The Benefits and Limits of Biomarkers". Canadian Institute for Human Development, Child and Youth Research, Montreal, Canada, December 6th, 2011.
165. "Rachel Carson: Clarity of Vision". SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA, January 6th, 2012.
166. "The Truth About Toxins: What Parents and Health Professionals Should Know". Environmental Influences on Neurodevelopment: Translating the Emerging Science into Public Health Policy". UCLA School of Public Health, Los Angeles, California, January 12th, 2012.
167. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Mattel Children's Hospital, Los Angeles, California, January 13th, 2012.
168. "Why Should We Share Data?", Data Sharing Strategies for Environmental Health Workshop, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, February 6th and 7th, 2012.
169. "The Science and Prevention of Lead Toxicity" (Keynote Presentation), Forum on Lead Toxicity: A Little is Still Too Much", Macquarie University, Sydney, Australia, June 5th, 2012
170. "Canada Environmental Health Atlas Knowledge Translation Workshop", Canadian Public Health Association, Edmonton, Alberta, June 13th, 2012.
171. "First Annual Controversies in Pediatric Environmental Health Debate: Should organophosphate pesticides be reduced or banned?" A debate with Brenda Eskenazi and Bruce Lanphear (Rob McConnell, Moderator). International Society for Environmental Epidemiology, Columbia, SC, August 28th, 2012.
172. "Supralinear Dose-Response Relationship of Environmental Toxicants: Research and Policy Implications." Moderator and Speaker, with Arden Pope, Roel Vermeulen and Bruce Lanphear. International Society for Environmental Epidemiology, Columbia, SC, August 29th, 2012.
173. Tanya Froehlich and Bruce Lanphear, "ADHD and Environmental Toxicants: Time for Prevention?", Society for Development and Behavioral Pediatrics, Phoenix, AZ, September 9th, 2012.
174. "The Epidemic of Childhood Disabilities: A Failure to Regulate". Workshop on Children's Rights and Corporate Responsibility, Green College, University of British Columbia, Vancouver, BC, October 19th, 2012.
175. "Low-level Toxicity: Much Ado About Nothing?", Department of Preventive Medicine Seminar, University of Southern , California, Los Angeles, California, October 23rd, 2012.
176. "Reflections on Silent Spring". (Invited Keynote). International Society for Exposure Sciences, Seattle, Washington, October 28th, 2012.

177. "Randomized Controlled Trials in Children's Environmental Health: Underutilized or Unethical?" The University of Washington Northwest Pediatric Environmental Health Specialty Unit and Center for Child Environmental Health, Seattle, Washington, February 26th, 2013.
178. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". Dali Lana School of Public Health and of School Environment, University of Toronto, Toronto, Ontario, March 26th, 2013.
179. "The Ongoing Search for a Threshold". International Conference of Toxicology, Seoul, Korea, July 1, 2013.
180. "Blood Lead Concentrations and Cardiovascular Mortality in the United States: The NHANES Mortality Follow-up Cohort Study". International Society for Environmental Epidemiology, Basel, Switzerland, August 2, 2013.
181. "The Conquest of Lead Poisoning: A Pyrrhic Victory". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
182. "Striking at the Root: Changing the Narrative on the Causes of Disease". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
183. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 26, 2013.
184. "Low-level Toxicity: Policy Implications for the 21st Century". Symposium on Policy Implications of Environmental Exposures in the 21st Century. Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 27, 2013.
185. "Excavating the Enigmas of Childhood Lead Toxicity". Network for Soil Contamination Research (INSCR), Delhi University, New Delhi, India. October 22nd, 2013.
186. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure", World Health Organization, New Delhi, India. October 24th, 2013. "The Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." National Institute of Environmental Health Sciences, Raleigh-Durham, NC, November 10th, 2013.
187. "Protecting Children from Environmental Toxins". Japan Dioxin and Endocrine Disruptors Preventive Action, Tokyo, Japan, November 24th, 2013.
188. "ADHD: A Preventable Epidemic?" Alberta Children's Hospital, Calgary, Alberta, December 16th, 2013.
189. "Little Things Matter: The Impact of Toxins on the Developing Brain". Early Years Conference, Vancouver, British Columbia, January 30th, 2014.
190. "Little Things Matter: The Impact of Toxins on the Developing Brain". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.

191. "Low-level Toxicity of Environmental Toxins: Much Ado About Nothing?". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.
192. "The Canadian Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." School of Occupational and Environmental Health, University of British Columbia, March 28th, 2014.
193. "Little Things Matter: The Impact of Toxins on the Developing Brain". British Columbia Healthy Child Alliance, Vancouver, British Columbia, April 2nd, 2014.
194. "Sixth Annual Controversies in Pediatric Environmental Health Debate, E-Cigarettes: A weapon in the war against tobacco or a threat to tobacco control. (Moderator). Featuring Greg Connelly and James Sargent. Pediatric Academic Societies, Vancouver, May 4th, 2014.
195. "Striking at the Root Causes of Chronic Disease in Children" (Moderator). James Sargent, Joel Bakan and David Kessler, May 5th, 2014.
196. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). OHKA Healthy Homes Alliance, Omaha, Nebraska, May 15th, 2014.
197. "Excavating environmental risk factors for autism: Suspects and strategies". A workshop on examining a multi-systems approach to autism and the environment: challenges and opportunities for research". Toronto, Ontario, June 23rd-24th, 2014.
198. "Lead Poisoning: Tackling a Global Problem" (Co-Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
199. "Interventions to Reduce Exposures to Environmental Hazards in Pregnant Women and Children", (Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
200. 3rd Annual ISCHE-Sponsored Debate: Should there be any restrictions on universities or academicians receiving payment from industry or other sources? (Moderator). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
201. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, September 5th, 2014.
202. "Environment Matters", Children's Environmental Health Panel. Society for Environmental Journalists, New Orleans, Louisiana, September 6th, 2014.
203. "Insidious Influence of Industry on Science: How Corporations Undermine Science", 5th Annual C. Everett Koop Distinguished Lecture, "Corporate Threats to Children's Health", with Joel Bakan and James Sargent, Dartmouth University, New Hampshire, October 6th, 2014.
204. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, Montefiore Medical Center, New York, New York, October 8th, 2014.

205. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). Prenatal Environmental Health Education (PEHE) Conference, University of Ottawa. Ottawa, Ontario, November 21st, 2014.
206. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). ISEE Asian Regional Meeting, Shanghai, China, November 30th, 2014.
207. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, ISEE Asian Regional Meeting, Shanghai, China, November 31st, 2014.
208. "Data Visualization", with Joe Braun and Allan Just, Pediatric Environmental Health Scholars Retreat, Reston, VA, December 6th, 2014.
209. "Victories in Public Health: Progress or Adaptation?" SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 8th, 2015.
210. "Food in the Industrial Era: Is Backward the Way Forward?" Children's Environmental Health Network, Austin, Texas, February 4th, 2015.
211. "Excavating the enigmas of childhood lead toxicity". Broken Hill City Council and Lead Reference Group, Broken Hill, New South Wales, Australia, March 3rd, 2015.
212. "Prevention Paradox: Why a Little Lead is Too Much". Unequal Exposure Symposium, Climate Change Research Center, University of New South Wales, March 5th, 2015, Sydney, Australia.
213. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 23rd, 2015.
214. "The Staggering Cost of Lead Toxicity and the Unbelievable Benefit of Preventing It". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 24th, 2015.
215. Seventh Annual Controversies in Pediatric Environmental Health Debate, "GMOs: A Hazard or Harvest of Health?" A debate with Joel Forman, MD and Daniel Goldstein, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, San Diego, California, April 27th, 2015.
216. "Impact of Dwellings on Child Health", Canadian Green Building Council Conference, Vancouver Convention Center, Vancouver, BC, April 28. 2015.
217. "Impact of Tobacco on the Developing Brain", Developmental Effects of Nicotine and Implications for Emerging Tobacco Products, Rockville, Maryland, May 5th, 2015.
218. "Impact of Toxins on the Developing Brain" India Tour (Bengaluru, Trivandrum, Kolkata, and Chandigarh) Sponsored by PAN-India, September 4th-11th, 2015.
219. "Impact of Dwellings on Child Health", Green School Summit, Calgary, Alberta, September 25th. 2015.

220. "Prevention Paradox: Why a Little Lead is Too Much", A debate with George Rhoads, Montefiore Medical Center, Tarrytown, October 2nd, 2015.
221. "Crime of the Century: Our Failure to Prevent the Lead Pandemic" (Keynote Presentation), University of Cincinnati Department of Environmental Health 50th Anniversary Gala, Cincinnati, Ohio, October 9th, 2015.
222. "Impact of Toxins on the Developing Brain" (Keynote Presentation) Children's Environmental Health Centers Annual Meeting, Washington, DC, October 31, 2015.
223. "The Impact of Toxins on the Developing Brain: Our Failure to Prevent Brain-based Disorders in Children", National Core for Neuroethics, UBC November 12th, 2015.
224. "Impact of Dwellings on Child Health", Canada Green Building Council, Toronto, ON Green, December 1st, 2015.
225. "The Tortuous Road to Prevention: Are We There Yet", Air Quality and Impacts on Health: Beyond the Heart and the Lungs, The Lung Association of BC, February 28th, 2016.
226. "Lead's Long Shadow: What the Story of Flint, Michigan Means for All of Us", with Bruce Lanphear, Mona Hanna-Attisha and Marc Edwards. Collaborative on Health and the Environment Webinar, March 8th, 2016.
227. "Little Things Matter: The Impact of Toxins on the Developing Brain", Collaborative on Health and Environmental Alaska Working Group Webinar, March 9th, 2016.
228. "Victories in Public Health: Progress or Adaptation?", Symposium Against Indifference, Ashland University, Ashland, Ohio, April 5th, 2016.
229. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote), Children's Environmental Health: New Findings from California Research, Sacramento, California, April 7th, 2016.
230. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Distinguished Visiting Professor in Health Law, Loyola University, Chicago, Illinois April 21st, 2016.
231. "The Population Impact of Toxins on Intellectual Abilities: Implications for Policy and Prevention", in Symposia on Environmental Toxins and the Brain: Growing Evidence of Risk, Pediatric Academic Societies, Baltimore, MD, May 2nd, 2016.
232. "Data Visualization and Video Production for Public Consumption", in Symposia on Innovative Tools to Enhance Knowledge Translation of Environmental Health: Data Visualization, Videos and Message Mapping, (co-Moderated by Mark Miller and Bruce Lanphear), Pediatric Academic Societies, Baltimore, MD, April 30th, 2016.
233. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Michigan State University, Flint, MI, May 7th, 2016.

234. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Johns Hopkins University School of Public Health, Baltimore, MD, May 7th, 2016.
235. "Little Things Matter: The Impact of Toxins on the Developing Brain", Baltimore, MD, International Medical Federation Autism Research (IMFAR), May 8th, 2016.
236. "Public Health Matters: Videos on Toxic Chemicals, Air Pollutants and the Prevention Paradox", Mongolian National University of Medical Sciences, June 23, 2016.
237. "Little Things Matter: The Impact of Toxins on the Developing Brain", USC Annenberg Center for Health Journalism, July 18th, 2016.
238. "Preventing Lead Toxicity", California Environmental Protection Agency, Occupational Environmental Health Hazard Assessment, September 23rd, 2016.
239. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease," World Issues Forum, Fairhaven College, University of Western Washington, (with Bob Lanphear), November 2, 2016.
240. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Pediatric Grand Rounds, Maimonides Hospital, November 15th, 2016.
241. "Little Things Matter: The Impact of Toxic Chemicals on the Child Health" (Keynote), Hudson Valley Perinatal Conference, November 16th, 2016.
242. "Little Things Matter: The Impact of Toxins on the Developing Brain", IPEN, San Francisco, CA, November 18th, 2016.
243. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", SFU, UBC and UW Annual Occupational and Environmental Health Conference Semiahmoo, WA, January 5th, 2017.
244. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", University of New Brunswick, January 25th, 2017.
245. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", New Brunswick Children's Environmental Health Collaborative, January 26th, 2017.
246. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Rockefeller Center, Bellagio, Italy, February 22nd, 2017.
247. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", The Science in Society Speaker Series, Okanagan College, Vernon, BC, April 6th, 2017.
248. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (invited plenary), Vancouver, British Columbia, Canadian Pediatric Society, June 3rd, 2017.
249. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Macquarie University, Sydney, Australia, September 29th, 2017.

250. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Brown University, Providence, Rhode Island, October 13th, 2017.
251. Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Health? University of Alaska, Alaska Tribal Health Consortium, Anchorage, Alaska, November 2nd, 2017.
252. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (Keynote), All Alaska Pediatric Conference, Anchorage, Alaska, November 3rd, 2017.
253. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", CINBIOSE 30th Anniversary, University of Quebec at Montreal, Montreal, November 9th, -10th, 2017.
254. "The Legacy of Lead Poisoning: Moving towards Prevention". East Chicago Community Meeting, Illinois, November 26th, 2017.
255. "Cause or Cure", NIEHS Environmental Health Seminar, University of Southern California, Los Angeles, California, December 1st, 2017.
256. "Little Things Matter: The Impact of Lead on Brain Development" (Keynote Presentation), Workshop on Lead-Free Schools, Pew Trust, Washington, DC, December 6th-7th, 2017.
257. "Low-level Toxicity of Chemicals: No Acceptable Threshold?" Risk Modeling, Mitigation and Modeling in Health Sciences, Centre de Recherches Mathematiques, Montreal, QC, December 11th, 2017.
258. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Department of Psychology and Neuroscience, York University, Toronto, ON, December 13th, 2017.
259. "The impact of Pollutants on Human Health: No Safe Levels?", Center for Energy and Environmental Contaminants, Macquarie University, Sydney, Australia, February 13th, 2018.
260. "Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Children's Health?", Department of Pediatrics, University of Wisconsin at Madison School of Medicine, Madison, Wisconsin, March 1st, 2018.
261. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Wisconsin Environmental Health Network, Madison, Wisconsin, March 2nd, 2018.
262. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Biennial Atlantic Symposium on Learning Disabilities Association, Fredericton, NB.
263. "Crime of the Century: The Failure to Prevent the Lead Pandemic" (Keynote). 11th UK and Ireland Environmental and Occupational Epidemiology, John Snow Lecture Hall, London School of Hygiene and Tropical Medicine, April 27th, 2018.
264. "The Impact of Pollutants on Human Health: No Safe Levels?" From Toxicology to Planetary Health, London School of Hygiene and Tropical Medicine, April 27th, 2018.

265. Topic Symposium: “Toxic Chemicals and the Rise of Chronic Disease in Childhood: A Preventable Epidemic?” (chair and speaker), Pediatric Academic Societies, May 7th, 2018.
266. “Prevention Paradox; Why a Little Lead is Too Much”, Ontario Water Advisory, Toronto, CA, May 7th, 2018.
267. “How the Secrets of Body Care and Cleaning Products Impact your Health”, Panel with Bruce Lanphear, Muhannad Malas and Janie McConnell, Centre for Free Expression, Ryerson University, Toronto, ON, May 7th, 2018.
268. “Prevention Paradox; Why a Little Lead is Too Much” (Keynote), Pittsburgh, PA, Get the Lead Out Conference, May 9th, 2018.
269. “Low-level Lead Exposure and Mortality”, Global Health Forum, Miami, FL, May 23rd, 2018.
270. “Unleashing the Power of Prevention: Targeting Toxic Chemicals and Pollutants”, Canadian Public Health Association, Montreal, QC, May 28th, 2018.
271. “The Impact of Pollutants on Human Health: No Safe Levels?” Chemicals Management Plan Stakeholder Advisory Council, Health Canada, May 30th, 2018.
272. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Pediatric Grand Rounds, University of California – Davis, Sacramento, CA, June 8th, 2018.
273. “Why a Little Lead is Too Much”, Health Canada, Ottawa, ON, August 29th, 2018.
274. “Unleashing the Power of Prevention: Mobilizing Science to Prevent Disease”, ISEE-ISES Workshop, Ottawa, ON, August 30th, 2018.
275. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, LA Lead Summit: A Strategy for Prevention, University of Southern California, September 14th, Los Angeles, CA.
276. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Children’s Hospital of Orange County, Orange County, CA, September 19th, 2018.
277. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, Hurley Medical Center, Flint, Michigan, October 3rd, 2018.
278. “Lead and The Mysterious Decline in Coronary Heart Disease”, National Institute of Occupational Safety and Health, Cincinnati, OH, October 11, 2018.
279. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Grand Rounds, Oregon State Health University, Portland, OR, October 23, 2018.
280. “The Impact of Pollutants on Human Health: No Safe Levels?” Oregon Environmental Council, Portland, OR, October 23, 2018.
281. “Little Things Matter: The Impact of Toxic Chemicals and Organic Food on Children’s Health”, HIPP Scientific Symposium on Organic Food, Kranzberg, Germany, October 30, 2018.

282. “The Mysterious Decline in Coronary Heart Disease”, Harvard University Lead Summit, Cambridge, MA, November 15th, 2018.
283. “The Impact of Pollutants on Human Health: No Safe Levels?” Department of Epidemiology, UMass, Amherst, MA, November 16th, 2018.
284. “Little Things Matter: The Impact of Toxic Chemicals on Human Health”, School of Public Health, Oregon State University, Corvallis, Oregon, April 12th, 2019.
285. Why A Little Lead is Too Much: An Intimate History”, “The Impact of Pollutants on Human Health: No Safe Levels?”, Graduate Course in Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.
286. “The Impact of Pollutants on Human Health: No Safe Levels?”, Department of Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.

Grants

Active Grant Awards

1. Consultant (Joseph Braun, PI). Early Life Perfluoroalkyl Substance Exposure and Obesity: Mechanisms and Phenotyping. 02/01/2016-01/31/2021. National Institutes of Health, \$523,725 (5% effort). The purpose of this award is to study the impact of exposure to perfluoroalkyl chemicals on the development of child obesity, adverse cardiometabolic markers and gene regulation. (2.5% effort)
2. Co-Applicant (Linda Booij, Maryse Bouchard PI). In utero exposure to Bisphenol-A and the developing brain in humans: A longitudinal study of epigenetic mechanisms. 03/01-2016 – 03/31/2019. Canadian Institutes of Health Research (CIHR), \$344,025. (2.5% effort).
3. Principal Investigator (Multiple PI Award with Christine Till). “Impact of early life fluoride exposure on cognitive and behavioural outcomes in children”. NIEHS, 09/30/16 – 05/01/19, \$296,683 (10% effort).
4. Consultant (Aimin Chen, Principal Investigator). Developmental neurotoxicity of organophosphate and novel brominated flame retardants in children. National Institute for Environmental Health Sciences. 1RO1ES028277. 09/30/2017-06/30/22 (10% effort).
5. Mentor (Cynthia Curl, Principal Investigator). Measurement of Agricultural and Dietary Glyphosate Exposure among Pregnant Women. National Institutes of Environmental Health Sciences. 1KO1ES028745-01A1. 09/01/2018-08/31/2022 (5% effort).

Past Grant Awards

1. Principal Investigator, "Dust-Lead and Blood Lead Levels among Urban Children". The National Center for Lead-Safe Housing, \$561,619, 06/15/93 to 08/31/94. Department of Housing and Urban Development Contract MDLPT0001-93. (25% effort).
2. Principal Investigator, "Determinants of Lead Exposure among Children in Monroe County, NY", NIEHS Pilot Grant, University of Rochester School of Medicine and Dentistry, Department of Environmental Medicine. \$7,600, 06/15/93 to 12/31/95. (0% effort)
3. Principal Investigator, "The Effectiveness of Dust Control in Reducing Children's Blood Lead Levels" U.S. Department of Housing and Urban Development, \$128,394, 04/01/94 to 05/30/95. (25% effort).
4. Principal Investigator, "Primary Prevention of Exposure to Lead". Centers for Disease Control and Prevention, \$832,228, 09/30/94 to 10/01/98. (25% effort)
5. Principal Investigator, "Lead-Contaminated House Dust and Children's Blood Lead Levels". National Center for Lead-Safe Housing, \$43,260, 10/01/96 to 03/30/96. (25% effort).
6. Co-investigator (Christy, PI), "Tuberculosis Screening in Children". New York Department of Health, \$15,000, 01/01/95 to 12/31/96. (0% effort)
7. Co-investigator (Weitzman, PI), "Fellowship Training in General Pediatrics" (Grant # D28PE50008). Bureau of Health Professions, HRSA, U.S. Public Health Service, \$1,752,816, 06/01/96 to 05/30/97. (10% effort).
8. Principal Investigator, "Neurobehavioral Effects of Low-Level Childhood Lead Exposure". University of Rochester School of Medicine & Dentistry, \$8,560, 06/01/96 to 05/30/97. (0% effort)
9. Principal Investigator, "Neurobehavioral Effects of low-level Lead Exposure in Children". NIEHS Pilot Grant, University of Rochester Department of Environmental Medicine, \$20,035, 09/01/97 to 08/30/97. (0% effort).
10. Co-investigator (Howard, PI), "Effect on Breastfeeding of Pacifiers and Bottle Feeding". Bureau of Maternal and Child Health, \$420,333, 10/01/96 to 09/30/00. (2.5% effort)
11. Co-investigator (Canfield, PI) "Lead and Children's Cognitive Functioning", Research Grants Program, Cornell University. \$17,000, 10/01/96 to 09/31/97 (0% effort).

12. Principal Investigator, "Neurobehavioral Effects of Low-Level Lead Exposure in Children" (RO1-ES 08338). National Institute of Environmental Health Sciences, 12/01/96 to 11/31/01, \$1,946,848. (25% effort).
13. Co-investigator, (Aligne, PI). "Reduction in Passive Smoking among Children with Asthma: A Randomized Trial of HEPA Air Filtration." 10/01/96 to 09/31/97, \$6,000. KIDD Grant, Rochester General Hospital (0% effort).
14. Co-investigator, (DeWitt, PI). "Faculty Development in General Pediatrics". Bureau of Health Professions, Health, Department of Health and Human Services 07/01/97 to 06/30/00, \$338,000. (15% effort).
15. Principal Investigator, "A Side-by-Side Comparison of Allergen Sampling Methods", U.S. Department of Housing and Urban Development, 01/02/98 to 12/31/98, \$163,065. (15% effort).
16. Principal Investigator, "National Research Service Award - Fellowship Training in General Pediatrics and Adolescent Medicine" (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/03. \$634,408. (0% effort).
17. Co-investigator, (Steiner, PI) "Survey of Directors and Graduates of NRSA Fellowship Training Programs", Health Resources and Services Administration, Department of Health and Human Services. 06/01/98 to 06/30/99.
18. Principal Investigator, "Effect of Soil Remediation on Children's Blood Lead Levels in Midvale, Utah". U.S. Environmental Protection Agency, 08/01/98 to 07/30/99. \$62,550. (15% effort).
19. Co-investigator, (Phelan, PI) Trends and Patterns in Playground Injuries among U.S. Children." Ambulatory Pediatric Association, 05/05/99 to 05/04/00. \$9,000 (0% effort).
20. Principal Investigator, "Risk Assessment for Residential Lead Hazards". U.S. Department of Housing and Urban Development, 09/01/99 to 08/30/00. \$102,435. (25% effort).
21. Principal Investigator, "Residential Exposures associated with Asthma in U.S. Children and Adolescents" U.S. Department of Housing and Urban Development, 07/16/99 to 03/15/00. \$30,400. (20% effort).
22. Principal Investigator, "Effectiveness of Lead Hazard Control Interventions – A Systematic Review" National Center for Lead-Safe Housing, 10/01/99 to 06/01/00. \$22,500 (10% effort).
23. Principal Investigator, "Racial Disparity in Blood Lead Levels due to Genetic Variation in Calcium Absorption". NIEHS Pilot Grant, Center for Environmental Genetics, University of Cincinnati, 04/01/00 to 03/31/01. \$28,130 (0% effort).
24. Principal Investigator, "International Pooled Analysis of Prospective, Lead-Exposed Cohorts". National Institute of Environmental Health Sciences, National Institutes of Health, 08/15/00 to 09/14/01, \$16,000. (2.5% effort).

25. Principal Investigator, "A Randomized Trial to Reduce ETS in Children with Asthma" (RO1-HL/ES65731). National Heart, Lung and Blood Institute, National Institutes of Health, 09/29/00 to 09/28/04, \$1,546,848. (25% effort).
26. Co-investigator, (Geraghty, PI) "Breastfeeding Practices of Mothers of Multiples". Ambulatory Pediatric Association, 05/01/01 to 04/30/02. \$5,000 (0% effort).
27. Principal Investigator (Subcontract), "A Longitudinal Study of Lead Exposure and Dental Caries". National Institute of Dental and Craniofacial Research, National Institutes of Health, 08/01/01 to 07/30/04. \$300,000 (10% effort).
28. Co-investigator (Phelan, PI), "Fatal and Non-Fatal Residential Injuries in U.S. Children and Adolescents" U.S. Department of Housing and Urban Development, 03/01/01 to 11/31/01. \$40,700. (5% effort).
29. Principal Investigator, "Prevalent Neurotoxicants in Children" (PO1-ES11261). National Institute for Environmental Health Sciences and U.S. Environmental Protection Agency, 09/01/01 to 09/31/06, \$5,000,000. (30% effort).
30. Principal Investigator, "International Pooled Analysis of Lead-Exposed Cohorts". Centers for Disease Control (RO1/CCR 521049). Centers for Disease Control, 09/15/01 to 09/14/02, \$28,473. (3% effort).
31. Principal Investigator, supplement to "Prevalent Neurotoxicants in Children" (PO1-ES11261). NIEHS, 09/01/02 to 09/31/07, \$1,800,000. (10% effort).
32. Co-Investigator, "ADHD Phenotype Network: Animal Model to Clinical Trial". National Institute of Neurologic Diseases, 09/15/02 to 06/30/05 (15% effort).
33. Principal Investigator, "Linkage of ADHD and Lead Exposure", Springfield, Ohio Department of Health, 02/01/03 to 06/01/04, \$25,000. (0% effort).
34. Co-investigator (Yolton, PI) "Explorations of ETS Exposure on Child Behavior and Sleep" NIEHS, 04/01/04 to 03/30/06, \$300,000. (5% effort).
35. Co-investigator (Haynes, PI) "MRI as a Biomarker of Manganese Exposure". NIEHS, 09/01/04 to 08/30/06, \$300,000. (5% effort).
36. Co-investigator (National Center for Healthy Housing, PI) "Development of a Standardized Housing Assessment for Asthma", U.S. Department of Housing and Urban Development, 11/01/05 to 10/31/07, \$50,000. (5% effort).
37. Co-Investigator (Hershey, PI) "Epithelial Genes in Allergic Inflammation" National Institutes of Allergy and Infectious Diseases", 07/01/06 to 06/30/07, \$4,787,541. (3% effort).

38. Co-Investigator and Mentor (Wilson, PI), "Racial Difference in DNA Adducts in Tobacco-Exposed Children". Dean's Scholar Award, University of Cincinnati, 02/22/06 to 01/21/09, \$150,000 (5% effort).
39. Principal Investigator, "National Research Service Award - Fellowship Training in Primary Care Research," (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/08. \$1,600,000. (0% effort).
40. Co-Investigator and Mentor (Kahn, PI). "Childhood Asthma in an Era of Genomics: Will the Generalist's Role be Recast?" Robert Wood Johnson Generalist Physician Faculty Scholars Program" 06/01/04 to 05/30/08, \$300,000.
41. Co-Investigator and Mentor (Spanier, PI), "Exhaled Nitric Oxide to Manage Childhood Asthma". National Heart, Lung and Blood Institute, 07/01/06 to 06/31/08, \$200,000 (10% effort).
42. Co-investigator (Sub-Contract PI), BYPL Vanguard Center (Specker, Principal Investigator), "National Children's Study", National Institute for Child Health and Development, 11/01/05 to 10/31/10, \$500,000. (20% effort). [Relinquished with relocation to SFU].
43. Associate Director and Co-Investigator, (Ho, PI). "Center for Environmental Genetics," NIEHS, 04/01/08 to 3/31/13, \$1,000,000 (10% effort). [Relinquished with relocation to SFU.]
44. Co-Investigator (Yolton, PI). "Tobacco Smoke and Early Human Behavior". Clinical Innovator Award, Flight Attendant Medical Research Institute", 07/01/07 to 06/30/10, \$300,000. (3% effort).
45. Co-Investigator (Spanier, PI). "Low Level Prenatal Tobacco Exposure and Infant Wheeze." Young Clinical Scientist Award, Flight Attendant Medical Research Institute, 07/01/07 to 06/30/12, \$300,000. (5% effort).
46. Co-Investigator and Mentor (Spanier, PI). K23, "Prenatal Low Level Tobacco & Phthalate Exposure and Childhood Respiratory Health". National Institute for Environmental Health Sciences, 12/1/07 to 11/30/12, \$623,679 (0% funded effort).
47. Co-investigator (Yolton, PI). "Neurobehavioral effects of insecticide exposure in pregnancy and early childhood." NIEHS, 09/01/09 to 08/31/12.
48. Principal Investigator (Bruce Lanphear, PI), "A Community-Based Trial to Prevent Lead Poisoning and Injuries," National Institute for Environmental Health Sciences, 04/01/07 to 03/30/13, \$2,000,000. (25% effort).
49. Co-Investigator (Kim N. Dietrich, PI). "Early Lead Exposure, ADHD & Persistent Criminality: Role of Genes & Environment," National Institute for Environmental Health Sciences, 04/01/07 to 3/31/2013, \$1,250,000. (2.5% funded effort).

50. Co-Investigator and Sub-Contract PI (Brenda Eskenazi, PI). This supplemental award was to conduct a pooled analysis of prenatal organophosphate pesticide exposures with birth outcomes and neurodevelopment in children using 4 US birth cohorts. NIEHS, 09/01/2009 to 08/31/2013, \$96,000 (0% effort).
51. Mentor and Supervisor (Glenys Webster, PI). Michael Smith Foundation for Health Research Postdoctoral Training Award, 03/01/12 to 02/28/15, \$134,500 (5% effort).
52. Co-Principal Investigator (Tye Arbuckle, PI). Maternal-Infant Research on Environmental Chemicals: Effects on Child Development (MIREC-CD). 06/26/11 to /5/25/14, Health Canada Chemical Management Program, \$283,000 (10% effort).
53. Co-Investigator (Patti Dods and Amanda Wheeler, co-PIs). Phthalate Exposure and the development of asthma in the CHILD Study. 06/01/11 to 05/30/14, Health Canada Chemical Management Program, \$204,000 (5% effort). Consultant (Stephanie Engel, PI). A pooled investigation of prenatal phthalate exposure and childhood obesity. 11/01/2012 – 10/31/15, NIEHS. \$275,000. (5% effort).
54. Co-Investigator (Ryan Allen, PI). A randomized air filter intervention study of air pollution and fetal growth in a highly polluted community. 06/08/2012 – 05/30/15, CIHR \$348,000 (10% effort).
55. Co-Investigator (William Fraser and Tye Arbuckle, co-PIs). MIREC-CD Biomonitoring Study in Vancouver. 09/01/2013 – 08/30/2014. Health Canada, \$120,138 (10% effort).
56. Principal Investigator. Knowledge translation tools for capacity building for an online Canadian Environmental Health Atlas. 03/01/12 – 02/28/13, Canadian Institutes of Health Research, \$98,974 (10% effort).
57. Principal Investigator (with Lawrence McCandless). Prenatal exposure to environmental contaminants and fetal growth: How to account for multiplicity when testing multiple statistical hypotheses?. 07/01/2015-06/30/2016. Canadian Institutes of Health Research (CIHR), \$12,000 (5% effort).
58. Principal Investigator, Canadian Environmental Health Atlas Knowledge Translation to produce videos and interactive tools. 06/01/2015-07/30/2016. Canadian Internet Registration Authority, \$50,000 (10% effort).
59. Co-Investigator (Kieran Phelan, PI). “Injury Prevention in a Home Visitation Population”. NICHD, 09/28/10 to 07/31/16, \$2,000,000 (total direct costs over 5 years) (10% effort).
60. Co-applicant (Timothy F. Oberlander, PI). Developmental origins of autism: A population level linked data study of prenatal antidepressant medication exposure. 09/01/2013 – 09/31/2016, Canadian Institutes of Health Research (CIHR), \$285,768.

61. Principal Investigator (Multiple PI Award with Aimin Chen and Kimberly Yoltan).
“Longitudinal study of exposures to PBDEs and PFCs and child behavior”. NIEHS,
04/30/11 – 05/01/17, \$2,150,000 (total direct costs over 5 years) (20% effort).
62. Principal Applicants (McCandless and Lanphear). Biostatistical methods for estimating the
cumulative impact of environmental contaminant exposures on preterm birth. Canadian
Institute for Human Development, Child and Youth Health. 12/06/16-12/05/18, \$200,000
(10% effort).
63. Co-investigator (Ryan Allen, PI). Randomized Interventions to Evaluate the Effects of Air
Pollution Exposure on Children's Health and Development. 03/01/2015 – 03/31/2019,
Canadian Institutes of Health Research (CIHR), \$720,535. (10% effort)
64. Co-investigator (Joseph Braun, PI). Endocrine Disrupting Chemicals, Thyroid Hormones
and Child Neurobehavior. 06/01/2015-03/31/2019. National Institutes of Health, \$471,241
(5% effort). The purpose of this study is test if and when early life exposures to phthalates,
triclosan, or bisphenol A adversely impacts children’s cognition and behavior.
- 65.

Ethics Training for Research

CITI (Collaborative Institutional Training Initiative) (Reference# 7159023). Academic and Regional
Health Centers Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 7160515), Canada GCP Curriculum
Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 8316270), Human Subjects Core
Curriculum, completed on August 17th, 2012.

CITI (Collaborative Institutional Training Initiative) (Reference# 13561457), Academic and Regional
Health Centers Core Curriculum, completed on September 1st, 2014.

CITI (Collaborative Institutional Training Initiative) (Reference# 16954900), Human Subjects Research
Core Curriculum, completed on October 31st, 2015.

Expert Declaration
of
Kathleen M. Thiessen, Ph.D.

May 20, 2020

Food & Water Watch et al. v. Environmental Protection Agency
No. 17-cv—02162

Oak Ridge Center for Risk Analysis, Inc.
102 Donner Drive
Oak Ridge, TN 37830



TABLE OF CONTENTS

I.	SUMMARY OF QUALIFICATIONS	3
II.	SUMMARY OF OPINIONS	4
III.	SUMMARY OF METHODOLOGY	5
	A. Risk Assessment	5
	B. Materials Relied Upon	7
	C. Literature Search for Animal Neurotoxicity Data	8
	D. Systematic Review.....	9
IV.	HISTORIC CONTEXT: 1930s to 2006.....	9
V.	HAZARD CHARACTERIZATION	11
	A. The “Sufficient Evidence” Standard.....	11
	1 Sufficient Evidence from Human Data.....	12
	2 Sufficient Evidence from Animal Data.....	12
	3 Data that EPA Has Found Sufficient for Hazard Determination.....	14
	B. Human Studies on Fluoride Neurotoxicity	17
	C. Animal Studies on Fluoride Neurotoxicity	19
	1 Studies Indexed by the National Library of Medicine (PubMed).....	19
	2 NTP Systematic Review (2015).....	22
	3 NTP Systematic Review (2016).....	23
	4 Assessment of NTP’s Review.....	24
	5 Developmental Studies Published Since NTP Review.....	25
	6 McPherson (2018) and Other “No Effect” Studies.....	25
	D. Other Considerations	27
	1 Dose Response	27
	2 Neuroendocrine Effects	28
	3 Toxicokinetics.....	30
	4 Mode of Action	31
	5 <i>In Vitro</i> Studies	32
	6 Validity of the Database.....	32
	7 Data Gaps.....	35
	E. Conclusion: Neurotoxicity Is a Hazard of Fluoride Exposure.....	35
VI.	QUANTITATIVE DOSE RESPONSE	36
	A. Basis for Using Animal Data	37
	B. Selecting Points of Departure (PODs)	39
	C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day).....	44
	D. Selecting the Uncertainty Factors	45
	1 <i>Intraspecies</i> Variability (UF _H).....	46
	2 <i>Interspecies</i> Variability (UF _A)	47
	3 LOAEL to NOAEL	51
	4 Composite Uncertainty Factor	51
	E. RfD Calculations from Animal Data	52
VII.	EXPOSURE ASSESSMENT	53

VIII.	RISK CHARACTERIZATION	56
A.	Characterization of Highly Exposed and/or Highly Susceptible Populations	56
1	Pregnant Women (Fetus)	57
2	Bottle-Fed Infants	59
3	Elderly	66
4	Renal Impairment.....	68
5	Other Predisposing Factors	68
B.	Margin of Exposure	70
1	Introduction to the MOE Approach and Similarity to the RfD Approach.....	70
2	MOE Analysis.....	71
C.	Assumptions and Key Sources of Uncertainty	77
IX.	RISK DETERMINATION	82
A.	Effects of Fluoridation Chemicals Under the Condition of Use.....	83
B.	Number of People Exposed to Fluoridation Chemicals.....	84
C.	Exposure of Susceptible Subpopulations to Fluoridation Chemicals	85
D.	The Severity of the Hazard (Cognitive Deficits/IQ Loss)	85
E.	Uncertainties	86
	REFERENCES	88
	APPENDIX A. Recent animal studies of fluoride neurotoxicity (Tables A-1 and A-2).....	112
	APPENDIX B. Resume of Kathleen M. Thiessen, Ph.D.	125

I, Kathleen Thiessen Ph.D., declare that:

1. I am a risk assessment scientist at Oak Ridge Center for Risk Analysis in Oak Ridge, Tennessee. For more than 30 years, I have been involved in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment, including fluoride, and in the use of uncertainty analysis for environmental and health risk assessment.

2. I was asked to apply risk assessment frameworks used by the Environmental Protection Agency (EPA) to the current scientific literature on fluoride neurotoxicity to determine whether neurotoxicity is a hazard of fluoride exposure, and whether this hazard is a risk at the levels of fluoride added to drinking water for fluoridation (0.7 mg/L).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 7 and attached herein.

4. In the course of my work as a risk assessment scientist, I have done work for the U.S. Environmental Protection Agency (EPA), the U.S. Department of Energy, the Centers for Disease Control and Prevention, the U.S. Nuclear Regulatory Commission, the National Cancer Institute, and the National Institute for Occupational Safety and Health, as well as a number of other government and private clients.

5. I have authored several reports for the EPA on the health effects of specific environmental contaminants, including Health Issue Assessments of fluorides (hydrogen fluoride and related compounds) and mercuric chloride.

6. More recently, I served on two subcommittees of the National Research Council, one which was asked by EPA to review the toxicologic literature on fluoride (which resulted in the 2006 publication *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*), and one

dealing with guidance levels for air contaminants in submarines. For the latter review, published in 2009, the NRC asked me to write much of the chapter on hydrogen fluoride.

7. Recently, I led the Working Group on Assessment of Exposures and Countermeasures in Urban Environments for the International Atomic Energy Agency's (IAEA) program on Development, Testing and Harmonization of Models and Data for Radiological Impact Assessment. I was also involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity.

8. Throughout my career, I have authored or contributed to a number of open literature publications in peer-reviewed journals such as *Environmental Science and Technology*, *Environmental Pollution*, *Atmospheric Environment*, *Journal of Environmental Radioactivity*, and the *International Journal of Occupational and Environmental Health*. I have also served as a peer reviewer for journals such as *American Journal of Preventive Medicine*, *Environment International*, *Environmental Pollution*, *Risk Analysis*, *Science of the Total Environment*, *Environmental Health Perspectives*, and *Journal of Environmental Radioactivity*, among others.

II. SUMMARY OF OPINIONS

9. Under EPA's *Guidelines for Neurotoxicity Risk Assessment*, there is sufficient evidence to conclude that neurotoxicity is a hazard of fluoride exposure.

10. The animal data on fluoride neurotoxicity are consistent with the epidemiological data in showing a risk of cognitive deficits at doses of fluoride ingested from fluoridated water.

11. Fluoridation chemicals present an "unreasonable risk" of neurotoxic effects, including IQ loss, if assessed under the same risk characterization and risk determination framework that EPA uses in its evaluations of other chemicals under TSCA.

III. SUMMARY OF METHODOLOGY

A. Risk Assessment

12. EPA has stated it “will follow” its *Guidelines on Neurotoxicity Risk Assessment* (hereafter, *Guidelines*) when “evaluating data on potential neurotoxicity associated with exposure to environmental toxicants.”¹ I conducted a risk assessment in accordance with these *Guidelines*, including a Hazard Characterization, Quantitative Dose Response Analysis, Exposure Assessment, and Risk Characterization.

13. Hazard Characterization: Pursuant to the *Guidelines*, I conducted a Hazard Characterization, in which I considered: (1) the animal studies on neuroanatomical, neurochemical, and behavioral effects, including effects on learning and memory; (2) human case reports, including clinician observations of occupationally exposed workers; (3) human epidemiology studies of fluoride and cognitive deficits, including all prospective cohort studies; (4) the literature on fluoride’s neuroendocrine effects; (5) animal and human research on possible modes of action (direct and indirect) by which fluoride affects the brain; (6) dose-response data on fluoride and neurotoxic outcomes in animal and epidemiological studies; (7) the toxicokinetics of fluoride, including data on placental transfer and uptake into the brain; and (8) *in vitro* studies investigating fluoride’s effects on brain cells, including several that used low concentrations.

14. Quantitative Dose Response Analysis: Since the literature demonstrates with high confidence that neurotoxicity is a hazard of fluoride exposure, I turned to the second step of an EPA neurotoxicity risk assessment: Quantitative Dose Response. In a quantitative dose-response analysis, a “Point of Departure” (POD) is identified from the available animal and human data in order to derive a dose that will be without appreciable risk (i.e., a Reference Dose, or RfD). For

¹ EPA (1998a), p. 1.

my analysis, I focused on the animal data, as I understood that Dr. Grandjean had already calculated a POD (i.e., BMDL) from the human birth cohort data.

15. To increase confidence in the risk characterization (a later step in the analysis, discussed below), I did not identify just one POD from the animal data. Instead, I identified the full range of PODs that can be justified, including the *least protective*. After converting these PODs into Human Equivalent Doses (HED), I applied different combinations of uncertainty factors (from non-conservative to conservative) to derive the *full range of reference doses that can be justified from the animal literature*.

16. Exposure Assessment: Consistent with the *Guidelines*, I conducted an Exposure Assessment that focused solely on the condition of use at issue in this case: fluoridation of drinking water. For my initial assessment, I relied primarily, but not solely, on the National Research Council's estimates of fluoride intake from water from the 2006 report. In response to criticisms that NRC's data may no longer be representative of contemporary exposures, I considered EPA's 2019 assessment of water intake data, in which the Agency identified the most scientifically sound and up-to-date data to use for risk assessment. I compared these updated values from EPA with the values I initially used to see if they have any material effect on my risk estimates (they did not).

17. Risk Characterization: Consistent with the *Guidelines*, I integrated the information on hazards and exposures in a risk characterization by, among other things, conducting a "Margin of Exposure" analysis for each of the PODs identified through the Quantitative Dose Response analysis.

18. Risk Determination: For the risk determination, I considered the risk-related factors that EPA has identified as relevant for risk determinations under TSCA. At the time of my initial report, EPA had not yet issued any draft risk evaluations under Section 6 of TSCA, so I relied for

guidance on risk evaluations that EPA had completed under Section 5. In response to criticism on this point, I reviewed the draft risk evaluations that EPA has subsequently issued under Section 6 to assess whether the factors EPA considers under Section 6 affect my initial determination (they do not).

B. Materials Relied Upon

19. For my risk assessment, I have relied upon my background, training and expertise in risk assessment, as well as my existing familiarity with the scientific literature on fluoride, which I first developed through extensive literature reviews for both the EPA and NRC. I also considered the following materials:

20. EPA documents, including (i) the *Guidelines* and other guidance documents that EPA has issued on risk assessment; (ii) risk assessments that EPA has conducted pursuant to the *Guidelines*;² (iii) risk evaluations that EPA has conducted under TSCA; and (iv) EPA's water intake data.

21. The NRC's review of the toxicologic literature on fluoride (NRC 2006), which I co-authored.

22. Animal studies on fluoride neurotoxicity that have been published since the NRC's 2006 review, which I obtained through a search of the National Library of Medicine's online database PubMed, as described further below.

23. The NTP's systematic review of studies addressing fluoride's impact on learning and memory in animals (NTP 2015, NTP 2016).

24. All prospective cohort studies on fluoride and neurodevelopment in humans

²I obtained the complete list of risk assessments that EPA has conducted pursuant to the *Guidelines* via an interrogatory response produced by EPA, which was provided to me by counsel.

(Bashash et al. 2017; Bashash 2018; Broadbent et al. 2015; Green et al. 2019; Shannon et al. 1986; Till et al. 2020; and Valdez-Jiminez et al. 2017).

25. Meta-analyses of the cross-sectional studies on fluoride and IQ (Choi 2012, Duan 2018).

26. The deposition of Dr. Kristina Thayer, the Director of EPA's Integrated Risk Information System (IRIS) and principal author of the NTP's 2015 and 2016 systematic reviews.

27. The deposition of Casey Hannan, the Acting Director of the Oral Health Division of the Centers for Disease Control and Prevention.

28. The deposition of Dr. Tala Henry, the Deputy Director of EPA's Office of Pollution Prevention and Toxics.

29. Studies provided by counsel—much of which I was already familiar with—which I understand were also provided to EPA's experts as well, including Dr. Tsuji.

C. Literature Search for Animal Neurotoxicity Data

30. For the animal literature, I conducted a search of the National Library of Medicine's online database PubMed to identify studies published since the NRC's 2006 review. The search terms used were: "fluoride and brain," "fluoride and learning," and "fluoride and memory."

31. The titles of all studies published since 2006 were reviewed to identify potentially relevant primary studies, and, among potentially relevant studies, abstracts were reviewed to verify relevance. Reviews, studies in Chinese for which translations were not available, and *in vitro* studies were excluded. Full-text copies of all relevant studies were obtained. In total, the search identified 110 papers. Papers that appeared to be reporting effects from the same underlying rodent experiment were treated as one study, leaving 105 distinct studies.

32. The 105 studies I identified are not an exhaustive list of the studies published since

2006, as they do not include studies that were not indexed in PubMed (e.g., studies published in the journal *Fluoride* or in certain Chinese-language journals such as the *Chinese Journal of Endemiology*). In addition, the search terms probably did not identify all relevant studies available on PubMed.

Nevertheless, the studies obtained through this pre-defined search protocol should be a reasonably representative sample of the recent literature.

D. Systematic Review

33. I did not conduct a formal systematic review, but a risk assessment under the *Guidelines* has been considered the effective equivalent of a systematic review.

IV. HISTORIC CONTEXT: 1930s to 2006

34. The early epidemiological studies in the U.S. that claimed to establish the safety of waterborne fluoride (fluoride concentrations ranging from 1 to 8 mg/L in drinking water) did not address the potential for fluoride to cause neurological effects, including IQ loss.³ The primary focus of these early studies was, instead, on skeletal health.

35. Although largely overlooked, some of the early studies of occupationally exposed workers,⁴ as well as some of the early studies of fluoride-exposed animals,⁵ reported central nervous system effects from fluoride exposure. In a 1953 study of monkeys, Wadhwani and Ramasway reported that monkeys with chronic fluorosis “did not conduct themselves with intelligence and agility of mind normally associated with them. There was a significant lack of co-ordination in their behaviour.”⁶ These early observations, some of which remained unpublished,

³ Call et al. (1965); Leone et al. (1954; 1955a; 1955b); McCauley and McClure (1954); McClure (1944); Schlesinger et al. (1956a; 1956b); Stevenson and Watson (1957).

⁴ Roholm (1937); Popov et al. (1974); Duan et al. (1995); Guo et al. (2001); Yazdi et al. (2011).

⁵ Wadhwani and Ramasway (1953); Lu et al. (1961); Rice and Lu (1963); Sadilova et al. (1968).

⁶ Wadhwani and Ramasway (1953).

were largely ignored at the time.

36. The first known study of fluoride and intelligence in humans was published in 1989 by Ren and colleagues in China.⁷ A flurry of similar studies were published in China in the 1990s.⁸ Most of these studies were published in Chinese, and they remained largely unknown outside of China until English translations started to become available after the NRC's report in 2006.

37. In 2006, the NRC concluded that "fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means."⁹ The NRC reached this conclusion based on the histological, biochemical, and molecular findings from animal studies published in the 1990s and early 2000s.¹⁰ The NRC also reviewed two studies that examined the impact of fluoride on learning and memory in animals, but the data were not yet sufficient to draw conclusions on cognitive effects.¹¹

38. As part of its report, the NRC also reviewed the 4 studies on fluoride and intelligence that were then available in English.¹² Various methodological limitations were identified with these studies, but the NRC concluded that the consistency of the results (i.e., reduced intelligence among children exposed to elevated fluoride) warranted further epidemiological research into the potential of fluoride to lower IQ.

39. The NRC also reviewed the toxicologic literature on fluoride's effects on the endocrine system, including the thyroid gland. The NRC concluded that fluoride is an endocrine-disrupting chemical which can alter thyroid function at estimated average intakes as low as 0.01 to

⁷ Ren et al. (1989).

⁸ Qin et al. (1990); Chen et al. (1991); Guo et al. (1991); Lin et al. (1991); Sun et al. (1991); An et al. (1992); Li et al. (1994); Xu et al. (1994); Yang et al. (1994); Duan et al. (1995); Li et al. (1995); Wang et al. (1996); Yao et al. (1996; 1997); Zhao et al. (1996).

⁹ NRC (2006), p. 222.

¹⁰ NRC (2006), pp. 221-222.

¹¹ NRC (2006), pp. 215-216, 221.

¹² Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a; 2003b).

0.03 mg/kg/day in individuals with iodine deficiency.¹³ The NRC recognized the potential relevance of fluoride's endocrine effects to neurotoxicity, noting that depressed thyroid function during pregnancy can lower the IQ of the offspring.¹⁴

40. The NRC's findings on the neurotoxic potential of fluoride have been accepted as an accurate summary of the hazard by the EPA and other federal agencies, including the CDC.

41. My risk assessment builds upon NRC's hazard determinations by considering the large volume of additional research that has been published since the NRC findings were released.

V. HAZARD CHARACTERIZATION

A. The "Sufficient Evidence" Standard

42. The focus of the Hazard Characterization is whether, at some level of exposure, the chemical has a credible potential to cause neurotoxic effects (i.e., whether neurotoxicity is a *hazard* of the chemical). The question of whether this hazard is a *risk* at environmentally relevant exposures is a separate question that is addressed in the Risk Characterization phase (as discussed below).

43. Under the *Guidelines*, hazard assessment is a qualitative determination in which the risk assessor must determine whether "sufficient evidence" of a neurotoxicity hazard exists.¹⁵ A "sufficient evidence" finding "can be based on either human or animal data."¹⁶ EPA has a preference for using human data if suitable data exist;¹⁷ in practice, however, animal data are almost always used.¹⁸

¹³ NRC (2006), pp. 262-263, 266.

¹⁴ NRC (2006), p. 263.

¹⁵ EPA (1998a), pp. 11, 53, 55-56.

¹⁶ EPA (1998a), p. 11.

¹⁷ EPA (2018a), p. 2-1.

¹⁸ EPA (1998a), p. 20.

1. Sufficient Evidence from Human Data

44. For human data, “sufficient evidence” of a neurotoxic hazard exists if epidemiologic studies show that “some neurotoxic effect is *associated* with exposure.”¹⁹ EPA contrasted this requirement of an “association” with what the Agency recognized to be the “more stringent requirement” of “causality.”²⁰ Under the *Guidelines*, there is no requirement to prove causality; evidence of an association is enough.

45. In assessing whether epidemiological studies demonstrate an association with neurotoxicity, EPA has stated that prospective cohort studies “should weigh heavily” in the assessment.²¹ The *Guidelines* recognize that prospective studies are “invaluable for determining the time course for development of dysfunction” and permit “direct estimate of risks attributed to a particular exposure.”²² The only drawback of prospective studies that the *Guidelines* identify are that they “can be very time-consuming and costly.”²³

2. Sufficient Evidence from Animal Data

46. For animal data, “sufficient evidence” of a neurotoxic hazard exists if experimental studies demonstrate a potential neurotoxic hazard in humans.²⁴ The “minimum evidence” necessary to demonstrate a potential hazard is “a single appropriate, well-executed study in a single experimental animal species.” If no individual study is sufficient to establish a hazard, “the total

¹⁹ EPA (1998a), p. 53.

²⁰ EPA (1998a), pp. 53.

²¹ EPA (1998a), pp. 18.

²² EPA (1998a), pp. 17.

²³ EPA (1998a), pp. 17.

²⁴ EPA (1998a), p. 53.

available data may support such a conclusion” including data on toxicokinetics²⁵ and mechanisms of action.²⁶

47. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical, neurochemical, and behavioral.²⁷

48. Neuroanatomical endpoints include changes to the brain, including damage to brain cells, that are detectable under a microscope (i.e., “histological”).²⁸ The *Guidelines* consider neuroanatomical changes to be “of concern,” and EPA has established reference doses for chemicals based on neuroanatomical effects.

49. Neurochemical effects include biochemical changes, such as alterations in neurotransmitter function and effects on enzymes. The *Guidelines* state that neurochemical changes “may be regarded as adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences.”²⁹

50. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, and impairments in learning, memory, and attention.³⁰ EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments.

51. In considering the relevance of the animal data to humans, the *Guidelines* provide four default assumptions. First, EPA assumes that “an agent that produces detectable adverse

²⁵ The *Guidelines* use the term pharmacokinetics. Both pharmacokinetics and toxicokinetics refer to the uptake, distribution, and retention of chemicals, with the former term being more frequently used in the context of pharmaceuticals, and the latter term more frequently used in the context of toxicants.

²⁶ EPA (1998a), p. 56.

²⁷ EPA (1998a), pp. 20-21.

²⁸ EPA (1998a), p. 21.

²⁹ EPA (1998a), p. 55.

³⁰ EPA (1998a), p. 21.

neurotoxic effects in experimental animal studies will pose a potential hazard to humans.”³¹ Second, EPA assumes that neuroanatomical, neurochemical, and behavioral changes “are of concern.”³² Third, EPA assumes that “the neurotoxic effects seen in animal studies may not always be the same as those produced in humans” due to “species-specific differences in maturation of the nervous system, differences in timing of exposure, metabolism, or mechanisms of action.”³³ Fourth, EPA assumes that “humans are as sensitive as the most sensitive animal species tested.”³⁴ These four assumptions are “plausibly conservative,” meaning that “they are protective of public health and are also well founded in scientific knowledge about the effects of concern.”³⁵

3. Data that EPA Has Found Sufficient for Hazard Determination

52. EPA has conducted 10 risk assessments pursuant to the *Guidelines*. In 9 of these risk assessments, EPA found sufficient evidence to make a hazard determination and established Reference Doses (RfDs) or Reference Concentrations (RfCs)³⁶ to protect against the hazard.³⁷ In each of these 9 assessments, EPA based its hazard determination on animal data. For 6 of these 9 assessments, the chemicals had *no* human data on neurotoxicity (Table 1). For the 3 chemicals with some human data, no prospective cohort studies were available.

53. The principal studies³⁸ which EPA has used to establish RfDs have not been

³¹ EPA (1998a), p. 6.

³² EPA (1998a), p. 6.

³³ EPA (1998a), p. 7.

³⁴ EPA (1998a), p. 7.

³⁵ EPA (1998a), p. 7.

³⁶ Reference Doses refer to oral exposures, while Reference Concentrations refer to inhalational exposure. Eight of the 9 neurotoxicity risk assessments established RfDs, while 1 set an RfC. For purposes of simplicity, I will refer to Reference Doses for the remainder of this declaration when discussing these assessments.

³⁷ These 9 risk assessments were performed for BDE-47 (EPA 2008a), BDE-99 (EPA 2008b), BDE-153 (EPA 2008c), BDE-209 (EPA 2008d), Chlorine Dioxide and Chlorite (EPA 2000b), 2-Hexanone (EPA 2009b), Methanol (EPA 2013a), RDX (EPA 2018a), and Trimethylbenzenes (EPA 2016).

³⁸ A principal study is the study that contributes most significantly to the assessment of risk and is generally the basis for the Point of Departure from which a reference value is derived.

“perfect” studies. In fact, in most of the neurotoxicity risk assessments, EPA has identified a number of methodological limitations with the studies. Some of the principal studies did not conform to EPA’s testing guidelines for animal studies; some used relatively small numbers of animals (e.g., 10 per group); and the principal studies that investigated effects from prenatal exposures did not always control for “litter effects,” a methodological deficiency that can skew the effect size in developmental studies. In light of these limitations, EPA had “low confidence” for the studies it relied upon for several of its risk assessments (see Table 1). This did not stop EPA from establishing RfDs for these chemicals.

54. In several of EPA’s neurotoxicity risk assessments, EPA established an RfD despite a relatively small number of animal studies. In the RDX risk assessment, for example, EPA identified 16 animal studies, only two of which had been published. EPA characterized these studies as showing “consistent evidence” of neurotoxicity because 11 of the 16 studies reported neurological effects³⁹ and the effects were generally dose-related (although inconsistencies existed across the studies in terms of the doses that produced effects).⁴⁰ EPA has thus recognized that “consistency” of the evidence is not synonymous with unanimity.

³⁹ EPA (2018a), p. 1-23.

⁴⁰ EPA (2018a), pp. 1-12, 1-18.

Table 1. Chemicals with oral RfDs based on neurological endpoints, assessed according to EPA's Guidelines for Neurotoxicity Risk Assessment.^a

Name of Chemical	Human Neurotoxicity Data? ^b	Principal Study	Confidence in Principal Study	Known Mode of Action?	Effect	Reference
BDE-47	No	Animal	Not given ^c	Inadequate data	Changes in spontaneous motor activity and habituation	EPA (2008a)
BDE-99	No	Animal	Not given ^d	Inadequate data	Neurobehavioral developmental effects; changes in motor activity	EPA (2008b)
BDE-153	No	Animal	Not given ^e	Inadequate data	Spontaneous behavior, learning and memory	EPA (2008c)
BDE-209	No	Animal	Low	Inadequate data	Changes in spontaneous behavior and habituation	EPA (2008d)
Chlorine Dioxide and Chlorite	No	Animal	Medium	No	Neurodevelopmental delay; lowered auditory startle amplitude	EPA (2000b)
2-Hexanone	No	Animal	Medium	Yes	Axonal swelling in peripheral nerves	EPA (2009b)
RDX	One cross-sectional study, 16 case reports	Animal	High	Yes	Convulsions	EPA (2018a)
Trimethylbenzenes	Occupational studies of solvent mixtures, controlled experiments with healthy adults	Animal	Low to Medium	Tentative, based on structurally similar compounds	Decreased pain sensitivity	EPA (2016)

^a EPA (1998a); Federal Register (1998). In addition, an inhalation RfC was derived for methanol based on animal data (EPA 2013a); the confidence in the RfC was considered medium to high.

^b Human studies of neurotoxicity endpoints.

^c Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment of BDE-47 is low" (EPA 2008a, p. 48).

^d Confidence in the principal study was not stated, but the "overall confidence in the RfD [for BDE-99] is low" (EPA 2008b, p. 67).

^e Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment for BDE-153 is low" (EPA 2008c, p. 37).

55. EPA has taken a similar approach to animal data in some of its draft risk evaluations under Section 6 of TSCA. In its NMP risk evaluation, for example, EPA based its risk calculations for chronic exposures in humans on animal data linking NMP to reduced fertility, despite the fact that there were only six animal studies available, three of which found no effect.⁴¹ These contradictory findings were considered a source of uncertainty, but did not stop EPA from using these animal data to assess risk in humans. In fact, EPA made findings of unreasonable risk in humans exposed to lower doses of NMP based on this small body of contradictory data.

B. Human Studies on the Neurotoxicity of Fluoride

56. As noted earlier, the *Guidelines* state that prospective cohort studies “should weigh heavily in the risk assessment process.”⁴² The *Guidelines* also identify other types of human studies that can inform the assessment, including case reports and cross-sectional studies.⁴³

57. In contrast to 9 chemicals for which EPA has established reference doses under the *Guidelines*, there are abundant human data on fluoride neurotoxicity, including 4 high-quality prospective cohort studies with individualized measurements of exposure during the prenatal period.⁴⁴

58. I understand that Dr. Hu and Dr. Lanphear will be addressing the ELEMENT and MIREC birth cohort studies, and I understand that Dr. Philippe Grandjean will be addressing the other epidemiological studies, so I will forego repeating the details here.

⁴¹ EPA (2019d), pp. 173-174.

⁴² EPA (1998a), p. 17.

⁴³ EPA (1998a), pp. 15-16.

⁴⁴ Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

59. As I described in my expert report, the human data on fluoride *strongly* support a hazard determination. Most importantly, each of the 4 prospective studies with measurements of *prenatal* exposure has found large and significant adverse associations with neurodevelopment, including IQ loss and inattention. An additional prospective study has found an association between IQ deficits and fluoride exposure during *infancy*.⁴⁵ These studies—which have consistently detected a significant association between early-life fluoride exposure and cognitive deficits using the most reliable study design identified by the *Guidelines*—are by themselves enough to constitute “sufficient evidence” of a hazard.

60. The consistency of the inverse association between fluoride and IQ in cross-sectional studies also adds important weight to the hazard assessment. Although cross-sectional studies are limited in their capacity to establish causal relationships, this limitation is lessened where the study examines stable populations and stable water fluoride levels.⁴⁶ In any event, the focus of the *Guidelines* is on assessing whether there is a reliable *association* with neurotoxicity, not on definitively proving causality.⁴⁷ As several meta-analyses have demonstrated, the cross-sectional studies show large and significant inverse *associations* between fluoride and IQ, with an average loss of about 7 IQ points.⁴⁸

61. Finally, the case reports of neurological symptoms following fluoride exposure (e.g., general malaise, fatigue, headaches, and difficulties with concentration and memory) add

⁴⁵ Till et al. (2020).

⁴⁶ Under these conditions, measurement of current water fluoride levels may be a reasonable, albeit imperfect, proxy for exposure from the prenatal period onward, and thus the temporality requirement for a causal inference is partially met. A number of the cross-sectional studies on fluoride and IQ have, in fact, expressly limited the study population to children who lived in the same area since birth, which increases the basis for inferring causation. Chen et al. (1991); Choi et al. (2015); Ding et al. (2011), Karimzade et al. (2014a; 2014b); Khan et al. (2015); Lu et al. (2000); Nagarajappa et al. (2013); Rocha Amador et al. (2007); Seraj et al. (2012); Sudhir et al. (2009); Wang et al. (2007); Yao et al. (1996; 1997); Zhang et al. (2015b).

⁴⁷ EPA (1998a), p. 53.

⁴⁸ Choi et al. 2012; Duan et al. 2018.

additional support to the hazard determination. While case reports are generally not sufficient, by themselves, to establish a hazard, the *Guidelines* consider them “useful when corroborating epidemiological data are available.”⁴⁹ Further, as the NRC noted, several of the case reports on fluoride can be characterized as “experimental studies,” since they involved “individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under ‘blind’ conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated.”⁵⁰ There is credible evidence, therefore, that for some sensitive individuals, fluoride exposure may cause overt neurological symptoms, although the NRC called for more research to better understand the issue.

C. Animal Studies on Fluoride Neurotoxicity

62. The animal research on fluoride neurotoxicity was sufficient to permit the NRC to conclude, in 2006, that fluoride interferes with the functions of the brain.⁵¹ The NRC based this finding on the neuroanatomical and neurochemical changes produced by fluoride in laboratory animals. These changes include: reduced protein and phospholipid content; inhibition of acetylcholinesterase; interference with neurotransmitters; increased production of free radicals in the brain (i.e., oxidative stress); neuronal deformations; increased uptake of aluminum; and enhancement of reactive microglia.⁵²

63. Many animal studies have been published since the NRC review which add further support to the hazard determination, as I will now discuss.

1. Studies Indexed by the National Library of Medicine (PubMed)

64. In my search of PubMed, I identified 105 studies that have been published since

⁴⁹ EPA (1998a), p. 15.

⁵⁰ NRC (2006), pp. 208-209.

⁵¹ NRC (2006), p. 222.

⁵² NRC (2006), pp. 221-222.

2006. Of these studies, all but 4 reported associations between fluoride exposure and neurotoxic outcomes.⁵³

65. Table A-1 in Appendix A to this declaration provides data from the 88 animal studies which investigated neuroanatomical and neurochemical endpoints (i.e., “structural” effects), while Table A-2 provides data from the 36 animal studies which investigated learning and memory endpoints (i.e., “functional” effects).⁵⁴ Twenty-nine studies investigated both types of effects and are in both lists.⁵⁵

66. As can be seen in Table A-1, rodent studies published since the NRC review have continued to document structural (e.g., neuroanatomical and neurochemical) changes in the brains of fluoride-treated rodents. These changes include oxidative stress, neuronal degeneration, mitochondrial disturbances, reductions in nicotinic receptors, impaired synaptic plasticity, and neuroinflammation.

67. Among the studies that have investigated both structural and functional effects of fluoride, the former have sometimes (but not always) occurred at lower exposures, suggesting that fluoride can cause cellular and biochemical changes in the brain prior to the manifestation of outwardly demonstrable deficits.⁵⁶ Put another way, deficits in learning and memory likely represent a relatively advanced stage of fluoride neurotoxicity. Nevertheless, both structural and

⁵³ Negative results were reported by Whitford et al. (2009), Pulangan et al. (2018), McPherson et al. (2018), and Jia et al. (2019, which I discuss later.

⁵⁴ For purposes of simplicity, I have used the term “structural” to refer to both neuroanatomical and neurochemical effects. While neurochemical effects are technically “functional” in nature, I use the word “functional” to refer solely to outward manifestations of neurotoxicity (i.e., learning/memory deficits). In this declaration, therefore, “structural” changes refer to all changes observed *in the brain*, while functional effects refer to all changes in *outward behavior* (e.g., learning and memory test performance, etc).

⁵⁵ To facilitate comparisons across these studies, Tables A-1 and A-2 exclude 2 studies of non-rodents as well as four studies in which the fluoride exposure was part of a mixture involving other potentially neurotoxic chemicals, one study involving exposure by a route other than ordinary ingestion, and two behavioral studies with endpoints that did not specifically involve learning and memory.

⁵⁶ See, for example, Agustina et al. (2018); Ma et al. (2015); Niu et al. (2018a); Sun et al. (2018); Wang et al. (2018a); Zhang et al. (2019); Zhao et al. (2019).

functional harms have repeatedly been observed in rodents at water fluoride concentrations between 5 mg/L and 23 mg/L.⁵⁷ As with the RDX literature,⁵⁸ there are some inconsistencies across the studies in the reported doses that can cause certain types of harm; these differences likely result, at least in part, from differences in study design, including differences in timing of exposure, duration of exposure, and strain and sex of animal.

68. Most of the animal studies to date have used subchronic exposure scenarios, which would tend to understate the effect from lifetime exposure. EPA's testing guidelines define a chronic exposure study in rodents as one that lasts at least 12 months.⁵⁹ None of the recent learning studies has lasted 12 months, and only 1 of the recent structural studies has lasted 12 months or more.⁶⁰ Among the studies that have tested animals at multiple points in time, the effects have tended to worsen with time, with some effects not appearing at all until 3 to 6 months of chronic exposure.⁶¹ Since most of the studies on fluoride neurotoxicity have lasted no longer than 3 months, the studies are likely not detecting the full spectrum of fluoride's effects.

69. I understand that EPA is asserting that systemic toxicity, as reflected by reduced body weight, may explain fluoride's observed effect on learning/memory in animals. The *Guidelines* provide that, "If several neurological signs are affected, but only at the high dose and in conjunction with other overt signs of toxicity, including systemic toxicity, *large decreases in body weight*, decreases in body temperature, or debilitation, there is less persuasive evidence of a direct neurotoxic effect."⁶² The *Guidelines* further provide that "At doses causing moderate

⁵⁷ These concentrations of fluoride *ion* correspond to a concentration of approximately 10 to 50 mg/L of *sodium* fluoride, as there are 2.2 parts sodium for each 1 part fluoride.

⁵⁸ EPA (2018a).

⁵⁹ EPA (1998b), p. 1.

⁶⁰ Teng et al. (2018).

⁶¹ For example, Güner et al. (2016); Liu et al. (2011); Yang et al. (2018a); Zhang et al. (2015a).

⁶² EPA (1998a), p. 38.

maternal toxicity (i.e., 20% or more reduction in weight gain during gestation and lactation), interpretation of developmental effects may be confounded.”⁶³ The fact that there is some effect on body weight, therefore, does not, by itself, negate a direct neurotoxic effect; the effect on body weight must be relatively large (i.e., >20%). While some of the animal studies on fluoride do show some body weight reductions, many do *not*—particularly at the lowest doses causing the effects. Systemic toxicity is thus an unlikely explanation of the neurotoxic effects reported.

2. NTP Systematic Review for Australian Government (2015)

70. In 2015, the National Toxicology Program (NTP) completed a systematic review of the animal literature on fluoride neurotoxicity and submitted a report to the Australian government.⁶⁴ The NTP limited its review to studies that have measured learning, memory, and other behavioral effects.⁶⁵ In total, the NTP identified 44 studies of learning and memory, 14 of which were excluded due to risk of bias from lack of randomization, lack of blinding at outcome assessment, or other design deficiencies.⁶⁶ From the remaining 30 studies, NTP concluded that there was “a moderate level-of-evidence for a pattern of findings suggestive of an effect on learning and memory in rats treated during development or adulthood.”⁶⁷ Moderate level of evidence is the second highest level of evidence under NTP’s 5-grade classification criteria.⁶⁸

⁶³ EPA (1998a), p. 46.

⁶⁴ NTP (2015a).

⁶⁵ NTP (2015a), pp. 1, 28.

⁶⁶ In addition to PubMed, NTP searched several additional databases. NTP (2015a), p. 1.

⁶⁷ NTP (2015a), p. 1.

⁶⁸ NTP (2015a), p. 11. Under NTP’s Hazard Identification Scheme, a chemical that has a moderate level of evidence of neurotoxicity in animals and a moderate level of evidence of neurotoxicity in humans is a “presumed” neurotoxicant (NTP 2015b, p. 67, Figure 8).

3. NTP Systematic Review (2016)

71. In 2016, the NTP published an updated version of its systematic review.⁶⁹ In the updated review, NTP identified an additional four studies on learning and memory, two of which were excluded for bias, resulting in a total of 32 studies for its analysis.⁷⁰ NTP maintained its conclusion that the animal evidence is “suggestive” that fluoride impairs learning and memory, but downgraded its confidence in the developmental studies to “low.”⁷¹ NTP had less confidence in the developmental studies due to their general failure to control for litter effects, as well as the relatively few developmental studies that used fluoride concentrations lower than 25 mg/L in drinking water.⁷²

72. The NTP identified several common methodological limitations with the learning and memory studies, including failure to rule out fluoride-induced motor effects as the cause of the apparent cognitive deficits; failure to control for “litter effects” in the developmental studies; lack of blinding; and lack of reported information on the study conditions, including the purity of the fluoride added to the water and the concentrations of fluoride in the rodent chow.

73. In contrast to NTP’s 2015 report, the 2016 report considered the absence of animal studies using 0.7 mg/L (the current recommended fluoride concentration for human drinking water⁷³) to be an important limitation in the research in terms of its relevance to human exposure levels.⁷⁴

⁶⁹ NTP (2016).

⁷⁰ NTP (2016), p. vi.

⁷¹ NTP (2016), p. vii.

⁷² NTP (2016), p. 57.

⁷³ USDHHS (2015).

⁷⁴ NTP (2016), pp. 55, 58.

4. Assessment of NTP's Review

74. The suggestion by NTP that rodent studies should use fluoride concentrations of 0.7 mg/L in order to be relevant to human exposures is at odds with EPA's approach to risk assessment.⁷⁵ As I discuss later, humans are considered much more sensitive to toxicants than are rats and mice, and the EPA has developed procedures to account for this increased sensitivity. The net effect of EPA's procedures is that what might initially seem to be a "high" dose in animal studies may be very relevant to assessing risk in humans at lower doses.

75. By limiting its review to studies investigating learning and memory, the NTP did not consider the much larger number of studies that have investigated neuroanatomical and neurochemical effects, endpoints that are more sensitive and also potentially less susceptible to bias associated with outcome assessment.

76. The NTP correctly identified a number of methodological limitations in the learning/memory studies. The lack of blinding in some studies, for example, does create some uncertainty because lack of blinding can bias results in the direction of the anticipated effect.⁷⁶ Some of the limitations, however, would not be expected to skew the results in a consistent direction across laboratories (e.g., lack of information on the purity of the fluoride compounds). Similarly, litter effects can produce false negatives as well as false positives, and can both inflate and deflate the true effect size.⁷⁷ The impact of these limitations on the reported results is thus unclear, particularly when considering that the studies also have limitations that will make it harder

⁷⁵ The principal author of the NTP study, Kristina Thayer, testified at her deposition that she is no longer comfortable with the assumption of a 1-to-1 equivalence between fluoride exposures in animals and humans; Thayer testified that she would approach the issue differently today, with greater attention to interspecies differences in toxicokinetics and toxicodynamics. (Thayer Deposition at 151:9-152:3, 302:21-303:23). These issues are discussed further below.

⁷⁶ Holman et al. (2015).

⁷⁷ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

to detect effects, including the absence of chronic studies and the absence of studies investigating neonatal exposures that are comparable to formula-feeding exposures in human infants, as discussed further below.

77. Although the NTP expressed concern about the difficulty of distinguishing fluoride's effects on learning/memory from its effects on the motor/sensory system, each of these effects is neurotoxic and a matter of concern.

5. Developmental Studies Published Since the NTP Review

78. Subsequent to the NTP's review, 11 additional developmental studies have reported learning and memory outcomes.⁷⁸ Ten of these studies found deficits in the fluoride-treated groups. Notably, the Bartos et al. studies, which controlled for litter effects, found impairments in learning and memory at a fluoride concentration of just 5 mg/L. I will discuss these studies further in the Quantitative Dose Response section below.

6. McPherson (2018) and Other "No Effect" Studies

79. McPherson et al. (2018) is the one developmental study published since the NTP review that did not find clear adverse effects on learning and memory, although it did find a significant increase in pain sensitivity (a neurotoxic effect).

80. There are several features of the McPherson study that may help to explain the absence of a clear effect on learning and memory. First, unlike the overwhelming majority of previous studies on fluoride neurotoxicity, the McPherson study used Long Evans Hooded rats, which some have suggested may have lower sensitivity to fluoride than other strains.⁷⁹ To date,

⁷⁸ Bartos et al. (2018; 2019); Chen et al. (2018a); Cui et al. (2017); Ge et al. (2018); McPherson et al. (2018); Sun et al. (2018); Wang et al. (2018a); Zhao et al. (2019); Zhu et al. (2017); Zhou et al. (2019).

⁷⁹ Elliott (1967).

three studies⁸⁰ have examined the effect of fluoride on learning in Long Evans rats, and all three have failed to find an effect.⁸¹

81. Second, in contrast to most of the other developmental studies, McPherson et al. did not start the exposure until the 6th day of gestation.⁸² As pregnancy in rats lasts approximately 21 days, any effects due to exposures early in, or preceding, the pregnancy may not have been detected by McPherson's study design.

82. Third, the offspring in the McPherson study had virtually no fluoride exposure during the neonatal period because the rat pups were breastfed during the pre-weaning period. This is important because the fluoride content of breast milk in rats (as with other mammals, including humans) is negligible, even when the mother is consuming large quantities of fluoride.⁸³ The rats in the McPherson study thus missed a potentially key period of vulnerability (early infancy)—an important limitation given the widespread use of infant formula among human neonates.⁸⁴

83. In addition to the McPherson study, three other studies (with weaker study designs) reported no neurotoxic effects from fluoride exposure.⁸⁵ These three studies include Whitford et al. and Pulungan et al. which started with adult animals, and an unusual study by Jia et al. which started at gestational day 9. All or part of the gestational period was thus missed in each of these studies.

⁸⁰ Elliott (1967); Varner et al. (1994); McPherson et al. (2018).

⁸¹ The plausibility of strain-specific differences between Long Evans and other rats is supported by other research which has found that Long Evans Hooded rats have different sensitivities to teratogenic substances in utero than Sprague-Dawley rats (Kang et al. 1986).

⁸² McPherson et al. (2018).

⁸³ Fluoride concentrations in mammalian milk are very low in comparison to the mother's fluoride intake, even when the mother's fluoride intake is quite high (NRC 2006, pp. 33, 36; Drinkard et al. 1985).

⁸⁴ This limitation is not unique to the McPherson study, as all other developmental studies on fluoride have failed to supplement the pup's exposure during the breastfeeding stage.

⁸⁵ Whitford et al. (2009); Pulungan et al. (2018); Jia et al. (2019).

84. According to the *Guidelines*, “To judge that an agent is unlikely to pose a hazard for neurotoxicity, the minimum evidence would include data from a host of endpoints that revealed no neurotoxic effects.”⁸⁶ This evidence does not exist for fluoride. To the contrary, almost all studies, including McPherson et al. (2018), have reported adverse effects on at least one of the endpoints measured.

D. Other Considerations

1. Dose Response

85. The *Guidelines* recognize that “determining a hazard often depends on whether a dose-response relationship is present,”⁸⁷ and thus “dose-response evaluation is a critical part of the qualitative characterization of a chemical’s potential to produce neurotoxicity.”⁸⁸ Because “human studies covering a range of exposures are rarely available,” the *Guidelines* state that the dose-response evaluation will typically be limited to animal data.⁸⁹

86. In contrast to the chemicals that EPA has evaluated under the *Guidelines*, there is abundant dose-response data for fluoride from *human* studies. Most importantly, the ELEMENT and MIREC birth cohort studies have found linear dose-response relationships between maternal urinary fluoride and IQ in the offspring.⁹⁰ The linearity of the dose-response relationships in these studies was not simply assumed—it was scrutinized through several methods, which I understand Drs. Hu and Lanphear will be explaining as part of their testimony.

87. Dose-response trends have also been observed in cross-sectional studies as a function of childhood urine and serum fluoride levels, although these are inherently less certain.⁹¹

⁸⁶ EPA (1998a), pp. 55-56.

⁸⁷ EPA (1998a), p. 2.

⁸⁸ EPA (1998a), p. 50.

⁸⁹ EPA (1998a), p. 50.

⁹⁰ Bashash et al. (2017; 2018); Green et al. (2019).

⁹¹ Cui et al. (2018); Ding et al. (2011); Xiang et al. (2011); Zhang et al. (2015b).

An important limitation with dose-response data from cross-sectional studies is that the exposures are tested after the effect (reduction in IQ) has occurred. The data, however, are not without value, as current exposures can be reflective of developmental exposures in areas with stable populations and stable water fluoride concentrations. In the Zhang study, for example, most of the children had been living in the same household and drinking from the same wells since birth.⁹²

88. In addition to dose-response data from human studies, there is also considerable dose-response data from animal studies. A prerequisite for dose-response analysis in animal studies is that there be multiple treatment groups with different exposures to the test substance. Many of the animal studies on fluoride have used multiple treatment doses, and thereby permit evaluation of dose response. Of the studies published since the NRC review (summarized in Table A-1), 1 used four treatment doses, 17 used three treatment doses, and 16 used two treatment doses (in addition to the control groups). Of these 34 studies, 30 show visually apparent dose-response trends for at least one of the effects being investigated.

2. Neuroendocrine Effects

89. EPA's *Guidelines* recognize the relevance of a chemical's ability to alter the function of the thyroid gland.⁹³ According to the *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone."⁹⁴ A thyroid disturbance during a specific developmental period may cause a "nervous system deficit, which could include cognitive dysfunction, altered neurological development, or visual deficits, [depending] on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred."⁹⁵ Elsewhere, EPA has recognized

⁹² Zhang et al. (2015b), p. 4.

⁹³ EPA (1998a), p. 50.

⁹⁴ EPA (1998a), p. 50.

⁹⁵ EPA (1998a), p. 50.

that “thyroid hormones are essential for normal brain development in humans and that hypothyroidism during fetal and early neonatal life may have profound adverse effects on the developing brain.”⁹⁶

90. Thyroid toxicity may be a significant mechanism by which fluoride affects neurodevelopment. In 2006, the NRC had enough information to conclude that fluoride is an “endocrine disrupter” which may lower thyroid function.⁹⁷ Sodium fluoride was once prescribed as a therapeutic agent for *lowering* thyroid activity in cases of *hyperthyroidism*.⁹⁸ The NRC reported that fluoride can lower thyroid function at estimated average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at estimated average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency.⁹⁹ Put differently, fluoride affects thyroid function at lower doses in people with iodine deficiency than in those with optimal intake of iodine.

91. Epidemiological research published subsequent to the NRC’s report is consistent with and further supports NRC’s findings. In 2018, Malin et al. reported a relationship between urinary fluoride and elevated TSH (thyroid stimulating hormone) among iodine-deficient adults in Canada, but not in the general population as a whole (excluding those with known thyroid disease and excluding pregnant individuals).¹⁰⁰ Elevated TSH is indicative of a decrease in thyroid function. Ten percent of women of child-bearing age in the US are iodine deficient.¹⁰¹

⁹⁶ EPA (2008a), p. 40, citing Morreale de Escobar et al. (2000) and Haddow et al (1999). See also EPA (2008b), p. 54, citing Morreale de Escobar et al. (2000). EPA’s Science Advisory Board in 2013 found that “the most sensitive life stages are the fetus, neonates and infants because these are the stages when thyroid-dependent brain development occurs” (EPA 2013b, cover letter, p. 2).

⁹⁷ NRC (2006), pp. 262-263.

⁹⁸ Galletti and Joyet (1958). Consistent with this thyroid use (i.e., lowering thyroid function), fluoride exposure has been associated with hypothyroidism in animal and human studies (Hillman et al. 1979; Peckham et al. 2015; Yang et al. 2019).

⁹⁹ NRC (2006), pp. 262-263.

¹⁰⁰ Malin et al. (2018). Barberio et al. (2017) found no association between fluoride exposure and thyroid status, but the iodine-deficient part of the population was not specifically addressed.

¹⁰¹ CDC (2008), Chapter 4a, pp. 91-100; see also Pearce (2015); Caldwell et al. (2011).

92. In 2015, a nationwide study from England reported a significant association between water fluoridation and increased prevalence of hypothyroidism.¹⁰²

3. Toxicokinetics

93. Under the *Guidelines*, consideration should be given to the toxicokinetics of the chemical with “particular importance” given to the chemical’s capacity to get through the blood-brain barrier.¹⁰³ The permeability of the blood brain barrier is particularly important when a chemical, such as fluoride, is able to make it through the placenta. Studies in humans have repeatedly demonstrated that fluoride crosses the placenta and reaches the fetus,¹⁰⁴ and thus it is generally accepted that “fluoride readily crosses the placenta.”¹⁰⁵ In general, measured concentrations of fluoride in umbilical cord blood and in blood of neonates are similar to concentrations in maternal blood.¹⁰⁶ In short, the fluoride that a mother ingests will cause exposure to the fetus.

94. Fluoride is also known to cross the blood-brain barrier,¹⁰⁷ and passage of fluoride into the brain can be expected to be higher during the fetal and neonatal life stages when the blood brain barrier is not yet fully developed.¹⁰⁸ As the EPA has recognized, “Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain.”¹⁰⁹ Consistent with EPA’s observation, the recent rat study by

¹⁰² Peckham et al. (2015).

¹⁰³ EPA (1998a), p. 47.

¹⁰⁴ See for example, Feltman and Kosel (1961); Gedalia et al. (1964); Blayney and Hill (1964); Armstrong et al. (1970); Hanhijärvi et al. (1974); Forsman (1974); Shen and Taves (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Brambilla et al. (1994); Shimonovitz et al. (1995).

¹⁰⁵ NRC (2006), p. 193.

¹⁰⁶ Feltman and Kosel (1961); Gedalia et al. (1964); Hudson et al. (1967); Armstrong et al. (1970); Hanhijärvi et al. (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Shimonovitz et al. (1995).

¹⁰⁷ Geeraerts et al. (1986); Mullenix et al. (1995); Zhang et al. (2013c); Niu et al. (2015b).

¹⁰⁸ EPA (2009b), p. 58.

¹⁰⁹ EPA (2009b), p. 58.

McPherson et al. found sharply elevated concentrations of fluoride in the brain following prenatal exposure.¹¹⁰

4. Mode of Action

95. EPA's *Guidelines* recognize that hazard identification is strengthened by, but not dependent upon, an identifiable mechanism by which the chemical can exert neurotoxic effects.¹¹¹ For most of the chemicals for which EPA has established RfDs pursuant to the *Guidelines*, the mode of action has not been known (see Table 1). As noted recently by the NAS, "solid conclusions about causality can be drawn without mechanistic information, for example, when there is strong and consistent evidence from animal or epidemiology studies."¹¹² The NAS added that "mechanistic frameworks today could probably be completed for only a few chemicals."¹¹³

96. Several plausible mechanisms—both indirect and direct—have been identified that could help explain the neurotoxicity of fluoride.

97. *Indirect Mechanisms:* Depression of thyroid function is likely a principal indirect mechanism and could account for some of the neurotoxic effects reported in the literature. A thyroid mechanism is particularly plausible as a cause of IQ loss among offspring born to women with suboptimal iodine intakes.

98. *Direct Mechanisms* A recent study by Zhao et al. provides *in vitro*, *in vivo*, and epidemiological data that, together, suggest that disturbances in hippocampal mitochondrial dynamics (marked by fission inhibition and fusion promotion) play an important role in fluoride-induced cognitive loss.¹¹⁴ The hippocampus is an important region in the brain for learning and

¹¹⁰ McPherson et al. (2018).

¹¹¹ EPA (1998a), pp. 10, 53.

¹¹² NAS (2018), p. 9.

¹¹³ NAS (2018), p. 9.

¹¹⁴ Zhao et al. 2019.

memory, and many of the studies investigating the neuroanatomical and neurochemical effects of fluoride exposure have identified adverse effects in this region (see Table A-1). Other potential modes of action have also been identified, including signaling disruption, oxidative stress, and selective reductions in nicotinic receptors.¹¹⁵

5. In Vitro Studies

99. EPA's *Guidelines* also call for consideration of *in vitro* data. While positive *in vitro* data are not sufficient, by themselves, to demonstrate a neurotoxic hazard in humans, the existence of such data helps enhance the reliability of *in vivo* data.¹¹⁶

100. Fluoride's ability to damage brain cells has been documented in *in vitro* experiments. While most of the *in vitro* studies have used high concentrations that are unlikely to be present in the human brain, several studies have examined environmentally realistic fluoride concentrations. Gao et al. found increased lipid peroxidation and reduced $\alpha 7$ nicotinic acetylcholine receptors in brain cells at fluoride concentrations (i.e., 9.5 parts per billion) that are commonly found in the blood of people living in fluoridated areas.¹¹⁷ Increases in markers of neuroinflammation have also been found at low concentrations.¹¹⁸ Under the *Guidelines*, these data do not demonstrate a hazard in humans, but they do enhance the reliability of the animal studies, as similar effects have been reported in fluoride-treated rodents.¹¹⁹

6. Validity of the Database

101. Under the *Guidelines*, the validity of the database should be evaluated by assessing

¹¹⁵ Bartos et al. (2018); Chen et al. (2003; 2018a); Gao et al. (2008); Liu et al. (2010); Long et al. (2002); Shan et al. (2004); Zhang (2017b); Zhu et al. (2017).

¹¹⁶ EPA (1998a), p. 49.

¹¹⁷ Gao et al. (2008), Figures 1A, 3A.

¹¹⁸ Goschorska et al. (2018).

¹¹⁹ Bartos et al. (2018); Dong et al. (2015); Yang et al. (2018a); Yan et al. (2016); Zhao et al. (2019).

the content validity, construct validity, concurrent validity, and predictive validity of the data.¹²⁰

102. *Content validity* addresses “whether the effects result from exposure.”¹²¹ This factor weighs decisively in favor of a neurotoxicity hazard determination for fluoride. The NRC concluded that fluoride interferes with the brain,¹²² and the evidence has gotten stronger since. Kristina Thayer, the Director of EPA’s IRIS Division, has explained that “experimental animal studies are designed to let you draw causal inferences,” and that the animal studies show that fluoride damages the brain at some level of exposure.¹²³ Further, while the human cross-sectional studies are limited in their ability to produce causal inferences, the *Guidelines* provide that prospective cohort studies permit “direct estimates of risk attributable to a particular exposure.”¹²⁴

103. *Construct validity* addresses whether the neurologic effects that have been observed “are adverse or toxicologically significant.”¹²⁵ This factor is satisfied in the fluoride database. Animal studies have linked fluoride to learning and memory deficits, which are an adverse effect upon which EPA has established reference doses for other neurotoxicants (e.g., BDE-153).¹²⁶ Further, the human epidemiological data have linked fluoride with IQ detriments, including an approximate 5 to 6 point drop in IQ as maternal urinary fluoride increased from 0 to 1 mg/L.¹²⁷ EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,¹²⁸ and EPA’s Clean Air Science Advisory Council has stated that “a population loss of 1-2 IQ points

¹²⁰ EPA (1998a), pp. 10-11.

¹²¹ EPA (1998a), pp. 10-11.

¹²² NRC (2006), p. 222.

¹²³ Thayer Deposition at 225:8-15, 226:13-16, 270:23-25.

¹²⁴ EPA (1998a), p. 17.

¹²⁵ EPA (1998a), pp. 10-11.

¹²⁶ EPA (2008c), p. 36. Effects on memory were also noted in the RfD determination for BDE-99 (EPA 2008b, p. 27).

¹²⁷ Bashash et al. (2017); Green et al. (2019).

¹²⁸ EPA (2008e), p. 5-28.

is highly significant from a public health perspective” and should be prevented in 99.5% of the population.¹²⁹

104. *Concurrent Validity* addresses “whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints.¹³⁰ Studies have correlated fluoride’s cognitive effects in animals with various neurochemical and neuroanatomical changes,¹³¹ and a few studies have correlated fluoride-associated cognitive loss in humans with increased TSH and alterations in mitochondrial dynamics.¹³² For example, Zhao et al.¹³³ reported lower circulating levels of a mitochondrial protein (fission-related protein-1, Fis1) in children from high fluoride areas (compared with children in low fluoride areas), and higher circulating levels of a second mitochondrial protein (mitofusin-2, Mfn2) in the same children. The levels of circulating Fis1 were positively associated with children's IQ scores, while the levels of circulating Mfn2 were negatively associated with the IQ scores. In addition, several plausible mechanisms of fluoride neurotoxicity have been described (discussed above).

105. *Predictive validity* addresses “whether the effects are predictive of what will happen under various conditions.”¹³⁴ The condition of perhaps greatest interest with respect to prediction of fluoride neurotoxicity is exposure during the prenatal period. Studies in both animals and humans have, with one exception,¹³⁵ reported neurologic effects following prenatal exposure. The database, therefore, does have some degree of predictive validity, although further research remains necessary to determine to what extent other conditions (e.g., nutrition, genetics, neonatal

¹²⁹ Federal Register (2008), p. 67000.

¹³⁰ EPA (1998a), pp. 10-11.

¹³¹ For example, see Bartos et al. (2018); Zhao et al. (2019); Zhou et al. (2019).

¹³² For example, Zhang et al. (2015b); Zhao et al. (2019).

¹³³ Zhao et al. (2019).

¹³⁴ EPA (1998a), pp. 10-11.

¹³⁵ McPherson et al. (2018).

exposure, and kidney function) may modify or predict outcomes. Exposure during the early postnatal period also requires further research.

7. Data Gaps

106. EPA's *Guidelines* point to the need to address "significant data gaps."¹³⁶ One of the major data gaps for fluoride is the lack of research on the impact of fluoride during the neonatal and early infancy period. EPA has recognized that the neonatal period represents a critical window of vulnerability to neurotoxicants,¹³⁷ yet most developmental rodent studies do not address neonatal exposures to fluoride (due to exclusive breastfeeding of the rat or mouse pups and absence of gavage exposures). Other data gaps include the absence of long-term animal studies, and the scarcity of epidemiological research into fluoride's neurologic effects in the elderly. Data gaps also remain with respect to how the dose which causes neurologic effects varies across susceptible subsets of the population, including those with nutrient deficiencies, genetic polymorphisms, kidney disease, and the elderly.

E. Conclusion: There Is Sufficient Evidence that Neurotoxicity Is a Hazard of Fluoride

107. The large and substantial body of evidence that now exists for fluoride, from both animal and human studies, satisfies EPA's "sufficient evidence" standard for hazard determination.

108. The *Guidelines* provide that "the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study."¹³⁸ The *Guidelines* also recognize that prospective cohort studies are the optimal type of epidemiological study that permit direct

¹³⁶ EPA (1998a), p. 12.

¹³⁷ See for example, EPA (2008a), p. 42.

¹³⁸ EPA (1998a), p. 55.

estimates of risk. The minimum evidence threshold is thus met for fluoride because there is not just one, but *four* high-quality prospective cohort studies that support the endpoint of IQ loss, and another high-quality prospective cohort study that supports the endpoint of inattention.¹³⁹

109. EPA's *Guidelines* also permit consideration of the collective evidence when no study, by itself, is sufficient to permit a hazard determination. This, again, supports a hazard determination for fluoride because the prospective studies are most compelling when viewed in the context of (i) the toxicokinetic data showing that fluoride crosses the placenta and enters the fetal brain; (ii) animal data showing neurochemical and neuroanatomical damage following fluoride exposure; (iii) animal data finding impairments in learning and memory following prenatal exposure to fluoride; (iv) cross-sectional studies consistently finding reductions in IQ in communities with elevated fluoride exposure; (v) *in vitro* studies reporting effects on brain cells at concentrations of fluoride found in the blood of individuals living in fluoridated communities; and (vi) animal and human studies finding that fluoride can depress thyroid function, a known risk factor for neurodevelopmental harm.

110. Based on the collective data—which are far more robust than the data EPA has relied upon for prior hazard determinations—I conclude with a reasonably high degree of confidence that neurotoxicity is a hazard of fluoride exposure.

VI. QUANTITATIVE DOSE RESPONSE

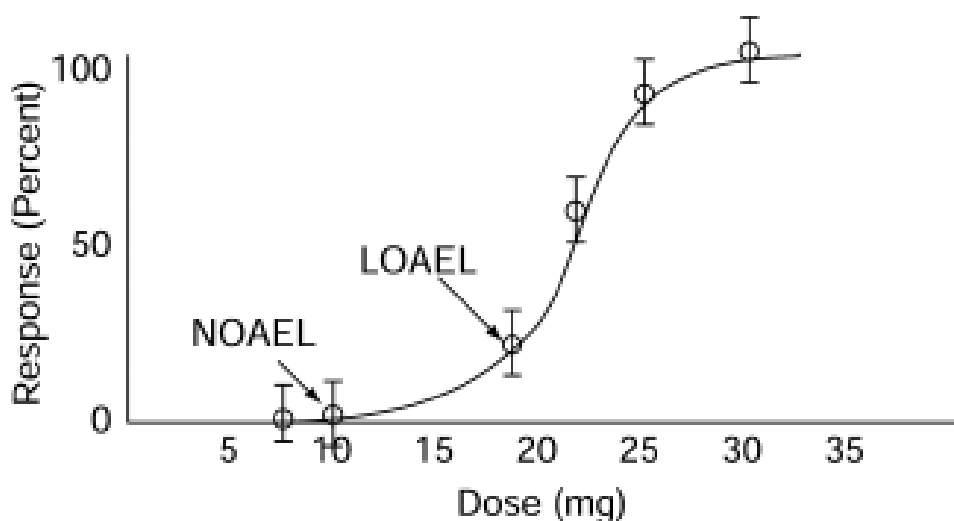
111. If a chemical is identified as posing a neurotoxic hazard, EPA's *Guidelines* call for a quantitative dose-response analysis to determine the reference dose (RfD). The RfD is “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the

¹³⁹ Bashash et al. (2017; 2018); Green et al. (2019); Till et al. (2020); Valdez-Jiménez et al. (2017).

human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”¹⁴⁰

112. In the Quantitative Dose Response analysis, human or animal data are assessed to determine an appropriate “Point of Departure” (POD). As the name implies, the Point of Departure (POD) is the datapoint from which the RfD is ultimately derived. The POD can be one of three types of values: the No Observed Adverse Effect Level (NOAEL), the Lowest Observed Adverse Effect Level (LOAEL) or the Benchmark Dose Level (BMDL). While EPA now has a preference for using BMD, it still uses both the NOAEL and LOAEL approaches in its assessments.

113. The following figure provides a visual illustration of the difference between a NOAEL and LOAEL on a dose-response curve.



A. Basis for Using Animal Data

114. When human data are available, EPA’s preference is to use human data for the Point of Departure.¹⁴¹ In the case of fluoride, the recent prospective cohort studies¹⁴² with individual-level biomonitoring data provide suitable data for this purpose. If one had to choose,

¹⁴⁰ EPA (1998a), p. 57. See also EPA (2009a).

¹⁴¹ EPA (2018a), p. 2-1.

¹⁴² Bashash et al. (2017; 2018); Valdez-Jiménez et al. (2017); Green et al. (2019).

therefore, between deriving the POD for fluoride from the human or animal data, *the choice would clearly be to use the human data*. But this does not mean that the animal data are without value. In EPA's assessment of methylmercury, for example, the EPA derived its RfD from human prospective cohort data, but it also considered what the RfD would be if it were derived from the animal literature.¹⁴³ As the EPA noted, "[i]t is informative to compare RfDs derived from animal studies with those derived from the epidemiological literature."¹⁴⁴ In the case of methylmercury, the animal-based RfD supported the human-based RfD, and EPA cited this as a factor that increased its "confidence" in the assessment.¹⁴⁵

115. In this case, Dr. Philippe Grandjean conducted a dose-response analysis of the prospective cohort data where he derived a BMDL. To avoid duplication of Dr. Grandjean's effort, and to determine whether Dr. Grandjean's BMDL is consistent with potential RfDs derived from the animal data, I focused my assessment on the animal literature.

116. In this assessment, I did not seek to select a single value for the RfD. Instead, I sought to identify the full range of RfDs that can be derived, including the *least* protective. If human exposures exceed RfDs that use non-protective assumptions, there would be greater confidence that a human risk does, in fact, exist.

117. There are several considerations that support the use of animal data to establish an RfD for fluoride. First, EPA has used animal studies as the principal studies for each of the neurotoxicity risk assessments it has thus far conducted under the *Guidelines*. Second, EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals,¹⁴⁶ thus this is an accepted endpoint to use in deriving an RfD. Third, a

¹⁴³ EPA (2001), pp. 17-18.

¹⁴⁴ EPA (2001), pp. 17.

¹⁴⁵ EPA (2001), pp. 18-19.

¹⁴⁶ For example, BDE-153 (EPA 2008c, p. 36).

substantial number of animal studies of fluoride neurotoxicity have used 2 or 3 treatment groups (in addition to control groups), and EPA has found this to be sufficient for identifying Points of Departure,¹⁴⁷ including in animal studies with as few as 10 rats per group (2-Hexanone).¹⁴⁸

B. Selecting Points of Departure

118. In the literature review discussed earlier, 37 rodent studies were identified that have investigated fluoride's impact on learning and memory since the NRC report (Table A-2). All but 3 of these studies found adverse effects in the fluoride-treated rodents, including 16 of the 17 studies that investigated prenatal fluoride exposures. Since the prenatal period represents a point of heightened vulnerability to neurotoxicants, the prenatal studies are a logical candidate for the point of departure.

119. To avoid studies at high risk of bias, the three studies that did not specifically mention using a randomization procedure were excluded from further consideration.¹⁴⁹ Further, in order to focus the analysis on those studies best suited for identifying a Point of Departure (POD), four studies that only used one treatment dose were excluded.¹⁵⁰

120. Table 2 and the figures below summarize the 10 prenatal studies that remained for POD consideration. Most of the studies used a similar dosing regimen with 2 or 3 treatment groups and at least 10 rodents per group, which is consistent with several of the principal studies that EPA has used to establish an RfD. The figures show the lowest-observed and no-observed effect levels in each study and help to visually compare the data across studies.

121. Nine of the 10 studies found dose response trends for one or more effects, which

¹⁴⁷ EPA (2000b; 2008a; 2008c; 2008d; 2009b).

¹⁴⁸ EPA (2009b).

¹⁴⁹ Bera et al. (2007); Basha et al. (2011b); Ge et al. (2018).

¹⁵⁰ Niu et al. (2014); Banala and Karnati (2015); Dong et al. (2015); Zhu et al. (2017).

adds confidence to a causative role of the fluoride treatment.¹⁵¹ Six of these studies also provide data on the body weights of the pups, and no bodyweight changes were seen in any of the studies at the lowest concentrations producing the effects.¹⁵² Only one of the six studies found any bodyweight changes among pups in the higher-dose groups.¹⁵³ Of the two studies that reported maternal weight, neither found any changes.¹⁵⁴

122. One limitation with these studies is that only three of them specifically mention controlling for litter effects,¹⁵⁵ which introduces some uncertainty since the failure to control for litter effects can result in false positives, as well as false negatives.¹⁵⁶ While a source of uncertainty, the failure to control for litter effects does not preclude use for risk assessment purposes. As noted earlier, EPA has used studies that do not control for litter effects as the principal studies upon which it has based RfDs for developmental neurotoxicity.¹⁵⁷

¹⁵¹ See for example, Jiang et al. (2014b), Table 3; Cui et al. (2017), Table 3; Chen et al. (2018a), Figure 1d,e; Sun et al. (2018), Tables 2 and 3; Wang et al. (2018a), Figure 4b,c; Zhao et al. (2019), Figure 5e.

¹⁵² Bartos (2018; 2019); Cui et al. (2017); Jiang et al. (2014b); Wang et al. (2018a). The study by McPherson (2018) also showed no changes in bodyweight, although it did not find effects on learning/memory.

¹⁵³ Jiang (2014b) found reduced body weight gain among the pups in the 23 mg/L and 45 mg/L groups.

¹⁵⁴ Bartos (2018; 2019).

¹⁵⁵ Bartos et al. (2018; 2019); McPherson et al. (2018).

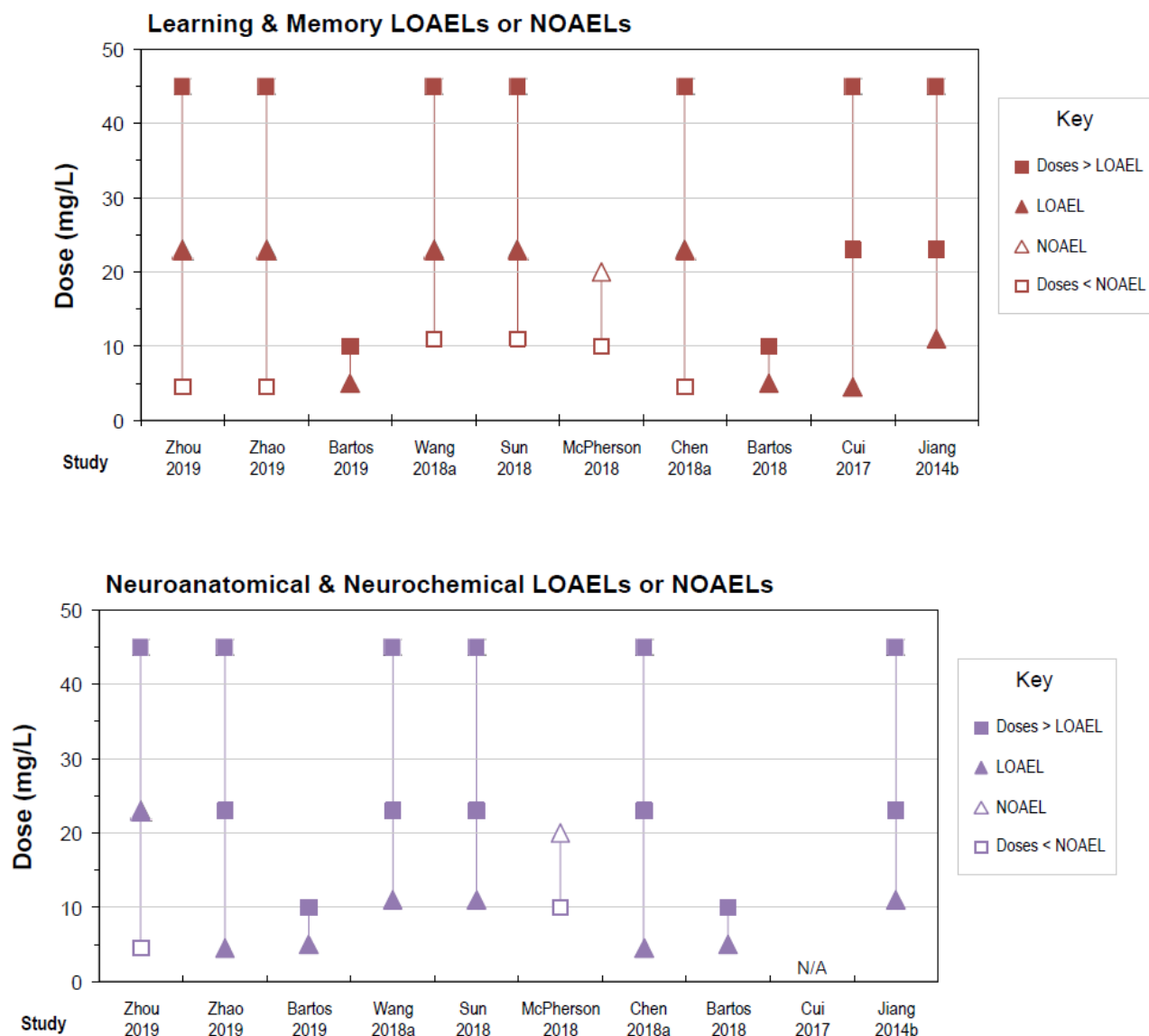
¹⁵⁶ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

¹⁵⁷ See for example EPA (2008a), pp. 44, A-4; EPA (2008b), pp. 59, A-3; EPA (2008c), pp. 32, A-3.

Table 2. Examples of rodent studies of prenatal exposure to fluoride that could provide LOAELs or NOAELs for neurotoxicity.

Study	Animal	Exposure period	[F ⁻] in drinking water ^a (mg/L)	Number of animals per group (n)	Learning and memory		Neuroanatomical or neurochemical effects	
					LOAEL (mg/L)	NOAEL (mg/L)	LOAEL (mg/L)	NOAEL (mg/L)
Zhou et al. (2019)	Rats, Sprague- Dawley	Prenatal ^b + 6 months	4.5, 23, 45	6	23	4.5	23	4.5
Zhao et al. (2019)	Rats, Sprague- Dawley	Prenatal ^b + 60 days	4.5, 23, 45	5	23	4.5	4.5	None
Bartos et al. (2019)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Wang et al. (2018a)	Mice, ICR (female)	Prenatal (from day 7) + 21 days	11, 23, 45	15	23	11	11	None
Sun et al. (2018)	Mice, Kunming	Prenatal + 21 days	11, 23, 45	6	23	11	11	None
McPherson et al. (2018)	Rats, Long Evans Hooded (male)	Prenatal (from day 6) + 90 days	10, 20 ^c	11-23	None	20	None	20
Chen et al. (2018a)	Rats, Sprague- Dawley	Prenatal ^b + 6 months	4.5, 23, 45	6	23	4.5	4.5	None
Bartos et al. (2018)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Cui et al. (2017)	Rats, Sprague- Dawley	Prenatal ^b + 60 days	4.5, 23, 45	12	4.5	None	N/A	N/A
Jiang et al. (2014b)	Rats, Sprague- Dawley	Prenatal ^b + 2 months	11, 23, 45	12	11	None	11	None

^a Treatment groups in addition to the control group.^b Exposure of the mother began before pregnancy.^c Animals were given 0, 10, or 20 mg/L fluoride in drinking water, plus 3.24 ppm fluoride in feed. An additional control group had 0 mg/L fluoride in drinking water plus 20.5 ppm fluoride in feed (McPherson et al. 2018).



123. Based on the dose-response data from these studies, the following values could be used as the Point of Departure.

124. **LOAEL of 5 mg/L:** The lowest observed adverse effect levels in the studies were fluoride concentrations of 4.5 and 5 mg/L. Of the six studies that used this concentration, three

found adverse effects on learning,¹⁵⁸ and two of the other three studies, which did not find effects on learning, *did find alterations in the brain*.¹⁵⁹ Two of the three studies reporting effects on learning at 5 mg/L controlled for litter effects, which suggests that the failure to control for litter effects is unlikely to explain the reported effects at this concentration.¹⁶⁰ A 5 mg/L LOAEL was selected, therefore, as one of the Points of Departure (PODs) for learning impairment from prenatal fluoride exposure.

125. **LOAEL of 23 mg/L**: Seven of the 10 studies used 23 mg/L as one of the treatment doses, and all 7 of these studies found impaired performance on the cognitive tests, with 6 of the 7 studies finding changes in the brain as well. 23 mg/L appears, therefore, to be a reliable “Observed Adverse Effect Level,” particularly in light of the six studies (discussed above) which found adverse effects at < 5 mg/L. Although not the *lowest* observed effect level, it is assumed to be one for purposes of this Point of Departure.

126. **LOAEL of 45 mg/L**: As can be seen in the above figures, 45 mg/L is clearly an “observed adverse effect level,” just as it has been in many other animal studies on fluoride neurotoxicity. It would be difficult to justify selecting 45 mg/L as the LOAEL because it is the *highest* observed adverse effect level in this group of studies, not the *lowest*. Nevertheless, for purposes of capturing the broadest possible range of RfDs that can be derived from the animal literature, a 45 mg/L LOAEL was selected as one of the Points of Departure.

¹⁵⁸ Cui et al. (2017); Bartos et al. (2018; 2019). In the Chen study (which had only six rats per group), there is some indication of an effect on learning in the 4.5 mg/L group, albeit not statistically significant (Chen et al. 2018a, Figure 1).

¹⁵⁹ Chen et al. (2018a); Zhao et al. (2019). Other studies have also found alterations in the brain at ≤ 5 mg/L, including Liu et al. (2010; 2011); Zhang et al. (2015a); Niu et al. (2018a); Varner et al. (1998); and Yu et al. (2019).

¹⁶⁰ Bartos et al. (2018; 2019).

127. **NOAEL of 11 mg/L:** Four of the prenatal studies used 10 or 11 mg/L for the low-dose group.¹⁶¹ The two studies of mice failed to find a significant effect on learning at this level,¹⁶² and, as such, 11 mg/L could be selected as a NOAEL. The fact that the two studies that did not find effects at 11 mg/L found them at higher concentrations (23 and 45 mg/L) would be a factor weighing in favor of this choice, as the animal models were sensitive enough to find an effect. It bears considering, however, that the two studies finding no effects on learning at 11 mg/L did find alterations in the brain at this level,¹⁶³ which is consistent with 11 mg/L being a LOAEL, rather than a NOAEL. However, for purposes of reflecting the spectrum of RfDs that can be derived from the animal literature, 11 mg/L was treated as a NOAEL for one of the PODs.

128. **NOAEL of 20 mg/L:** The highest possible NOAEL that can be selected from these prenatal studies is the 20 mg/L no-effect finding from McPherson et al.¹⁶⁴ As discussed earlier, there are limitations with the McPherson study that may have made it less sensitive to detecting an effect, including strain of rat used and lack of first trimester exposure. Further, the study did find an adverse neurotoxic effect in the 20 mg/L group (i.e., increased pain sensitivity), and, as such, 20 mg/L is not a true NOAEL in the study. Nevertheless, for the purpose of illustrating the upper-bound range of RfDs that can be derived from the animal literature, a 20 mg/L NOAEL will be treated as a POD for the analysis.

C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day)

129. Reference Doses (RfDs) are expressed in terms of dose (i.e., milligrams per kilogram of bodyweight, or mg/kg/day), not in terms of water concentration. To calculate RfDs from the Points of Departure, therefore, the unit of measurement (i.e., water fluoride concentration)

¹⁶¹ Wang et al. (2018a); Sun et al. (2018); McPherson et al. (2018); Jiang et al. (2014b).

¹⁶² Sun et al. (2018); Wang et al. (2018a).

¹⁶³ Sun et al. (2018); Wang et al. (2018a).

¹⁶⁴ McPherson et al. (2018).

needs to be converted into a dosage metric.

130. The NTP's 2016 review provides data that facilitate this analysis.¹⁶⁵ In its review, the NTP estimated the doses for dozens of rodent studies by using EPA's default water consumption rates and body weight data for the species, strain, and sex of the animals studied.¹⁶⁶ A review of NTP's data shows that the average ratio of fluoride concentration (mg/L) to intake rate or dose (mg/kg/day) is 6.8, and that this ratio is generally higher for rats (typically 6 to 10) than for mice (typically 3.8 to 5). For purposes of this analysis, the low end of this range was chosen for each species (6 for rats, 3.8 for mice). The practical effect of selecting the low-end of this range, is that the estimated doses will likely *overestimate* the actual dose, and thereby *inflate* the RfDs derived from these Points of Departure.¹⁶⁷ The net result of this non-conservative approach will be RfDs that are *less* protective of human health.

D. Selecting the Uncertainty Factors

131. Consistent with EPA's standard risk assessment procedures,¹⁶⁸ the *Guidelines* provide that "uncertainty factors" (UFs) should be applied to the point of departure (POD) to ensure that the resulting RfD is protective of health.¹⁶⁹

132. Uncertainty factors are applied to account for expected variations in susceptibility among humans (*intraspecies* variability, or UF_H), expected differences in susceptibility between animals and humans (*interspecies* variability, or UF_A), and, where applicable, differences in the

¹⁶⁵ NTP (2016), Appendix 19.

¹⁶⁶ NTP (2016), p. 118.

¹⁶⁷ For example, using this method gives an intake rate of 0.83 mg/kg/day for rats for the 5 mg/L fluoride concentration (Table 5). However, Bartos et al. (2018; 2019) give an estimate of 0.6 mg/kg/day for their rats at this fluoride concentration. Using the same approach described below with Table 5 for a LOAEL of 5 mg/L, equivalent to an intake rate of 0.6 mg/kg/day, gives an RfD of 0.0005, compared with 0.0007 in Table 5.

¹⁶⁸ EPA (2018a), pp. xvii-xxiv.

¹⁶⁹ EPA (1998a), pp. 58-59.

length of exposure between the study and human conditions (subchronic to chronic, or UF_S), research gaps in the overall database (database deficiency, UF_D), and converting from a LOAEL to a NOAEL.¹⁷⁰ These uncertainty factors are “typically multiples of 10,” although they can be reduced to factors of 3 or 1 if warranted by available information.^{171,172}

1. Intraspecies Variability (UF_H)

133. EPA recognizes that susceptibility to toxic substances is not uniform across the human population, and that due to differences in *toxicokinetics* and/or *toxicodynamics* some subsets of the population will be more vulnerable to harm than others.¹⁷³

134. *Toxicokinetics* refers to the “processes which determine the extent and duration of exposure of the target organ or site of toxicity to the active chemical species,” while *toxicodynamics* refers to the “processes involved in the translation of such exposure of the target organ or site of action into the generation of a toxic effect.”¹⁷⁴ Put more simply, toxicokinetics governs how much of the chemical gets to the target site (i.e., access), while toxicodynamics governs how much of the chemical is necessary at the target site to cause the adverse effect (i.e., sensitivity).

135. If there are no chemical-specific data on toxicokinetics and toxicodynamics, EPA uses a default UF_H of 10.¹⁷⁵ This default factor of 10 is “considered to be appropriate in the absence of convincing data to the contrary.”¹⁷⁶ Consistent with this, EPA has used a UF_H of 10 in each of

¹⁷⁰ EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), pp. xix-xx.

¹⁷¹ EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), p. xix.

¹⁷² As discussed by Martin et al. (2013), default uncertainty factors, while sometimes viewed as overly protective, do not represent worst-case situations and cannot be safely assumed to be adequately protective of the most exposed individuals or the most susceptible individuals, nor can they be safely assumed to be protective for effects of mixtures of chemicals.

¹⁷³ EPA (2011b), p. 14; EPA (2016), p. 2-15; EPA (2018a), p. 2-12.

¹⁷⁴ Renwick (1993), p. 276.

¹⁷⁵ EPA (2018a), pp. 2-12, 2-13.

¹⁷⁶ EPA (2013a), p. 5-17.

the nine risk assessments where it has established an RfD or RfC pursuant to the *Guidelines* (Table 3).

136. In the case of fluoride, there is evidence that affirmatively demonstrates substantial variability in how humans respond to fluoride, including differences in retention (toxicokinetics) and differences in response (toxicodynamics). These data are discussed below in the Risk Characterization. While the magnitude of this variability is difficult to quantify, the data *support* the need for an uncertainty factor as opposed to providing “convincing data” *against* one. Accordingly, pursuant to standard EPA procedure, a value of 10 for UF_H was assigned.

Table 3. Summary of RfDs or RfCs developed in compliance with EPA's Guidelines for Neurotoxicity Risk Assessment.

Chemical	LOAEL	NOAEL	Uncertainty Factors					RfD or RfC ^a	Reference
			UF _H	UF _A	UF _S	UF _D	Composite		
BDE-47	10.5 mg/kg	0.7 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008a)
BDE-99	0.8 mg/kg	0.4 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008b)
BDE-153	0.9 mg/kg	0.45 mg/kg	10	10	3	10	3000	0.2 µg/kg/day	EPA (2008c)
BDE-209	20.1 mg/kg	2.22 mg/kg	10	10	3	1	300	7 µg/kg/day	EPA (2008d)
Chlorine Dioxide and Chlorite	6 mg/kg/day	3 mg/kg/day	10	10	1	1	100	0.03 mg/kg/day	EPA (2000b)
2-Hexanone	143 mg/kg/day	Not observed	10	10	1	10	1000	0.005 mg/kg/day	EPA (2009b)
Methanol	1000 ppm (1310 mg/m ³)	500 ppm (655 mg/m ³)	10	3	1	3	100	20 mg/m ³	EPA (2013a)
RDX	8 mg/kg/day	4 mg/kg/day	10	3	1	10	300	0.004 mg/kg/day	EPA (2018a; 2018h)
Trimethylbenzenes	492 mg/m ³	123 mg/m ³	10	3	3	3	300	0.01 mg/kg/day	EPA (2016)

^a Where EPA established both an RfD (mg/kg/day) and an RfC (mg/m³) for a chemical, the RfD is presented.

Table 4. Comparison of BW^{1/1} and BW^{3/4} in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.^a

Absolute animal intake or administered dose	Species	BW(h)/BW(a)	Scaling = BW ^{1/1}		Scaling = BW ^{3/4}	
			BW scaling factor	BW scaled human intake or oral dose (mg/kg)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)
0.25 mg / 0.025 kg	Mouse	70 / 0.025 = 2800	2800 ^{1/1} = 2800	(2800 × 0.25 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	2800 ^{3/4} = 385	(385 × 0.25 mg = 96 mg) 96 mg / 70 kg = 1.4 mg/kg
2.5 mg / 0.25 kg	Rat	70 / 0.25 = 280	280 ^{1/1} = 280	(280 × 2.5 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	280 ^{3/4} = 68	(68 × 2.5 mg = 170 mg) 170 mg / 70 kg = 2.4 mg/kg
120 mg / 12 kg	Dog	70 / 12 = 5.8	5.8 ^{1/1} = 5.8	(5.8 × 120 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	5.8 ^{3/4} = 3.7	(3.7 × 120 mg = 444 mg) 444 mg / 70 kg = 6.4 mg/kg

^a Taken from Table A-1 in EPA (2011b), p. 29.

2. Interspecies Variability (UF_A)

137. EPA recognizes that susceptibility to toxic substances can differ across species. As with human-to-human variability, animal-to-human variability is also rooted in principles of toxicokinetics and toxicodynamics.

138. To adjust for differences in toxicokinetics between animals and humans, EPA has developed a hierarchical framework of approaches for ascertaining the “human equivalent dose” (HED) of doses given to animals.¹⁷⁷ EPA’s “optimal” approach for determining the HED is to use a physiologically based toxicokinetic model (PBTk).¹⁷⁸ Where a PBTk model is not available, the “intermediate” approach is to use chemical-specific information that, while falling short of a full PBTk model, provides some reliable guidance.¹⁷⁹ Where there is no reliable chemical-specific information on kinetics, EPA uses a default allometric scaling method.¹⁸⁰

139. Allometric scaling is “scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another species.”¹⁸¹ Under EPA’s recommended method for allometric scaling (BW^{3/4} Method), the HED equates to 24% of the dose given to rats, and 14% of the dose given to mice (see Table 4 above).¹⁸²

140. The BW^{3/4} Method “predominantly addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors.”¹⁸³ EPA thus maintains a residual default UF of 3 to allow for residual uncertainty from toxicodynamics, unless there is chemical-specific information available.¹⁸⁴

¹⁷⁷ EPA (2011b), pp. 18-21; EPA (2018a), p. 2-10.

¹⁷⁸ EPA (2011b), p. 19.

¹⁷⁹ EPA (2011b), p. 19.

¹⁸⁰ EPA (2011b), p. 19.

¹⁸¹ EPA (2011b), p. 1.

¹⁸² EPA (2011b), p. 29, Table A-1; EPA (2018a), p. 2-12.

¹⁸³ EPA (2011b), p. 17.

¹⁸⁴ EPA (2011b), p. 21; EPA (2016), p. 2-15; EPA (2018a), pp. 2-12, 2-13.

141. The following factors were considered to account for interspecies differences in both the toxicokinetics and toxicodynamics of fluoride.

142. *Toxicokinetic Considerations:* A full PBTK model has not yet been developed for fluoride that would allow for the calculation of HEDs from doses given to animals. As such, EPA's preferred approach for controlling for interspecies toxicokinetics is not available. By contrast, there is chemical-specific information for fluoride that could support application of EPA's intermediate approach. As discussed by the NRC, rats require higher levels of fluoride in their water to achieve the same level of fluoride in their blood.¹⁸⁵ Dunipace estimated that rats require about 5 times more fluoride in water than humans to reach the same plasma concentration of fluoride,¹⁸⁶ while Den Besten's team has reported a larger margin for mice, with a difference of about a factor of 10.¹⁸⁷ The data from Dunipace and Den Besten support a toxicokinetics adjustment of 5 for rats and 10 for mice, which are slightly *higher* than, but roughly consistent with, the adjustments under the default BW^¾ Method (4 for rats, 7 for mice). The chemical-specific information for fluoride thus supports the general validity of the BW^¾ Method, but would be more protective. The BW^¾ Method, which is roughly consistent with the chemical-specific information, but slightly *less* protective, was selected as the method for the toxicokinetics adjustment.

¹⁸⁵ NRC (2006), pp. 98-99; pp. 442-446, Appendix D; NRC (2009), pp. 88-89.

¹⁸⁶ NRC (2006), pp. 98, 442.

¹⁸⁷ Zhang et al. (2014).

143. *Toxicodynamic Considerations*: It has long been recognized that rodents are less susceptible (i.e., more resistant) to certain toxic effects from fluoride ingestion than are humans.¹⁸⁸ Rats, for example, have been reported to require 10 to 25 times more fluoride than humans to develop dental fluorosis.¹⁸⁹ Differences in toxicokinetics contribute to rodents being less sensitive to fluorosis, but the differences appear larger than would be expected if they were due solely to kinetics. The fluorosis data support the existence of differential toxicodynamics between rodents and humans, but it is unclear if this difference would also apply to neurotoxicity, as this has not yet been the subject of study. Conversely, there are no data to suggest that humans are *more resistant* to fluoride neurotoxicity than animals. In the absence of data, EPA's default uncertainty factor of 3 was selected to account for interspecies differences in toxicodynamic differences.

3. LOAEL to NOAEL

144. When EPA uses a LOAEL from animal data as the Point of Departure, it applies an additional uncertainty factor of 10 to convert the LOAEL into an estimated NOAEL.¹⁹⁰ Consistent with EPA practice, the three LOAEL-based PODs were adjusted by a factor of 10.

4. Composite Uncertainty Factor

145. The "composite" uncertainty factor is the product of all uncertainty factors used in an analysis. The composite uncertainty factor applied here to the NOAEL-based PODs is **30**, which is the same value that EPA has been using in its draft risk evaluations under TSCA.¹⁹¹ The

¹⁸⁸ Roholm (1937), pp. 265, 318; Lehman and Fitzhugh (1954), p. 33; Angmar-Mansson and Whitford (1982), p. 339.

¹⁸⁹ Roholm (1937), pp. 265, 318; Angmar-Mansson and Whitford (1982), p. 339.

¹⁹⁰ EPA (1998a), p. 59.

¹⁹¹ In my expert report, I also calculated alternate RfDs where I applied additional uncertainty factors that EPA uses to account for subchronic animal exposures and deficiencies in the fluoride database (e.g. no data on formula-feeding during the neonatal period). For purposes of simplicity, I have not included those calculations in this declaration.

composite uncertainty factor applied here to the LOAEL-based PODs is **300**, which is on the low-end of the range of the composite uncertainty factors that EPA has used in its neurotoxicity risk assessments (see Table 3 above).

E. RfD Calculations from Animal Data

146. Table 5 summarizes the RfD calculations for each of the five Points of Departure (POD) listed above. The RfDs range from 0.0007 to 0.006 mg/kg/day for the LOAEL-based PODs, and 0.01 to 0.03 mg/kg/day for the NOAEL-based PODs. The least protective RfD that can be derived from the literature in a manner consistent with EPA practice is thus **0.03 mg/kg/day**.

Table 5. Calculation of the RfD from the selected Points of Departure (POD), based on the studies summarized in Table 2.

A Observation	B Intake rate	C POD _{HED}	D NOAEL	E UF _H = 10	F UF _A = 3	G RfD
LOAEL or NOAEL from Table 6 mg/L	Column A / 6 (rats) or 3.8 (mice) mg/kg/day	Column B × 0.24 (rats) or 0.14 (mice) mg/kg/day	Column C / 10 (LOAEL) or 1 (NOAEL) mg/kg/day	Column D / 10 mg/kg/day	Column E / 3 mg/kg/day	Column F mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	0.020	0.0020	0.00067	0.0007
23 mg/L, LOAEL (rats)	3.8	0.91	0.091	0.0091	0.0030	0.003
45 mg/L, LOAEL (rats)	7.5	1.8	0.18	0.018	0.0060	0.006
11 mg/L, NOAEL (mice)	2.9	0.41	0.41	0.041	0.014	0.01
20 mg/L, NOAEL (rats)	3.3	0.79	0.79	0.079	0.026	0.03

Column A: The observed LOAEL or NOAEL from Table 2.

Column B: The observed LOAEL or NOAEL converted from mg/L to an intake rate (dose) in mg/kg/day. For rats, the LOAEL or NOAEL is divided by 6; for mice, the NOAEL is divided by 3.8 (see explanation in text).

Column C: The intake rate for rats or mice converted to a human equivalent dose (HED) using the BW^{3/4} method (see explanation in text). The HED = 24% of the intake rate for rats or 14% of the intake rate for mice.

Column D: NOAEL as already obtained (NOAEL / 1) or as estimated from a LOAEL (LOAEL / 10).

Column E: The estimated NOAEL after application of an intraspecies uncertainty factor (UF_H), where UF_H = 10. The NOAEL from Column D is divided by UF_H (i.e., NOAEL / 10).

Column F: The estimated NOAEL after application of an additional uncertainty factor for interspecies variability (UF_A), where UF_A = 10. The adjusted NOAEL from Column E is divided by UF_A (i.e., NOAEL / 3).

Column G: The value of the Reference Dose (RfD) obtained with only UF_H and UF_A. RfD = the NOAEL value in Column F, rounded to 1 significant digit.

VII. EXPOSURE ASSESSMENT

147. The only condition of use at issue in this case, as I understand it, is the addition of fluoridation chemicals to drinking water. Because of this, I limited the scope of my exposure assessment to exposures directly attributable to fluoridated water (0.7 mg/L). The purpose of my assessment was to enable a comparison of the doses people ingest from fluoridated water with the toxicity values (LOAELS and NOAELs) derived from the animal studies. I did not consider fluoride intake from dental products, pesticides, industrial pollution, occupational exposures, black tea, or other sources.

148. In my assessment, I considered fluoride exposures among both the general public as well as subsets of the population known to consume elevated amounts of water. For the source data, I relied primarily on the NRC's 2006 report which presented estimates of fluoride intake from water containing 0.7 mg/L fluoride. The NRC's estimates were based on an EPA analysis of community water intake data that were collected in a national survey by the US Department of Agriculture (USDA) in the 1990s.¹⁹² The USDA survey was "designed to obtain a statistically representative sample of the United States population," and EPA stated that data from this survey "may be used in risk assessment analyses where exposures that occur through ingestion of water are of concern."¹⁹³

149. Based on NRC's data, human exposure to fluoride from fluoridated water is estimated to range from an average of 0.011 mg/kg/day for adults to a "high" of 0.14 mg/kg/day for 95th percentile-exposed infants.

150. Following my initial report, a criticism was raised that I should have conducted a

¹⁹² The USDA survey is called the "Continuing Survey of Food Intakes by Individuals," or CSFII for short.

¹⁹³ EPA (2000a), p. 5-5.

systematic review of all water intake data published subsequent to the NRC's report. In response to this criticism, I reviewed an updated and comprehensive review of water intake data that EPA published in 2019. The review was published as an update to EPA's *Exposure Factors Handbook* ("*Handbook*"), which is a document "intended for use by exposure and risk assessors both within and outside the U.S. EPA as a reference tool and primary source of exposure factor information."¹⁹⁴

151. In its 2019 report, EPA presented the results of its "comprehensive review of the scientific literature [on water intake] through 2017" and provided EPA's determination as to "the most up-to-date and scientifically sound" data¹⁹⁵ to use for tap water consumption in the US.¹⁹⁶ The report thus provides the community water intake values¹⁹⁷ that EPA now recommends using for risk assessment for each age group in the population.¹⁹⁸

152. The water intake data that EPA identifies in its 2019 report are consistent with EPA's older water intake data that I relied upon in my initial assessment. For example, whereas I selected 0.011 mg/kg/day as an average adult exposure, the EPA's updated data produce mean intakes by adults of 0.011-0.013 mg/kg/day (i.e., the same as or slightly higher than my estimate).¹⁹⁹ Further, whereas I selected 0.14 mg/kg/day as the 95th percentile exposure among

¹⁹⁴ EPA (2011a), p. 1-3.

¹⁹⁵ EPA (2019b), p. 1-5.

¹⁹⁶ EPA selected its own analysis of water intake data from NHANES's 2005-2010 surveys as the "key study" to use for all age groups in the general population and for pregnant and lactating women. For formula-fed babies, EPA selected an analysis by Kahn of the USDA's CSFII survey, which is the same survey that the NRC relied upon for its estimates in 2006.

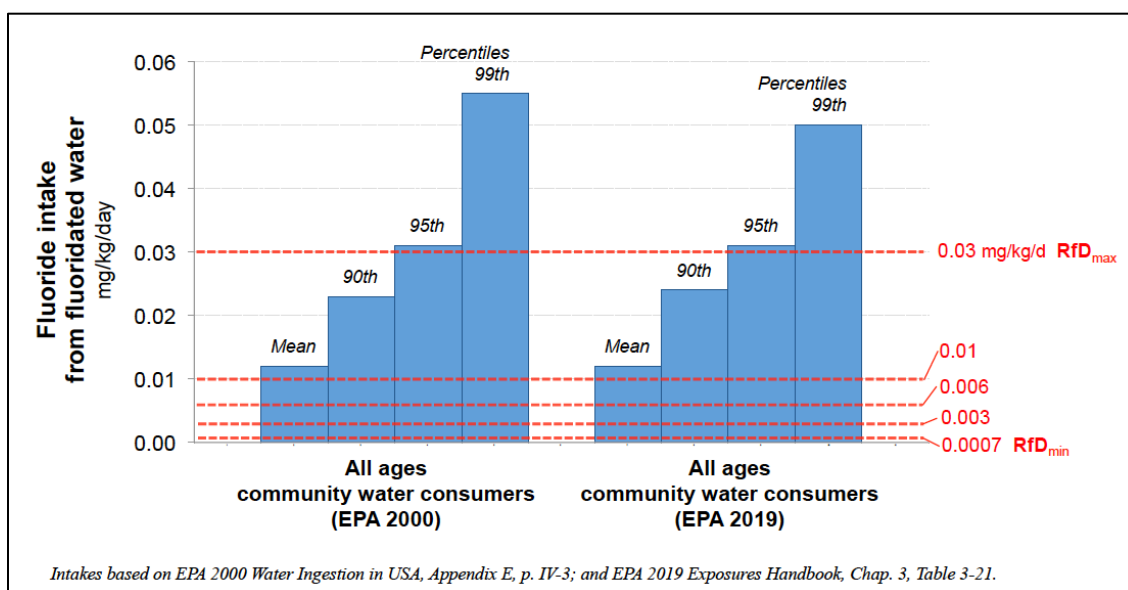
¹⁹⁷ EPA's report presents water intake in terms of milliliters of water consumed per kilogram of bodyweight per day (mL/kg/day). This permits a direct estimation of fluoride exposure from fluoridated water because the concentration of fluoride is known (0.7 micrograms per milliliter). By way of example, if a person drinks 100 milliliters of fluoridated water per kilogram of bodyweight, they will receive a dose of 70 micrograms of fluoride per kilogram, which is more commonly expressed as 0.07 milligrams per kilogram (i.e., 0.07 mg/kg/day).

¹⁹⁸ EPA (2019b), pp. 3-1, 3-4, 3-7, & 3-9.

¹⁹⁹ EPA (2019b), pp. 3-4.

bottle-fed infants, EPA's updated data produce 95th percentile values ranging from 0.13 mg/kg/day to 0.2 mg/kg/day (i.e., higher than my estimate).²⁰⁰

153. The similarity between the two EPA datasets can be seen in the following figure. The figure shows the fluoride exposure from water for *all* community water consumers for *all* age groups combined. The left side of the figure shows EPA's 2000 data (that NRC and I relied upon), while the right side of the figure shows EPA's 2019 data. To help put these exposures in context, the figure also shows the five reference doses from the animal neurotoxicity data (Table 5).



154. As can be seen in the figure, the two datasets show that a *substantial* percentage of the population that consume fluoridated tap water exceed each of the 5 RfDs for neurotoxicity, including the least protective RfD.

155. One limitation with EPA's water intake data (from both 2000 and 2019) is that they do not include consumption of community water that is added to commercial beverages, such as soda and juice.²⁰¹ This underestimates actual exposure to fluoridated water, since commercial

²⁰⁰ EPA (2019b), pp. 3-9.

²⁰¹ EPA (2000a), p. viii.

beverages have become a significant source of exposure to fluoridated water for many people.²⁰²

156. Another limitation with EPA's water intake data is that they are based on short-term surveys (i.e., surveys taken on two non-consecutive days), which creates a source of uncertainty when extrapolating to long-term exposures. This uncertainty is minimized, however, by the large numbers of people surveyed in the studies, and the use of non-consecutive days for the survey. While not perfect, EPA has recognized these data as the most scientifically sound data to use for risk assessment.

VIII. RISK CHARACTERIZATION

157. The risk characterization step of a risk assessment integrates the evidence of hazard, exposure, and dose-response in a clear and transparent manner, and provides a description of the risk. The *Guidelines* recognize multiple ways of describing risk, including (i) characterization of highly-exposed and/or susceptible individuals; (ii) estimation of the number of individuals exposed; (iii) comparing human exposures against the RfD; and (iv) "Margin of Exposure" analysis.²⁰³

A. Characterization of Highly Exposed and/or Highly Susceptible Populations

158. Susceptibility to a chemical may be "intrinsic" (biological, e.g., life stage) or "extrinsic" (acquired, e.g., lifestyle),²⁰⁴ although many individuals may have *both* intrinsic *and* extrinsic susceptibility.

159. EPA has recognized that life stage is an important source of intrinsic susceptibility to neurotoxicants, and has identified the prenatal, infant, and elderly stages of life as "critical periods for exposure."²⁰⁵ According to the EPA, "It is a well-established principle that there are

²⁰² E.g., Heilman et al. (1999); Kiritsy et al. (1996); Turner et al. (1998).

²⁰³ EPA (1998a), pp. 63-66.

²⁰⁴ EPA (2017).

²⁰⁵ EPA (1998a), p. 65.

critical developmental periods for the disruption of functional competence, which include both the prenatal and postnatal periods to the time of sexual maturation, and the effect of a toxicant is likely to vary depending on the time and degree of exposure.”²⁰⁶ In light of this, a “population subgroup is susceptible if exposure occurs during a period of sensitivity.”²⁰⁷

160. As described below, there are large, identifiable subsets of the population that are likely more susceptible to the neurotoxic effects of fluoride than the general population, including pregnant women and their fetuses, bottle-fed infants, the elderly, and individuals with renal impairment.

1. Pregnant Women and Their Fetuses

161. Multiple converging lines of evidence support the fetal period as a critical period of susceptibility to fluoride’s neurotoxic effects. First, it is well established that fluoride crosses the placenta and reaches the fetus.²⁰⁸ Second, due to the absence of an effective blood brain barrier,²⁰⁹ the fluoride that reaches the fetus also reaches the brain—a fact that has been confirmed by both animal and human studies.²¹⁰ Third, fluoride has the capacity to lower thyroid function, particularly among individuals with low iodine intakes, and EPA has recognized that alterations to thyroid function (e.g., reductions in thyroid hormone concentrations) during pregnancy can cause cognitive disorders and other neurological harm to the child.²¹¹ Fourth, most studies of prenatal fluoride exposures in animals have documented neuroanatomical, neurochemical, and/or cognitive problems. Fifth, all prospective cohort studies that included individual measurements of

²⁰⁶ EPA (1998a), p. 46.

²⁰⁷ EPA (2008a), p. 42.

²⁰⁸ NRC (2006), p. 193.

²⁰⁹ EPA (2009b), p. 58.

²¹⁰ E.g., McPherson et al. (2018); Mullenix et al. (1995); Du et al. (1992).

²¹¹ EPA (1998a), p. 50; EPA (2008a), p. 40; EPA (2008b), p. 54; EPA (2013b), cover letter, p. 2. See also Rodier (1995); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Bellinger (2018).

prenatal fluoride exposure have found significant adverse associations with neurocognitive harm, including IQ loss and inattention.²¹²

162. The number of pregnant women exposed to fluoridated water each year is large. The CDC estimates that there are approximately 4 million children born in the U.S. each year, and therefore about 4 million pregnancies.²¹³ With approximately two-thirds of the U.S. population living in communities where fluoridation chemicals are added to water, about 2.5 million pregnancies can be expected to occur each year in fluoridated areas.

163. Of paramount concern are pregnant women who have an iodine deficiency. The CDC considers the average iodine status (median urinary iodine concentration) of women of childbearing age (12-19 years and 20-39 years) in the U.S. to be in the “adequate intake” range, but the 10th percentiles by ethnicity and for the total population are in the “insufficient intake” range, indicating that more than 10% of women of childbearing age in the U.S. are deficient in iodine.²¹⁴ Caldwell et al. report that 35% of pregnant women and 38% of nonpregnant women in the U.S. have urinary iodine concentrations below the level considered adequate.²¹⁵ In addition, the CDC notes that even higher intakes of iodine are required for pregnant and lactating women; thus an even greater percentage of American women are likely to be deficient in iodine with respect to the demands of pregnancy and lactation.²¹⁶ Pearce suggests that iodine deficiency in the U.S. may be becoming more prevalent, especially among pregnant women.²¹⁷

164. While the effects of fluoride exposure among pregnant women with iodine

²¹² Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

²¹³ Centers for Disease Control. Births and Natality. Available at: <http://www.cdc.gov/nchs/fastats/births.htm>

²¹⁴ CDC (2008), Chapter 4a, pp. 90-100.

²¹⁵ Caldwell et al. (2011).

²¹⁶ CDC (2008), Chapter 4a, pp. 90-100.

²¹⁷ Pearce (2015).

deficiency have not yet been specifically studied, there is a clear basis for concern. The NRC reported that high fluoride intake appears to exacerbate the effects of low iodine intake on thyroid function in both animals and humans.²¹⁸ Consistent with this, Malin et al. found that an increase in urinary fluoride was associated with an increase in thyroid stimulating hormone (TSH)—an indicator of decreased thyroid function—among iodine-deficient adults in Canada.²¹⁹ A decrease in thyroid function during pregnancy, even in the absence of clinical symptoms in the mother, is associated with reduced IQ and other neurological effects in the offspring.²²⁰

2. Bottle-Fed Infants

165. A bottle-fed infant has a combination of *both* intrinsic *and* extrinsic susceptibility to fluoridated water.

166. *Intrinsic Susceptibility:* The blood brain barrier does not finish developing until 6 months of age,²²¹ and, as such, the fluoride ingested during early infancy will likely reach the brain more readily than during the later childhood and adult years. The brain is also undergoing “rapid development” during infancy, with the growth rate of the brain peaking at 4 months of age.²²² The EPA has thus described the neonatal stage of life as “a critical window of development.”²²³

167. *Extrinsic Susceptibility:* Infants have the highest intake of fluid per unit body weight of any age group among humans, given their mostly liquid diet at that age. This can be seen in the following figure, which uses EPA’s 2000 water intake data to compare the community water

²¹⁸ NRC (2006), pp. 227, 234, 262.

²¹⁹ Malin et al. (2018).

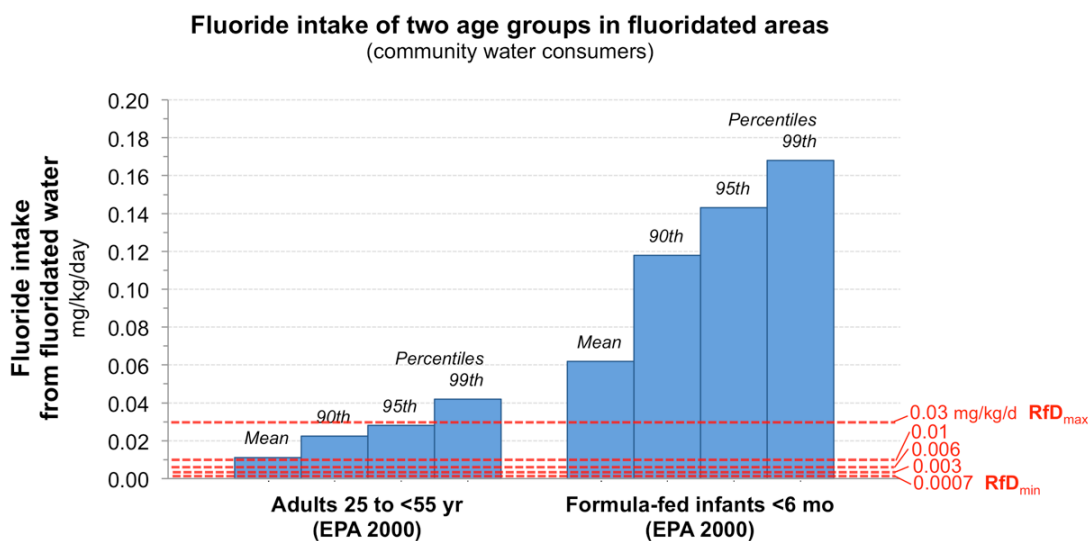
²²⁰ For example, see Haddow et al. (1999); Pop et al. (1999; 2003); Morreale de Escobar et al. (2000; 2004); Klein et al. (2001); Vermiglio et al. (2004); LaFranci et al. (2005); Kooistra et al. (2006); Roman (2007); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Moleti et al. (2016).

²²¹ EPA (2009b), p. 58.

²²² EPA (2013a), p. 5-4; EPA (2008a), p. 42.

²²³ EPA (2008a), p. 42.

intake of adults (on the left) with the community water intake of bottle-fed infants (on the right).



Intakes based on EPA 2000 Water Intake Estimates in US, p. IV-3.

168. According to the CDC, 75% of infants born in 2015 were formula-fed at least partially during their first six months, including 17% of infants who were *exclusively* formula-fed.²²⁴ Data vary by ethnicity, with Hispanics, whites and Asians having breastfeeding rates similar to or greater than the national averages and African Americans having substantially lower rates. Breastfeeding rates tend to be highest for higher family income and maternal education levels.

169. Breastfeeding rates in the U.S. have increased substantially in recent years from a low point in the early 1970s.²²⁵ While increased breastfeeding rates are to be encouraged for a number of reasons, it is important to remember that for many infants in the U.S., breastfeeding is not an option; these include cases of infant adoption or fostering, as well as cases of death or illness of the mother.

²²⁴ CDC (2018; n.d.).

²²⁵ DHEW (1979), pp. 2-6, especially Tables A and B.

170. Most commercial infant formula, historically and currently, has been in powder form, for which the cost is approximately half that of ready-to-feed formula, per unit volume of formula as fed.²²⁶ Based on national data collected during 2005-2007, the CDC reported that approximately 83-93% of babies are fed formula prepared from powder from cans.²²⁷ For approximately 70-78% of infants in the same national survey, formula is reconstituted with tap water at least some of the time.²²⁸

171. Based on the available information, it can reasonably be assumed that the majority of formula-fed infants in the U.S. are fed powdered formula reconstituted with water, often or usually tap water. Especially for low-income homes (where breastfeeding is less likely), it is reasonable to assume that many or most infants are fed formula prepared from powder using tap water, which in much of the country is fluoridated. In addition, for approximately 20% of infants, tap water is boiled before it is used to prepare formula;²²⁹ if this tap water is fluoridated, the resulting fluoride concentration in the formula will be higher than if the water had not been boiled.²³⁰

172. Fomon et al. estimated that infants consuming powdered formula prepared with fluoridated water (1 mg/L) will ingest between 0.116 and 0.164 mg/kg/day.²³¹ If Fomon's estimate is adjusted to account for the lower concentration of fluoride now added to water (0.7 mg/L), the result is a daily intake of 0.08 to 0.115 mg/kg/day, which is 80 to 115 times higher than the amount that Fomon et al. estimated for breast-fed infants (0.001 mg/kg/day).²³² By Fomon's estimates,

²²⁶ O'Connor (2009).

²²⁷ CDC (2017), Table 3.16.

²²⁸ CDC (2017), Table 3.97.

²²⁹ CDC (2017), Table 3.98.

²³⁰ For example, see Juárez-López et al. (2011).

²³¹ Fomon et al. (2000), Table 2.

²³² Fomon et al. (2000), Table 2.

essentially all formula-fed infants will exceed the RfDs for neurotoxicity if their formula is prepared with fluoridated tap water.

173. Fomon's estimates agree well with recent data from Harriehausen et al., who surveyed 114 parents in Houston to determine brand and type of formula, total volume of formula consumed over 24 hours, and infant weight.²³³ Most of the parents in the study (corresponding to 92.1% of the infants) reported using powdered formula, which is consistent with the literature described above.²³⁴ Harriehausen et al. estimated that over 50% of infants fed formula made with fluoridated water will exceed 0.1 mg/kg/day during the first 4 months of life (Table 6).

Table 6. Estimated fluoride ingestion from infant formula, assuming fluoridated water at 0.7 mg/L.^a

Category	Age				
	2 months	4 months	6 months	9 months	12 months
Number of infants	32	23	27	21	11
Predicted fluoride intake					
Mean (mg/kg/day)	0.110	0.112	0.090	0.066	0.053
Variance	0.0033	0.0016	0.0018	0.0012	0.0009
Standard deviation ^b	0.057	0.040	0.042	0.035	0.03
Distribution of fluoride intake					
> 0.1 mg/kg/day (%)	59.4	56.5	33.3	14.3	9.1
< 0.1 mg/kg/day (%)	40.6	43.5	66.7	85.7	90.9

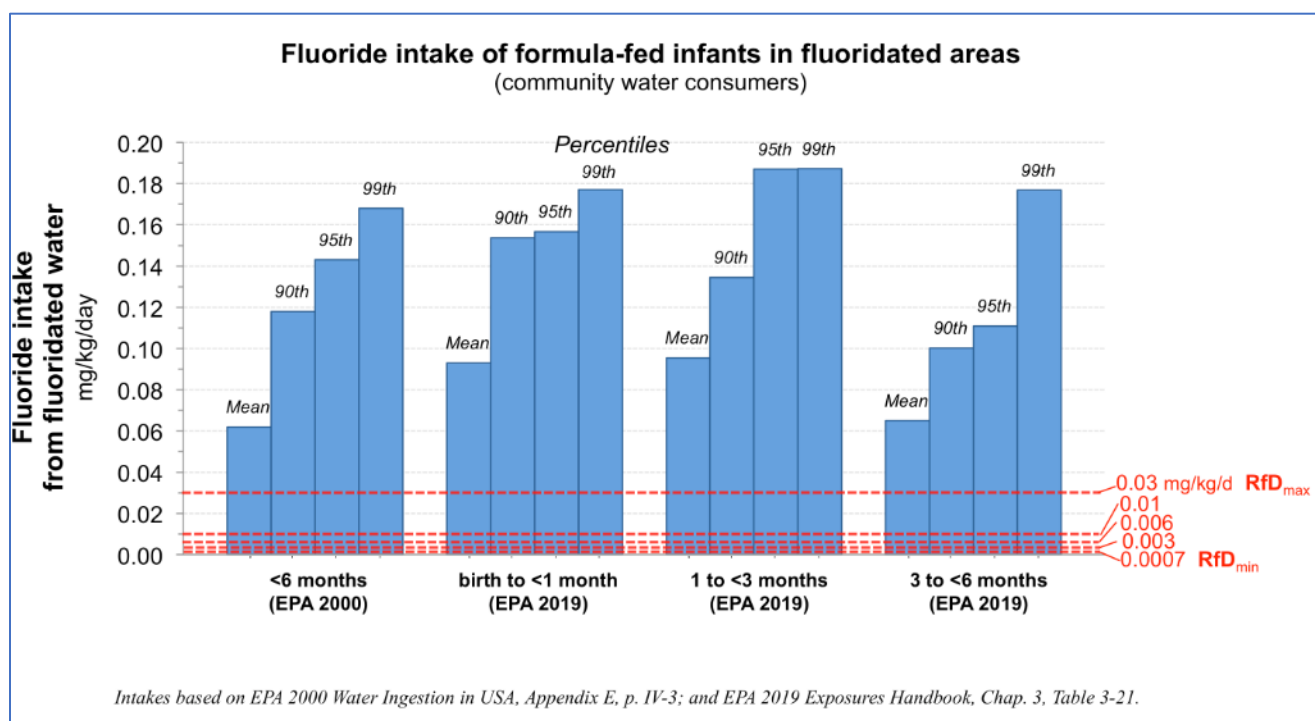
^a Data from Harriehausen et al. (2019), Table 3.

^b Calculated from the variance reported by Harriehausen et al. (2019), Table 3.

²³³ Harriehausen et al. (2019).

²³⁴ Harriehausen et al. (2019), Table 2.

174. The estimates from both Harriehausen and Fomon are consistent with EPA's most up-to-date and scientifically sound estimates for formula-fed infants.²³⁵ According to EPA's updated estimates, mean fluoride exposures during the first 6 months of life for infants receiving formula reconstituted with fluoridated water are **0.07 to 0.10 mg/kg/day** (age-dependent), with 95th percentile exposures of **0.13 to 0.2 mg/kg/day** for the first 3 months and **0.13 mg/kg/day** for the next three months.²³⁶ These intakes are very high, and far exceed even the least protective RfD, as shown in the following figure.



175. In its *Guidelines*, EPA considers the potential for postnatal toxicant exposures to interact with breastmilk composition.²³⁷ EPA was referring to animal studies, but the principle would apply to humans as well: Replacement of the mother's milk with a substitute that contains a toxic agent would be an extremely important source of postnatal exposure for infants and children

²³⁵ EPA (2019b), p. 3-9.

²³⁶ EPA (2019b), p. 3-9.

²³⁷ EPA (1998a), p. 46.

to that toxic agent. Few, if any, animal studies reproduce the effect of formula-feeding of human infants, in terms of a water-based formula containing fluoride being substituted for the mother's milk; thus this very important developmental period is routinely missed in most developmental studies on fluoride.

176. Consistent with the high fluoride intakes produced by formula feeding, studies have found that bottle-fed babies have higher rates of dental fluorosis (a disorder of enamel caused by excess fluoride intake) in their permanent teeth.²³⁸ Studies have also documented an increased prevalence and severity of dental fluorosis in the African American community, which is consistent with the high rate of formula feeding in this population.²³⁹

177. While fluoride exposure during infancy is known to produce abnormal physiological changes in the body (e.g., dental fluorosis), there has been a paucity of research on the neurodevelopmental effects of this exposure. In the developmental studies on fluoride neurotoxicity to date, the pups have been *breastfed*. Consequently, the existing animal data do not reflect the neurotoxic effects that may occur during the neonatal period.

178. Studies in humans have found lower IQ scores among formula-fed babies versus breastfed babies,²⁴⁰ but up until this year,²⁴¹ no study had investigated the role that fluoridated water may have in this association. Specific differences in brain activation and regional volumes of gray matter have been reported among formula-fed children, indicating developmental changes in children in comparison with breastfed children.²⁴² Such effects (and other adverse effects of

²³⁸ Hong et al. (2006a; 2006b); Forsman (1977); Walton and Messer (1981); Fomon and Ekstrand (1999); Fomon et al. (2000).

²³⁹ EPA (2010), pp. 33-34; Exhibit 34 to Casey Hannan Deposition; CDC (2005), Table 23.

²⁴⁰ For example, see Fomon (2001); Wolf 2003; Belfort et al. (2013); Horta et al. (2015; 2018); Victora et al. (2015; 2016); Kanazawa (2015); Boutwell et al. (2018). Many studies have controlled for possible confounders such as maternal IQ, maternal education, and family income.

²⁴¹ Till et al. (2020).

²⁴² Ou et al. (2016).

formula-feeding compared with breastfeeding, especially compared with exclusive breastfeeding for at least the first several months) could, in principle, be due to loss of the enhanced mother-child bonding associated with breast-feeding,²⁴³ to deficiency of an essential nutrient (e.g., long-chain saturated fatty acids) in the formula,²⁴⁴ to the presence of a toxic contaminant in the water used to prepare the infant formula,²⁴⁵ or to some combination of these factors.

179. Given the *a priori* basis for concern that fluoridated water may adversely affect the neurological system of bottle-fed infants, the recent findings from Till et al. must be taken very seriously.²⁴⁶ Using a prospective cohort study design, Till et al. found that fluoridated water consumption during infancy is associated with a large and significant reduction in non-verbal IQ at age 4 (i.e., a loss of 9.3 non-verbal IQ points for each 0.5 mg/L increase in exposure). Although the study did not find a statistically significant association with Full-Scale IQ after excluding several outliers, this could be a result of imprecision in the exposure estimates, or might reflect differential impacts of pre- and post-natal exposure.

180. As noted earlier, CDC data indicate that 17% of babies are *exclusively* fed formula for their first six months of life (i.e., never breast-fed).²⁴⁷ Assuming 2.5 million live births per year in fluoridated areas, approximately 1.9 million infants living in fluoridated areas will be formula-fed for at least part of the time during their first six months, including 425,000 infants who are *exclusively* formula-fed.²⁴⁸ Approximately 70-78% of these infants will have their formula made

²⁴³ Horta et al. (2018).

²⁴⁴ Horta et al. (2018).

²⁴⁵ Goyer (1995).

²⁴⁶ Till et al. (2020).

²⁴⁷ CDC (2018; n.d.).

²⁴⁸ CDC (2018; n.d.).

with fluoridated tap water (some of which will be boiled and have higher concentrations), at least part of the time.²⁴⁹

3. Elderly

181. The elderly have also been identified by the EPA as an at-risk group for neurotoxicity.²⁵⁰ According to the EPA, the elderly are “at particular risk because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult.”²⁵¹

182. The NRC has described the possible relationship of fluoride exposure, especially exposure to aluminum fluoride complexes, to the development of Alzheimer’s disease.²⁵² The NRC based its concern, in part, on studies reporting pathological lesions in the brain of fluoride-treated rodents that parallel the changes in humans with dementia.²⁵³ A recent study by Cao et al. found that exposure to fluoride for 3 months among mice genetically prone to degenerative brain changes, produced more severe, and earlier development of, neuropathological lesions than in controls, including lesions associated with Alzheimer’s.²⁵⁴ Goschorska et al. have recently postulated that fluoride plays a likely role in the initiation and progression of Alzheimer’s disease, based largely on the neuroanatomical and neurochemical changes seen in the brains of fluoride-treated animals.²⁵⁵

183. While epidemiological data on fluoride and cognition in the elderly remain relatively sparse, Li et al. reported a very high rate of cognitive impairment (81.1%) in an endemic fluorosis area.²⁵⁶ Li did not find a linear relationship between urinary fluoride and the severity of

²⁴⁹ CDC (2017), Table 3.97; Juárez-López et al. (2011).

²⁵⁰ EPA (1998a), p. 65; see also NRC (2006), p. 351.

²⁵¹ EPA (1998a), p. 65.

²⁵² NRC (2006), pp. 210-212.

²⁵³ NRC (2006), pp. 222.

²⁵⁴ Cao et al. (2019).

²⁵⁵ Goschorska et al. (2018).

²⁵⁶ Li et al. (2016), p. 59.

cognitive impairment within the endemic fluorosis area; however urinary fluoride levels among those with any form of cognitive impairment were significantly higher than those with normal cognition.²⁵⁷ Russ et al. described a longitudinal study involving nearly all people born in Scotland in 1921, who were passively followed for diagnoses of dementia after 2004.²⁵⁸ Residential locations after age 60 (or at death or at time of diagnosis of dementia) were used to estimate exposure to aluminum and fluoride (separately) in drinking water. The authors found that even relatively low levels of aluminum and fluoride were associated with an increased prevalence of dementia and suggested further research.²⁵⁹

184. While more research is needed to clarify fluoride's effects in the elderly population, there are a multitude of factors which support an increased vulnerability to fluoride's neurological effects among the elderly. Studies have found that water fluoridation significantly increases the level of fluoride in bone, and these levels increase with age.²⁶⁰ In the post-menopausal and elderly years, the fluoride that is taken into bone can be released back into the blood stream as bones begin to break down, leading to increased levels of fluoride in the blood.²⁶¹ Compounding this, renal function declines with age, and because of this the elderly kidney can be expected to be less efficient in clearing fluoride from the bloodstream. The net result is that more fluoride will be circulating in the bloodstream, and due to age-related increases in the permeability of the blood-brain barrier, will reach the brain more readily.²⁶²

185. Although the impact of fluoride on the elderly brain has not received as much

²⁵⁷ Li et al. (2016), Figure 2, Table 3.

²⁵⁸ Russ et al. (2019).

²⁵⁹ Russ et al. (2019).

²⁶⁰ Alhava et al. (1980); Arnala et al. (1985); Eble et al. (1992); Chachra et al. (2010).

²⁶¹ Itai et al. (2010).

²⁶² Increased permeability of the blood-brain barrier is associated with ordinary aging, as well as with diseases such as Alzheimer's and Parkinson's, both of which are common among elderly people. For example, see Mooradian (1994); Zeevi et al. (2010); Rosenberg (2014); and Pan and Nicolazzo (2018).

scholarly attention as the impact on the developing brain, this population is likely at higher risk of toxicity than healthy adults, particularly among those with elevated accumulation of fluoride in the bone following long-term residence in a fluoridated area.

Renal Impairment

186. It is well recognized that people with renal impairment (kidney disease) are less able to excrete fluoride, resulting in higher concentrations of fluoride in the body and greater susceptibility to adverse health effects from fluoride exposure.²⁶³ The World Health Organization states that it “is known that persons suffering from certain forms of renal impairment have a lower margin of safety for the effects of fluoride than the average person.”²⁶⁴ In addition, a number of papers report an association between renal impairment and reduced IQ or other cognitive impairment,²⁶⁵ which is consistent with higher fluoride retention (and often higher water intake and consequent higher fluoride intake). The role of fluoride in these IQ deficits has not yet been the subject of epidemiological study.

4. Other Predisposing Factors

187. There are a number of other factors that are known, or reasonably anticipated, to increase susceptibility to the chronic toxic effects of fluoride exposure, including neurotoxicity. These factors include:

188. *Diseases that Increase Water Intake*: The NRC identified population subgroups whose water intake “is likely to be substantially above the national average for the corresponding sex and age group” as susceptible subpopulations with respect to fluoride exposure.²⁶⁶ Health

²⁶³ For example, see Marumo and Iwanami (2001); NRC (2006), pp. 30, 292, 351; Ibarra-Santana (2007); Schiff (2008).

²⁶⁴ WHO (2004), p. 6.

²⁶⁵ For example, see Madero et al. (2008); Mendley et al. (2015); Chen et al. (2018b).

²⁶⁶ NRC (2006), p. 30.

conditions that affect water intake include “diabetes mellitus, especially if untreated or poorly controlled; disorders of water and sodium metabolism, such as diabetes insipidus; [and] renal problems resulting in reduced clearance of fluoride.”²⁶⁷ According to the NRC, adults with diabetes mellitus can ingest 0.05 mg/kg/day from fluoridated water alone, while children with diabetes mellitus can have fluoride intakes as high as 0.07 mg/kg/day.²⁶⁸ For children and adults with nephrogenic diabetes insipidus, NRC estimated waterborne fluoride intakes of 0.11 mg/kg/day.^{269,270} Each of these intakes exceeds the least protective RfD.

189. *Nutrient Deficiencies:* Nutritional deficiencies can contribute to increased susceptibility to fluoride toxicity.²⁷¹ Calcium deficiency and iodine deficiency are expected to be particularly important in terms of vulnerability to neurotoxic effects of fluoride, but deficiencies of magnesium, vitamin C, protein, and other nutrients have also been associated with increased susceptibility to the effects of fluoride exposure.

190. *Genetic Susceptibilities:* A number of studies have shown associations between specific genetic arrangements and a greater susceptibility to the chronic effects of fluoride exposure,²⁷² including dental fluorosis and alterations to reproductive hormones.²⁷³ While a complete picture of the relationship between genes, gene regulation, and adverse effects of fluoride exposure remains to be developed, it is already quite clear that some people or groups of people

²⁶⁷ NRC (2006), p. 30.

²⁶⁸ NRC (2006), p. 35, Table 2-4.

²⁶⁹ NRC (2006), p. 35, Table 2-4.

²⁷⁰ Consistent with this, case reports have documented moderate to severe dental fluorosis among children with diabetes insipidus who drank water with 0.5 to 1 mg/L NRC (2006), p. 33.

²⁷¹ See for example, NRC (2006), p. 265; Pandit et al. (1940); Marier (1977).

²⁷² Reviewed by Pramanik and Saha (2017). See also Lavryashina et al. (2003); Tu et al. (2011); Liu et al. (2006); Huang et al. (2008); Ba et al. (2011); Zhao et al. (2015); Zhou et al. (2016); Zhang et al. (2013b); Pei et al. (2017); Jiang et al. (2015); Zhang et al. (2015b); Cui et al. (2018); K  chler et al. (2018); Bhagavatula Naga (2009).

²⁷³ Zhao et al. (2015); Zhou et al. (2016); Ma et al. (2017); An et al. (2019).

are inherently more vulnerable than others to adverse effects of fluoride exposure and require a greater level of protection from fluoride exposures.²⁷⁴ The implications to neurotoxicity have not yet been extensively studied, but two recent studies from China, including one with extensive control for covariates, suggest that certain genotypes may significantly magnify fluoride's impact on IQ in some individuals.²⁷⁵ A third, smaller study reported a contrary result.²⁷⁶ More research is needed to clarify this issue, but in light of the broader literature on genetic susceptibility to chronic fluoride toxicity, it is reasonable to suspect that genetics plays a role in rendering some individuals more vulnerable to fluoride's neurological effects.

B. Margin of Exposure (MOE)

1. Introduction to the MOE Approach and Its Similarity to the RfD Approach

191. Under the *Guidelines*, neurotoxic risk can be described either through a comparison of the human exposures to the RfD, or by calculating the “Margin of Exposure” (MOE).²⁷⁷ Although the two approaches use slightly different frameworks, they produce the same results. If comparison of human exposure with the RfD shows a risk, a risk will be shown by MOE as well, and vice versa.

192. RfD and MOE analyses produce the same results because they use the same Point of Departure (i.e., NOAEL, LOAEL, or BMDL) for the toxicity value, the same data for human exposure, and the same composite uncertainty factor to assess whether human exposure poses a risk. Where the two methods differ is in how they put these three pieces together and the terminology they use, as will now be discussed.

193. In an RfD analysis, human exposure is compared against the Reference Dose. As

²⁷⁴ Wu et al. (2015); Yang et al. (2016); Pei et al. (2017); Li et al. (2017); Yang et al. (2018b).

²⁷⁵ Cui et al. (2018); Zhang et al. (2015b).

²⁷⁶ Pang et al. (2018).

²⁷⁷ EPA (1998a), pp. 65-66; Federal Register (1998), pp. 26949-26950.

discussed earlier, the Reference Dose is the Point of Departure (i.e., NOAEL, LOAEL, or BMDL) divided by the composite uncertainty factor. In an MOE analysis, by contrast, human exposure is *compared directly against the Point of Departure*. If the ratio (i.e., Actual MOE) between the Point of Departure and human exposure is less than the composite uncertainty factor (i.e., Acceptable MOE), an unacceptable risk is presumed to exist.^{278,279} In short, the composite uncertainty factor is the standard for judging whether human exposure is unacceptably close to the toxicity value under both frameworks.

2. MOE Analysis

194. As part of the risk assessment, I conducted an MOE analysis to characterize risk because this is EPA's preferred method to characterize non-cancer risk under TSCA, as evident by its risk evaluations under both Section 5 (new chemicals)²⁸⁰ and Section 6 (existing chemicals).²⁸¹

195. *Points of Departure*: The same five Points of Departure (converted into Human Equivalent Doses) that were used for the derivation of the Reference Doses, as discussed above (see Table 5), were used for the MOE analysis.

196. *Acceptable MOEs (Benchmark MOEs)*: The same composite uncertainty factors that were used for the RfD derivation were selected as the Acceptable MOEs: 30 for the NOAEL-based PODs, and 300 for the LOAEL-based PODs. In EPA's draft risk evaluations under Section 6 of TSCA, EPA has used composite uncertainty factors of 30 for NOAEL-based PODs, and has

²⁷⁸ EPA (2016), p. 61; EPA (2012), p. 13-8.

²⁷⁹ EPA sometimes refers to the risk as a "risk of concern." EPA (2007), p. 13; EPA (2000c), p. C-12.

²⁸⁰ See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

²⁸¹ In its draft risk evaluations under Section 6 thus far, EPA has used MOE to characterize non-cancer risk. (EPA 2019c; 2019d; 2020). In its Final Rule for Risk Evaluation under Section 6, however, EPA described the MOE method as "just one of several approaches to risk characterization" that may be used under TSCA (Federal Register 2017, p. 33735).

characterized this as a relatively small uncertainty factor that “indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD . . . were applied).”²⁸² EPA has contrasted this with a composite uncertainty factor of 1,000, which “would indicate more uncertainty in risk estimation and extrapolation.”²⁸³

197. *Human Exposure:* At the time I conducted this analysis, EPA had not yet released any of its Section 6 draft risk evaluations. I relied, therefore, on EPA’s risk evaluations under Section 5 for guidance on the human exposure assessment. In the Section 5 risk evaluations, EPA considers the highest-exposed group in the population. When dealing with chemicals that may be present in drinking water, therefore, EPA’s MOE analyses separately consider the exposures of *infants*.²⁸⁴

198. Based on the guidance from the Section 5 risk evaluations, I relied on the NRC’s 2006 data to calculate a range of exposures representing the general adult population along with highly exposed population subgroups, including bottle-fed infants and individuals with high water intakes (for example, due to medical conditions or to physical exertion).²⁸⁵

199. In EPA’s draft risk evaluations under Section 6, EPA has used the 95th percentile exposure to represent highly exposed individuals.²⁸⁶ This is the same percentile exposure I used

²⁸² EPA (2019d), p. 301.

²⁸³ EPA (2019d), p. 301.

²⁸⁴ See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

²⁸⁵ For the general adult population, I combined NRC’s estimates for adult consumers of municipal water, ages 20-24 and 25-54 years (0.011 mg/kg/day). As an example of elderly adults (ages 65+), I included the 90th percentile of adult consumers of municipal water (0.022 mg/kg/day). To account for individuals with high water intakes, I used the NRC’s waterborne fluoride intake estimates (at 0.7 mg/L) for adult athletes and physical laborers (0.05 mg/kg/day), children with diabetes mellitus (0.07 mg/kg/day), and individuals with nephrogenic diabetes insipidus (0.1 mg/kg/day). For bottle-fed infants, I estimated a typical (0.1 mg/kg/day) and high (0.14 mg/kg/day) exposure based on the data from Fomon et al. (2000), Harriehausen et al. (2019), and NRC (2006). None of these exposure estimates, even those labeled “high,” is an upper bound or maximum exposure.

²⁸⁶ E.g., EPA (2019d), pp. 266, 300; EPA (2020), p. 108.

for high exposures among bottle-fed infants, and a higher percentile exposure than I used for the elderly (90th percentile).

200. Table 7 and the two figures below show the results of the MOE analyses. The first figure shows the results using the three LOAEL-Based PODs, while the second figure shows the results using the NOAEL-based PODs. As can be seen, the Actual MOEs are below the Acceptable MOEs for each group using every POD (including the least protective), with the exception of *average* adults and 90th percentile elderly when using the NOAEL-based PODs. If EPA's recommended 95th percentile exposure data (0.031 mg/kg/day) is used as the exposure for adults, risks are present even when using the least protective PODs.

201. The margins between the neurotoxicity levels in animals and the exposure levels in humans are far smaller than what EPA considers "acceptable." In fact, the Actual MOEs are so small that unacceptable risks would still be indicated for infants for each POD if the doses from animal studies had no adjustment to convert to the Human Equivalent Doses (HEDs) (i.e., no allometric scaling). Under EPA's framework for characterizing risk, therefore, it is apparent that fluoridation chemicals in drinking water present an unacceptable risk of neurotoxicity.²⁸⁷

²⁸⁷ EPA (2016), p. 61.

Table 7. Calculated Margins of Exposure (MOEs)^a for selected subgroups of the human population for the NOAELs and LOAELs for fluoride in Table 5.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Estimated human exposures ^e					
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

^a A Margin of Exposure (MOE) is equal to the LOAEL or NOAEL (mg/kg/day) divided by an estimated human exposure (mg/kg/day). Usually, the benchmark MOE = 1000 for assessments based on a LOAEL and 100 for assessments based on an NOAEL. Since allometric scaling between animals and humans has been used to obtain the Human Equivalent Dose, the benchmark MOE is 300 for LOAELs and 30 for NOAELs. An MOE less than the benchmark MOE indicates an “unacceptable risk.”

^b These LOAEL and NOAEL values (mg/L) for fluoride are summarized in Table 2.

^c The intake rates (mg/kg/day) in this column correspond to the LOAELs and NOAELs in the first column (mg/L), converted to intake rates (mg/kg/day) as summarized in Table 5. For rats, the intake rate equals the LOAEL or NOAEL divided by 6. For mice, the intake rate equals the NOAEL divided by 3.8.

^d The Human Equivalent Dose (HED) is calculated from the intake rate for rats or mice as summarized in Table 5. The HED = the intake rate for rats × 0.24 or the intake rate for mice × 0.14.

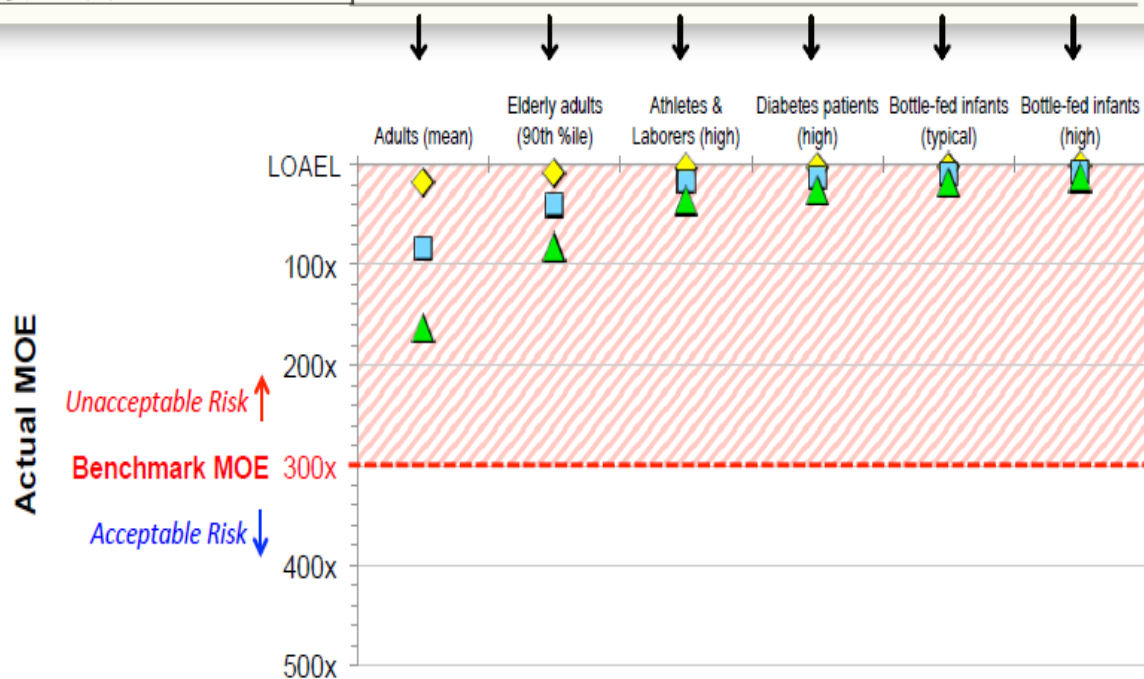
^e The estimated human exposures are for fluoride exposures from drinking water alone, assuming a fluoride concentration of 0.7 mg/L in the drinking water. Sources are as follows: Adults (average), NRC (2006), p. 430, Table B-11, average consumers ages 20-54; Elderly adults (90th percentile), NRC (2006), p. 431, Table B-12, 90th percentile consumers ages 65+; Athletes and laborers (high), NRC (2006), p. 35, Table 2-4, high consumers (but not upper bound); DM patients (high), NRC (2006), p. 35, Table 2-4, patients with diabetes mellitus, high consumers (but not upper bound); Bottle-fed infants (typical), based on Fomon et al. (2000) and Harriehausen et al. (2019); NDI patients (high), NRC (2006), p. 35, Table 2-4, patients with nephrogenic diabetes insipidus, high consumers (but not upper bound); and Bottle-fed infants (high), NRC (2006), p. 432, Table B-13, infants < 0.5 years old, 95th percentile consumers (but not upper bound).

Food and Water Watch v. EPA

Thiessen Report

Table 8. Calculated Margins of Exposure (MOEs)^a for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Actual MOEs					
			Estimated human exposures ^e					
LOAELs from animal studies								
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	 0.83	0.20	 18	 9.1	 4.0	 2.9	 2.0	 1.4
23 mg/L, LOAEL (rats)	 3.8	0.91	 83	 41	 18	 13	 9.1	 6.5
45 mg/L, LOAEL (rats)	 7.5	1.8	 163	 82	 36	 26	 18	 13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

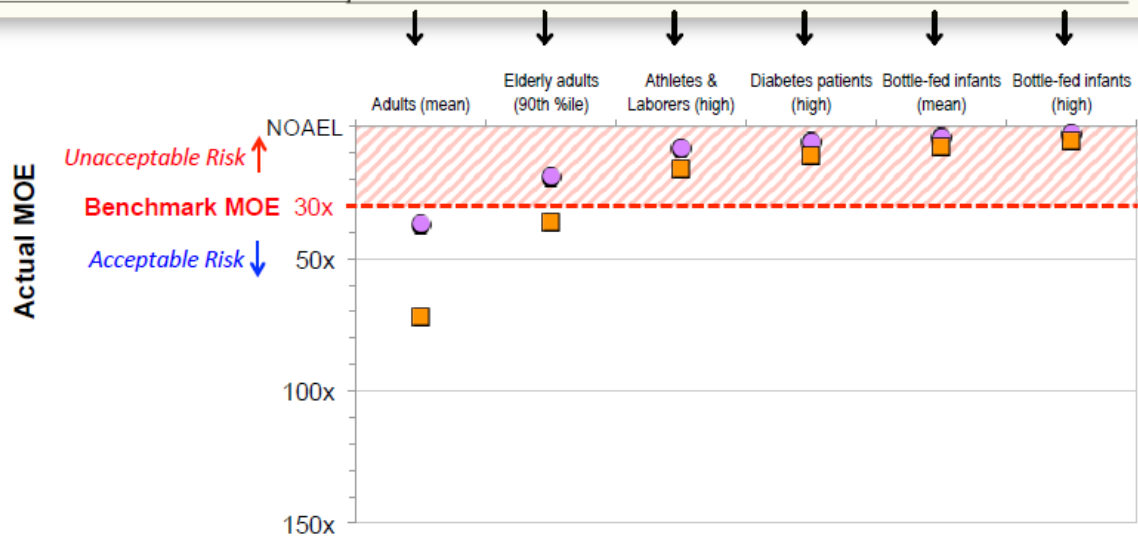


Food and Water Watch v. EPA

Thiessen Report

Table 8. Calculated Margins of Exposure (MOEs)^a for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Actual MOEs					
			Estimated human exposures ^e					
NOAELs from animal studies								
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice) 	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats) 	3.3	0.79	72	36	16	11	7.9	5.6



C. Assumptions and Key Sources of Uncertainty

202. Uncertainties are inherent to the field of risk assessment; they are to be expected. As discussed throughout my expert report, there are uncertainties involved in a risk assessment of fluoride neurotoxicity,²⁸⁸ including:

203. *Uncertainties in the Animal Data:* The Points of Departure for both the RfDs and MOEs are derived from developmental animal studies that, while published in the peer-reviewed biomedical literature, have methodological limitations, including lack of control for litter effects, lack of blinding, lack of exposure during the full window of vulnerability (in utero *and* infancy), lack of long-term chronic exposures, and failure to rule out a contributing role of motor and sensory effects in the observed learning/memory deficits. As discussed earlier, the net effect of these limitations is uncertain. On one hand, lack of blinding can inflate the effect size, while on the other hand, lack of exposure during the full window of vulnerability and lack of chronic exposures can deflate it. Similarly, while lack of control for litter effects can create false positives, it can also create false negatives as well.²⁸⁹ Further, to the extent that fluoride is causing the learning/memory deficits indirectly through a motor/sensory mechanism,²⁹⁰ this would still be a neurotoxic effect and is thus not a basis to forego risk assessment, particularly since body weight changes do not appear to be a mediating mechanism in the studies from which the Points of Departure have been derived.

²⁸⁸ For purposes of brevity, my initial expert report did not reiterate each of these uncertainties in the risk characterization section, although I considered them as part of my assessment.

²⁸⁹ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

²⁹⁰ NTP (2016), p. vii.

204. While there are some uncertainties in the animal data (which is not unusual²⁹¹), there is reasonable confidence that the observed effects are both real and relevant. First, the animal studies have been overwhelmingly consistent—across numerous laboratories and study designs—in finding adverse effects on the brain, both structural and functional, which supports the conclusion that the effects are not an artifact of a methodological limitation. Second, the effect of fluoride on cognition has been detected in studies that have specifically controlled for litter effects and body weight changes, thus suggesting that fluoride’s effect on the brain is independent of these concerns.²⁹² Third, there are extensive human epidemiological data reporting associations between fluoride and reduced IQ, and the existence of these data adds plausibility to the animal data, and vice versa. Fourth, the finding of unacceptable risk through an MOE analysis of the animal toxicity values is consistent with Dr. Grandjean’s BMD analysis of the human data, which shows that the level of exposure associated with reduced IQ in humans is well below the levels of exposure produced by fluoridation. The confluence of the animal and human data thus adds strong overall confidence to the assessment.

205. *Uncertainties in the Extrapolation to Humans:* As discussed above, the extrapolation of animal data to humans involves some inherent uncertainty. There does not yet exist a physiologically based toxicokinetic model (PBTK) for fluoride, which would be the optimal method for adjusting for toxicokinetics.²⁹³ This uncertainty has been accounted for by EPA’s use of allometric scaling method which accounts for the expected difference in

²⁹¹ As discussed earlier, the principal animal studies that EPA has relied upon for its neurotoxicity risk assessments have also had methodological limitations, including failure to control for litter effects. There was also significant uncertainty in the animal data that EPA used for its unreasonable risk determinations for its draft NMP evaluation (e.g., there were only 6 studies available for the endpoint of concern, and three found no effect).

²⁹² Bartos (2018; 2019).

²⁹³ EPA (2011b), p. 19.

toxicokinetics), and use of an uncertainty factor of 3 (to address the expected difference in toxicodynamics). The use of default allometric scaling for fluoride is consistent with chemical-specific research on fluoride showing that rats and mice require approximately 5 to 10 times more fluoride, respectively, to obtain the same concentration of fluoride in the blood.²⁹⁴ The allometric scaling thus has a chemical-specific justification for fluoride, which provides confidence to the assessment. But, importantly, even if *no* allometric scaling is done to assess the risk of infant exposures, the MOEs still indicate unacceptable risks for *all* PODs.

206. The use of non-protective (i.e., non-conservative) assumptions provides additional confidence to the assessment. These non-protective assumptions include: (1) the use of 45 mg/L as a LOAEL, despite the fact that studies have found adverse effects well below this concentration; (2) the use of 20 mg/L as a NOAEL in McPherson (2018), despite the fact that the study found a neurotoxic effect at this concentration (i.e., increased pain sensitivity); and (3) conversion of water fluoride concentrations (mg/L) into doses (mg/kg/day) using the lowest end of the reported ratio, which results in Points of Departure that are likely higher than the actual dosages the animals received.

207. *Uncertainties in the Exposure Assessment:* As discussed above, I obtained most of my initial exposure estimates from the NRC's 2006 report, which in turn were based on EPA's own water intake data from 2000,²⁹⁵ and have also reviewed EPA's 2019 report in which the Agency identified the "most up-to-date and scientifically sound" water intake data to use for risk assessment. Both of EPA's water intake reports (from 2000 and 2019) are based on short-term (2-day) surveys, which introduces some uncertainty when extrapolating to long-term exposures.

²⁹⁴ NRC (2006), pp. 98, 442; Zhang et al. (2014).

²⁹⁵ NRC (2006), Appendix B; EPA (2000a).

Long-term surveys, however, do not exist, and the uncertainty of using 2-day surveys is minimized by the large, nationally-representative scale of the survey data. EPA has stated that it has medium-to-high confidence in the reliability of these data, and that the data are well suited for risk assessment of water-based exposures.²⁹⁶

208. *Uncertainties in the Human Data:* One of the major strengths of the database on fluoride neurotoxicity is that there is a large body of human data, including five prospective cohort studies that have individual measurements of exposure during the fetal and neonatal period. The large extent of human data for fluoride far surpasses what EPA has used for its draft risk assessments of other chemicals under Section 6,²⁹⁷ where the Agency has often had to rely *solely* on animal data.

209. The emergence of prospective cohort data on early life exposures to “optimal” levels of fluoride (from salt and water fluoridation programs)²⁹⁸ addresses the two primary criticisms that have been made with respect to the cross-sectional studies of populations with elevated levels of fluoride in water: i.e., (1) that cross-sectional studies are limited in establishing causation because the exposures are measured after the effect (i.e., IQ loss) has occurred; and (2) the cross-sectional studies involve exposures that are generally higher than what people receive through artificially fluoridated water. The fact that the prospective cohort studies have found cognitive deficits at “optimal” levels of exposure that are consistent with the effects observed in the cross-sectional studies adds *substantial* confidence to the risk characterization.

210. While the human data are very robust, data gaps do remain, particularly with

²⁹⁶ EPA (2000a), p. 5-5; EPA (2019b), pp. 3-6 & 3-10.

²⁹⁷ As discussed earlier, the data available for fluoride are also substantially more robust than the data EPA has considered in making hazard determinations for other neurotoxicants.

²⁹⁸ I understand that Dr. Hu and Dr. Lanphear will be addressing the criticisms with respect to imprecise exposure estimates, and thus I do not address that issue here.

respect to how the causative doses may vary across the population based on life-stage (e.g., the elderly), and other intrinsic sources of susceptibility, such as renal impairment, nutritional deficiencies, and genetic predisposition. These data gaps make it difficult to quantify the extent to which susceptibility varies across the population; the available data on chronic fluoride toxicity, however, provide a high level of confidence that human susceptibility to fluoride varies by a considerable margin, particularly in a population as large and diverse as the United States. Of particular concern are individuals with co-existing susceptibilities, such as pregnant women with iodine deficiencies, neonates that are bottle-fed with fluoridated water, and elderly individuals with diabetes.

211. To account for the *known* (but not yet quantified) variability in human susceptibility, I utilized EPA's default uncertainty factor of 10. This is consistent with EPA's standard practice, including EPA's Section 6 risk evaluations under TSCA. While I derived the Points of Departure from studies on susceptible (i.e., prenatally exposed) animals, the studies did not account for the full range of expected susceptibility in the human population. The studies did not, for example, attempt to replicate the formula-feeding practices of human infants, as all rodents were breast-fed during the critical neonatal period. Nor did the studies attempt to examine the effect of a co-existing iodine deficiency in the mother, or any other factor (e.g., renal impairment, calcium deficiency, etc) that would be expected to exacerbate the effects of prenatal fluoride exposure. Since hundreds of millions of Americans are now exposed to fluoridation chemicals on a regular basis, the spectrum of susceptibility will likely exceed the susceptibility examined in the available animal studies. An uncertainty factor of 10 is thus appropriate and necessary.

IX. RISK DETERMINATION

212. Under TSCA, a risk evaluation has a fifth and final step that is not included within the *Guidelines*: the Risk Determination. In the Risk Determination, EPA assesses whether the risks identified by the Margin of Exposure (MOE) analysis are “unreasonable.” In making this determination, EPA considers “relevant risk-related factors,” including (i) the effects of the chemical substance under the conditions of use; (ii) number of people exposed; (iii) whether susceptible subpopulations are exposed; (iv) the severity of the hazard; and (v) uncertainties in the data.

213. In practice, EPA’s Risk Determination analyses do not address each of the “relevant risk factors” identified above. Severity of the hazard, for example, is rarely discussed. Assessments of uncertainties in EPA’s Risk Determinations has also been rather cursory. In the NMP risk evaluation, for instance, the discussion of uncertainties in the analysis was largely limited to the assumptions involved in estimating worker exposure to chemicals in the absence of actual monitoring data.²⁹⁹ Although EPA’s risk estimates were based on an endpoint for which there were only 6 animal studies (with only 3 showing an effect), EPA did not re-address the underlying uncertainties in these data. The Risk Determination should thus not be mistaken as an exhaustive re-examination of all issues previously addressed; instead they tend to be brief and written in summary form.

214. At the time I conducted my initial assessment in this case, EPA had not yet released any risk evaluations under Section 6. For guidance, therefore, I relied on the risk characterization

²⁹⁹ EPA (2019d), pp. 301-335.

considerations identified in the *Guidelines*,³⁰⁰ as well as risk evaluations that EPA had recently completed on “new chemicals” under Section 5.

215. The factors that EPA considers under Section 5 substantially overlap with the factors that EPA considers under Section 6. Specifically, EPA considers the following three factors: (i) the hazardous nature of the chemical (as determined by toxicity values in animal studies);³⁰¹ (ii) the extent of human exposure to the chemical, and (iii) the Margin of Exposure (MOE). As I described in my report, fluoride meets each of these three criteria for unreasonable risk.

216. Importantly, whether one considers the factors under Section 5 or Section 6, the risk of neurotoxicity posed by fluoridation chemicals constitutes a clear and unreasonable risk, as will now be discussed.

A. Effects of Fluoridation Chemicals Under the Condition of Use

217. In most of the risk evaluations that EPA has conducted thus far under Section 6, the Agency did not have actual human data on health effects associated with the condition of use. EPA had to rely, therefore, on animal data alone. This is not the case with fluoridation. Critically, there are four prospective cohort studies that have examined the impact of optimal fluoride exposures, including two that examined the specific condition of use (water fluoridation) at issue.³⁰² Under the *Guidelines*, prospective cohort data permit “direct estimates of risks attributed to a particular

³⁰⁰ EPA (1998a), pp. 63-66.

³⁰¹ Under Section 5, a chemical is “considered to have high human health hazard if there is evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies with a **NOAEL** of less than or equal to 10 mg/kg/day.” EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a). This criterion is readily satisfied with fluoride, as the **LOAELs** for cognitive deficits and brain abnormalities are below 10 mg/kg/day. Fluoride is thus a “high human health hazard” under Section 5.

³⁰² Bashash et al (2017, 2018); Green et al. (2019); Till et al. (2020).

exposure.”³⁰³ The effects of fluoridation chemicals under the condition of use are thus well characterized, particularly in comparison to chemicals (e.g., NMP, 1-BP) for which EPA has made unreasonable risk findings under TSCA.

B. Number of People Exposed to Fluoridation Chemicals

218. EPA has recognized that “the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and *the extent of exposure* to the substance.”³⁰⁴ Although EPA made this statement in the context of Section 5, EPA considers the extent of exposure to be a relevant factor under Section 6 as well. In the Section 6 risk determinations, the number of people (usually workers) who are exposed to the chemical are identified under each condition of use.³⁰⁵

219. This factor weighs in favor of an unreasonable risk finding for fluoridation chemicals. The extent of human exposure to fluoridation chemicals is nothing short of massive, much like lead exposure was during the era of leaded gasoline. Today, approximately 200 million Americans, or nearly 2/3 of the population, have municipal water to which fluoridation chemicals are added. Moreover, most of the remaining population living in “non-fluoridated” areas will routinely consume fluoridation chemicals in processed beverages and foods, as many beverages and foods are produced in fluoridated areas.³⁰⁶ To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046³⁰⁷ and 1,900 occupationally-

³⁰³ EPA (1998a), p. 17.

³⁰⁴ EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

³⁰⁵ EPA (2019d), pp. 299, 303-335; EPA (2019c), pp. 255-289.

³⁰⁶ See, for example, Kiritsy et al. (1996); Turner et al. (1998); Heilman et al. (1999).

³⁰⁷ EPA (2019c), p. 264.

exposed workers.³⁰⁸ With such widespread exposure to fluoridation chemicals among the general population, even small risks can amount to widespread harm.

C. Exposure of Susceptible Subpopulations to Fluoridation Chemicals

220. One of the consequences from widely dispersing a toxicant through the environment (versus the use of industrial chemicals *within* manufacturing facilities) is that susceptible members of the general public may be exposed. This is the case with fluoridation chemicals. Each year, there are approximately **2.5 million pregnancies** in fluoridated areas; *in utero* exposures are thus widespread. Many of those exposed *in utero* will also be exposed during the sensitive neonatal period, with upwards of **1.9 million infants** living in fluoridated areas being fed formula at least part of the time, including **400,000 infants** who are *exclusively* formula-fed for their first six months. While these numbers do not account for those who use bottled water, the numbers will be substantial regardless.

D. The Severity of the Hazard (Cognitive Deficits/IQ Loss)

221. The principal hazard at issue from exposure to fluoridation chemicals is IQ loss. The prospective studies have found an approximate 5 to 6 point drop in IQ as maternal urinary fluoride levels increase from 0 to 1 mg/L.³⁰⁹ To put this in perspective, EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,³¹⁰ and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points is highly significant from a public health perspective" and should be prevented in 99.5% of the population.³¹¹

³⁰⁸ EPA (2019d), pp. 307, 311.

³⁰⁹ Bashash et al. (2017); Green et al. (2019).

³¹⁰ EPA (2008e), p. 5-28.

³¹¹ Federal Register (2008), p. 67000.

Consistent with this, EPA has established reference doses for chemicals based on observed cognitive deficits in animal studies (see Table 1 above). Cognitive deficits, including in the range observed in fluoridated areas, are a sufficiently severe effect on human health to warrant prevention, as EPA has recognized in other contexts.

E. Uncertainties

222. Uncertainties are a pervasive aspect of risk assessment; their existence does not negate a finding of risk. As would be expected, there are uncertainties in the fluoride dataset, arising in part from methodological limitations in the available animal studies (e.g., lack of control for litter effects, lack of blinding, lack of studies on neonatal exposures, lack of chronic experiments, etc.). The impact of these limitations on the observed learning and memory deficits is not yet defined. The clear suggestion from the observed findings, however, is that fluoride causes alterations to the brain and behavior. Further, the uncertainties that remain in the animal data are largely offset by the existence of high-quality prospective studies that have *consistently* detected significant associations between “optimal” fluoride exposures and cognitive deficits. While I understand that EPA’s experts in this case question whether the “causal” relationship between fluoridation and IQ loss has been proven, the *Guidelines* do not require proof of causation; they require sufficient evidence of association.³¹²

223. Another factor weighing in favor of an unreasonable risk finding is that the exposure estimates are more straightforward—and permit greater confidence—than the exposure estimates that EPA has had to extrapolate for other chemicals under TSCA. In its NMP risk evaluation, for example, EPA had to make “assumptions about glove use, glove effectiveness,

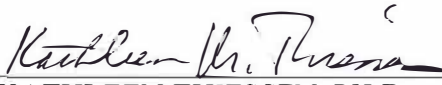
³¹² EPA (1998a), p. 53.

duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP” in order to come up with estimates of human exposure under the conditions of use.³¹⁵ Estimating exposure to fluoridation chemicals involves much less uncertainty, as the concentration of fluoride in the water is defined (0.7 mg/L), and the EPA has extensive empirical data on water consumption in the U.S. that the Agency has described as “scientifically sound.”

224. Based on the available scientific evidence that now exists on the hazards, exposures, and risks of fluoride ingestion, the widespread addition of fluoridation chemicals to drinking water and processed foods in the United States presents an unreasonable risk to human health.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Oak Ridge, Tennessee.


KATHLEEN THIESSEN, PH.D.

³¹⁵ EPA (2019d), Table 5-1.

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Appendix A

Recent Animal Studies of Fluoride Neurotoxicity (Tables A-1 and A-2)

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity.

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Adebayo et al. 2013	Albino Rats	Male	Post-Weaning ^f	1 week	6
Adedara et al. 2017a & b	Wistar Rats	Male	8 weeks old	45 days	12
Agustina et al. 2018	Wistar Rats	Male	Adults	30 days	8
Akinrinade et al. 2015a & b	Wistar Rats	Male	Adults	30 days	5
Ameeramja et al. 2018	Wistar Albino Rats	Female	2 to 3 months old	30 days	6
Atmaca et al. 2014	Wistar Rats	Male	Post-Weaning ^f	21 days	7
Balaji et al. 2015	Swiss Albino Mice	Female	Adults	30 days	6 (of 7)
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 14, 21 & 30 days	5
Banji et al. 2013	Wistar Rats	Both	Gestational day 6	Prenatal + 15 days	6
Bartos et al. 2018	Wistar Rats	Female	Prenatal	Prenatal + 21 days	5
Bartos et al 2019	Wistar Rats	Both	Pre-Pregnancy	Prenatal + 21 days	5
Basha and Madhusudhan 2010	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 21 days	6
Basha et al. 2011a & b	Wistar Albino Rats	Both	Multigenerational	Prenatal + 12 weeks (3rd generation)	6
Basha and Sujitha 2012a & b	Wistar Rats	Male	3 months old	1 month	6
Basha and Saumya 2013	Albino Mice	Both	Adults	45 days	6
Bharti and Srivastava 2009	Wistar Rats	Female	Adults	28 days	6
Bharti et al. 2012	Wistar Rats	Female	Adults	7 days	6
Chauhan et al. 2013	Sprague-Dawley Rats	Female	6 months old	3 to 6 weeks	4 (of 8)
Chen et al. 2018a	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Chouhan and Flora 2008	Albino Rats	Male	Adults	10 weeks	6
Chouhan et al. 2010	Wistar Albino Rats	Male	Adults	12 weeks	5-6 (of 6)
Dec et al. 2019	Wistar Rats	Males	Pre-Pregnancy	Prenatal + 90 days	6 (of 12)
Dong et al. 2015	Sprague-Dawley Rats	Both	1 month old	>10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1, 7, 14, 21, & 28 days	10
Flora et al. 2009	Swiss Mice	Male	Adults	10 weeks	5
Flora et al. 2012	Swiss Mice	Male	Adults	28 weeks	5 (of 12)
Ge et al. 2011	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 20 days	8
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 90 days	6
Güner et al. 2016	Wistar Albino Rats	Both	Adult	Prenatal + 1, 3, & 5 months	5

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Treatment groups	LOAEL ^b	Specific Effect	Hippocampus?
Adebayo et al. 2013	100 mg/L	100 mg/L	Oxidative stress, reduced brain weight	No
Adedara et al. 2017a & b	6.8 mg/L	6.8 mg/L	Oxidative stress, reduced AChE activity, inflammation, Caspase-3 activity	No
Agustina et al. 2018	2.3, 4.5 & 9 mg/kg/day	4.5 mg/kg/day	Reduced number of Purkinje cells	No
Akinrinade et al. 2015a & b	1 & 5 mg/L	1 mg/L	Oxidative stress, inflammation, neuronal damage	No
Ameeramja et al. 2018	136 mg/L	136 mg/L	Oxidative stress	No
Atmaca et al. 2014	100 mg/L	100 mg/L	Oxidative stress & neuronal degeneration	Yes
Balaji et al. 2015	45 & 90 mg/L	45 mg/L	Inhibition of cholinesterase & increased oxidative stress	No
Banala and Karnati 2015	9 mg/L	9 mg/L	Oxidative stress	No
Banji et al. 2013	9 mg/kg/day	9 mg/kg/day	Oxidative stress	No
Bartos et al. 2018	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Decreased nicotinic receptors & oxidative stress	Yes
Bartos et al. 2019	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Increased oxidative stress as reflected by decreased CAT, GPT, and GOT	Yes
Basha and Madhusudhan 2010	50 & 150 mg/L	50 mg/L	Oxidative stress & reduced brain protein content	No
Basha et al. 2011a & b	100 & 200 mg/L	100 mg/L	Oxidative stress, reduced brain weight, and histological changes	Yes
Basha and Sujitha 2012a & b	270 mg/L	270 mg/L	Oxidative stress & decreased acetylcholinesterase activity	No
Basha and Saumya 2013	270 mg/L	270 mg/L	Mitochondrial disturbances & Oxidative stress	No
Bharti and Srivastava 2009	150 mg/L	150 mg/L	Oxidative stress	No
Bharti et al. 2012	150 mg/L	150 mg/L	Decreased acetylcholinesterase activity	No
Chauhan et al. 2013	11.3 mg/kg/day	11.3 mg/kg/day	Oxidative stress	No
Chen et al. 2018a	4.5, 23, 45 mg/L	4.5 mg/L	Impaired synaptogenesis	Yes
Chouhan and Flora 2008	10, 50, & 100 mg/L	100 mg/L ^c	Oxidative stress	No
Chouhan et al. 2010	1, 10, 50 & 100 mg/L	1 mg/L	Oxidative stress, alterations in neurotransmitters, neuronal lesions, & increased AChE activity	No
Dec et al. 2019	23 mg/L	23 mg/L	Evidence of inflammatory processes (reduced activity of cyclooxygenases (COX1 & COX2) and increase in prostaglandins)	Yes
Dong et al. 2015	50 mg/L (adults)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Dong et al. 2015	50 mg/L (offspring)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Flora et al. 2009	50 mg/L	50 mg/L	Oxidative stress, alteration in neurotransmitters, DNA damage, increased AChE activity	No
Flora et al. 2012	50 mg/L	50 mg/L	Oxidative stress, neuronal degeneration, DNA damage, Protein interaction	Yes
Ge et al. 2011	100 mg/L (+25 mg/kg in food)	100 mg/L	Alteration in protein expression	No
Ge et al. 2018	50 & 100 mg/L	50 mg/L	Alterations of synapse-related proteins	No
Güner et al. 2016	13.6 & 45 mg/L	13.6 mg/L	Neurodegenerative changes & catalase immunoreactivity	Yes

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Hamza et al. 2015	Wistar Albino Rats	Male	Adults	30 days	10
Han et al. 2014	Kumming Mice	Male	Sexually matured mice	180 days	4 (of 15)
Hassan and Abdel-Aziz 2010	Wistar Albino Rats	Male	Adults	5 weeks	6
Inkielwicz-Stepniak and Czarnowski 2010	Wistar Han Rats	Male	6 weeks old	4 weeks	6
Jia et al. 2019	CD1 Mice	Both	Prenatal	Prenatal (day 9) + 19 days	5 (of 20)
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	3-12 (of 12)
Jiang et al. 2019	Sprague-Dawley Rats	Male	Post-weaning ^f	10 weeks	7
Kaur et al. 2009	Sprague-Dawley Rats	Female	Adults	8 weeks	6-7 (of 8)
Khan et al. 2018	Wistar Rats	Both	Post-weaning ^f	28 days	6
Kinawy 2019	Rats	Male	Prenatal (6th day)	Prenatal + Weaning or 70 days	8
Li et al. 2019	Kumming Mice	Both	Adults	90, 120 & 150 days	8 (of 30)
Liu et al. 2010	Sprague-Dawley Rats	Both	Post-weaning ^f	6 months	10 (of 24)
Liu et al. 2011	Sprague-Dawley Rats	Both	Post-weaning ^f	3 & 6 months	12 (of 24)
Lou et al. 2013	Sprague-Dawley Rats	Both	Post-weaning ^f	6 months	20
Ma et al. 2015	C57/BL Mice	Male	4 weeks old	4 weeks	8
Mansour and Tawfik 2012	Albino Rats	Male	Adults	5 weeks	6
McPherson et al. 2018	Long Evans Hooded Rats	Male	Prenatal	Prenatal (day 6) + 90 days	6 (of ~23)
Nabavi et al. 2012a	Wistar Rats	Male	8 to 12 weeks old	1 week	10
Nabavi et al. 2012b	Wistar Rats	Male	Post-weaning ^f	1 week	10
Nabavi et al. 2013	Wistar Rats	Male	7 days old	7 days	10
Niu et al. 2009	Wistar Albino Rats	Both	Day of birth	6, 8, 10, & 12 weeks	8
Niu et al. 2014	Kumming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2015a	Kumming Mice	?	Adults	60 days	5 (of 15)
Niu et al. 2015b	Kumming Mice	Both	Prenatal	Prenatal + 56 days	6
Niu et al. 2018a	Sprague-Dawley Rats	Female	Post-weaning ^f	60 days	3 (of 10)
Niu et al. 2018b	Kumming Mice	Both	Adults	60 days	5 (of 12)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Hamza et al. 2015	4.7 mg/kg/day	4.7 mg/kg/day	Increased oxidative stress	No
Han et al. 2014	11, 23, and 45	23 mg/L ^c	Altered mRNA expression	Yes
Hassan and Abdel-Aziz 2010	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
Inkielwicz-Stepniak and Czarnowski 2010	25 mg/L	25 mg/L	Oxidative stress	No
Jia et al. 2019	6 & 113 mg/L	None	No reduction in neuronal density	No
Jiang et al. 2014a	54 mg/L	54 mg/L	Decreased glutamate levels	Yes
Jiang et al. 2014b	11, 23, and 45 mg/L	11 mg/L	Neuronal degeneration, decreased glucose utilization	Yes
Jiang et al. 2019	23 & 45 mg/L	23 mg/L	Impaired neurogenesis & synaptic plasticity	Yes
Kaur et al. 2009	125 mg/L	125 mg/L	Oxidative stress, alteration in neurotransmitters, & neuronal degeneration	No
Khan et al. 2018	20 mg/L	20 mg/L	Inhibition of AChE and increase in oxidative stress	No
Kinawy 2019	678 mg/L	678 mg/L	Oxidative stress	Yes
Li et al. 2019	68 mg/L	68 mg/L	Altered mRNA expression of anxiety & depression-related genes	Yes
Liu et al. 2010	5 & 50 mg/L	5 mg/L	Reductions in nicotinic receptors & activation of photoho-ERK1/2	No
Liu et al. 2011	5 & 50 mg/L	5 mg/L	Increased apoptosis & phosphorylation	No
Lou et al. 2013	10 & 50 mg/L	10 mg/L	Mitochondrial disturbances in neurons, altered protein expression	No
Ma et al. 2015	23 & 45.6 mg/L	23 mg/L	Increased BDNF expression	Yes
Mansour and Tawfik 2012	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
McPherson et al. 2018	10 & 20 mg/L (+ food exposure group)	None	No neuronal damage or glia reactivity	Yes
Nabavi et al. 2012a	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2012b	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2013	270 mg/L	270 mg/L	Oxidative stress	No
Niu et al. 2009	68 mg/L	68 mg/L	Decreased glutamate levels & altered enzyme activity	Yes
Niu et al. 2014	68 mg/L	68 mg/L	Altered protein expression	Yes
Niu et al. 2015a	11, 23, and 45 mg/L	23 mg/L	Microtubule lesions in neurons	Yes
Niu et al. 2015b	68 mg/L	68 mg/L	Alterations in protein expression	No
Niu et al. 2018a	4.5, 23, and 45 mg/L	4.5 mg/L	Endoplasmic reticulum stress	Yes
Niu et al. 2018b	11, 23, and 45 mg/L	11 mg/L	Myelin damage, and alteration to synaptic structure	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Pal and Sarkar 2014	Wistar Rats	Male	Post-weaning ^f	30 days	6 to 8
Pan et al. 2015	Sprague-Dawley Rats	Male	3 weeks after weaning	30 days	15
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	4-10 (of 15)
Pulungan et al. 2018	Wistar Rats	Male	12-16 weeks old	30 days	8
Qian et al. 2013	Sprague-Dawley Rats	Male	Newly weaned	6 months	2-20 (of 20)
Reddy et al. 2009	Swiss Albino Mice	Female	Adults	14 days	6
Reddy et al. 2014	Wistar Rats	Male	4 months old	90 days	6
Rogalska et al. 2017	Wistar Rats	Both	8 weeks old	4 weeks	6-8
Samanta et al. 2016	Sprague-Dawley Rats	Female	Post-weaning ^f	16 weeks	5
Sarkar et al. 2014	Wistar Rats	Male	Post-weaning ^f	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2014	Swiss Albino Mice	Male	1.5 months old	30 days	7
Sharma et al. 2018	Swiss Albino Mice	Both	1 month old	30 days	7
Shen et al. 2019	Wistar Rats	Both	1 month old	12 & 24 weeks	30
Sun et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	10
Sun et al. 2018	Kumming Mice	Female	Prenatal	Prenatal + 21 days	6 (of 12)
Teng et al. 2018	Sprague-Dawley Rats	Male	Recently weaned	18 months	6-7 (of 13)
Trivedi et al. 2007	Swiss Albino Rats	Male	Young adults	30 days	10
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (7th day) + 21 days	6 (of 15)
Wang et al. 2018b	Wistar Albino Rats	Male	12-weeks old	8 weeks	10 (of 24)
Wei et al. 2018	Sprague-Dawley Rats	Both	1 month old	>6 months	15
Wei et al. 2018	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 28 days	6-10 (of 10)
Yan et al. 2016	Wistar Rats	Both	5 weeks old	10 weeks	20
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 & 12 weeks	4-6 (of 10)
Yu et al. 2019	ICR Mice	Male	Newly weaned	3 & 6 months	20
Yuan et al. 2019	Kumming Mice	Male	7 weeks old	90 days	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2015a	Sprague-Dawley Rats	Both	2 months old	3 months & 6 months	10 (of 20)

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Pal and Sarkar 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, altered neurotransmitters, reduced protein content	No
Pan et al. 2015	9 mg/kg/day	N/A ^d	Altered protein expression	Yes
Pereira et al. 2011	45 mg/L	45 mg/L	Alterations in neurotransmitters	Yes
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	none	No reduction in number of pyramidal cells in medial prefrontal cortex	No
Qian et al. 2013	23 mg/L	23 mg/L	Impaired synaptic plasticity, oxidative stress, altered protein expression	Yes
Reddy et al. 2009	9 mg/kg/day	9 mg/kg/day	Oxidative stress & altered enzyme activity	No
Reddy et al. 2014	9, 27, & 45 mg/L	9 mg/L	Oxidative stress, alterations in neurotransmitters, and immunosuppression	No
Rogalska et al. 2017	4.5 & 23 mg/L	23 mg/L ^c	Increased glucose uptake	Yes
Samanta et al. 2016	5.9 mg/kg/day	5.9 mg/kg/day	Oxidative stress, cellular degeneration, apoptosis	No
Sarkar et al. 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, & reduced protein content	No
Shalini and Sharma 2015	10 mg/L	10 mg/L	Oxidative stress, reduced protein content & AChE activity	No
Sharma et al. 2014	120 mg/L	120 mg/L	Oxidative stress & cellular degeneration	Yes
Sharma et al. 2018	54 mg/L	54 mg/L	Oxidative stress and neuronal damage	Yes
Shen et al. 2019	200 mg/L	200 mg/L	Apoptosis and degeneration of nerve cells in spinal cord	No
Sun et al. 2017	45 mg/L	45 mg/L	Altered gene expression & apoptosis	Yes
Sun et al. 2018	11, 23, and 45 mg/L	11 mg/L (Fig 3b)	Altered mRNA expression	Yes
Teng et al. 2018	8.25, 16.5, & 33 mg/L	16.5 mg/L ^c	Elevated calcium in hippocampus	Yes
Trivedi et al. 2007	2.7 & 5.4 mg/kg/day	2.7 mg/kg/day	Reduced protein content	No
Wang et al. 2018a	11, 23, and 45 mg/L	11 mg/L (Fig 4b)	Altered expression of mi-RNAs	No
Wang et al. 2018b	45 mg/L	45 mg/L	Cellular degeneration, DNA damage	Yes
Wei et al. 2018	50 mg/L (adults)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Wei et al. 2018	50 mg/L (offspring)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Yan et al. 2016	60 & 120 mg/L	60 mg/L	Increased apoptosis & inflammation	Yes
Yang et al. 2018a	60 & 120 mg/L	60 mg/L	Apoptosis, altered protein expression, increased inflammation	Yes
Yu et al. 2019	2.3 & 13.6 mg/L	2.3 mg/L	Alterations of L-type calcium channels	Yes
Yuan et al. 2019	23, 45, 68 mg/L	23 mg/L	Reduced brain protein content, impaired insulin signaling pathway, reduced brain organ coefficient	Yes
Zhang et al. 2013a	45 mg/L	45 mg/L	Oxidative stress, neuronal loss, altered protein expression	Yes
Zhang et al. 2015a	5 & 50 mg/L	5 mg/L	Increased oxidative stress & activation of AGE/RAGE Pathway	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Zhang et al. 2017a	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	15-20 (of 20)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	2-3 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	2-5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2011 & Zhang et al. 2011	Sprague-Dawley Rats	Male	Just weaned	9 months	6 (of 12)
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 21 or 42 days	6 (of 8)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Zhang et al. 2017a	45 mg/L	45 mg/L	Impaired synaptic plasticity	No
Zhang et al. 2019	25, 50, 100 mg/L	50 mg/L ^e	Autophagy in hippocampus	Yes
Zhao et al. 2019	4.5, 23, 45 mg/L	4.5 mg/L [Fig 6e]	Mitochondrial disturbances	Yes
Zheng et al. 2016	45 mg/L	45 mg/L	Increased apoptosis	Yes
Zhou et al. 2019	4.5, 23, 50 mg/L	23 mg/L ^c	Decreased neurons, suppressed autophagy, and enhanced apoptosis in hippocampus	Yes
Zhu et al. 2011 & Zhang et al. 2011	7, 13.6, & 27 mg/L	13.6 mg/L ^c	Decrease in synaptic membrane fluidity & increased calcium	Yes
Zhu et al. 2017	34 mg/L	34 mg/L	Altered protein expression in ERK/CREB signaling pathway	Yes

^a Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

^b A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

^c At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

^d The authors did not perform a statistical analysis to determine if the observed changes were statistically significant.

^e Ultrastructural observations of the rat hippocampal CA1 cells identified changes in the 25 mg/L group (i.e., increased lipofuscin content), but a statistical analysis of these changes was not performed.

^f Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning.

Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory

Paper	Strain	Sex ^a	Maturity at Start of Exposure	Length of Exposure	Animals per group
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 30 days	5
Bartos et al. 2018	Wistar Rats	Female	Prenatal (day 0)	Prenatal + 21 days	9-10
Bartos et al. 2019	Wistar Rats	Both	Prenatal (day 0)	Prenatal + 21 days	9-10
Basha et al. 2011b	Wistar Albino Rats	Both	Prenatal/Multigenerational	Prenatal + 30 days	6
Basha & Sujitha 2012b	Wistar Rats	Male	3 months old	1 month	6
Bera et al. 2007	Wistar Rats	Both	Prenatal (day 1)	Prenatal (day 1) + 9 days	6-12
Chen et al. 2018a	Sprague-Dawley Rats	Female	2 months pre-gestation	Prenatal + 6 months	6
Chioca et al. 2008	Wistar Rats	Male	Adult	30 days	15 (of 18)
Cui et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	12
Dong et al. 2015	Sprague-Dawley Rats	Both	One month old	10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1 to 28 days	10
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 60 days	6
Han et al. 2014	Kunming Mice	Male	Sexually matured mice	180 days	15
Jetti et al. 2016	Wistar Rats	Male	Adult	30 days	6
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	12
Liu et al. 2010	Sprague-Dawley Rats	Both	Adult	6 months	10 (of 24)
Liu et al. 2014	BaB/C Mice	Male	4 weeks old	4 weeks	11-12 (of 12)

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Strain	Sex ^a	Maturity at Start of Exposure	Length of Exposure	Animals per group
McPherson et al. 2018	Long-Evans Hooded Rats	Male	Prenatal (day 6)	Prenatal (day 6) + 90 days	11-23 (of ~23)
Niu et al. 2009	Wistar Albino Rats	Both	Postnatal (day 0)	6 to 12 weeks	8
Niu et al. 2014	Kunming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2018a	Sprague Dawley Rats	Female	Post-weaning ^g	2 months	6 (of 10)
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	14-15
Pulungan et al. 2018	Wistar Rats	Male	12 to 16 weeks old	30 days	8
Raghu et al. 2013	Wistar Rats	Male	1 month old	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2018	Swiss Albino Mice	Male	1 month old	30 days	7
Sun et al. 2018	Kunming Mice	Both	Prenatal	Prenatal + 21 days	6 (of 12)
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (day 7) + 21 days	15
Whitford et al. 2009	Sprague-Dawley Rats	Female	8 days after weaning	8 months	8
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 to 12 weeks	10
Yuan et al. 2019	Kunming Mice	Male	7 weeks old	12 weeks	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	15 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 42 days	8

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL ^b
Banala and Karnati 2015	20 mg/L	Maze Learning	20 mg/L
Bartos et al. 2018	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Bartos et al. 2019	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Basha et al. 2011b	100 & 200 mg/L	T Maze	100 mg/L
Basha & Sujitha 2012b	270 mg/L	T Maze	270 mg/L
Bera et al. 2007	1.13 & 2.3 mg/kg/day	Active Avoidance / Novel Object Recognition	2.3 mg/kg
Chen et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Chioca et al. 2008	23 & 45 mg/L (5.15 & 10.77 mg/kg/day)	Open Field / Two-Way Active Avoidance	23 mg/L
Cui et al. 2017	4.5, 23, & 45 mg/L	Morris Water Maze	4.5 mg/L
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (adults)
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (pups)
Ge et al. 2018	50 & 100 mg/L	Morris Water Maze	50 mg/L
Han et al. 2014	11, 23, and 45 mg/L	Novel Object Recognition / Open Field	45 mg/L ^d
Jetti et al. 2016	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Jiang et al. 2014a	55 mg/L	Morris Water Maze	55 mg/L
Jiang et al. 2014b	11, 23, & 45 mg/L	Morris Water Maze	11 mg/L
Liu et al. 2010	2.3 & 23 mg/L	Morris Water Maze	2.3 mg/L
Liu et al. 2014	0.9, 2.3, and 4.5 mg/L	Morris Water Maze / Novel Object Recognition / Elevated-Plus Maze	2.3 mg/L ^c

Table continued next page

Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL ^b
McPherson et al. 2018	10 & 20 mg/L (+food exposure group)	Open Field / Elevated Plus Maze / Passive Avoidance / Morris Water Maze / Y Maze	None
Niu et al. 2009	68 mg/L	Y Maze	68 mg/L
Niu et al. 2014	68 mg/L	Novel Object Recognition	68 mg/L ^e
Niu et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Pereira et al. 2011	45 mg/L	Open Field	45 mg/L
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	Y Maze	None ^f
Raghu et al. 2013	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Shalini and Sharma 2015	10 mg/L	Maze Test	10 mg/L
Sharma et al. 2018	68 mg/L	Morris Water Maze / Classic Maze	68 mg/L
Sun et al. 2018	11, 23, & 45 mg/L	Radial Arm Maze / Open Field	23 mg/L ^c
Wang et al. 2018a	11, 23, & 45 mg/L	Open Field / Eight-Arm Maze	23 mg/L ^c
Whitford et al. 2009	2.9, 5.7, & 11.5 mg/kg/day	Appetitive Based Learning	None
Yang et al. 2018a	60 & 120 mg/L	Morris Water Maze / Open Field	60 mg/L
Yuan et al. 2019	23, 45, & 68 mg/L	Y Maze	23 mg/L
Zhang et al. 2013a	45 mg/L	Y Maze	45 mg/L
Zhang et al. 2019	25, 50, & 100 mg/L	Morris Water Maze	100 mg/L ^c
Zhao et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L
Zheng et al. 2016	45 mg/L	Morris Water Maze / Open Field	45 mg/L
Zhou et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Zhu et al. 2017	45 mg/L (8 to 11 mg/kg/day)	Morris Water Maze	45 mg/L

^a Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

^b A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

^c At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

^d At least one statistically significant effect was seen at lower treatment doses but for a neurological endpoint that is not specific to learning or memory impairments.

^e The effect in the fluoride + lead treatment group was statistically significant, but the effect in the fluoride-only treatment group did not reach statistical significance.

^f A statistically significant effect was observed in the low treatment dose group (5 mg/kg/day) when compared to the control, but there were no significant differences between the control and mid/high dose treatment groups (10 mg/kg/day & 20 mg/kg/day).

^g Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning

Appendix B

KATHLEEN M. THIESSEN, Ph.D.
Senior Scientist
Oak Ridge Center for Risk Analysis, Inc.

Education

Ph.D. 1986 Genetics, University of Tennessee-Oak Ridge, Graduate School of Biomedical Sciences, Oak Ridge, TN
B.A. 1981 Biology and Chemistry (*Summa cum laude*), Covenant College, GA

Capabilities

Health Effects Assessment
Dose and Risk Assessment
Analysis of Environmental Transport and Exposure Pathways
Uncertainty and Sensitivity Analysis
Technical Writing/Editing, Technical and Public Presentations

Experience Summary

Dr. Thiessen is experienced in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment and in the use of uncertainty analysis for environmental and health risk assessment. She has served on two National Research Council subcommittees, one charged with the review of fluoride exposure and toxicology, and one dealing with guidance levels for air contaminants (including hydrogen fluoride) in submarines. Dr. Thiessen has also written two reports for the U.S. Environmental Protection Agency, one on the health effects of hydrogen fluoride and related compounds, and one on the health effects of mercuric chloride. Dr. Thiessen has led several working groups on urban contamination and dose reconstruction for the International Atomic Energy Agency's programs on environmental transport modeling and has served on the coordinating committees of the programs; she currently leads a working group on assessment of exposures and countermeasures in urban environments. She also serves on a committee for the preparation of a new International Atomic Energy Agency report on modeling the impacts of planned discharges or radioactivity, and she is involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity. Dr. Thiessen participated in two symposia on reconstruction of internal doses from Fukushima releases organized by Japan's National Institute of Radiological Sciences, and she has served as a consultant on environmental modeling issues to the Korea Atomic Energy Research Institute and on uncertainty analysis to the National Council on Radiation Protection and Measurements. Dr. Thiessen contributed to the development of a risk-based screening approach to prioritize further investigation of contaminants and exposure situations in various assessment contexts, and she led in the application of risk-based screening techniques for the reconstruction of doses and health risks associated with releases of chemicals and radionuclides from the U.S. Department of Energy's Oak Ridge (Tennessee) facilities. Dr. Thiessen also led an analysis of human exposures, doses, and health risks to off-site individuals associated with historic releases of radionuclides to the Clinch River from the Oak Ridge facilities.

Experience

- 1992-present Senior Scientist and Director, Oak Ridge Center for Risk Analysis, Inc. (Formerly *SENES* Oak Ridge, Inc., Center for Risk Analysis), Oak Ridge, TN.
- Review of data on contaminant exposure and toxicology.
 - Analysis of environmental transport and exposure pathways.
 - Screening techniques for environmental assessment.
 - Dose reconstruction.
 - Uncertainty analysis for environmental assessment.
 - International model validation using Chernobyl data sets.
 - Working Group Leader for International Atomic Energy Agency research programs.
 - Project coordination.
 - Technical review.
- 1991-1992 Consultant and Technical Writer. Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN.
- 1987-1992 Lecturer in Genetics. University of Tennessee, Oak Ridge Graduate School of Biomedical Sciences.
- 1986-1989 Oak Ridge National Laboratory, Health and Safety Research Division, Chemical Hazard Evaluation Program.
- Assessment of health effects from chemicals.
 - Risk assessment.
 - Technical review.

Publications and Technical Reports

Periáñez, R., Thiessen, K.M., Chouhan, S.L., Mancini, F., Navarro, E., Sdouz, G., and Trifunović, D. 2016. Mid-range atmospheric dispersion modelling. Intercomparison of simple models in EMRAS-2 project. *Journal of Environmental Radioactivity* 162-163:225-234.

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THE WORLD-WIDE MOVEMENT AGAINST WATER FLUORIDATION



In stark contrast to the Center for Disease Control's claim that fluoridation is one of the top ten public health achievements of the 20th century, it is **one of the most widely rejected health interventions in the world.**

Out of 196 nations, only 24 have any fluoridation, and only 10, like the U.S., for more than half their population. Over 95% of the world's population is fluoridation-free. The U.S. fluoridates as many people as the rest of the world combined.

None of the largest Asian nations, including China, India and Japan, fluoridate. Out of 54 countries in Africa, only one fluoridates – Libya, and only for a small percent of its population. In Europe, only four out of 48 countries fluoridate (less than 2% of the population). A few have fluoridated salt, but only as a consumer choice.

France, Germany, Belgium, the Netherlands, Denmark, Norway and Sweden have all prohibited fluoridation, many citing the ethical problem of putting any drug in drinking water.

For dozens of nations that haven't banned it, thousands of major cities and smaller towns don't fluoridate, including **Athens, Barcelona, Budapest, Geneva, Helsinki, London, Madrid, Prague, Rome, Vienna and Warsaw**. Ireland is the only European nation mandating fluoridation. But despite the mandate, 13 town and county councils, including Dublin and Cork, have voted for its immediate cessation.

Many organizations still support fluoridation, but **those opposing it grows year by year**. They include:

- American Academy of Environmental Medicine • Center for Health, Environment and Justice
- Children's Health Defense • Eau Secours (Canadian coalition of 234 groups promoting clean, safe water)
- Council of Canadians • Environmental Working Group • Food and Water Watch
- * Institute of Neurotoxicology & Neurological Disorders • International Academy of Biological Dentistry and Medicine
- International Academy of Oral Medicine and Toxicology • League of United Latin American Citizens
- Moms Against Fluoridation • Organic Consumers Association

In addition, **many organizations once endorsing fluoridation have pulled back**, no longer taking a position. They include the Alzheimer's Association, American Academy of Allergy, Asthma and Immunology, Center for Science in the Public Interest, Consumers Union (Consumer Reports), National Association of Social Workers, National Down Syndrome Congress, National Down Syndrome Society and National Kidney Foundation.

The trend is clear. And as the scientific data accumulate, more and more nations, cities and organizations are challenging the safety, efficacy, costs and ethics of fluoridation.



Full length article

Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth

Julia K. Riddell^{a,*}, Ashley J. Malin^b, David Flora^a, Hugh McCague^c, Christine Till^a

^a Faculty of Health, York University, Ontario, Canada

^b Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States

^c Institute for Social Research, York University, Ontario, Canada



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ABSTRACT

Background: Exposure to fluoride has been linked with increased prevalence of attention deficit hyperactivity disorder (ADHD) in the United States and symptoms of inattention in Mexican children. We examined the association between fluoride exposure and attention outcomes among youth living in Canada.

Method: We used cross-sectional data collected from youth 6 to 17 years of age from the Canadian Health Measures Survey (Cycles 2 and 3). Urinary fluoride concentration adjusted for specific gravity (UF_{SG}) was available for 1877 participants. Water fluoride concentration measured in tap water samples was available for 980 participants. Community water fluoridation (CWF) status was determined by viewing reports on each city's website or contacting the water treatment plant. We used logistic regression to test the association between the three measures of fluoride exposure and ADHD diagnosis. Linear regression was used to examine the relationship between the three measures of fluoride exposure and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

Results: UF_{SG} did not significantly predict ADHD diagnosis or hyperactive/inattentive symptoms. A 1 mg/L increase in tap water fluoride level was associated with a 6.1 times higher odds of an ADHD diagnosis (95% CI = 1.60, 22.8). A significant interaction between age and tap water fluoride level ($p = .03$) indicated a stronger association between tap water fluoride and hyperactivity/inattention symptoms among older youth. A 1 mg/L increase in water fluoride level was associated with a 1.5 SDQ score increase (95% CI: 0.23, 2.68, $p = .02$) for youth at the 75th percentile of age (14 years old). Similarly, there was a significant interaction between age and CWF. At the 75th percentile of age (14 years old), those living in a fluoridated region had a 0.7-point higher SDQ score (95% CI = 0.34, 1.06, $p < .01$) and the predicted odds of an ADHD diagnosis was 2.8 times greater compared with youth in a non-fluoridated region (aOR = 2.84, 95% CI: 1.40, 5.76, $p < .01$).

Discussion: Exposure to higher levels of fluoride in tap water is associated with an increased risk of ADHD symptoms and diagnosis of ADHD among Canadian youth, particularly among adolescents. Prospective studies are needed to confirm these results.

1. Introduction

Fluoride is beneficial in the prevention of dental caries (Health Canada, 2010). It can naturally occur in water, but often at levels that are too low to prevent tooth decay. In the middle of the 20th century, the concept of adding fluoridation chemicals (usually hexafluorosilicic acid) to water supplies was introduced. Currently, approximately 38% of Canadians on public water supplies receive community water fluoridation (CWF; Public Health Agency of Canada, 2017) compared with 74% of Americans and only 3% of Europeans (Centers for Disease Control and Prevention, 2014). Consumption of optimally fluoridated

water (i.e., 0.7 mg fluoride per liter of water) accounts for approximately 40 to 70% percent of daily fluoride ingestion (United States Environmental Protection Agency, 2010).

Fluoride has been classified as a developmental neurotoxin (Grandjean and Landrigan, 2014) – a claim that is uncontested at high exposure levels, but remains debated at the exposure levels associated with water fluoridation. Epidemiological studies conducted in endemic fluorosis areas (i.e., naturally occurring water fluoride concentrations > 1.5 mg/L) have reported a negative association between fluoride concentrations in drinking water and intellectual ability in children (Das and Mondal, 2016; Rocha-Amador et al., 2007; Seraj

* Corresponding author at: Department of Psychology, York University, 4700 Keele Street, M3J 1P3 Toronto, ON, Canada.

E-mail address: jriddell@yorku.ca (J.K. Riddell).

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et al., 2012; Xiang et al., 2003; Zhao et al., 1996). A meta-analysis of 27 studies concluded that children who lived in areas with high fluoride exposure had IQ scores that were approximately seven points lower than those who lived in low-exposure areas (Choi et al., 2012). Most of the studies included in this review were cross-sectional and had deficient reporting of key information; however, the consistency of their findings supports the potential for fluoride-mediated developmental neurotoxicity at elevated levels of exposure. Recently, three longitudinal birth cohort studies addressed these limitations by examining the associations between maternal fluoride exposure indicators in pregnancy and offspring cognitive abilities. These prospective studies reported a negative association between prenatal fluoride exposure and cognitive development in infants (Jiménez et al., 2017), children living in Mexico (Bashash et al., 2017), and children living in Canada (Green et al., 2019).

Experimental and epidemiologic studies have also reported an association between early-life fluoride exposure and adverse behavioural outcomes. One study demonstrated that prenatal fluoride exposure caused greater hyperactivity in male rat pups whereas females were more sensitive to postnatal exposures (Mullenix et al., 1995). In an ecological study, higher prevalence of water fluoridation was associated with increased prevalence of Attention Deficit Hyperactivity Disorder (ADHD) diagnoses among youth in the United States (Malin and Till, 2015). In a cohort study, higher levels of fluoride exposure during pregnancy were associated with more inattentive symptoms and total ADHD symptoms in Mexican children aged 6 to 12 years (Bashash et al., 2018). In contrast, a study using data from the Canadian Health Measures Survey (CHMS; Statistics Canada, 2013; 2015) did not report an association between urinary fluoride corrected for dilution and a diagnosis of a learning disability in children aged 3 to 12 years (Barberio et al., 2017).

We examined the relationship between urinary and tap water fluoride concentrations and attention-related outcomes in a national sample of Canadian youth aged 6 to 17 years. We hypothesized that higher levels of urinary and water fluoride would be associated with increased odds of an ADHD diagnosis and more symptoms of hyperactivity and inattention.

2. Methods

2.1. Data source and participants

We used data from Cycle 2 (2009–2011) and Cycle 3 (2012–2013) of the CHMS collected by Statistics Canada. All aspects of the CHMS were reviewed and approved by Health Canada's Research Ethics Board (Day et al., 2006); the current study was approved by the York University Research Ethics Board.

The CHMS randomly selected participants aged 3 to 79 years who lived in private households across Canada. A total of 6395 people participated in Cycle 2 of the CHMS, with 2520 people providing urine samples analyzed for fluoride concentration. Among those who provided urine samples, 909 (36%) were between 6 and 17 years of age. For Cycle 3, a total of 5785 people were enrolled, with 2667 people providing urine samples analyzed for fluoride concentration; 968 (36%) were between 6 and 17 years of age. In Cycle 3 only, 980 youth ages 6 to 17 were selected to provide a tap water sample to be analyzed for fluoride content. Full details about the survey can be found at www.statcan.gc.ca.

Approximately half of the sites included in Cycles 2 and 3 received CWF, which was determined by viewing reports on each city's website or contacting the water treatment plant (see Supplemental Table 1). In total, 13 of 25 sites received CWF (eight from Cycle 2 and five from Cycle 3), corresponding to approximately 1400 (51.9%) of 2700 participants included in the study (rounded due to Statistics Canada data release requirements). Nine additional sites were considered to have mixed fluoridation status, corresponding to approximately 650 (24.0%)

participants. A site was classified as mixed for one of five reasons: unclear site boundaries ($n = 150$), having some municipalities within the site add fluoride while others did not ($n = 250$), and stopping CWF during the period spanning CHMS data collection ($n = 50$). We excluded all mixed sites from any analysis using city fluoridation status as a variable. We also excluded sites which were labeled as fluoridated or non-fluoridated, but had an average water fluoride level that was either 2.5 times lower ($n = 100$) or higher ($n = 100$) than other fluoridated or non-fluoridated sites, respectively.

We utilized three participant samples for our analyses; see Fig. 1 for a participant flow chart. The first sample, collapsed across both cycles, included 1877 youth ages 6 to 17 who had urinary fluoride measurements. The second sample categorized 1722 youth who were on a municipal water system (instead of a well) as either living in a fluoridated region ($n = 932$; 54.1%) or a non-fluoridated region ($n = 790$; 45.9%). This sample only included youth who primarily drank tap water (instead of bottled water), did not have a home filtration system that removes fluoride (i.e., reverse osmosis or distillation), and have lived in their current residence for three or more years. The third sample consisted of 710 youth from Cycle 3 who primarily drank tap water (instead of bottled water) and had fluoride levels measured in their tap water.

2.2. Measurement of urinary fluoride concentration

Urine spot samples were collected under normal (non-fasting) conditions and were not standardized with respect to collection time. Fluoride concentrations in spot urine samples were analyzed using an Orion PH meter with a fluoride ion selective electrode after being diluted with an ionic adjustment buffer (Statistics Canada, 2013). Urinary analyses were performed at the Human Toxicology Laboratory of the Institut National de Santé Publique du Québec (INSPQ; accredited under ISO 17025) under standardized operating procedures (Statistics Canada, 2013; 2015). The precision and accuracy of the fluoride analyses, including quality control measures and quality assurance reviews, are described in previous publications (Health Canada, 2015). The limit of detection (LoD) for urinary fluoride was 20 µg/L for Cycle 2 and 10 µg/L for Cycle 3 (Health Canada, 2015). No urinary fluoride values in the Cycle 2 or Cycle 3 samples were below the LoD. Urinary fluoride concentrations were adjusted for specific gravity (UF_{SG} ; mg/L); specific gravity shows no systematic variation within a day and is less dependent on body size, age, and gender than creatinine (Barr et al., 2005; Nermell et al., 2008; Moriguchi et al., 2005; Suwazono et al., 2005).

2.3. Measurement of water fluoride concentration

Tap water samples were collected at respondents' homes and were available for Cycle 3 only. Samples were analyzed for fluoride concentrations (mg/L) via a basic anion exchange chromatography procedure with a LoD of 0.006 mg/L. Concentrations at the LoD were assigned a missing value code by Statistics Canada, and these values were subsequently replaced with an imputed value of $LoD/\sqrt{2}$ (Hornung and Reed, 1990); 150 of 980 (16%) water samples had fluoride levels below the LoD.

2.4. Measurement of attention-related outcomes

Primary outcomes included the hyperactivity/inattention subscale score from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001) and a physician-made diagnosis of ADHD; these outcomes were measured in both Cycles 2 and 3. Data are presented for youth ages 6 to 17 because the SDQ was only administered to youth under age 18 and 90% of youth with ADHD are diagnosed after age 6 (Kessler et al., 2005). For children aged 6 to 11 years, information about ADHD diagnosis and SDQ ratings were provided by parents or guardians, whereas youth aged 12 to 17 years completed the questionnaire

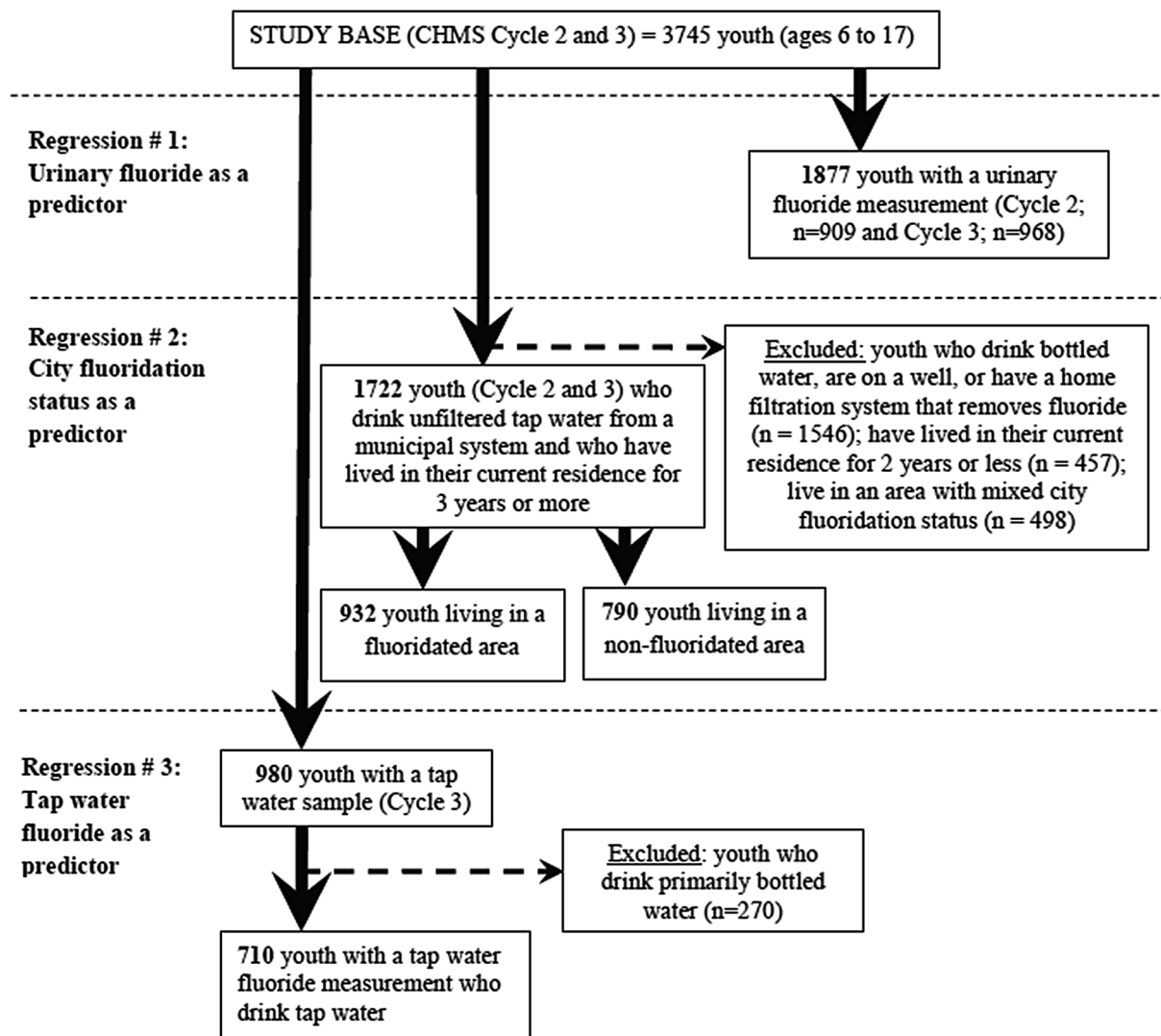


Fig. 1. Subject inclusion in each regression analysis.

themselves, including the question about having a diagnosis of ADHD.

The SDQ consists of 25 items with a 3-point response scale (0 = *not true*, 1 = *somewhat true*, and 2 = *certainly true*). These items are divided among five subscales: emotional problems, conduct problems, hyperactivity-inattention, peer problems, and prosocial behaviour. Possible scores on each subscale range from 0 to 10. The five-item hyperactivity-inattention subscale was used in the current study to test the association between fluoride and ADHD-like symptoms.

The item pertaining to a physician-made diagnosis of ADHD differed between Cycles 2 and 3. In Cycle 2, respondents were asked *Do you have a learning disability?*, and if they responded *yes*, they were asked to specify the type of learning disability from among four options: (1) Attention Deficit Disorder, no hyperactivity [ADD]; (2) Attention Deficit Hyperactivity Disorder [ADHD]; (3) Dyslexia; and (4) Other. In Cycle 3, parents of children aged 6 to 11 were asked directly whether their child had ADHD, and if so, which subtype. Similarly, youth age 12 or older were asked whether they have received a physician-diagnosis of ADHD, and if so, which subtype. Across both cycles, all subtypes were combined into a single dichotomous variable of ADHD diagnosis (*no* = 0, *yes* = 1) as per current diagnostic classification schemes (American Psychiatric Association, 2013).

2.5. Covariates

Covariates related to ADHD diagnosis and to fluoride metabolism were selected based on literature review and consultation with an ADHD expert. The following covariates were included in each regression model: sex, age of child at household interview, ethnicity (white or ethnic minority), Body Mass Index (BMI), highest level of education obtained by either parent (less than a bachelor's degree vs. bachelor's degree or greater), total household income (Canadian dollars), exposure to cigarette smoke inside the home (yes or no), and $\log_{10}$ -transformed value of concurrent level of blood lead ($\mu\text{g}/\text{dL}$).

2.6. Statistical analysis

Outliers that had high Studentized residuals, leverage, or Cook's distance values were removed from all analyses with UF_{SG} as a predictor; these outliers (0.27% of values) represented individuals with urinary fluoride levels that were over 30 times the mean UF_{SG} level, likely representing an acute fluoride ingestion (e.g., swallowing toothpaste). Further, individuals with the highest incomes were identified as extreme observations; these values were replaced with the next highest income value (only 0.01% of income values were adjusted).

We used robust logistic regression to examine the associations between each fluoride exposure measure (UF_{SG} , CWF status, tap water

fluoride) and ADHD diagnosis with the same set of covariates in each model. Box-Tidwell tests were used to check the linearity of the relationship between the log-odds of the dependent variable (ADHD diagnosis) and all continuous predictors; none of the non-linear terms were significant. Next, we used robust linear regression models with the same set of covariates to examine the associations between the three measures of fluoride exposure and the SDQ hyperactivity/inattention subscale score. Because the regression models produced heteroscedastic and non-normal residuals, all significance tests and confidence intervals were based on robust Huber-White standard errors. No issues with multicollinearity were detected from variance inflation factor (VIF) statistics. All regression analyses tested interactions between age and fluoride and between sex and fluoride, as hyperactivity is more common in younger boys and sex-dependent fluoride effects have been previously reported (Mullenix et al., 1995; Green et al., 2019). If an interaction with age was significant, we probed the interaction by calculating the predicted association between fluoride and the outcome at the 25th and 75th percentiles of age. When a tested interaction was non-significant, the model was re-estimated without the interaction term and the overall associations were interpreted. Finally, we conducted sensitivity analyses to test whether the associations between the fluoride exposure variables and ADHD diagnosis differed between cycles given that the question about ADHD diagnosis was posed differently across the two cycles. A two-tailed $\alpha = 0.05$ was used as the threshold for statistical significance.

3. Results

3.1. Descriptive statistics

Of all variables included in the CHMS, missing data were highest for household income (missing among 29% and 23% of CHMS respondents in Cycle 2 and 3, respectively); however, Statistics Canada provided imputed estimates for all participants missing the household income variable. Across Cycle 2 and 3 combined, most demographic variables (including sex, age, ADHD diagnosis, SDQ score, and length of residence) had less than 2% missing data. For highest household education, 2.6% of data were missing, and 7.4% of participants did not report their height or weight, which are needed to calculate BMI.

Table 1 presents descriptive statistics for the different samples used for the regression models. Among the 1877 youth in Cycles 2 and 3 with a urinary fluoride measurement, 51.2% were male, 72.6% were white, and 47.0% had at least one parent with a university degree or higher. In this sample, 137 (7.3%) reported having received a diagnosis of ADHD; the mean for the SDQ Hyperactivity-Inattention subscale score was 2.7 ($SD = 2.7$; range: 0 to 10) with 201 (11.4%) youth having scores in the clinical range (i.e., above 90th percentile; Goodman, 2001). As expected, participants with an ADHD diagnosis had significantly higher scores on the SDQ Hyperactivity-Inattention subscale ($M = 6.5$, $SD = 2.5$) than those without a diagnosis ($M = 2.5$, $SD = 2.4$), $t = 24.8$, $p < .01$. Table 2 provides descriptive statistics for the 1877 youth aged 6 to 17 years with and without an ADHD diagnosis.

3.2. Fluoride measurements

The mean UF_{SG} concentration was 0.61 mg/L ($Mdn = 0.51$; $SD = 0.39$; 10th to 90th percentile range = 0.27–1.06 mg/L) among the 1877 youth from Cycles 2 and 3. Mean UF_{SG} concentration was significantly higher among youth who lived in communities with fluoridated drinking water ($M = 0.82$ mg/L, $SD = 0.54$) than among youth who lived in communities without fluoridated drinking water ($M = 0.46$ mg/L, $SD = 0.32$), $t = 15.1$, $p < .01$. The mean water fluoride concentration was 0.23 mg/L ($Mdn = 0.12$; $SD = 0.24$; 10th–90th percentile = 0.01–0.65 mg/L) among the 710 youth for whom tap water measures were available, excluding those who reported drinking bottled water as their main source of water. As expected, water fluoride

Table 1

Demographic characteristics, fluoride exposure variables, and attention outcomes for youth included in the three different samples.

Variable	Participants in Cycles 2 and 3 with:		Participants in Cycle 3 with:
	Urinary fluoride Mean (SD) or %	CWF status [†] Mean (SD) or %	Water fluoride Mean (SD) or %
N	1877	1722	710
Child sex			
Male	51.2	50.8	52.7
Female	48.8	49.2	47.3
Child age at interview (years)	11.3 (3.4)	11.3 (3.3)	11.2 (3.5)
Ethnicity			
White	72.6	67.6	69.0
Non-white	27.3	32.5	31.0
Parental Education			
High School/College	53.0	43.4	44.9
University or higher	47.0	56.6	55.1
Smoking in the home			
Yes	11.5	7.7	8.3
No	88.5	92.4	91.7
Household income (per \$1000 CDN)	91.7 (82.7)	97.3 (70.6)	104.0 (134.6)
Body Mass Index	19.8 (4.7)	19.7 (4.7)	19.6 (4.6)
Blood lead (µg/dL)	0.83 (0.41)	0.83 (0.41)	0.83 (0.41)
Lived in residence			
2.99 years or less	19.2	Excluded	21.1
3.00 years or more	80.8	100.0	78.9
Fluoride measures			
UF_{SG} (mg/L)	0.61 (0.39)	0.64 (0.45)	0.62 (0.48)
Water fluoride (mg/L)	0.23 (0.24)	0.26 (0.26)	0.23 (0.24)
Site adds fluoride			
Yes	50.9	53.3	53.7
No	48.1	46.7	46.3
Outcome Variables			
Diagnosis of ADHD	7.3	5.5	6.3
SDQ H/I Subscale Score	2.8 (2.7)	2.6 (2.6)	2.9 (2.6)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; BMI = Body Mass Index; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity Inattention.

[†] Youth who drink tap water and have a stable residence.

levels were significantly higher among those living in a fluoridated region ($M = 0.49$ mg/L, $SD = 0.22$) than non-fluoridated region ($M = 0.04$ mg/L, $SD = 0.06$), $t = 34.9$, $p < .01$. Table 3 presents the urinary fluoride and water fluoride levels across demographic characteristics, fluoride exposure variables, and attention outcomes.

3.3. Association between fluoride exposure and ADHD diagnosis

No planned interactions were significant in the logistic regression of ADHD diagnosis on UF_{SG} concentration; thus, the final model did not include interaction terms. UF_{SG} did not significantly predict an ADHD diagnosis (adjusted Odds Ratio [aOR] = 0.96; 95% CI: 0.63, 1.46, $p = .84$) adjusting for covariates (Table 4). In the regression of ADHD diagnosis on CWF, there was a significant interaction between age and CWF ($B = 0.19$, $p = .02$), such that the association between CWF and the odds of an ADHD diagnosis was stronger among older youth. Specifically, at the 75th percentile of age (14 years old), the predicted odds of an ADHD diagnosis was 2.8 times greater among youth in a fluoridated region compared with youth in a non-fluoridated region (aOR = 2.84, 95% CI: 1.40, 5.76, $p < .01$), whereas among youth at the 25th percentile of age (9 years old), the predicted odds of an ADHD

Table 2

Comparison of youth with a urinary and water fluoride measurement with and without a diagnosis of ADHD.

Variable	ADHD Diagnosis (n = 137) Mean (SD)/%	No ADHD Diagnosis (n = 1740) Mean (SD)/%
Sex		
Male	69.7	49.6
Female	30.3	50.4
Ethnicity		
White	85.1	72.4
Non-white	14.9	27.6
Parental Education		
High School/College	68.7	53.1
University or higher	31.3	46.9
Smoking in the home		
Yes	26.9	10.0
No	73.1	90.0
Age	12.0 (3.2)	11.2 (3.5)
Household income (per \$1000 CND)	70.6 (54.1)	97.9 (95.4)
BMI	19.4 (4.1)	19.9 (4.8)
Blood lead (µg/dL)	0.83 (0.41)	0.83 (0.41)
Fluoride measures		
Tap water fluoride concentration [†] (mg/L)	0.29 (0.28)	0.22 (0.24)
UF _{SG} (mg/L)	0.57 (0.32)	0.62 (0.45)
Site adds fluoride – Yes	47.1	52.8
Site adds fluoride – No	52.9	47.2
Outcome		
SDQ H/I Subscale Score	6.74 (2.5)	2.51 (2.4)

ADHD = Attention Deficit Hyperactivity Disorder; BMI = Body Mass Index; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity concentration; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity-Inattention.

[†] Cycle 3 only.

diagnosis was similar across CWF status (aOR = 0.91, 95% CI: 0.41, 1.99, $p = .81$; Table 4). Finally, tap water fluoride concentration was significantly associated with having an ADHD diagnosis, adjusting for covariates; this effect did not significantly interact with sex or age. Specifically, a 1 mg/L increase in tap water fluoride was associated with a 6.1 times higher odds of ADHD diagnosis (95% CI: 1.60, 22.8, $p < .01$; Table 4).

Estimating the models with UF_{SG} and CWF for Cycle 2 and 3 separately showed a similar pattern (Supplemental Table 2). For the regression with CWF, the interaction with age was not significant using Cycle 2 data only ($B = 0.12$, $p = .35$), but was significant using data from Cycle 3 only ($B = 0.30$, $p = .03$).

3.4. Association between fluoride exposure and SDQ hyperactive/inattentive scores

No planned interactions were significant in the regression of SDQ hyperactive/inattentive subscale scores on UF_{SG} concentration; thus, the final model did not include interaction terms. UF_{SG} did not significantly predict SDQ hyperactive/inattentive subscale scores ($B = 0.31$, 95% CI = -0.04 , 0.66, $p = .08$; Table 4).

Next, there was a significant interaction between age and CWF status ($B = 0.11$, $p = .01$) such that the association between CWF and hyperactivity/inattention scores was stronger among older youth. Specifically, the regression model predicted that for youth at the 75th percentile of age (14 years old), living in a fluoridated region was associated with a 0.7-point higher SDQ hyperactivity/inattention score (95% CI = 0.34, 1.06, $p < .01$). In contrast, among youth at the 25th percentile of age (9 years old), CWF status was not significantly associated with SDQ hyperactivity/inattention scores ($B = 0.04$, 95% CI = -0.38 , 0.46, $p = .85$).

Table 3

Urinary fluoride and tap water fluoride levels across binary demographic characteristics and fluoride exposure variables.

Variable	UF _{SG} (mg/L) Mean (SD)	Water fluoride (mg/L) Mean (SD)
Child sex		
Male	0.61 (0.36)	0.23 (0.24)
Female	0.63 (0.51)	0.23 (0.24)
Ethnicity		
White	0.60 (0.42)	0.21 (0.23)
Non-white	0.68 (0.51)	0.28 (0.26)
Parental Education		
High School/College	0.62 (0.49)	0.21 (0.23)
University or higher	0.61 (0.38)	0.24 (0.25)
Smoking in the home		
Yes	0.57 (0.36)	0.17 (0.21)
No	0.63 (0.45)	0.24 (0.24)
Lived in residence		
2.99 years or less	0.64 (0.50)	0.23 (0.24)
3.00 years or more	0.61 (0.42)	0.23(0.24)
Type of water consumed		
Tap water	0.62 (0.44)	0.23 (0.24)
Bottled water	0.62 (0.45)	0.22 (0.23)
Source of water		
Municipal water system	0.63 (0.45)	0.25 (0.25)
Private well	0.54 (0.34)	0.13 (0.13)
Fluoride measures		
Site adds fluoride		
Yes	0.82 (0.54)	0.49 (0.22)
No	0.46 (0.32)	0.05 (0.06)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; SD = standard deviation; UF_{SG} = urinary fluoride adjusted for specific gravity.

Table 4

Adjusted Odds Ratio (aOR) and effect estimates for the association between fluoride exposure, ADHD diagnosis, and attention symptoms.

	ADHD diagnosis		SDQ H/I subscale score	
	aOR ^a	95% CI	aOR ^a	95% CI
UF _{SG} (mg/L) ^b	0.96	0.63, 1.46	0.31	-0.04 , 0.66
Fluoride in tap water (mg/L) ^c	6.10*	1.60, 22.8	0.31*	0.04, 0.58
75th percentile age	– ^d	–	1.52*	0.23, 2.80
25th percentile age	–	–	–0.33	-1.51 , 0.84
CWF status ^e	1.21*	1.03, 1.42	0.11*	0.02, 0.20
75th percentile age	2.84*	1.40, 5.76	0.70*	0.34, 1.06
25th percentile age	0.91	0.41, 1.99	0.04	-0.38 , 0.46

Abbreviations: ADHD = Attention Deficit/Hyperactivity Disorder; CWF = community water fluoridation; aOR = adjusted odds ratio; SDQ H/I = Strengths and Difficulties Questionnaire Hyperactivity-Inattention.

* $p < .05$.

^a Adjusted for child's sex, age at interview, ethnicity (white or other), body mass index, highest level of parental education, total household income, exposure to cigarette smoke inside the home (yes/no), concurrent blood lead level (log₁₀-transformed).

^b Non-significant main effect of urinary fluoride level predicting ADHD diagnosis ($B = -0.04$, $p = .84$) or SDQ subscale score ($B = 0.31$, $p = .08$).

^c Interaction between age and water fluoride level predicting SDQ subscale score ($B = 0.31$, $p = .03$).

^d Since the interaction between age and water fluoride was not significant, only the main effects are presented for the logistic regression predicting ADHD diagnosis from fluoride in tap water (mg/L).

^e Significant interaction between age and CWF status predicting ADHD diagnosis ($B = 0.19$, $p = .03$) and SDQ subscale score ($B = 0.11$, $p = .01$).

Finally, the interaction between age and tap water fluoride level was also significant ($B = 0.31$, $p = .03$) such that the association between tap water fluoride and SDQ hyperactivity/inattention score was

stronger among older youth. In particular, among youth at the 75th percentile of age (14 years old), an increase of 1 mg/L in water fluoride level was associated with a 1.52 increase in the SDQ hyperactivity/inattention subscale score (95% CI: 0.23, 2.68, $p = .02$). However, for youth at the 25th percentile of age (8 years old), the association between water fluoride level and SDQ hyperactivity/inattention subscale score was not significant ($B = -0.33$, 95% CI: $-1.51, 0.84$, $p = .58$).

4. Discussion

We found that Canadian youth exposed to higher tap water fluoride levels had a higher risk of receiving an ADHD diagnosis and reported more symptoms of hyperactivity and inattention. Specifically, an increase of 1.0 mg/L in water fluoride concentration was associated with a 6.1 times higher odds of an ADHD diagnosis after accounting for potential confounding variables, such as exposure to second-hand smoke, household income, and blood lead level. Likewise, water fluoride concentration was positively associated with hyperactive/inattentive symptoms, especially among older youth. To contextualize these results, the difference in water fluoride concentration between cities with and without fluoridation is approximately 0.5 mg/L. Our finding of a 1.5-point increase in the SDQ hyperactive/inattentive symptom subscale for each increase of 1 mg/L in water fluoride level implies a 0.75-point increase per 0.5 mg/L water fluoride; this result is remarkably consistent with our finding of a 0.7-point increase on the SDQ's hyperactivity/inattention subscale observed among older youth living in a fluoridated versus non-fluoridated region.

In contrast, urinary fluoride levels were not significantly associated with a diagnosis of ADHD or hyperactive/inattentive symptoms. Water fluoride concentration and CWF status may be more strongly associated with attention-related outcomes than urinary fluoride levels because fluoride concentrations in municipal water supplies vary within a limited range and therefore may serve as a proxy for early-life and chronic fluoride exposure. In contrast, urinary fluoride levels in spot samples are more likely to fluctuate due to the rapid elimination kinetics of fluoride. Additionally, urinary fluoride values may capture acute exposures due to behaviours that were not controlled in this study, such as professionally applied varnish, consumption of beverages with high fluoride content (e.g., tea), or swallowing toothpaste prior to urine sampling. Finally, the association between urinary fluoride and attention-related outcomes could be obscured due to reduced fluoride excretion (i.e., increased fluoride absorption) during a high growth spurt stage (Jha et al., 2011; World Health Organization, 1997). Despite these limitations, use of individualized biomarkers is considered an improvement over past ecologic studies (Malin and Till, 2015) examining the association between ADHD and fluoride exposure and it has the advantage of examining all sources of fluoride exposure, not just from drinking water.

Our findings are consistent with earlier studies showing a relationship between fluoride exposure and ADHD. In particular, Malin and Till (2015) found that a 1% increase in community water fluoridation prevalence in 1992 was associated with approximately 67,000 to 131,000 additional ADHD diagnoses from 2003 to 2011 among children and adolescents in the United States. Conversely, Barberio and colleagues (2017) did not find a significant relationship between fluoride exposure and learning disabilities (including ADHD) using data from the CHMS Cycles 2 and 3. A direct comparison of our results to the results found by Barberio and colleagues is challenged by the differences in how the data were analyzed between the two studies. Our sample included youth between ages 6 and 17, whereas Barberio and colleagues restricted their sample to youth ages 3 to 12. Further, Barberio and colleagues included participants with learning disabilities instead of selecting only those with a diagnosis of ADHD. Finally, the current study accounted for whether youth in both Cycles 2 and 3 drank unfiltered municipal tap water. It may be that the effects of fluoride exposure are most pronounced in older youth, or that fluoride is

specifically associated with ADHD-related behaviours as opposed to learning disabilities. Finally, inclusion of learning disabilities may also introduce selection bias due to differences in how learning disabilities and ADHD are diagnosed in Canada.

Our findings showed that age modified the association between fluoride exposure and the likelihood of ADHD diagnosis and symptoms of hyperactivity and inattention, such that the associations were stronger among older youth. The method used in the CHMS may not be as sensitive for young children who are at risk of an ADHD diagnosis but have not yet been diagnosed; given that 90% of youth with ADHD are diagnosed after age 6 (Kessler et al., 2005), we restricted our minimum age to 6 years. Cumulative exposure to fluoride over time may also impact neurobehavioural development such that youth show more symptoms as they age. Alternatively, because the developing brain is highly sensitive to environmental toxins (Grandjean and Landrigan, 2006; 2014) and because gene expression later in life is impacted by epigenetic changes that occur earlier in development (Roth, 2012), changes produced by early exposure to environmental toxins may manifest later in development.

While ADHD is known to have a strong genetic component with an estimated heritability of 70% to 80% (Larsson et al., 2014), environmental risk factors are also believed to contribute to the development of ADHD. Prenatal substance exposures, heavy metal and chemical exposures, and nutritional factors have been proposed to contribute to the rise in ADHD in the United States (Xu et al., 2018; Sciberras et al., 2017) and an increase in behavioural difficulties as assessed by the SDQ (Philippat et al., 2017; Oulhote et al., 2016; Luk et al., 2018). A recent systematic review (Donzelli et al., 2019) reported a significant association between lead exposure and risk of ADHD in 12 out of 17 studies; the adjusted odds ratios ranged from 1.09 to 7.25, which is within the range of the current study findings. Although the precise mechanism by which fluoride affects neurodevelopment is unclear, several possible mechanisms have been proposed. Animal studies have shown alterations in acetylcholine or cholinergic receptors due to fluoride exposure (Chouhan et al., 2010; Liu et al., 2010; Reddy et al., 2014). In particular, both nicotinic acetylcholine receptors and cholinesterase expression appear to play a role in attentional processes (Levin et al., 2011). Other studies have shown morphological changes in neurons (Bhatnagar et al., 2011), mitochondria (Zhao et al., 2019), increased catalase immunoreactivity (Güner et al., 2016), more oxidative stress (Zhang et al., 2015), and increases in apoptotic neurons and abnormal mitochondrial dynamics (Lou et al., 2013, 2014). Further, some studies have suggested that fluoride may suppress thyroid function (Trabelsi et al., 2001); subclinical hypothyroidism during pregnancy has been linked with increased risk for attention disorders (Modesto et al., 2015; Pääkkilä et al., 2014).

Our study has some limitations. First, tap water fluoride was measured in Cycle 3 only, which decreased the sample size for analyses using this predictor. However, we were able to determine CWF status for participants in both Cycle 2 and 3, which permitted examining the concordance between the effects associated with tap water fluoride level, CWF status, and urinary fluoride level. Second, use of exposure metrics obtained at the same time as the outcome of interest (cross-sectional data) is limited for making conclusions about the causal association between fluoride and attention-related outcomes. Exposure misclassification may have occurred for some participants due to changes in a city's water fluoridation status over the youth's lifetime. Tap water samples were collected between 2012 and 2013 when approximately 37.4% of Canadians had access to fluoridated water as compared with 42.6% in 2007 (Public Health Agency of Canada, 2017). Thus, water fluoride measures obtained at the time of CHMS data collection may not be consistent with water fluoride levels that were antecedent to the outcomes in our study. Because the CHMS only measured postnatal fluoride exposure, we were not able to distinguish the effects of fluoride exposure during different developmental periods (e.g., prenatal versus postnatal). Recent studies have identified

pregnancy as a critical period during which fluoride exposure is linked to lowered IQ (Bashash et al., 2017; Green et al., 2019) and attention-related behaviours (Bashash et al., 2018) in offspring. Third, the method used by CHMS may not completely capture true ADHD prevalence. Because of the way that the CHMS items were phrased, the Cycle 2 sample may identify youth with a comorbid learning disability and ADHD, but not those who have ADHD and no learning disability. Nonetheless, the prevalence of ADHD in the current study (7.3%) is similar to the prevalence rate found in other studies. A meta-analysis including 175 studies from across the world obtained an overall ADHD prevalence rate of 7.2% (Thomas et al., 2015). In a 2012 sample of Canadian youth under age 24, the prevalence of ADHD was 5.4% (Hauck et al., 2017). Relatedly, the number of youth with ADHD in our study was relatively small, ranging from approximately 45 to 140 depending on the sample used for a given analysis, which limited statistical power and precision. Finally, the SDQ relies on youth or parent perceptions of symptoms. Future studies would benefit from prospective designs and more rigorous symptom assessment, particularly a structured diagnostic interview that assesses DSM-5 criteria for ADHD.

In conclusion, we found that higher tap water fluoride levels and fluoridation of municipal water supplies were associated with a higher risk of an ADHD diagnosis as well as increased symptoms of hyperactivity and inattention, especially among adolescents. These findings, which point to a potential cumulative effect of fluoride exposure, highlight the need for further investigation of the potential for fluoride-mediated developmental neurotoxicity in populations with water fluoridation.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.105190>.

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Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada

Rivka Green, MA; Bruce Lanphear, MD; Richard Hornung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Rachel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD

IMPORTANCE The potential neurotoxicity associated with exposure to fluoride, which has generated controversy about community water fluoridation, remains unclear.

OBJECTIVE To examine the association between fluoride exposure during pregnancy and IQ scores in a prospective birth cohort.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter birth cohort study used information from the Maternal-Infant Research on Environmental Chemicals cohort. Children were born between 2008 and 2012; 41% lived in communities supplied with fluoridated municipal water. The study sample included 601 mother-child pairs recruited from 6 major cities in Canada; children were between ages 3 and 4 years at testing. Data were analyzed between March 2017 and January 2019.

EXPOSURES Maternal urinary fluoride (MUF_{SG}), adjusted for specific gravity and averaged across 3 trimesters available for 512 pregnant women, as well as self-reported maternal daily fluoride intake from water and beverage consumption available for 400 pregnant women.

MAIN OUTCOMES AND MEASURES Children's IQ was assessed at ages 3 to 4 years using the Wechsler Primary and Preschool Scale of Intelligence-III. Multiple linear regression analyses were used to examine covariate-adjusted associations between each fluoride exposure measure and IQ score.

RESULTS Of 512 mother-child pairs, the mean (SD) age for enrollment for mothers was 32.3 (5.1) years, 463 (90%) were white, and 264 children (52%) were female. Data on MUF_{SG} concentrations, IQ scores, and complete covariates were available for 512 mother-child pairs; data on maternal fluoride intake and children's IQ were available for 400 of 601 mother-child pairs. Women living in areas with fluoridated tap water ($n = 141$) compared with nonfluoridated water ($n = 228$) had significantly higher mean (SD) MUF_{SG} concentrations (0.69 [0.42] mg/L vs 0.40 [0.27] mg/L; $P = .001$; to convert to millimoles per liter, multiply by 0.05263) and fluoride intake levels (0.93 [0.43] vs 0.30 [0.26] mg of fluoride per day; $P = .001$). Children had mean (SD) Full Scale IQ scores of 107.16 (13.26), range 52-143, with girls showing significantly higher mean (SD) scores than boys: 109.56 (11.96) vs 104.61 (14.09); $P = .001$. There was a significant interaction ($P = .02$) between child sex and MUF_{SG} (6.89; 95% CI, 0.96-12.82) indicating a differential association between boys and girls. A 1-mg/L increase in MUF_{SG} was associated with a 4.49-point lower IQ score (95% CI, -8.38 to -0.60) in boys, but there was no statistically significant association with IQ scores in girls ($B = 2.40$; 95% CI, -2.53 to 7.33). A 1-mg higher daily intake of fluoride among pregnant women was associated with a 3.66 lower IQ score (95% CI, -7.16 to -0.14) in boys and girls.

CONCLUSIONS AND RELEVANCE In this study, maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years. These findings indicate the possible need to reduce fluoride intake during pregnancy.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christine Till, PhD, Department of Psychology, York University, 4700 Keele St, Toronto, ON M3J 1P3, Canada (ctill@yorku.ca).

For decades, community water fluoridation has been used to prevent tooth decay. Water fluoridation is supplied to about 66% of US residents, 38% of Canadian residents, and 3% of European residents.¹ In fluoridated communities, fluoride from water and beverages made with tap water makes up 60% to 80% of daily fluoride intake in adolescents and adults.²

Fluoride crosses the placenta,³ and laboratory studies show that it accumulates in brain regions involved in learning and memory⁴ and alters proteins and neurotransmitters in the central nervous system.⁵ Higher fluoride exposure from drinking water has been associated with lower children's intelligence in a meta-analysis⁶ of 27 epidemiologic studies and in studies^{7,8} including biomarkers of fluoride exposure. However, most prior studies were cross-sectional and conducted in regions with higher water fluoride concentrations (0.88–31.6 mg/L; to convert to millimoles per liter, multiply by 0.05263) than levels considered optimal (ie, 0.7 mg/L) in North America.⁹ Further, most studies did not measure exposure during fetal brain development. In a longitudinal birth cohort study involving 299 mother-child pairs in Mexico City, Mexico, a 1-mg/L increase in maternal urinary fluoride (MUF) concentration was associated with a 6-point (95% CI, –10.84 to –1.74) lower IQ score among school-aged children.¹⁰ In this same cohort, MUF was also associated with more attention-deficit/hyperactivity disorder-like symptoms.¹¹ Urinary fluoride concentrations among pregnant women living in fluoridated communities in Canada are similar to concentrations among pregnant women living in Mexico City.¹² However, it is unclear whether fluoride exposure during pregnancy is associated with cognitive deficits in a population receiving optimally fluoridated water.

This study examined whether exposure to fluoride during pregnancy was associated with IQ scores in children in a Canadian birth cohort in which 40% of the sample was supplied with fluoridated municipal water.

Methods

Study Cohort

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from 10 cities across Canada. Women who could communicate in English or French, were older than 18 years, and were within the first 14 weeks of pregnancy were recruited from prenatal clinics. Participants were not recruited if there was a known fetal abnormality, if they had any medical complications, or if there was illicit drug use during pregnancy. Additional details are in the cohort profile description.¹³

A subset of 610 children in the MIREC Study was evaluated for the developmental phase of the study at ages 3 to 4 years; these children were recruited from 6 of 10 cities included in the original cohort: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Owing to budgetary restraints, recruitment was restricted to the 6 cities with the most participants who fell into the age range required for

Key Points

Question Is maternal fluoride exposure during pregnancy associated with childhood IQ in a Canadian cohort receiving optimally fluoridated water?

Findings In this prospective birth cohort study, fluoride exposure during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.

Meaning Fluoride exposure during pregnancy may be associated with adverse effects on child intellectual development, indicating the possible need to reduce fluoride intake during pregnancy.

the testing during the data collection period. Of the 610 children, 601 (98.5%) completed neurodevelopmental testing; 254 (42.3%) of these children lived in nonfluoridated regions and 180 (30%) lived in fluoridated regions; for 167 (27.7%) fluoridation status was unknown owing to missing water data or reported not drinking tap water (Figure 1).

This study was approved by the research ethics boards at Health Canada, York University, and Indiana University. All women signed informed consent forms for both mothers and children.

Maternal Urinary Fluoride Concentration

We used the mean concentrations of MUF measured in urine spot samples collected across each trimester of pregnancy at a mean (SD) of 11.57 (1.57), 19.11 (2.39), and 33.11 (1.50) weeks of gestation. Owing to the variability of urinary fluoride measurement and fluoride absorption during pregnancy,¹⁴ we only included women who had all 3 urine samples. In our previous work, these samples were moderately correlated; intraclass correlation coefficient (ICC) ranged from 0.37 to 0.40.¹²

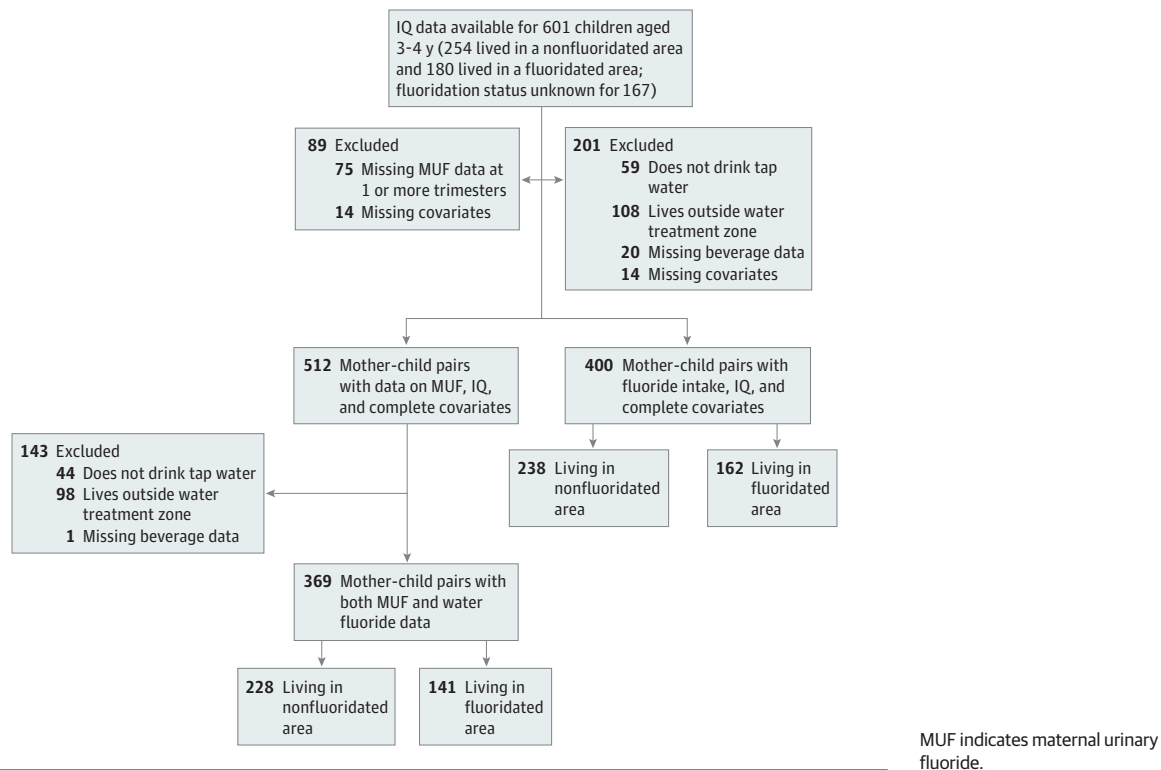
Urinary fluoride concentration was analyzed at the Indiana University School of Dentistry using a modification of the hexamethyldisiloxane (Sigma Chemical Co) microdiffusion procedure¹⁵ and described in our previous work.¹² Fluoride concentration could be measured to 0.02 mg/L. We excluded 2 samples (0.002%) because the readings exceeded the highest concentration standard (5 mg/L) and there was less certainty of these being representative exposure values.

To account for variations in urine dilution at the time of measurement, we adjusted MUF concentrations for specific gravity (SG) using the following equation: $MUF_{SG} = MUF_i \times (SG_M - 1) / (SG_i - 1)$, where MUF_{SG} is the SG-adjusted fluoride concentration (in milligrams of fluoride per liter), MUF_i is the observed fluoride concentration, SG_i is the SG of the individual urine sample, and SG_M is the median SG for the cohort.¹⁶ For comparison, we also adjusted MUF using the same creatinine adjustment method that was used in the 2017 Mexican cohort.¹⁰

Water Fluoride Concentration

Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water.¹² We matched

Figure 1. Flowchart of Inclusion Criteria



participants' postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) during the duration of pregnancy. We only included women who reported drinking tap water during pregnancy.

Daily Fluoride Intake in Mothers

We obtained information on consumption of tap water and other water-based beverages (tea and coffee) from a self-report questionnaire completed by mothers during the first and third trimesters. This questionnaire was used in the original MREC cohort and has not been validated. Also, for this study, we developed methods to estimate and calculate fluoride intake that have not yet been validated. To estimate fluoride intake from tap water consumed per day (milligrams per day), we multiplied each woman's consumption of water and beverages by her water fluoride concentration (averaged across pregnancy) and multiplied by 0.2 (fluoride content for a 200-mL cup). Because black tea contains a high fluoride content (2.6 mg/L),^{17,18} we also estimated the amount of fluoride consumed from black tea by multiplying each cup of black tea by 0.52 mg (mean fluoride content in a 200-mL cup of black tea made with deionized water) and added this to the fluoride intake variable. Green tea also contains varying levels of fluoride; therefore, we used the mean for the green teas listed by the US Department of Agriculture (1.935 mg/L).¹⁸ We multiplied each cup of green tea by 0.387 mg (fluoride content in a 200-mL cup of green tea made with deionized water) and added this to the fluoride intake variable.

Primary Outcomes

We assessed children's intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition. Full Scale IQ (FSIQ), a measure of global intellectual functioning, was the primary outcome. We also assessed verbal IQ (VIQ), representing verbal reasoning and comprehension, and performance IQ (PIQ), representing nonverbal reasoning, spatial processing, and visual-motor skills.

Covariates

We selected covariates from a set of established factors associated with fluoride metabolism (eg, time of void and time since last void) and children's intellectual abilities (eg, child sex, maternal age, gestational age, and parity) (Table 1). Mother's race/ethnicity was coded as white or other, and maternal education was coded as either bachelor's degree or higher or trade school diploma or lower. The quality of a child's home environment was measured by the Home Observation for Measurement of the Environment (HOME)-Revised Edition¹⁹ on a continuous scale. We also controlled for city and, in some models, included self-reported exposure to secondhand smoke (yes/no) as a covariate.

Statistical Analyses

In our primary analysis, we used linear regression analyses to estimate the associations between our 2 measures of fluoride exposure (MUF_{SG} and fluoride intake) and children's FSIQ scores. In addition to providing the coefficient corresponding to a 1-mg difference in fluoride exposure, we also estimated coefficients corresponding to a fluoride exposure

Table 1. Demographic Characteristics and Exposure Outcomes for Mother-Child Pairs With MUF_{SG} (n = 512) and Fluoride Intake Data (n = 400) by Fluoridated and Nonfluoridated Status^a

Variable ^b	No. (%)		
	MUF _{SG} Sample (n = 512) ^c	Nonfluoridated (n = 238)	Fluoridated (n = 162)
Mothers			
Age of mother at enrollment, mean (SD), y	32.33 (5.07)	32.61 (4.90)	32.52 (4.03)
Prepregnancy BMI, mean (SD)	25.19 (6.02)	25.19 (6.35)	24.33 (5.10)
Married or common law	497 (97)	225 (95)	159 (98)
Born in Canada	426 (83)	187 (79)	131 (81)
White	463 (90)	209 (88)	146 (90)
Maternal education			
Trade school diploma/high school	162 (32)	80 (34)	38 (24)
Bachelor's degree or higher	350 (68)	158 (66)	124 (76)
Employed at time of pregnancy	452 (88)	205 (86)	149 (92)
Net income household >\$70 000 CAD	364 (71)	162 (68)	115 (71)
HOME total score, mean (SD)	47.32 (4.32)	47.28 (4.48)	48.14 (3.90)
Smoked in trimester 1	12 (2)	7 (3)	2 (1)
Secondhand smoke in the home	18 (4)	9 (4)	2 (1)
Alcohol consumption, alcoholic drink/mo			
None	425 (83)	192 (81)	136 (84)
<1	41 (8)	23 (10)	11 (7)
≥1	46 (9)	23 (10)	15 (9)
Parity (first birth)	233 (46)	119 (50)	71 (44)
Children			
Female	264 (52)	118 (50)	83 (51)
Age at testing, mean (SD), y	3.42 (0.32)	3.36 (0.31)	3.49 (0.29)
Gestation, mean (SD), wk	39.12 (1.57)	39.19 (1.47)	39.17 (1.81)
Birth weight, mean (SD), kg	3.47 (0.49)	3.48 (0.48)	3.47 (0.53)
FSIQ	107.16 (13.26)	108.07 (13.31)	108.21 (13.72)
Boys ^d	104.61 (14.09)	106.31 (13.60)	104.78 (14.71)
Girls ^d	109.56 (11.96)	109.86 (12.83)	111.47 (11.89)
Exposure variables			
MUF_{SG} concentration, mg/L^e			
No.	512	228	141
Mean (SD)	0.51 (0.36)	0.40 (0.27)	0.69 (0.42)
Fluoride intake level per day, mg			
No.	369 ^a	238	162
Mean (SD)	0.54 (0.44)	0.30 (0.26)	0.93 (0.43)
Water fluoride concentration, mg/L			
No.	369 ^a	238	162
Mean (SD)	0.31 (0.23)	0.13 (0.06)	0.59 (0.08)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, Canadian dollars; FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUF_{SG}, maternal urinary fluoride adjusted for specific gravity.

SI conversion factor: To convert fluoride to millimoles per liter, multiply by 0.05263.

^a Owing to missing water treatment plant data and/or MUF data, the samples are distinct with some overlapping participants in both groups (n = 369).

^b All of the listed variables were tested as potential covariates, as well as the following: paternal variables (age, education, employment status, smoking status, and race/ethnicity); maternal chronic condition during pregnancy and birth country; breastfeeding duration; and time of void and time since last void.

^c Maternal urinary fluoride (averaged across all 3 trimesters) and corrected for specific gravity.

^d The FSIQ score has a mean (SD) of 100 (15); US population norms used.

^e Owing to missing water treatment plant data, the samples in the fluoridated and nonfluoridated regions do not add up to the MUF sample size.

difference spanning the 25th to 75th percentile range (which corresponds to a 0.33 mg/L and 0.62 mg F/d difference in MUF_{SG} and fluoride intake, respectively) as well as the 10th to 90th percentile range (which corresponds to a 0.70 mg/L and 1.04 mg F/d difference in MUF_{SG} and fluoride intake, respectively).

We retained a covariate in the model if its *P* value was less than .20 or its inclusion changed the regression coefficient of the variable associated factor by more than 10% in any of the IQ models. Regression diagnostics confirmed that there were no collinearity issues in any of the IQ models

with MUF_{SG} or fluoride intake (variance inflation factor <2 for all covariates). Residuals from each model had approximately normal distributions, and their Q-Q plots revealed no extreme outliers. Plots of residuals against fitted values did not suggest any assumption violations and there were no substantial influential observations as measured by Cook distance. Including quadratic or natural-log effects of MUF_{SG} or fluoride intake did not significantly improve the regression models. Thus, we present the more easily interpreted estimates from linear regression models. Additionally, we examined separate models with 2 linear splines to test

whether the MUF_{SG} association significantly differed between lower and higher levels of MUF_{SG} based on 3 knots, which were set at 0.5 mg/L (mean MUF_{SG}), 0.8 mg/L (threshold seen in the Mexican birth cohort),¹⁰ and 1 mg/L (optimal concentration in the United States until 2015).²⁰ For fluoride intake, knots were set at 0.4 mg (mean fluoride intake), 0.8 mg, and 1 mg (in accordance with MUF_{SG}). We also examined sex-specific associations in all models by testing the interactions between child sex and each fluoride measure.

In sensitivity analyses, we tested whether the associations between MUF_{SG} and IQ were confounded by maternal blood concentrations of lead,²¹ mercury,²¹ manganese,^{21,22} perfluoro-octanoic acid,²³ or urinary arsenic.²⁴ We also conducted sensitivity analyses by removing IQ scores that were greater than or less than 2.5 standard deviations from the sample mean. Additionally, we examined whether using MUF adjusted for creatinine instead of SG affected the results.

In additional analyses, we examined the association between our 2 measures of fluoride exposure (MUF_{SG} and fluoride intake) with VIQ and PIQ. Additionally, we examined whether water fluoride concentration was associated with FSIQ, VIQ, and PIQ scores.

For all analyses, statistical significance tests with a type I error rate of 5% were used to test sex interactions, while 95% confidence intervals were used to estimate uncertainty. Analyses were conducted using R software (the R Foundation).²⁵ The *P* value level of significance was .05, and all tests were 2-sided.

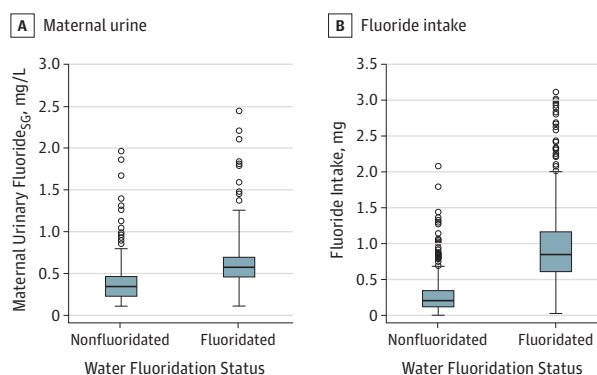
Results

For the first measure of fluoride exposure, MUF_{SG} , 512 of 601 mother-child pairs (85.2%) who completed the neurodevelopmental visit had urinary fluoride levels measured at each trimester of the mother's pregnancy and complete covariate data (Figure 1); 89 (14.8%) were excluded for missing MUF_{SG} at 1 or more trimesters (*n* = 75) or missing 1 or more covariates included in the regression (*n* = 14) (Figure 1). Of the 512 mother-child pairs with MUF_{SG} data (and all covariates), 264 children were female (52%).

For the second measure of fluoride exposure, fluoride intake from maternal questionnaire, data were available for 400 of the original 601 mother-child pairs (66.6%): 201 women (33.4%) were excluded for reporting not drinking tap water (*n* = 59), living outside of the predefined water treatment plant zone (*n* = 108), missing beverage consumption data (*n* = 20), or missing covariate data (*n* = 14) (Figure 1).

Children had mean FSIQ scores in the average range (population normed) (mean [SD], 107.16 [13.26], range = 52-143), with girls (109.56 [11.96]) showing significantly higher scores than boys (104.61 [14.09]; *P* < .001) (Table 1). The demographic characteristics of the 512 mother-child pairs included in the primary analysis were not substantially different from the original MIREC cohort or subset of mother-child pairs without 3 urine samples (eTable 1 in the Supplement). Of the 400 mother-child pairs with fluoride intake data (and all covariates), 118 of

Figure 2. Distribution of Fluoride Levels in Maternal Urine and for Estimated Fluoride Intake by Fluoridation Status



To convert fluoride to millimoles per liter, multiply by 0.05263.

238 (50%) in the group living in a nonfluoridated region were female and 83 of 162 (51%) in the group living in a fluoridated region were female.

Fluoride Measurements

The median MUF_{SG} concentration was 0.41 mg/L (range, 0.06-2.44 mg/L). Mean MUF_{SG} concentration was significantly higher among women (*n* = 141) who lived in communities with fluoridated drinking water (0.69 [0.42] mg/L) compared with women (*n* = 228) who lived in communities without fluoridated drinking water (0.40 [0.27] mg/L; *P* < .001) (Table 1; Figure 2).

The median estimated fluoride intake was 0.39 mg per day (range, 0.01-2.65 mg). As expected, the mean (SD) fluoride intake was significantly higher for women (162 [40.5%]) who lived in communities with fluoridated drinking water (mean [SD], 0.93 [0.43] mg) than women (238 [59.5%]) who lived in communities without fluoridated drinking water (0.30 [0.26] mg; *P* < .001) (Table 1; Figure 2). The MUF_{SG} was moderately correlated with fluoride intake (*r* = 0.49; *P* < .001) and water fluoride concentration (*r* = 0.37; *P* < .001).

Maternal Urinary Fluoride Concentrations and IQ

Before covariate adjustment, a significant interaction (*P* for interaction = .03) between MUF_{SG} and child sex (*B* = 7.24; 95% CI, 0.81-13.67) indicated that MUF_{SG} was associated with FSIQ in boys; an increase of 1 mg/L MUF_{SG} was associated with a 5.01 (95% CI, -9.06 to -0.97; *P* = .02) lower FSIQ score in boys. In contrast, MUF_{SG} was not significantly associated with FSIQ score in girls (*B* = 2.23; 95% CI, -2.77 to 7.23; *P* = .38) (Table 2).

Adjusting for covariates, a significant interaction (*P* for interaction = .02) between child sex and MUF_{SG} (*B* = 6.89; 95% CI, 0.96-12.82) indicated that an increase of 1 mg/L of MUF_{SG} was associated with a 4.49 (95% CI, -8.38 to -0.60; *P* = .02) lower FSIQ score for boys. An increase from the 10th to 90th percentile of MUF_{SG} was associated with a 3.14 IQ decrement among boys (Table 2; Figure 3). In contrast, MUF_{SG} was not significantly associated with FSIQ score in girls (*B* = 2.43; 95% CI, -2.51 to 7.36; *P* = .33).

Table 2. Unadjusted and Adjusted Associations Estimated From Linear Regression Models of Fluoride Exposure Variables and FSIQ Scores

Variable	Difference (95% CI)			
	Unadjusted	Adjusted Estimates, Regression Coefficients Indicate Change in Outcome per ^a		
MUF _{SG} ^{b,c}	-2.60 (-5.80 to 0.60)	1 mg	25th to 75th Percentiles	10th to 90th Percentiles
Boys	-5.01 (-9.06 to -0.97)	-4.49 (-8.38 to -0.60)	-1.48 (-2.76 to -0.19)	-3.14 (-5.86 to -0.42)
Girls	2.23 (-2.77 to 7.23)	2.40 (-2.53 to 7.33)	0.79 (-0.83 to 2.42)	1.68 (-1.77 to 5.13)
Fluoride intake ^{d,e}	-3.19 (-5.94 to -0.44)	-3.66 (-7.16 to -0.15)	-2.26 (-4.45 to -0.09)	-3.80 (-7.46 to -0.16)

Abbreviations: FSIQ, Full Scale IQ; HOME, Home Observation for Measurement of the Environment; MUF_{SG}, maternal urinary fluoride adjusted for specific gravity.

^a Adjusted estimates pertain to predicted FSIQ difference for a value spanning the interquartile range (25th to 75th percentiles) and 80th central range (10th to 90th percentiles): (1) MUF_{SG}: 0.33 mg/L, 0.70 mg/L, respectively; (2) fluoride intake: 0.62 mg, 1.04 mg, respectively.

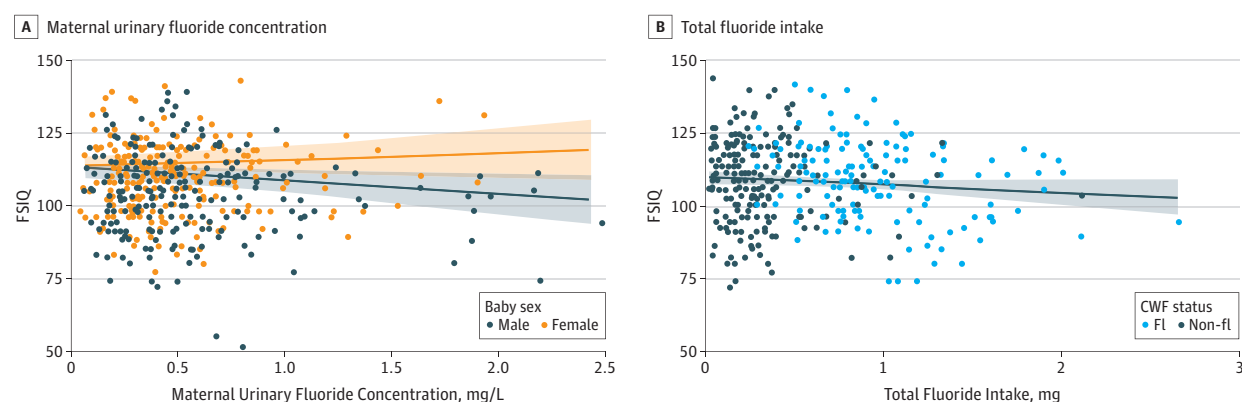
^b n = 512.

^c Adjusted for city, HOME score, maternal education, race/ethnicity, and including child sex interaction.

^d n = 400.

^e Adjusted for city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure.

Figure 3. Covariate Results of Multiple Linear Regression Models of Full Scale IQ (FSIQ) from Maternal Urinary Fluoride Concentration by Child Sex (n = 512) and Total Fluoride Intake Estimated from Daily Maternal Beverage Consumption (n = 400)



B, Community fluoridation status (CWF) is shown for each woman; black dots represent women living in nonfluoridated (non-FL) communities and blue dots represent women living in fluoridated (FL) communities.

Estimated Fluoride Intake and IQ

A 1-mg increase in fluoride intake was associated with a 3.66 (95% CI, -7.16 to -0.15; $P = .04$) lower FSIQ score among boys and girls (Table 2; Figure 3). The interaction between child sex and fluoride intake was not statistically significant ($B = 1.17$; 95% CI, -4.08 to 6.41; P for interaction = .66).

Sensitivity Analyses

Adjusting for lead, mercury, manganese, perfluorooctanoic acid, or arsenic concentrations did not substantially change the overall estimates of MUF_{SG} for boys or girls (eTable 2 in the Supplement). Use of MUF adjusted for creatinine did not substantially alter the associations with FSIQ (eTable 2 in the Supplement). Including time of void and time since last void did not substantially change the regression coefficient of MUF_{SG} among boys or girls.

Estimates for determining the association between MUF_{SG} and PIQ showed a similar pattern with a statistically significant interaction between MUF_{SG} and child sex (P for interaction = .007). An increase of 1 mg/L MUF_{SG} was associated with a 4.63 (95% CI, -9.01 to -0.25; $P = .04$) lower PIQ score in boys, but the association was not statistically significant in girls

($B = 4.51$; 95% CI, -1.02 to 10.05; $P = .11$). An increase of 1 mg/L MUF_{SG} was not significantly associated with VIQ in boys ($B = -2.85$; 95% CI, -6.65 to 0.95; $P = .14$) or girls ($B = 0.55$; 95% CI, -4.28 to 5.37; $P = .82$); the interaction between MUF_{SG} and child sex was not statistically significant (P for interaction = .25) (eTable 3 in the Supplement).

Consistent with the findings on estimated maternal fluoride intake, increased water fluoride concentration (per 1 mg/L) was associated with a 5.29 (95% CI, -10.39 to -0.19) lower FSIQ score among boys and girls and a 13.79 (95% CI, -18.82 to -7.28) lower PIQ score (eTable 4 in the Supplement).

Discussion

Using a prospective Canadian birth cohort, we found that estimated maternal exposure to higher fluoride levels during pregnancy was associated with lower IQ scores in children. This association was supported by converging findings from 2 measures of fluoride exposure during pregnancy. A difference in MUF_{SG} spanning the interquartile range for the entire sample (ie, 0.33 mg/L), which is roughly the difference in

MUF_{SG} concentration for pregnant women living in a fluoridated vs a nonfluoridated community, was associated with a 1.5-point IQ decrement among boys. An increment of 0.70 mg/L in MUF_{SG} concentration was associated with a 3-point IQ decrement in boys; about half of the women living in a fluoridated community have a MUF_{SG} equal to or greater than 0.70 mg/L. These results did not change appreciably after controlling for other key exposures such as lead, arsenic, and mercury.

To our knowledge, this study is the first to estimate fluoride exposure in a large birth cohort receiving optimally fluoridated water. These findings are consistent with that of a Mexican birth cohort study that reported a 6.3 decrement in IQ in preschool-aged children compared with a 4.5 decrement for boys in our study for every 1 mg/L of MUF.¹⁰ The findings of the current study are also concordant with ecologic studies that have shown an association between higher levels of fluoride exposure and lower intellectual abilities in children.^{7,8,26} Collectively, these findings support that fluoride exposure during pregnancy may be associated with neurocognitive deficits.

In contrast with the Mexican study,¹⁰ the association between higher MUF_{SG} concentrations and lower IQ scores was observed only in boys but not in girls. Studies of fetal and early childhood fluoride exposure and IQ have rarely examined differences by sex; of those that did, some reported no differences by sex.^{10,27-29} Most rat studies have focused on fluoride exposure in male rats,³⁰ although 1 study³¹ showed that male rats were more sensitive to neurocognitive effects of fetal exposure to fluoride. Testing whether boys are potentially more vulnerable to neurocognitive effects associated with fluoride exposure requires further investigation, especially considering that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities.³² Adverse effects of early exposure to fluoride may manifest differently for girls and boys, as shown with other neurotoxicants.³³⁻³⁶

The estimate of maternal fluoride intake during pregnancy in this study showed that an increase of 1 mg of fluoride was associated with a decrease of 3.7 IQ points across boys and girls. The finding observed for fluoride intake in both boys and girls may reflect postnatal exposure to fluoride, whereas MUF primarily captures prenatal exposure. Importantly, we excluded women who reported that they did not drink tap water and matched water fluoride measurements to time of pregnancy when estimating maternal fluoride intake. None of the fluoride concentrations measured in municipal drinking water were greater than the maximum acceptable concentration of 1.5 mg/L set by Health Canada; most (94.3%) were lower than the 0.7 mg/L level considered optimal.³⁷

Water fluoridation was introduced in the 1950s to prevent dental caries before the widespread use of fluoridated dental products. Originally, the US Public Health Service set the optimal fluoride concentrations in water from 0.7 to 1.2 mg/L to achieve the maximum reduction in tooth decay and minimize the risk of enamel fluorosis.³⁸ Fluorosis, or mottling, is a symptom of excess fluoride intake from any source occurring during the period of tooth development. In

2012, 68% of adolescents had very mild to severe enamel fluorosis.³⁹ The higher prevalence of enamel fluorosis, especially in fluoridated areas,⁴⁰ triggered renewed concern about excessive ingestion of fluoride. In 2015, in response to fluoride overexposure and rising rates of enamel fluorosis,^{39,41,42} the US Public Health Service recommended an optimal fluoride concentration of 0.7 mg/L, in line with the recommended level of fluoride added to drinking water in Canada to prevent caries. However, the beneficial effects of fluoride predominantly occur at the tooth surface after the teeth have erupted.⁴³ Therefore, there is no benefit of systemic exposure to fluoride during pregnancy for the prevention of caries in offspring.⁴⁴ The evidence showing an association between fluoride exposure and lower IQ scores raises a possible new concern about cumulative exposures to fluoride during pregnancy, even among pregnant women exposed to optimally fluoridated water.

Strengths and Limitations

Our study has several strengths and limitations. First, urinary fluoride has a short half-life (approximately 5 hours) and depends on behaviors that were not controlled in our study, such as consumption of fluoride-free bottled water or swallowing toothpaste prior to urine sampling. We minimized this limitation by using 3 serial urine samples and tested for time of urine sample collection and time since last void, but these variables did not alter our results. Second, although higher maternal ingestion of fluoride corresponds to higher fetal plasma fluoride levels,⁴⁵ even serial maternal urinary spot samples may not precisely represent fetal exposure throughout pregnancy. Third, while our analyses controlled for a comprehensive set of covariates, we did not have maternal IQ data. However, there is no evidence suggesting that fluoride exposure differs as a function of maternal IQ; our prior study did not observe a significant association between MUF levels and maternal education level.¹² Moreover, a greater proportion of women living in fluoridated communities (124 [76%]) had a university-level degree compared with women living in nonfluoridated communities (158 [66%]). Nonetheless, despite our comprehensive array of covariates included, this observational study design could not address the possibility of other unmeasured residual confounding. Fourth, fluoride intake did not measure actual fluoride concentration in tap water in the participant's home; Toronto, for example, has overlapping water treatment plants servicing the same household. Similarly, our fluoride intake estimate only considered fluoride from beverages; it did not include fluoride from other sources such as dental products or food. Furthermore, fluoride intake data were limited by self-report of mothers' recall of beverage consumption per day, which was sampled at 2 points of pregnancy, and we lacked information regarding specific tea brand.^{17,18} In addition, our methods of estimating maternal fluoride intake have not been validated; however, we show construct validity with MUF. Fifth, this study did not include assessment of postnatal fluoride exposure or consumption. However, our future analyses will assess exposure to fluoride in the MIREC cohort in infancy and early childhood.

Conclusions

In this prospective birth cohort study from 6 cities in Canada, higher levels of fluoride exposure during preg-

nancy were associated with lower IQ scores in children measured at age 3 to 4 years. These findings were observed at fluoride levels typically found in white North American women. This indicates the possible need to reduce fluoride intake during pregnancy.

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Author Affiliations: Faculty of Health, York University, Toronto, Ontario, Canada (Green, Flora, Neufeld, Till); Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada (Lanphear); Child and Family Research Institute, British Columbia Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada (Lanphear); Pediatrics and Environmental Health, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Hornung); School of Dentistry, Indiana University, Indianapolis (Martinez-Mier); Department of Social and Preventive Medicine, Laval University, Québec City, Québec, Canada (Ayotte); Centre de Recherche du CHU de Québec, Université Laval, Québec City, Québec, Canada (Ayotte, Muckle); School of Psychology, Laval University, Québec City, Québec, Canada (Muckle).

Author Contributions: Ms Green and Dr Till had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Green, Lanphear, Martinez-Mier, Ayotte, Muckle, Till.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Green, Flora, Martinez-Mier, Muckle, Till.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Green, Hornung, Flora, Till.

Obtained funding: Lanphear, Muckle, Till.

Administrative, technical, or material support: Green, Lanphear, Martinez-Mier, Ayotte, Till.

Supervision: Flora, Till.

Conflict of Interest Disclosures: Dr Lanphear reports serving as an expert witness in an upcoming case involving the US Environmental Protection Agency and water fluoridation, but will not receive any payment. Dr Hornung reported personal fees from York University during the conduct of the study. Dr Martinez-Mier reported grants from the National Institutes of Health during the conduct of the study. No other disclosures were reported.

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Fluoride exposure from infant formula and child IQ in a Canadian birth cohort

Christine Till^{a,*}, Rivka Green^a, David Flora^a, Richard Hornung^b, E. Angeles Martinez-Mier^c, Maddy Blazer^a, Linda Farmus^a, Pierre Ayotte^{d,e}, Gina Muckle^{d,f}, Bruce Lanphear^{g,h}

^a Faculty of Health, York University, Ontario, Canada

^b Pediatrics and Environmental Health, Cincinnati Children's Hospital Medical Center, OH, USA

^c School of Dentistry, Indiana University, IN, USA

^d Centre de Recherche du CHU de Québec, Université Laval, Québec, Canada

^e Department of Social and Preventive Medicine, Laval University, Quebec, Canada

^f School of Psychology, Laval University, Quebec, Canada

^g Faculty of Health Sciences, Simon Fraser University, British Columbia, Canada

^h Child & Family Research Institute, BC Children's Hospital, University of British Columbia, Canada

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ABSTRACT

Background: Infant consumption of formula reconstituted with fluoridated water can lead to excessive fluoride intake. We examined the association between fluoride exposure in infancy and intellectual ability in children who lived in fluoridated or non-fluoridated cities in Canada.

Methods: We examined 398 mother-child dyads in the Maternal-Infant Research on Environmental Chemicals cohort who reported drinking tap water. We estimated water fluoride concentration using municipal water reports. We used linear regression to analyze the association between fluoride exposure and IQ scores, measured by the Wechsler Primary and Preschool Scale of Intelligence-III at 3–4 years. We examined whether feeding status (breast-fed versus formula-fed) modified the impact of water fluoride and if fluoride exposure during fetal development attenuated this effect. A second model estimated the association between fluoride intake from formula and child IQ.

Results: Thirty-eight percent of mother-child dyads lived in fluoridated communities. An increase of 0.5 mg/L in water fluoride concentration (approximately equaling the difference between fluoridated and non-fluoridated regions) corresponded to a 9.3- and 6.2-point decrement in Performance IQ among formula-fed (95% CI: −13.77, −4.76) and breast-fed children (95% CI: −10.45, −1.94). The association between water fluoride concentration and Performance IQ remained significant after controlling for fetal fluoride exposure among formula-fed ($B = -7.93$, 95% CI: −12.84, −3.01) and breastfed children ($B = -6.30$, 95% CI: −10.92, −1.68). A 0.5 mg increase in fluoride intake from infant formula corresponded to an 8.8-point decrement in Performance IQ (95% CI: −14.18, −3.34) and this association remained significant after controlling for fetal fluoride exposure ($B = -7.62$, 95% CI: −13.64, −1.60).

Conclusions: Exposure to increasing levels of fluoride in tap water was associated with diminished non-verbal intellectual abilities; the effect was more pronounced among formula-fed children.

1. Introduction

Fluoride can occur naturally in water and, in some communities, is added to water supplies to reach the recommended concentration of 0.7 mg/L for the prevention of tooth decay (Health Canada, 2010).

About 74% of Americans and 38% of Canadians on municipal water are supplied with fluoridated drinking water. Water fluoridation has been reported to reduce the prevalence of tooth decay by 26% to 44% (Iheozor-Ejiofor et al., 2015; National Health and Medical Research Council (NHMRC), 2017) in youth and by 26% (Iheozor-Ejiofor et al.,

Abbreviations: BF, breastfed; FF, formula fed; CI, confidence intervals; HOME, home observation for measurement of the environment; IQ, intelligence quotient; FSIQ, full scale IQ; PIQ, performance IQ; VIQ, verbal IQ; MIREC, maternal-infant research on environmental chemicals; MUF, maternal urinary fluoride; SD, standard deviation

* Corresponding author at: Department of Psychology, York University, 4700 Keele Street, M3J 1P3 Toronto, ON, Canada.

E-mail address: ctill@yorku.ca (C. Till).

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2015) to 27% (NHMRC, 2017) in adults. Infants who are fed formula reconstituted with fluoridated water have approximately three to four times greater exposure to fluoride than adults (National Research Council (NRC), 2006) on a per body-weight basis. Formula-fed infants residing in fluoridated areas have an approximate 70-fold higher fluoride intake than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010).

The prevalence of enamel fluorosis, a discoloration of enamel resulting from chronic, excessive ingestion of fluoride during tooth development (Brothwell and Limeback, 2003; Buzalaf et al., 2001), is higher among formula-fed infants than breastfed infants (Buzalaf et al., 2001; Do et al., 2012; Fv et al., 2012; Hong et al., 2006; Walton and Messer, 1981). While enamel fluorosis develops from excess fluoride exposure during the first four years of life, (Levy et al., 2010) the first 12 months are the most vulnerable period (Hong et al., 2006). The risk of fluorosis increases with higher levels of fluoride in the water supply for formula-fed infants (Hujoel et al., 2009).

Breastmilk contains extremely low concentrations of fluoride (0.005–0.01 mg/L) due to the limited transfer of fluoride in plasma into breastmilk (Dabeka et al., 1986; Ekstrand, 1981; Ekstrand and Hardell, 1984; Esala et al., 1982; Faraji et al., 2014; Zohoori et al., 2018). Exclusive breastfeeding for six months, which is recommended by current practice guidelines (Critch, 2013; Eidelman, 2012), is reported by 25% of mothers in the United States (Breastfeeding Report Card, United States, 2018) and Canada (Health Canada, 2001). Ninety percent of bottle-fed infants are fed powdered formula (Infant Feeding Practices Survey II) and 75% of mothers report using tap water to reconstitute formula (Van Winkle et al., 1995). Thus, reconstituted formula is the major source of nutrition for many infants in the United States and Canada.

Despite growing concerns about excessive exposure to fluoride during infancy and the vulnerability of the developing brain (Rice and Barone, 2000; Grandjean and Landrigan, 2006), no studies have tested the potential neurotoxicity of using optimally fluoridated drinking water to reconstitute formula during infancy (Harriehausen et al., 2019). Increased fluoride exposure during fetal brain development was associated with diminished IQ scores in two birth cohort studies (Bashash et al., 2017; Green et al., 2019; Valdez Jiménez et al., 2017), among a number of recent studies conducted in endemic fluorosis areas (Karimzade et al., 2014; Dong et al., 2018; Zhang et al., 2015), as well as a 2012 meta-analysis of 27 ecologic studies (Choi et al., 2012). Increased fluoride exposure has also been linked with ADHD-related behaviors in children (Malin and Till, 2015; Bashash et al., 2018; Riddell et al., 2019).

We investigated the association between water fluoride concentration and intellectual abilities of Canadian children who were formula-fed or breastfed. In addition, we tested whether postnatal effects of fluoride exposure on child IQ remained after controlling for fetal exposure.

2. Materials and methods

2.1. Study population

Between 2008 and 2011, the Maternal-Infant Research on Environmental Chemicals (MIREC) program recruited 2001 pregnant women from ten Canadian cities to participate in a longitudinal pregnancy cohort study. Women who could communicate in English or French, were > 17 years, and were < 14 weeks gestation were recruited from prenatal clinics. Participants were excluded if there was a known fetal abnormality, if they had any medical complications, or if there was known illicit drug use during pregnancy. Additional details are in the cohort profile description (Arbuckle et al., 2013).

Of the 610 children who were recruited to participate in the developmental follow-up phase of the study (MIREC-Child Development

Plus), 601 completed all testing. Children were recruited from six of the cities in the original cohort (Vancouver, Toronto, Hamilton, Halifax, Kingston, Montreal); approximately half of the children lived in non-fluoridated cities and half lived in fluoridated cities.

This study received ethics approval from Health Canada and York University.

2.2. Infant feeding assessment

When children were between 30 and 48 months of age, mothers completed an infant feeding questionnaire asking, “How old was your baby when you ceased breastfeeding exclusively? At what age did you introduce other type of milk or food to your baby?”. Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

To explore the possibility of recall or response bias of mothers completing the questionnaire, we compared information reported by mothers when their children were between 30 and 48 months of age (i.e. time when the questionnaire was completed for classifying the BF and FF groups) with information reported by a subset of women at an earlier visit when their children were between 6 and 8 months of age. Information about infant feeding was only available for 11% of the sample at the infant visit (note that responses could only be matched for women who had stopped breastfeeding at the time the questionnaire was completed at the infant visit). Among women who provided information at both occasions, the median difference for when breastfeeding was reported to be ceased was 0 months; responses were within 1.5 months of each other for two-thirds of this subsample.

We dichotomized feeding status at six months because the Canadian Pediatric Society and American Academy of Pediatrics both recommend exclusive breastfeeding for six months (Critch, 2013; Eidelman, 2012). Moreover, formula-fed infants who are younger than six-months derive most of their nutrition from formula, placing this group at highest risk of exceeding the recommended upper limit (0.7 mg/d) for fluoride (Harriehausen et al., 2019; Institutes of Medicine, 1997; National Research Council (NRC), 2006). Finally, fluoride intake differences become less evident when other dietary sources of fluoride are introduced at around six months (Zohoori et al., 2018).

2.3. Infant fluoride exposure

We estimated fluoride concentrations in drinking water by accessing daily or monthly reports provided by water treatment plants. Water reports were first linked with mothers' postal codes and the daily or weekly amounts were averaged over the first six-months of the child's life. We only included participants whose postal codes could be linked to a water treatment plant that provided water fluoride measurements. We also excluded participants who reported that their primary drinking source was from a well or ‘other’ (e.g. bottled water) (Table S1). Further details can be found in our previous report (Till et al., 2018).

To obtain a continuous fluoride exposure estimate collapsed across the BF and FF groups, we estimated fluoride intake from formula (in mg F/day) by multiplying water fluoride concentration by the amount of time that the infant was not exclusively breastfed in the first year using the following equation:

$$\text{Fluoride intake from formula} = (\text{water_F mg/L}) * (1 - \#mo_excl_BF / 11.99) * 0.80 \text{ L/day}$$

where *water_F mg/L* refers to the average water fluoride concentration and *1-#mo_excl_BF/11.99* represents the proportion over the 12-month period the infant was not exclusively breastfed. A value near one indicates that an infant was primarily formula-fed over the 12 months whereas a value near zero indicates an infant primarily breastfed. We

estimated fluoride intake based on an average of 0.80 L of water used to reconstitute powdered formula as suggested by an infant food diary completed for infants in a prior study (Carignan et al., 2015); the average milk intake at 3 months of age is 0.812 L per day, ranging from 0.523 to 1.124 L (Dewey et al., 1991). Because we did not know the type of formula used (i.e. soy- or milk-based), we did not add fluoride derived from formula to our fluoride intake estimate. Previous studies have indicated that fluoride from water used in formula is a greater source of fluoride than fluoride found in formula (Buzalaf et al., 2004).

2.4. Fetal fluoride exposure

We used maternal urinary fluoride (MUF) adjusted for specific gravity as a proxy of fetal fluoride exposure. MUF, which was derived by averaging three spot samples collected across all three trimesters of pregnancy, was considered our most reliable measure of exposure (Till et al., 2018). Urinary fluoride concentrations were analyzed at the Indiana University School of Dentistry using a modification (Martínez-Mier et al., 2011) of the hexamethyldisiloxane (Sigma Chemical Co., USA) micro-diffusion procedure previously described (Green et al., 2019).

2.5. Intelligence assessment

We assessed children's intellectual abilities between ages 3.0 and 4.0 years with the Wechsler Preschool and Primary Scale of Intelligence-III (Wechsler, 2002) using United States population-based normative data ($mean = 100$, $SD = 15$). Outcomes included Full Scale IQ (FSIQ), a measure of global intellectual functioning, Verbal IQ (VIQ), a measure of verbal reasoning, and Performance IQ (PIQ), a measure of non-verbal reasoning and visual-motor coordination skills.

2.6. Covariates

We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates included child's sex and age at testing, maternal education (dichotomized as either a bachelor's degree or higher versus trade school diploma or lower), maternal race (white or not), second-hand smoke in the home (yes, no), and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME) - Revised Edition (Caldwell and Bradley, 1984). For each analysis, a covariate was retained in the final model if its p -value was < 0.20 or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10% (Kleinbaum et al., 1982). City was not included as a covariate in Model 1 because it was strongly multi-collinear with water fluoride concentration ($VIF > 20$). City was also excluded from Model 2 because fluoride intake from formula is a function of water fluoride concentration and was therefore deemed redundant.

2.7. Statistical analyses

We used linear regression to model differences in child IQ by water fluoride concentration while controlling for covariates. In our first model, we examined whether feeding status (BF or FF) modified the impact of water fluoride. In our second model, we estimated the association between fluoride intake from formula and child IQ. We controlled potential confounders by including them simultaneously with predictors.

In secondary analyses, we controlled for MUF during pregnancy in both models to account for fetal exposure. We also tested for sex-specific effects because we previously found that MUF concentration was only associated with diminished FSIQ in males (Green et al., 2019).

Regression diagnostics indicated no assumption violations

pertaining to linearity, normality, or homogeneity of variance. Specifically, QQ-plots of residuals were consistent with a normal distribution and plots of residuals against fitted values did not suggest any assumption violations. Two observations were investigated based on a plot of Cook's D that suggested they may be influential; these cases had extremely low IQ scores that were more than 2.5 standard deviations from the sample mean. In a sensitivity analyses, we re-estimated the models after removing these two observations. Finally, variance inflation factors indicated no concerns with excessive multicollinearity.

To aid interpretation, we divided all regression coefficients by 2 so that they represent the predicted IQ difference per 0.5 mg/L of fluoride in tap water or 0.5 mg fluoride from formula; 0.5 mg/L corresponds to the approximate difference between mean water fluoride level in fluoridated versus non-fluoridated regions in our sample.

3. Results

Of the 601 children who completed neurodevelopmental testing, 591 (99%) mother-child pairs completed the infant feeding questionnaire and IQ testing (BF: $n = 296$; FF: $n = 295$). Of these, 398 (67.3%) pairs reported drinking tap water, had water fluoride data and complete covariate data (BF: $n = 200$; FF: $n = 198$). The demographic characteristics of women included in the current analyses ($n = 398$) were not substantially different from the original MIREC cohort ($N = 1945$) or the subset without complete water fluoride and covariate data ($n = 203$) (Table S2, Mcknight-hanes et al., 1988).

Among the BF group, more women who lived in a fluoridated region had a bachelor's degree or higher compared with those in a non-fluoridated region (86 vs. 74%, $p = .001$) (Table 1). Compared with the FF group, women in the BF group were more educated, more likely to be married or common law, and had higher HOME scores (all $ps < 0.05$). The BF group had significantly higher FSIQ and VIQ scores relative to the FF group (Table 1; Fig. S1). Children living in a fluoridated region had a significantly lower PIQ score, but higher VIQ score, relative to children living in a non-fluoridated region (Table 1; Fig. S1).

Water fluoride concentration was correlated with MUF ($r = 0.37$, $p < .001$) and estimated fluoride intake from formula ($r = 0.79$, $p < .001$); MUF was correlated with fluoride intake from formula ($r = 0.55$, $p < .001$).

3.1. Feeding status

The mean duration of exclusive breastfeeding was 4.98 months ($SD = 3.48$); 54 (13.6%) women reported never breastfeeding, 32 (8%) reported discontinuing breastfeeding after the first three months, and 200 (50.2%) reported continuing to breastfeed at six months or longer. Water fluoride concentration did not significantly differ between the BF ($M = 0.32$ mg/L) and FF groups ($M = 0.29$ mg/L; $p = .18$).

3.2. Model 1: IQ scores and water fluoride concentration by feeding status

A 0.5 mg/L increase in water fluoride concentration was associated with a decrease of 4.4 FSIQ points (95% CI: -8.34 , -0.46 , $p = .03$) in the FF group, but it was not significantly associated with FSIQ in the BF group ($B = -1.34$, 95% CI: -5.04 , 2.38 , $p = .48$) (Table 2; Fig. 1A); the interaction between water fluoride and feeding status was not statistically significant ($p = .26$). Controlling for fetal exposure by adding MUF to the model resulted in non-significant associations between water fluoride concentration and FSIQ in both the FF ($B = -3.58$, 95% CI: -7.83 , 0.66 , $p = .098$) and BF groups ($B = -1.69$, 95% CI: -5.66 , 2.27 , $p = .40$). Removing two cases with extreme IQ scores from the models resulted in non-significant associations between water fluoride concentration and FSIQ in both groups (Table S3).

Water fluoride concentration was significantly associated with lower PIQ in the FF ($B = -9.26$, 95% CI: -13.77 , -4.76 , $p < .001$) and the BF groups ($B = -6.19$, 95% CI: -10.45 , -1.94 , $p = .004$)

Table 1
Demographic characteristics and exposure outcomes for mother-child pairs by infant feeding status.

	Breastfed ≥ 6 mo. (n = 200)		Formula-fed (n = 198)		
Characteristic	Fluoridated (n = 83)	Non-fluoridated (n = 117)	Fluoridated (n = 68)	Non-fluoridated (n = 130)	p value comparing BF and FF groups
	Mean (SD)/%	Mean (SD)/%	Mean (SD)/%	Mean (SD)/%	
Maternal characteristics					
Years of age at delivery	32.54 (3.64)	32.86 (4.79)	32.91 (4.42)	32.39 (5.11)	.73
Net household income > \$70 K	70.3	72.9	79.7	68	.88
Caucasian	88	93	88	84	.11
Maternal education					
Trade school diploma/high school	14	26*	28	42*	< .001
Bachelor's degree or higher	86	74*	72	58*	< .001
Employed at time of pregnancy	92	90	94	84*	.40
Married/common-law (at time of testing)	100	99	96	92	.001
Smoked in trimester 1	0	1.7	2.9	3.8	.17
Parity (first birth)	45	51	43	47	.61
Number of months exclusively breastfeeding	7.54 (2.95)	7.45 (2.46)	2.63 (2.08)	2.37 (2.13)	< .001
Child characteristics					
Years of age at IQ testing	3.48 (0.29)	3.34 (0.31)*	3.53 (0.28)	3.37 (0.3)*	.32
Female sex	51	53	54	47	.32
HOME total score	48.71 (3.42)	48.09 (3.86)	47.59 (4.33)	46.55 (4.76)	< .001
Second hand smoke in home	2.5	3.4	4.4	5.4	.43
Gestational age in weeks	39.22 (1.55)	39.17 (1.52)	38.68 (2.48)	39.15 (1.53)	.24
Birth weight (kg)	3.42 (0.50)	3.49 (0.46)	3.43 (0.62)	3.46 (0.52)	.75
Full Scale IQ	109.9 (12.4)	108.9 (13.6)	106.1 (15.8)	106.8 (13.5)	.03 ^a
Verbal IQ ^b	115.1 (11.3)	110.4 (12.4)*	110.9 (14.9)	107.1 (13.3)	.00 ^a
Performance IQ ^b	102.0 (15.2)	105.6 (15.8)	99.7 (15.1)	105.6 (13.4)*	.69
Exposure variables					
Water fluoride concentration (mg/L)	0.58 (0.08)	0.13 (0.06)*	0.59 (0.07)	0.13 (0.05)*	.18
% living in fluoridated region	41.5		34.3		.14
Infant fluoride intake (mg F/day)	0.12 (0.07)	0.02 (0.02)*	0.34 (0.12)	0.08 (0.04)*	< .001
MUF concentration (mg/L)	0.70 (0.39)	0.42 (0.28)*	0.64 (0.37)	0.38 (0.27)*	.07

Abbreviations: HOME = Home Observation for Measurement of the Environment; MUF = Maternal urinary fluoride, adjusted for specific gravity; SD = standard deviation.

* $p < .05$ for comparing participants in the breastfed or formula-fed group living in a fluoridated versus non-fluoridated region.

^a p -value reported for main effect of feeding status from 2×2 ANCOVA, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and water fluoridation status (fluoridated versus non-fluoridated).

^b Main effect of fluoridation status, adjusting for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), second-hand smoke status in the child's house (yes, no), and feeding status (BF vs. FF); VIQ: $p = .02$; PIQ: $p < .001$.

Table 2
Adjusted difference in IQ scores at 3–4 years of age per 0.5 mg/L water fluoride concentration and 0.5 mg infant fluoride intake from formula per day, with and without adjusting for maternal urinary fluoride (MUF).

Exposure variable	N	FSIQ B (95% CI)	N	PIQ B (95% CI)	N	VIQ B (95% CI)
Model 1						
Water FI (mg/L)	398		393		397	
Formula-fed		−4.40 (−8.34, −0.46)*		−9.26 (−13.77, −4.76)*		0.89 (−2.87, 4.65)
Breastfed		−1.34 (−5.04, 2.38)		−6.19 (−10.45, −1.94)*		3.06 (−0.49, 6.61)
Water FI (mg/L) adjusted for MUF ^a	350		345		349	
Formula-fed		−3.58 (−7.83, 0.66)		−7.93 (−12.84, −3.01)*		2.60 (−1.98, 7.16)
Breastfed		−1.69 (−5.66, 2.27)		−6.30 (−10.92, −1.68)*		4.20 (−0.06, 8.45)
Model 2						
Fluoride intake from formula	398	−2.69 (−7.38, 2.01)	393	−8.76 (−14.18, −3.34)*	397	3.08 (−1.40, 7.55)
Fluoride intake from formula adjusted for MUF ^b	350	−1.94 (−7.09, 3.21)	345	−7.62 (−13.64, −1.60)*	349	3.05 (−1.89, 7.98)

Abbreviations: FI = fluoride; MUF = maternal urinary fluoride; Regression model adjusted for maternal education (binary), maternal race (binary), child's age at IQ testing (continuous), child's sex, HOME total score (continuous), and second-hand smoke status in the child's house (yes, no).

* $p < .05$.

^a MUF was not significantly associated with FSIQ score ($B = -1.08$, 95% CI: $-1.54, 0.47$, $p = .29$), PIQ score ($B = -1.31$, 95% CI: $-3.63, 1.03$, $p = .27$), or VIQ score ($B = -0.34$, 95% CI: $-2.21, 1.59$, $p = .73$). Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for water FI is 2.41 for FSIQ, 2.41 for PIQ, and 2.40 for VIQ when MUF is entered in the model.

^b MUF is significantly associated with PIQ score ($B = -2.38$, 95% CI: $-4.62, -0.27$, $p = .04$), but not FSIQ score ($B = -1.50$, 95% CI: $-3.41, 0.43$, $p = .13$) or VIQ score ($B = -0.11$, 95% CI: $-1.94, 1.74$, $p = .91$). Note: regression coefficients represent the predicted IQ difference per 0.5 mg/L MUF; effect for both sexes is reported. Variance inflation factor (VIF) for infant fluoride intake is 1.10 for FSIQ, 1.12 for PIQ, and 1.10 for VIQ when MUF is entered in the model.

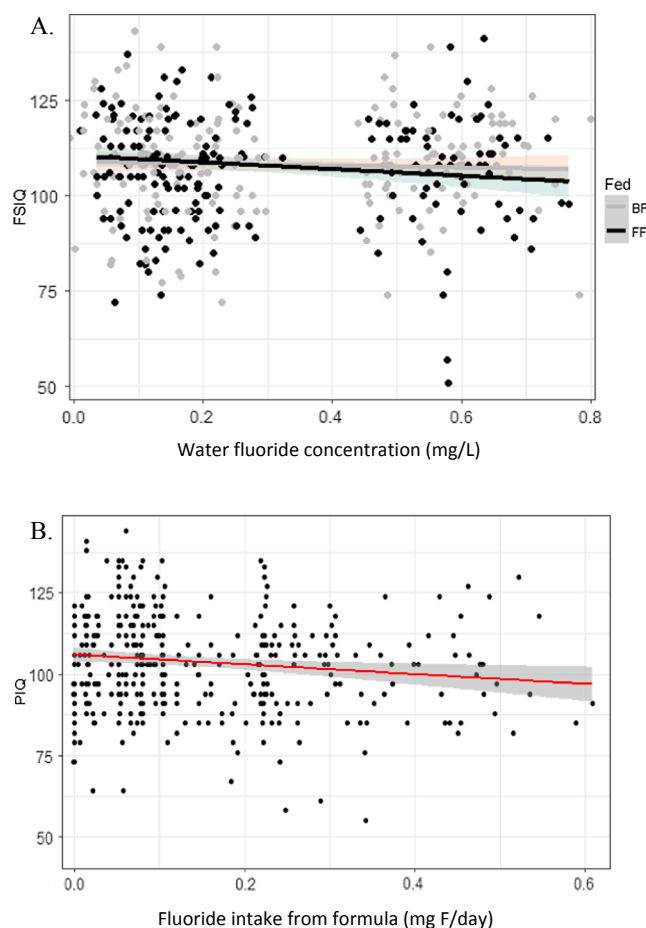


Fig. 1. A. Water fluoride concentration as a predictor of Full Scale IQ with an interaction by formula-fed (FF) vs. breastfed (BF) group. Black data points represent the FF group and grey data points represent the BF group. B. Fluoride intake from formula (mg F/day) as a predictor of Performance IQ score.

(Table 2); the interaction was not significant ($p = .26$). Controlling for MUF, water fluoride concentration remained significantly associated with PIQ in the FF ($B = -7.93$ 95% CI: $-12.84, -3.01, p = .002$) and BF groups ($B = -6.30$, 95% CI: $-10.92, -1.68, p = .008$). Likewise, the associations between water fluoride concentration and PIQ remained significant for both groups after removing two cases with extreme IQ scores (Table S3).

In contrast, water fluoride concentration was not associated with VIQ in the FF ($B = 0.89$, 95% CI: $-2.87, 4.65, p = .64$) or BF group ($B = 3.06$, 95% CI: $-0.49, 6.61, p = .09$); these associations remained non-significant after controlling for MUF (Table 2) and removing two cases with extreme IQ scores (Table S3).

3.3. Model 2: IQ scores and fluoride intake from formula

Fluoride intake from formula was not significantly associated with FSIQ ($B = -2.69$, 95% CI: $-7.38, 2.01, p = .26$) or VIQ ($B = 3.08$, 95% CI: $-1.40, 7.55, p = .18$) (Table 2). In contrast, a 0.5 mg increase in fluoride intake predicted an 8.76-point decrement in PIQ score (95% CI: $-14.18, -3.34, p = .002$; Fig. 1B). Adding MUF to the PIQ model slightly attenuated the association between fluoride intake and PIQ ($B = -7.62$, 95% CI: $-13.64, -1.60, p = .01$) (Table 2). Removing two cases with extreme IQ scores did not appreciably alter the association between fluoride intake and PIQ score, with and without adjustment for MUF (Table S3).

4. Discussion

For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 FSIQ points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among exclusively breastfed children. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became non-significant when two outliers were removed. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in PIQ in both the formula-fed (9.3-points) and the breastfed groups (6.2-points). Adjusting for fetal exposure or removing two extreme scores did not appreciably alter these results.

We observed converging results using fluoride intake from formula, which is a continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an 8.8-point decrement in PIQ; adjusting for fetal exposure using MUF attenuated the association only slightly (7.6-point decrement in PIQ). MUF was also negatively associated with PIQ (2.4-point decrement for each 0.5 mg/L increase in MUF). The fluoride intake estimate may reflect a more refined measure of exposure in infancy because it captures differences in both water fluoride level and the proportion of time each child was given formula over the first year of life. Yet, our binary classification of whether a child was exclusively breastfed for 6 months may better capture children who are most vulnerable to neurotoxic effects of fluoride because it subsets those exposed to fluoride during the early infancy period when the brain undergoes significant development (Huttenlocher and Dabholkar, 1997; Kostovic, 2006). Taken together, these findings suggest that using optimally fluoridated water (0.7 mg/L) to reconstitute infant formula may diminish the development of intellectual abilities in young children, particularly for non-verbal abilities. The findings also suggest that both prenatal and postnatal fluoride exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence. Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern (Bashash et al., 2017; Green et al., 2019).

Consistent with prior studies showing a positive effect of breastfeeding on cognition (Horta et al., 2015), children in the breastfed group had higher FSIQ and VIQ scores relative to the formula-fed group, regardless of fluoridation status (Table 1); higher education and income levels in the breastfed group likely accounts for part of this association (Walfisch et al., 2013). In contrast, the breastfed group did not differ significantly from the formula-fed group with respect to PIQ score. Children who lived in non-fluoridated regions showed higher PIQ scores than children who lived in fluoridated regions, though this difference was significant only for the formula-fed group, perhaps reflecting a higher vulnerability of nonverbal abilities to fluoride exposure in infancy.

Most studies of fluoride exposure from infant formula consumption have focused on risk for later development of dental enamel fluorosis (Brothwell and Limeback, 2003; Hong et al., 2006; Berg et al., 2011). Beyond fluorosis, the safety of fluoride exposure from infant formula has not been rigorously tested, despite warnings of overexposure (Diesendorf and Diesendorf, 1979). A recent study showed that up to 59% of infants younger than four months exceed the upper limit (0.1 mg/kg/day) (Institutes of Medicine, 1997) when optimally fluoridated water is used to reconstitute infant formula (Harriehausen et al., 2019); 33% and 14.3% of six- and nine-month old infants exceeded the upper limit threshold, respectively. Conversely, breastfed infants receive very low fluoride intake (generally less than 0.01 mg/L), even in communities with fluoridated water (Dabeka et al., 1986; Ekstrand, 1981; Fomon et al., 2000). Our estimate of fluoride intake (0.34 mg F/day) among formula-fed infants who live in a fluoridated region is an

underestimate of actual fluoride intake because we did not include fluoride from other sources, such as the fluoride found in the formula or foods; thus, the association between fluoride intake and IQ scores among formula-fed infants may be stronger than the association obtained in our analysis.

Our results, which showed that higher fluoride exposure in infancy was associated with diminished IQ scores in young children, are consistent with two longitudinal birth cohort studies. In one study involving 299 mother–child pairs living in Mexico City, there was a decrement of 3.2 IQ points in preschool aged children for every 0.5 mg/L of MUF level during pregnancy (Bashash et al., 2017). In the other study, which we conducted using the same Canadian cohort, we reported a decrement of 2.2 IQ points among preschool aged boys for every 0.5 mg/L of MUF level during pregnancy (Green et al., 2019). When MUF was included as a covariate in the current study, the association between MUF and FSIQ was not significant (see Table 2, note a). This discrepancy arises because (1) Green et al. (2019) did not include fluoride exposure in infancy as a covariate and (2) Green et al. (2019) estimated sex-specific MUF effects whereas the current study estimated an overall MUF effect.

The beneficial effects of fluoride predominantly occur at the tooth surface, after teeth have erupted (Limeback, 1999). Fluoride contributes to the prevention of dental caries primarily when it is topically applied to teeth, such as brushing with fluoridated toothpaste (Featherstone, 2001; Limeback, 1999; NRC, 2006; Pizzo et al., 2007; Warren and Levy, 2003). Because fluoride is not essential for growth and development (Scientific Committee on Health and Environmental Risks (SCHER), 2011), there is no recommended intake level of fluoride during fetal development or in the first six months of life before teeth have erupted. Accordingly, the Canadian Pediatric Society recommends administering supplemental fluoride (i.e. systemic exposure) only when primary teeth begin to erupt (American Dental Association) (at approximately 6 months) and only if the child is susceptible to high caries activity and is not exposed to other fluoride-based interventions, such as toothbrushing or water fluoridation (Godel, 2002).

The American Dental Association (Berg et al., 2011; American Dental Association, 2018) advises parents to use optimally fluoridated drinking water to reconstitute concentrate infant formulas, while being cognizant of the potential risk of mild enamel fluorosis development. This recommendation is echoed by the Centers for Disease Control and Prevention (Community Water Fluoridation. Infant Formula) as well as the U.S. Department of Health and Human Services (2015). The Canadian Dental Association (2019) recommends using water with low fluoride concentration (or ready-to-feed formula) when the fluoride level in drinking water is above the optimal level. In addition to tap water, which is reportedly used by 93% of caregivers who feed formula to infants (Brothwell and Limeback, 2003), “nursery” water (which may contain up to 0.7 mg F/L) is marketed for reconstituting formula and sold in Canada and the United States. The availability of fluoridated nursery water gives the false impression that fluoride exposure during early infancy is beneficial prior to teeth eruption.

Formula-fed infants who reside in fluoridated areas have a 70-fold higher intake of fluoride than exclusively breastfed infants (Ekstrand, 1981; Zohoori et al., 2018; United States Environmental Protection Agency, 2010). Formula-fed infants also retain more fluoride than breastfed infants (Zohoori et al., 2018; Ekstrand and Hardell, 1984) because infants have a limited capacity to excrete fluoride before renal function reaches its full capacity at about two years of age (National Research Council (NRC), 2006; Zohoori et al., 2018). Fluoride absorption also depends on the presence of other nutrients (Health Canada, 2010); when fluoride intake is exclusively from reconstituted formula, the bioavailability of fluoride is 65%, whereas a varied diet reduces fluoride absorption in tissues and bone to about 47% (Ekstrand and Ehrnebo, 1979). These factors place formula-fed infants at an even higher risk of fluoride toxicity.

Our study has some limitations. First, infant formulas vary in

fluoride content. Ready-to-use formulas typically have less fluoride than powdered formula (Dabeka and McKenzie, 1987; Fomon et al., 2000); information about formula type was only available for 100 of 198 (50.5%) participants in the formula group; of those, 75% reported using powdered formula, which is the most common type of formula used by the general population (Infant Feeding Practices Survey II; Fomon et al., 2000). Variability in fluoride content is also seen across different types of powdered formula (United States Environmental Protection Agency, 2010; Harriehausen et al., 2019; Mahvi et al., 2010). Additionally, soy-based formula reconstituted with distilled water has more fluoride (0.24–0.30 mg/L depending on whether it is ready-to-feed or concentrated) than milk-based powdered formulas (0.12–0.17 mg/L) (Harriehausen et al., 2019; Van Winkle et al., 1995). Although we lacked data on brand of formula, we have no reason to expect that use of powdered versus ready-to-feed or soy- versus milk-based formula would differ by fluoridation status. Moreover, our effects were primarily based on water fluoride content, which is the major source of fluoride (Buzalaf et al., 2001). Second, we did not have specific information on the type of water (bottled versus tap) used to reconstitute formula. However, mothers typically report using tap water for reconstituting formula (Van Winkle et al., 1995) and we only included children of women who reported drinking tap water in our analyses. Third, there is potential for non-differential misclassification of the feeding status variable because mothers may have been confused by the definition of exclusive breastfeeding on the questionnaire or the responses may have been affected by recall or response bias. As with any survey, women could be confused by the question, but given the demographic of the sample – highly educated, English speaking, and non-teenage mothers – confusion seems less likely. Fourth, our method of estimating infant fluoride intake has not been validated. Finally, children were tested between 3 and 4 years of age and we have no information regarding other possible sources of fluoride that occurred between post-weaning and the age of testing. Thus, other sources of fluoride (e.g. dental products) or more frequent brushing, might differ between participants who lived in fluoridated versus non-fluoridated communities or among those in the breastfeeding versus formula-feeding group. To control for these potential differences, we included maternal education in all models. In addition, the design of our study compares water fluoride level and IQ scores in the formula-fed children using the breast-fed children as a control.

In summary, fluoride intake among infants younger than 6 months may exceed the tolerable upper limits if they are fed exclusively with formula reconstituted with fluoridated tap water. After adjusting for fetal exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children. In the absence of any benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water or water with lower fluoride content as a formula diluent.

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Contributors statement

Dr Till conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms Green designed the study, curated the data, carried out the initial data analysis,

reviewed and revised the manuscript. Drs Flora and Hornung supervised data analysis, reviewed and revised the manuscript. Ms. Farmus assisted with data analysis, reviewed and revised the manuscript. Dr Martinez-Mier reviewed and revised the manuscript and supervised the analysis of maternal urinary fluoride. Mr Blazer collected the water fluoride data from water treatment plants and reviewed the manuscript. Drs Ayotte and Muckle assisted with initial data collection, and critically reviewed and revised the manuscript. Dr Lanphear conceptualized the study, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2019.105315>.

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Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico

Morteza Bashash,¹ Deena Thomas,² Howard Hu,¹ E. Angeles Martinez-Mier,³ Brisa N. Sanchez,² Niladri Basu,⁴ Karen E. Peterson,^{2,5,6} Adrienne S. Ettinger,² Robert Wright,⁷ Zhenzhen Zhang,² Yun Liu,² Lourdes Schnaas,⁸ Adriana Mercado-García,⁹ Martha María Téllez-Rojo,⁹ and Mauricio Hernández-Avila⁹

¹Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

²University of Michigan School of Public Health, Ann Arbor, Michigan, USA

³Indiana University School of Dentistry, Indiana University-Purdue University Indianapolis, Indianapolis, Indiana, USA

⁴Faculty of Agricultural and Environmental Sciences, McGill University, Montreal, Quebec, Canada

⁵Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan, USA

⁶Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

⁷Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁸Instituto Nacional de Perinatología, Mexico City, Mexico

⁹Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico

BACKGROUND: Some evidence suggests that fluoride may be neurotoxic to children. Few of the epidemiologic studies have been longitudinal, had individual measures of fluoride exposure, addressed the impact of prenatal exposures or involved more than 100 participants.

OBJECTIVE: Our aim was to estimate the association of prenatal exposure to fluoride with offspring neurocognitive development.

METHODS: We studied participants from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project. An ion-selective electrode technique was used to measure fluoride in archived urine samples taken from mothers during pregnancy and from their children when 6–12 y old, adjusted for urinary creatinine and specific gravity, respectively. Child intelligence was measured by the General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities at age 4 and full scale intelligence quotient (IQ) from the Wechsler Abbreviated Scale of Intelligence (WASI) at age 6–12.

RESULTS: We had complete data on 299 mother–child pairs, of whom 287 and 211 had data for the GCI and IQ analyses, respectively. Mean (SD) values for urinary fluoride in all of the mothers ($n=299$) and children with available urine samples ($n=211$) were 0.90 (0.35) mg/L and 0.82 (0.38) mg/L, respectively. In multivariate models we found that an increase in maternal urine fluoride of 0.5 mg/L (approximately the IQR) predicted 3.15 (95% CI: –5.42, –0.87) and 2.50 (95% CI: –4.12, –0.59) lower offspring GCI and IQ scores, respectively.

CONCLUSIONS: In this study, higher prenatal fluoride exposure, in the general range of exposures reported for other general population samples of pregnant women and nonpregnant adults, was associated with lower scores on tests of cognitive function in the offspring at age 4 and 6–12 y. <https://doi.org/10.1289/EHP655>

Introduction

Community water, salt, milk, and dental products have been fluoridated in varying degrees for more than 60 y to prevent dental caries, while fluoride supplementation has been recommended to prevent bone fractures (Jones et al. 2005). In addition, people may be exposed to fluoride through the consumption of naturally contaminated drinking water, dietary sources, dental products, and other sources (Doull et al. 2006). Whereas fluoride is added to drinking water [in the United States at levels of 0.7–1.2 mg/L (Doull et al. 2006)] to promote health, populations with exceptionally high exposures, often from naturally contaminated drinking water, are at risk of adverse health effects, including fluorosis.

In the United States, the U.S. Environmental Protection Agency (EPA) is responsible for establishing maximum permissible concentrations of contaminants, including fluoride, in public drinking-water systems. These standards are guidelines for restricting the amount of fluoride contamination in drinking water, not

standards for intentional drinking-water fluoridation. In 2006 the U.S. EPA asked the U.S. National Research Council (NRC) to reevaluate the existing U.S. EPA standards for fluoride contamination, including the maximum contaminant level goal (MCLG, a concentration at which no adverse health effects are expected) of 4 mg/L, to determine if the standards were adequate to protect public health (Doull et al. 2006). The committee concluded that the MCLG of 4 mg/L should be lowered because it puts children at risk of developing severe enamel fluorosis, and may be too high to prevent bone fractures caused by fluorosis (Doull et al. 2006). The Committee also noted some experimental and epidemiologic evidence suggesting that fluoride may be neurotoxic (Doull et al. 2006).

The National Toxicology Program (NTP) recently reviewed animal studies on the effects of fluoride on neurobehavioral outcomes and concluded that there was a moderate level of evidence for adverse effects of exposures during adulthood, a low level of evidence for effects of developmental exposures on learning and memory, and a need for additional research, particularly on the developmental effects of exposures consistent with those resulting from water fluoridation in the United States (Doull et al. 2006; NTP 2016). Human studies have shown a direct relationship between the serum fluoride concentrations of maternal venous blood and cord blood, indicating that the placenta is not a barrier to the passage of fluoride to the fetus (Shen and Taves, 1974). Fluoride was shown to accumulate in rat brain tissues after chronic exposures to high levels, and investigators have speculated that accumulation in the hippocampus might explain effects on learning and memory (Mullenix et al. 1995). An experimental study on mice has shown that fluoride exposure may have adverse effects on neurodevelopment, manifesting as both cognitive and behavioral abnormalities later in life (Liu et al. 2014).

Please send correspondence to M. Bashash, Dalla Lana School of Public Health, 6th floor, 155 College St., Toronto, Ontario M5R3M7 Canada. Telephone: +1-416-978-6512. Email: m.bashash@utoronto.ca. Supplemental Material is available online (<https://doi.org/10.1289/EHP655>).

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Most epidemiologic studies demonstrating associations between fluoride exposure and lower neuropsychological indicators have been conducted in populations living in regions with endemic fluorosis that are exposed to high levels of fluoride in contaminated drinking water. The epidemiologic evidence is limited, however, with most studies using an ecologic design to estimate childhood exposures based on neighborhood measurements of fluoride (e.g., drinking water levels) rather than personal exposure measures. Moreover, almost all existing studies of childhood outcomes are cross-sectional in nature, rendering them weak contributors towards causal inference.

The main objective of this study was to assess the potential impact of prenatal exposures to fluoride on cognitive function and test hypotheses related to impacts on overall cognitive function. We hypothesized that fluoride concentrations in maternal urine samples collected during pregnancy, a proxy measure of prenatal fluoride exposure, would be inversely associated with cognitive performance in the offspring children. Overall, to our knowledge, this is one of the first and largest longitudinal epidemiologic studies to exist that either address the association of early life exposure to fluoride to childhood intelligence or study the association of fluoride and cognition using individual biomarker of fluoride exposure.

Methods

This is a longitudinal birth cohort study of measurements of fluoride in the urine of pregnant mothers and their offspring (as indicators of individual prenatal and postnatal exposures to fluoride, respectively) and their association with measures of offspring cognitive performance at 4 and 6–12 y old. The institutional review boards of the National Institute of Public Health of Mexico, University of Toronto, University of Michigan, Indiana University, and Harvard T.H. Chan School of Public Health and participating clinics approved the study procedures. Participants were informed of study procedures prior to signing an informed consent required for participation in the study.

Participants

Mother–child pairs in this study were participants from the successively enrolled longitudinal birth cohort studies in Mexico City that comprise the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project. Of the four ELEMENT cohorts [that have been described elsewhere (Afeiche et al. 2011)], Cohort 1 and Cohort 2B recruited participants at birth and did not have archived maternal-pregnancy urine samples required for this analysis; they were thus excluded. Mothers for Cohort 2A ($n = 327$) and 3 ($n = 670$) were all recruited from the same three hospitals in Mexico City that serve low-to-moderate income populations. Cohort 2A was an observational study of prenatal lead exposure and neurodevelopmental outcomes in children (Hu et al. 2006). Women who were planning to become pregnant or were pregnant were recruited during May 1997–July 1999 and were considered eligible if they consented to participate; were ≤ 14 wk of gestation at the time of recruitment; planned to stay in the Mexico City study area for at least 5 y; did not report a history of psychiatric disorders, high-risk pregnancies, gestational diabetes; did not report current use of daily alcohol, illegal drugs, and continuous prescription drugs; and were not diagnosed with preeclampsia, renal disease, circulatory diseases, hypertension, and seizures during the index pregnancy.

Cohort 3 mothers were pregnant women (≤ 14 wk of gestation) recruited from 2001 to 2003 for a randomized trial of the effect of calcium supplementation during pregnancy on maternal

blood lead levels (Ettinger et al. 2009). Eligibility criteria were the same as for Cohort 2A, and 670 agreed to participate.

Exposure Assessment

By virtue of living in Mexico, individuals participating in the study have been exposed to fluoridated salt (at 250 ppm) (Secretaría-de-Salud 1995, 1996) and to varying degrees of naturally occurring fluoride in drinking water. Previous reports, based on samples taken from different urban and rural areas, indicate that natural water fluoride levels in Mexico City may range from 0.15 to 1.38 mg/L (Juárez-López et al. 2007; Martínez-Mier et al. 2005). Mean fluoride content for Mexico City's water supply is not available because fluoride is not reported as part of water quality control programs in Mexico.

Mother–child pairs with at least one archived urine sample from pregnancy and measures of neurocognitive function in the offspring were included in this study. In terms of when the archived samples were collected, the pregnant mothers were invited for assessments with the collection of samples during trimester 1 (13.6 ± 2.1 wk for Cohort 3 and 13.7 ± 3.5 wk for Cohort 2A), trimester 2 (25.1 ± 2.3 wk for Cohort 3 and 24.4 ± 2.9 wk for Cohort 2A), and trimester 3 (33.9 ± 2.2 wk for Cohort 3 and 35.0 ± 1.8 wk for Cohort 2A).

A spot (second morning void) urine sample was targeted for collection during each trimester of pregnancy of ELEMENT mothers as well as the offspring children at the time of their measurements of intelligence at 6–12 y old. The samples were collected into fluoride-free containers and immediately frozen at the field site and shipped and stored at -20°C at the Harvard T. H. Chan School of Public Health (HSPH), and then at -80°C at the University of Michigan School of Public Health (UMSPH).

A procedure for urine analysis of fluoride described elsewhere (Martínez-Mier et al. 2011) was adapted and modified for this study. The fluoride content of the urine samples was measured using ion-selective electrode-based assays. First, 3 M sulfuric acid saturated with hexamethyldisiloxane (HMDS) was added to the sample to allow fluoride to diffuse from the urine for 20–24 hr. The diffused fluoride was allowed to collect in 0.05 M of sodium hydroxide on the interior of the petri dish cover. Once the diffusion was complete, 0.25 M of acetic acid was added to the sodium hydroxide to neutralize the solution and then analyzed directly using a fluoride ion-selective electrode (Thermo Scientific Orion, Cat#13-642-265) and pH/ISE meter (Thermo Scientific Orion, Cat#21-15-001). All electrode readings (in millivolts) were calculated from a standard curve. Analyses were performed in a Class 100/1,000 clean room. Quality control measures included daily instrument calibration, procedural blanks, replicate runs, and the use of certified reference materials (Institut National de Santé Publique du Québec, Cat #s 0910 and 1007; NIST3183, Fluoride Anion Standard). Urinary fluoride concentrations were measured at the UMSPH and the Indiana University Oral Health Research Institute (OHRI) as previously described (Thomas et al. 2016). A validation study comparing measures taken by the two labs in the same samples revealed a between-lab correlation of 0.92 (Thomas et al. 2016).

There were a total of 1,484 prenatal samples measured at the UMSPH lab. All of these samples were measured in duplicate. Of these, 305 (20%) of them did not meet the quality control criteria for ion-selective electrode-based methods (i.e., $\text{RSD} < 20\%$ for samples with $\text{F level} < 0.2$ ppm or $\text{RSD} < 10\%$ when $\text{F level} > 0.2$ ppm) (Martínez-Mier et al. 2011). Of these 305, 108 had a second aliquot available and were successfully measured at the OHRI lab in Indiana (sufficient urine volume was not available for the remaining 197 samples). The OHRI lab in Indiana also measured an additional 289 samples. Of the 397

total samples measured at the OHRI lab in Indiana, 139 (35%) were measured in duplicate, for which >95% complied with the quality control criteria above; thus, all 139 values were retained. The remaining 258 (65%) were not measured in duplicate because of limitations in available urine volume, but were included in the study given the excellent quality control at the OHRI lab. In total, we ended up with 1,576 prenatal urine samples with acceptable measures of fluoride.

Of these 1,576 urine samples, 887 also had data on urinary creatinine and were associated with mother–offspring pairs who had data on the covariates of interest and GCI or IQ in the offspring. The urinary creatinine data were used to correct for variations in urine dilution at the time of measurement (Baez et al. 2014). Creatinine-adjusted urinary fluoride concentrations were obtained for each maternally derived sample by dividing the fluoride concentration (MUF) in the sample by the sample's creatinine concentration (MUC), and multiplying by the average creatinine concentration of samples available at each trimester ($MUC_{average}$) using the formula: $(MUF/MUC) \times MUC_{average}$. The values of average creatinine concentration used for the $MUC_{average}$ at each trimester were derived from the larger pool of trimester-1, -2, and -3 samples from Cohorts 2A and 3 examined in our previous report on maternal fluoride biomarker levels (Thomas et al. 2016): 100.81, 81.60, and 72.41 (mg/L), respectively. For each woman, an average of all her available creatinine-adjusted urinary fluoride concentrations during pregnancy (maximum three samples and minimum one sample) was computed and used as the exposure measure (MUF_{cr}). For children, as creatinine measurements were not available, urinary fluoride values (CUF) were corrected for specific gravity (SG) using the formula $CUF_{sg} = CUF(1.02 - 1)/(SG - 1)$ (Usuda et al. 2007).

After calculating MUF_{cr} for the 887 urine samples noted above, 10 values of MUF_{cr} were identified as extreme outliers (>3.5 SDs) and were dropped, leaving 877 measures of MUF_{cr} . These 877 measures of MUF_{cr} stemmed from 512 unique mothers. Of these 512, 71 participants had measurements from each of the three trimesters; 224 had measurements from two of the three trimesters (74, T1 and T2; 131, T1 and T3; and 19, T2 and T3); and 217 had measurements from only one of the trimesters (159, T1; 34, T2; and 24, T3).

Measurement of Outcomes

At age 4 y, neurocognitive outcomes were measured using a standardized version of McCarthy Scales of Children's Abilities (MSCA) translated into Spanish (McCarthy 1991). MSCA evaluates verbal, perceptual-performance, quantitative, memory, and motor abilities of preschool-aged children, and it has previously been successfully used in translated versions (Braun et al. 2012; Julvez et al. 2007; Kordas et al. 2011; Puertas et al. 2010). For this analysis, we focused on the General Cognitive Index (GCI), which is the standardized composite score produced by the MSCA (McCarthy 1991). For children 6–12 y old a Spanish-version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) was administered. WASI includes four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning), which provide estimates of Verbal, Performance, and Full-Scale IQ (Wechsler 1999). Both tests were administered by a team of three psychologists who were trained and supervised by an experienced developmental psychologist (L.S.). This team of three psychologists applied all of the McCarthy tests as well as the WASI-FSIQ tests. At the time of follow-up visits (age 4 and 6–12 y), each child was evaluated by one of the psychologists who was blind to the children's fluoride exposure. The inter-examiner reliability of the psychologists was

evaluated by having all three psychologists participate in assessments on a set of 30 individuals. For these 30, the inter-examiner reliability of the psychologists was evaluated by calculating the correlation in GCI scores by two of the psychologists with the scores of a third psychologist whom they observed applying the test in all three possible combinations with 10 participants for each observers–examiner pair (i.e., psychologist A (applicant) was observed by psychologist B and psychologist C; psychologist B (applicant) was observed by psychologist A and psychologist C; and psychologist C (applicant) was observed by psychologist A and psychologist B). The mean observer–examiner correlation was 0.99. All raw scores were standardized for age and sex (McCarthy 1991). Inter-examiner reliability was not examined on the WASI test.

Measurement of Covariates

Data were collected from each subject by questionnaire on maternal age (and date of birth), education, and marital status at the first pregnancy visit; on birth order, birth weight, and gestational age at delivery; and on maternal smoking at every prenatal and postnatal visit. Gestational age was estimated by registered nurses. Maternal IQ was estimated using selected subtests of the Wechsler Adult Intelligence Scale (WAIS)-Spanish (Information, Comprehension, Similarities, and Block Design), which was standardized for Mexican adults (Renteria et al. 2008; Wechsler et al. 1981). Maternal IQ was measured at the study visit 6 mo after birth or at the 12-mo visit if the earlier visit was not completed.

The quality of the children's individual home environments was assessed using an age-appropriate version of the HOME score. However, the measure was not available for all observations because it was only added to on-going cohort evaluation protocols beginning in April 2003, when a version of the HOME score instrument that is age-appropriate for children 0–5 y old was adopted, following which a version of the HOME score instrument that is age-appropriate for children ≥6 y old was adopted in September 2009 (Caldwell and Bradley 2003). Thus, we adjusted for HOME score using the measures for 0- to 5-y-old children in the subset of children who had this data in our analyses of GCI, and we adjusted for HOME score using the measures for >6-y-old children in the subset of children who had this data in our analyses of IQ.

Statistical Analyses

Univariate distributions and descriptive statistics were obtained for all exposure variables, outcome variables, and model covariates. For each variable, observations were classified as outliers if they were outside the bounds of the mean ± 3.5 SDs. Primary analyses were conducted with exposure and outcome outliers excluded. Statistical tests of bivariate associations were conducted using chi-square tests for categorical variables and analysis of variance (ANOVA) to compare the means of the outcomes or exposure within groups defined according to the distribution of each covariate. Spearman correlation coefficients were used to measure the correlation between MUF_{cr} and CUF_{sg} . Regression models were used to assess the adjusted associations between prenatal fluoride and each neurocognitive outcome separately. Generalized additive models (GAMs) were used to visualize the adjusted association between fluoride exposure and measures of intelligence [SAS statistical software (version 9.4; SAS Institute Inc.)]. Because the pattern appeared curvilinear, and because GAMs do not yield exact *p*-values for deviations from linearity, we used a Wald *p*-value of a quadratic term of fluoride exposure to test the null hypothesis that a quadratic model fit the data better

STUDY SUBJECT INCLUSION FLOWCHART

STUDY BASE (Element Cohorts mothers recruited at trimester 1 of pregnancy; i.e. prenatal data available)

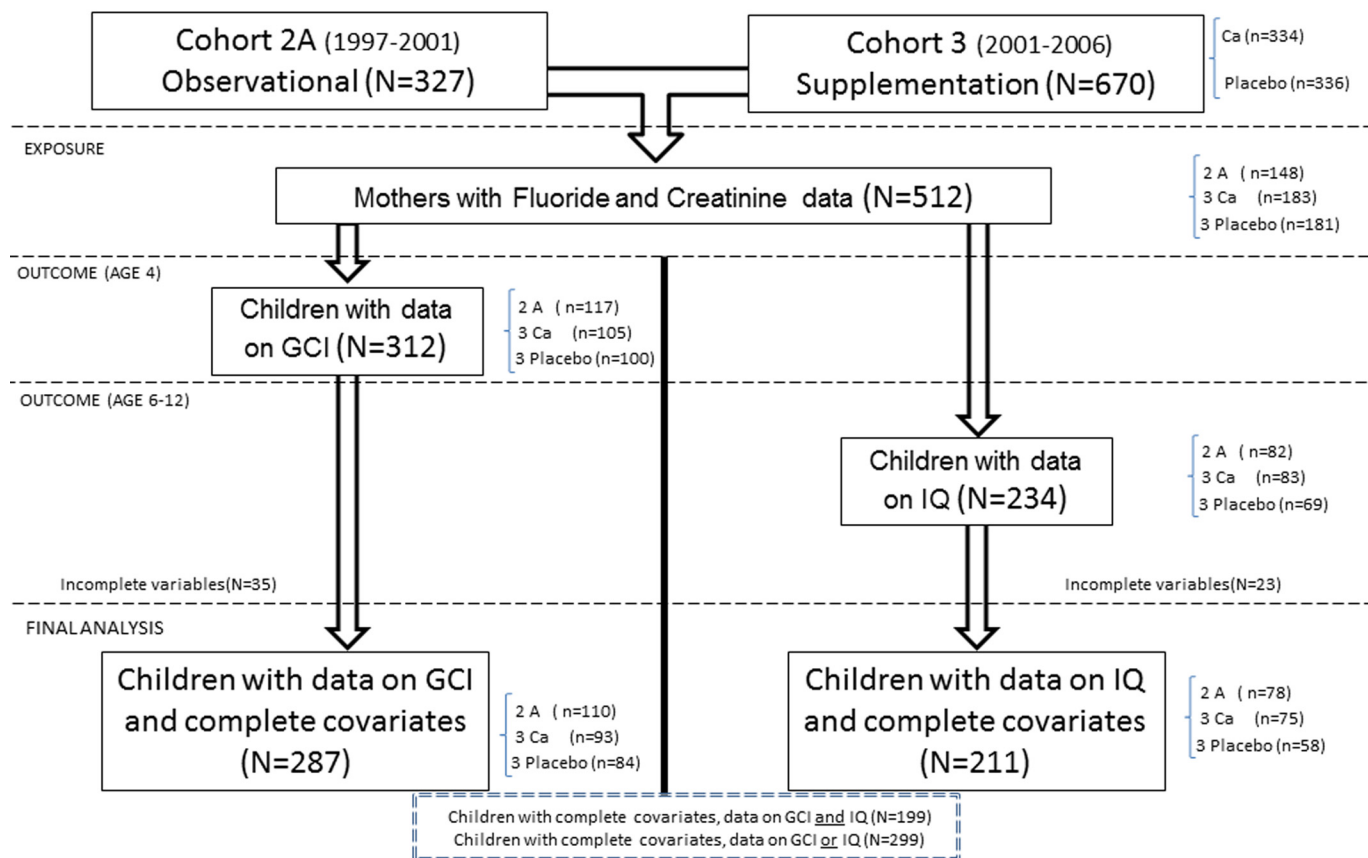


Figure 1. Flowchart describing source of mother-offspring subject pairs, fluoride and cognition study. Cohort 2A was designed as an observational birth cohort of lead toxicodynamics during pregnancy, with mothers recruited early during pregnancy from 1997 to 2001. Cohort 3 was designed as a randomized double-blind placebo-controlled trial of calcium supplements, with mothers recruited early during pregnancy from 2001 to 2006. “Ca” denotes subjects who were randomized to the calcium supplement; “placebo” denotes subjects who were randomized to the placebo. GCI is the McCarthy Scales General Cognitive Index (administered at age 4 y). IQ is the Wechsler Abbreviated Intelligence Scales Intelligence Quotient (administered at age 6–12 y and age-adjusted).

than the model assuming a linear relationship, and thus obtained a *p*-value for deviation from linearity of the fluoride–outcome associations. Residual diagnostics were used to examine other model assumptions and identify any additional potentially influential observations. Visual inspection of default studentized residual versus leverage plot from SAS PROC REG did not identify potential influential observations. Visual inspection of the histogram of the residuals did not indicate lack of normality; however, a fanning pattern in the residual versus predicted value plot indicated lack of constant variance (data not shown). Hence, robust standard errors were obtained using the “empirical” option in SAS PROC GENMOD.

Our overall strategy for selecting covariates for adjustment was to identify those that are well known to have potential associations with either fluoride exposure or cognitive outcomes and/or are typically adjusted for as potential confounders in analyses of environmental toxicants and cognition. All models were adjusted for gestational age at birth (in weeks), birthweight (kilograms), birth order (first born yes vs. no), sex, and child’s age at the time of the neurocognitive test (in years). All models were also adjusted for maternal characteristics including marital status (married vs. others), smoking history (ever-smoker vs. never-

smoker), age at delivery, IQ, and education (itself also a proxy for socioeconomic status). Finally, all models adjusted for potential cohort effects by including indicator variables denoting from which cohort (Cohort 2A, Cohort 3 + Ca supplement, and Cohort 3 -placebo) the participants came. We used 0.5 mg/L, which was close to the interquartile range of MUF_{cr} for the analyses of both GCI (IQR = 0.45) and IQ (IQR = 0.48), as a standard measure of incremental exposure. SAS statistical software (version 9.4; SAS Institute Inc.) was used for all data analyses described.

Sensitivity Analyses

Models were further adjusted for variables that relate to relatively well-known potential confounders (but for which we were missing a significant amount of data) and variables that were less-well known but possible confounders. The HOME scores were subject to sensitivity analyses because, as noted in the “Methods” section, they were not added to the subject evaluation protocols until 2003, resulting in a significantly smaller subsample of participants with this data. Models of the association between prenatal fluoride exposure (MUF_{cr}) and IQ at 6–12 y old were also adjusted for the child’s urine fluoride concentration at 6–12 y of

Table 1. Comparisons across cohorts with respect to the distributions of biomarkers of exposure to prenatal fluoride (MUF_{cr}), prenatal lead (maternal bone Pb), prenatal mercury (maternal blood Hg), and contemporaneous childhood fluoride (CUF_{sg}); and cognitive outcomes (GCI and IQ).

Analysis	Measurement	Cohort	N	Mean	SD	Min	Percentiles			Max	p-Value ^a
							25	50	75		
GCI Analysis	GCI	Cohort 3-Ca	84	96.88	14.07	50	88	96	107	124	0.997
		Cohort 3-placebo	93	96.80	13.14	50	89	96	105	125	
		Cohort 2A	110	96.95	15.46	56	88	98	110	125	
		Total ^b	287	96.88	14.28	50	88	96	107	125	
	MUF _{cr} (mg/L)	Cohort 3-Ca	84	0.92	0.41	0.28	0.60	0.84	1.14	2.36	0.57
		Cohort 3-placebo	93	0.87	0.34	0.23	0.62	0.82	1.10	2.01	
		Cohort 2A	110	0.92	0.33	0.23	0.68	0.86	1.11	2.14	
		Total ^b	287	0.90	0.36	0.23	0.65	0.84	1.11	2.36	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	62	7.30	7.37	0.05	0.75	4.40	12.93	26.22	<0.01
		Cohort 3-placebo	43	9.21	7.31	0.11	1.50	8.60	13.97	27.37	
		Cohort 2A	62	13.60	11.36	0.15	5.35	10.52	19.46	47.07	
		Total ^c	167	10.13	9.41	0.05	2.37	8.22	15.37	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	38	3.32	1.40	0.73	2.40	3.00	4.15	7.06	0.12
		Cohort 3-placebo	28	2.80	1.33	1.27	1.89	2.53	3.40	7.22	
		Cohort 2A	75	4.53	5.61	0.77	2.30	3.24	4.37	35.91	
		Total ^c	141	3.86	4.25	0.73	2.20	3.08	4.15	35.91	
IQ Analysis	IQ	Cohort 3-Ca	58	94.91	9.86	76	87	96	100	120	0.69
		Cohort 3-placebo	75	96.29	9.63	75	89	97	102	124	
		Cohort 2A	78	96.47	13.20	67	87	96	107	131	
		Total ^d	211	95.98	11.11	67	88	96	107	131	
	MUF _{cr} (mg/L)	Cohort 3-Ca	58	0.89	0.38	0.29	0.57	0.84	1.10	1.85	0.86
		Cohort 3-placebo	75	0.87	0.35	0.23	0.61	0.82	1.11	2.01	
		Cohort 2A	78	0.90	0.34	0.23	0.67	0.85	1.09	2.14	
		Total ^d	211	0.89	0.36	0.23	0.64	0.82	1.07	2.14	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	67	6.97	7.20	0.05	0.76	4.36	11.73	26.22	<0.01
		Cohort 3-placebo	48	9.07	7.42	0.11	1.00	8.49	14.41	27.37	
		Cohort 2A	62	13.60	11.36	0.15	5.35	10.52	19.46	47.07	
		Total ^e	177	9.86	9.33	0.05	2.29	7.95	15.22	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	43	3.25	1.41	0.51	2.43	2.87	4.02	7.06	0.067
		Cohort 3-placebo	31	2.66	1.36	0.78	1.81	2.40	3.26	7.22	
		Cohort 2A	75	4.53	5.61	0.77	2.30	3.24	4.37	35.91	
		Total ^e	149	3.77	4.16	0.51	2.19	2.90	4.11	35.91	
	CUF _{sg} (mg/L)	Cohort 3-Ca	71	0.84	0.4	0.31	0.53	0.78	1.12	2.8	0.29
		Cohort 3-placebo	53	0.85	0.38	0.35	0.57	0.75	1.14	1.85	
		Cohort 2A	65	0.76	0.34	0.18	0.51	0.7	0.89	1.76	
		Total ^e	189	0.82	0.38	0.18	0.54	0.73	1.01	2.8	
All available measurements	GCI	Cohort 3-Ca	133	97.32	13.67	50	88	96	107	124	0.57
		Cohort 3-placebo	149	95.99	13.07	50	88	96	106	125	
		Cohort 2A	150	97.57	14.63	56	88	99	109	131	
		Total ^f	432	96.95	13.80	50	88	96	107	131	
	IQ	Cohort 3-Ca	91	95.92	10.15	76	88	95	103	120	0.92
		Cohort 3-placebo	114	96.56	9.84	75	89	96	102	124	
		Cohort 2A	111	96.25	12.67	67	87	95	105	131	
		Total ^f	316	96.27	10.97	67	88	96	103	131	
	MUF _{cr} (mg/L)	Cohort 3-Ca	181	0.89	0.36	0.28	0.64	0.83	1.09	2.36	0.11
		Cohort 3-placebo	183	0.84	0.31	0.02	0.61	0.81	1.02	2.01	
		Cohort 2A	148	0.91	0.35	0.23	0.67	0.86	1.10	2.15	
		Total ^f	512	0.88	0.34	0.02	0.64	0.82	1.07	2.36	
	Maternal bone Pb (μg/g)	Cohort 3-Ca	97	7.07	7.26	0.01	0.83	4.36	11.78	26.22	<0.01
		Cohort 3-placebo	74	9.15	8.38	0.11	0.85	8.62	13.41	40.8	
		Cohort 2A	86	13.77	11.30	0.15	5.49	10.52	20.58	47.07	
		Total ^f	257	9.91	9.51	0.01	2.01	7.64	15.31	47.07	
	Maternal blood Hg (μg/L)	Cohort 3-Ca	55	3.03	1.41	0.51	2.12	2.77	3.62	7.06	0.09
		Cohort 3-placebo	48	2.87	2.09	0.34	1.82	2.37	3.34	13.47	
		Cohort 2A	104	4.06	4.88	0.77	2.14	3.10	4.16	35.91	
		Total ^f	207	3.51	3.70	0.34	2.07	2.80	3.79	35.91	
	CUF _{sg} (mg/L)	Cohort 3-Ca	104	0.84	0.39	0.31	0.56	0.75	1.07	2.80	0.227
		Cohort 3-placebo	84	0.90	0.46	0.35	0.58	0.75	1.09	2.89	
		Cohort 2A	96	0.79	0.34	0.18	0.53	0.73	0.92	2.11	
		Total ^f	284	0.84	0.40	0.18	0.57	0.74	1.00	2.89	

^aAnalysis of variance across cohorts.

^bTotal number of subjects included in GCI main analysis.

^cTotal number of subjects included in GCI sensitivity analysis.

^dTotal number of subjects included in IQ main analysis.

^eTotal number of subjects included in IQ sensitivity analysis.

^fTotal number of subjects with available measurements, combining Cohort 2A and Cohort 3.

Table 2. Analysis comparing subjects with and without data of interest [*n* (%) or mean $\pm$ SD] with respect to characteristics of mothers and children and sensitivity analysis covariates.

Characteristic	GCI analysis		IQ analysis	
	Included	Excluded	Included	Excluded
Total number ^a	287	710	211	786
Sex				
Female	160 (56%)	244 (47%)	116 (55%)	288 (48%)
Male	127 (44%)	275 (53%)	95 (45%)	307 (52%)
Birth order				
First child	96 (33%)	184 (35%)	93 (32%)	279 (36%)
≥ 2 nd child	191 (67%)	335 (65%)	118 (68%)	507 (65%)
Birth weight (kg)	3.11 $\pm$ 0.45	3.11 $\pm$ 0.44	3.11 $\pm$ 0.46	3.11 $\pm$ 0.43
Gestational age (wk)	38.66 $\pm$ 1.84	38.58 $\pm$ 1.68	38.56 $\pm$ 1.80	38.63 $\pm$ 1.72
Age at outcome assessment (y)	4.04 $\pm$ 0.05	4.05 $\pm$ 0.05	8.50 $\pm$ 1.31	8.83 $\pm$ 1.64
Maternal age at delivery (y)	26.78 $\pm$ 5.53	26.49 $\pm$ 5.37	27.16 $\pm$ 5.61	26.41 $\pm$ 5.36
Maternal education (y) ^b	10.63 $\pm$ 2.76	10.75 $\pm$ 3.08	10.80 $\pm$ 2.85	10.69 $\pm$ 3.03
Maternal IQ ^c	88.63 $\pm$ 12.17	89.27 $\pm$ 14.6	89.01 $\pm$ 12.45	88.27 $\pm$ 13.00
Marital status ^d	3.11 $\pm$ 0.45	3.11 $\pm$ 0.44	3.11 $\pm$ 0.46	3.11 $\pm$ 0.43
Married	201 (70%)	493 (70%)	149 (71%)	544 (69%)
Other	86 (30%)	216 (30%)	62 (29%)	240 (31%)
Maternal smoking ^e				
Ever	141 (49%)	335 (51%)	102 (48%)	374 (51%)
Never	146 (51%)	325 (49%)	109 (52%)	362 (49%)
Cohort				
Cohort 3-Ca	93 (32%)	241 (34%)	76 (36%)	259 (33%)
Cohort 3-placebo	84 (29%)	252 (36%)	59 (28%)	278 (35%)
Cohort 2A	110 (38%)	217 (31%)	78 (37%)	249 (32%)
Sensitivity Analyses				
HOME score ^f	<i>N</i> [†] = 138 35.24 $\pm$ 6.31	<i>N</i> [‡] = 87 33.23 $\pm$ 6.55	<i>N</i> [†] = 124 35.54 $\pm$ 7.46	<i>N</i> [‡] = 55 35.8 $\pm$ 7.44
SES ^g	<i>N</i> [†] = 188 6.35 $\pm$ 2.43	<i>N</i> [‡] = 110 6.94 $\pm$ 2.72	<i>N</i> [†] = 199 6.36 $\pm$ 2.41	<i>N</i> [‡] = 98 6.98 $\pm$ 2.79
Maternal Bone Pb (μ g/g) ^h	<i>N</i> [†] = 167 9.26 $\pm$ 10.55	<i>N</i> [‡] = 91 8.97 $\pm$ 10.32	<i>N</i> [†] = 177 9.02 $\pm$ 10.43	<i>N</i> [‡] = 80 9.48 $\pm$ 10.55
Maternal Blood Hg (μ g/L) ⁱ	<i>N</i> [†] = 141 3.86 $\pm$ 4.25	<i>N</i> [‡] = 67 2.76 $\pm$ 1.95	<i>N</i> [†] = 149 3.77 $\pm$ 4.16	<i>N</i> [‡] = 58 2.83 $\pm$ 2.01
CUF _{sg} ^j (mg/L)			<i>N</i> [†] = 124 35.54 $\pm$ 7.46	<i>N</i> [‡] = 55 35.8 $\pm$ 7.44

^aThe total number of subjects (*n* = 997) are all mother–offspring pairs who participated in the original Cohort 2A and Cohort 3 studies.

^bMaternal education at the time of the child's birth.

^cMaternal IQ measured at 6 mo after child's birth.

^dMother's marital status at the time of the child's birth.

^eHistory of any maternal smoking.

^fHOME score measured using the separate age-appropriate instruments pertaining to children of ≤ 5 y old; and children > 5 y old.

^gFamily socioeconomic status (SES) measured by questionnaire of family possessions at follow-up.

^hMaternal patella bone lead measured by KXRF after birth.

ⁱMaternal average blood mercury during pregnancy.

^jChildren's specific gravity–corrected urinary fluoride measured at the time of each child's IQ test (6–12 y old).

N[†] Number of subjects with measurements of MUF_{cr}, cognitive outcome, main covariates, and sensitivity covariates (they are included in the sensitivity model).

N[‡] Number of subjects with measurements of sensitivity covariates, but missing data on exposure, outcomes, or main covariates (they are excluded from the sensitivity model).

age (CUF_{sg}), a measure that was collected in a significantly smaller subset of individuals, to evaluate the potential role of contemporaneous exposure. Associations between prenatal fluoride exposure (MUF_{cr}) and GCI at 4 y old could not be adjusted for contemporaneous fluoride exposure because urine samples were not collected from children when the MSCA (from which the GCI is derived) was administered. Maternal bone lead measured by a 109-Cd K-X-ray fluorescence (KXRF) instrument at 1 mo postpartum, a proxy for lead exposure from mobilized maternal bone lead stores during pregnancy (Hu et al. 2006), was included in the model to test for the possible confounding effect of lead exposure during pregnancy. We focused on the subset of women who had patella bone lead values because these were found to be most influential on our previous prospective study of offspring cognition (Gomaa et al. 2002). Average maternal mercury level during pregnancy was also tested for being a potential confounder (Grandjean and Herz 2011). Mercury was measured as total mercury content in the subsample of women who had samples of archived whole blood samples taken during pregnancy

with sufficient volume to be analyzed using a Direct Mercury Analyzer 80 (DMA-80, Milestone Inc., Shelton, CT, USA) as previously described (Basu et al. 2014).

To address the potential confounding effect of socioeconomic status (SES) we conducted sensitivity analyses that adjusted our model for SES (family possession score). The socioeconomic questionnaire asked about the availability of certain items and assets in the home. Point values were assigned to each item, and SES was calculated based on the sum of the points across all items (Huang et al. 2016). Given that the calcium intervention theoretically could have modified the impact of fluoride, in examining our results, we repeated the analyses with and without the Cohort 3 participants who were randomized to the calcium intervention to omit any potential confounding effect of this intervention. Another sensitivity test was performed to examine the potential effect of the psychologist who performed the WASI test by including tester in the regression model. The information about psychologists who performed the WASI was available for 75% of participants, as recording this data was

Table 3. Distributions of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and offspring cognitive scores across categories of main covariates.

Covariate	GCI Analysis					IQ Analysis				
	<i>n</i>	MUF _{cr} ^a	<i>p</i> -Value	GCI (Age 4)	<i>p</i> -Value	<i>n</i>	MUF _{cr} ^a	<i>p</i> -Value	IQ (Age 6–12)	<i>p</i> -Value
Mothers										
Age										
≥25 y	123	0.88 ± 0.36	0.45	96.22 ± 14.12	0.50	88	0.89 ± 0.37	0.98	95.75 ± 11.64	0.80
<25 y	164	0.92 ± 0.36		97.37 ± 14.43		123	0.89 ± 0.35		96.15 ± 10.76	
Education										
<12 y	153	0.91 ± 0.4	0.92	94.22 ± 14.23	0.001	111	0.87 ± 0.37	0.53	93.09 ± 10.54	<0.001
12 y	97	0.89 ± 0.34		98.56 ± 14.46		70	0.93 ± 0.35		98.29 ± 10.72	
>12 y	37	0.89 ± 0.42		103.49 ± 11.21		30	0.85 ± 0.31		101.3 ± 11.16	
Marital status										
Married	201	0.90 ± 0.37	0.81	96.40 ± 14.46	0.39	62	0.90 ± 0.35	0.79	96.55 ± 11.06	0.63
Other	86	0.91 ± 0.33		98.00 ± 13.88		149	0.88 ± 0.36		95.74 ± 11.16	
Smoking										
Ever smoker	141	0.90 ± 0.36	0.80	97.77 ± 13.9	0.30	102	0.90 ± 0.36	0.56	97.21 ± 10.7	0.12
Nonsmoker	146	0.91 ± 0.35		96.01 ± 14.63		109	0.87 ± 0.35		94.83 ± 11.41	
HOME score^b										
Mid-low ≤30	49	0.88 ± 0.37	0.47	90.73 ± 13.36	<0.001	32	0.87 ± 0.36	0.85	89.88 ± 8.45	0.011
High >30	137	0.92 ± 0.38		99.29 ± 14.61		92	0.88 ± 0.38		99.05 ± 11.65	
Maternal IQ										
Mid-low ≤85	116	0.95 ± 0.35	0.09	93.16 ± 15.04	<0.001	86	0.92 ± 0.36	0.23	91.26 ± 9.72	<0.001
High >85	171	0.87 ± 0.36		99.4 ± 13.21		125	0.86 ± 0.35		99.23 ± 10.87	
Children										
Sex										
Boy	127	0.94 ± 0.36	0.09	93.93 ± 13.98	0.002	95	0.96 ± 0.38	0.008	96.82 ± 12.02	0.32
Girl	160	0.87 ± 0.36		99.22 ± 14.12		116	0.83 ± 0.32		95.29 ± 10.31	
Birthweight										
≥3.5 kg	241	0.91 ± 0.36	0.57	96.52 ± 14.36	0.33	201	0.89 ± 0.36	0.88	95.66 ± 11.29	0.58
<3.5 kg	46	0.87 ± 0.35		98.76 ± 13.88		10	0.88 ± 0.34		97.38 ± 9.42	
Gestational age										
≤39 wk	192	0.90 ± 0.35	0.90	96.66 ± 14.23	716	146	0.89 ± 0.36	0.712	95.71 ± 11.62	0.65
>39 wk	95	0.90 ± 0.37		97.32 ± 14.46		65	0.88 ± 0.34		96.58 ± 9.91	
First child										
Yes	96	0.91 ± 0.38	0.75	99.97 ± 12.87	0.009	68	0.88 ± 0.36	0.91	97.00 ± 11.00	0.36
No	191	0.90 ± 0.35		95.32 ± 14.73		143	0.89 ± 0.36		95.50 ± 11.17	
CUF_{sg}^c										
≥0.80 mg/L						112	0.86 ± 0.32	0.49	96.80 ± 11.16	0.37
<0.80 mg/L						77	0.90 ± 0.38		95.37 ± 10.31	

^aMaternal creatinine-adjusted urinary fluoride (mg/L).^bHome Observation for the Measurement of the Environment (HOME) score, measured using the separate age-appropriate instruments pertaining to children of ≤5 y old; and children >5 y old.^cChild contemporaneous specific gravity-adjusted urinary fluoride (available at the time of each child's IQ test).

added later to the study protocol. We also re-ran models with exposure outliers included as a sensitivity step. Finally, we ran models that focused on the cross-sectional relationship between children's exposure to fluoride (reflected by CUF_{sg}) and IQ score, unadjusted; adjusting for the main covariates of interest; and adjusting for prenatal exposure (MUF_{cr}) as well as the covariates of interest.

Results

Flow of Participants

Of the 997 total mothers from two cohorts evaluated, 971 were eligible after removing mothers <18 y old. Of these 971, 825 had enough urine sample volume to measure fluoride in at least one trimester urine sample, and of these 825 participants, 515 participants had urine samples with previously measured creatinine values, enabling calculation of creatinine-adjusted urinary fluoride (MUF_{cr}) concentrations. Of these 515, 3 participants were excluded based on the 10 extreme outlier values identified for MUF_{cr} (see the "Methods" section, "Exposure Assessment" subsection) and not having any other MUF_{cr} values to remain in the analysis. Thus, we had a total of 512 participants (mothers) with at least one value of MUF_{cr} for our analyses (Figure 1).

Of these 512 mothers, 312 had offspring with outcome data at age 4 (i.e., GCI), and 234 had offspring with outcome data at age

6–12 (i.e., IQ). Of these, complete data on all the covariates of main interest (as specified in the "Methods" section) were available on 287 mother–child pairs for the GCI analysis and 211 mother–child pairs for the IQ analysis. A total of 299 mother–child pairs had data on either GCI or IQ, and 199 mother–child pairs had data on both GCI and IQ (Figure 1).

Number of Exposure Measures per Subject

In terms of repeated measures of MUF_{cr} across trimesters, of the 287 participants with data on GCI outcomes; 25 participants had MUF_{cr} data for all three trimesters (11 from Cohort 2A and 14 from Cohort 3), 121 participants had MUF_{cr} data from two trimesters (48 from Cohort 2A and 73 from Cohort 3), and 141 participants had MUF_{cr} data from one trimester (51 from Cohort 2A and 90 from Cohort 3). Of the 211 participants with data on IQ outcomes, 10 participants had MUF_{cr} data for all three trimesters (6 from Cohort 2A and 4 from Cohort 3), 82 participants had data from two trimesters (32 from Cohort 2A and 50 from Cohort 3), and 119 participants had data from one trimester (40 from Cohort 2A and 79 from Cohort 3).

Comparisons across the Cohorts

In terms of the mother–child pairs who had data on all covariates as well as data on either GCI or IQ (*n* = 299), the mean (SD)

Table 4. Multivariate regression models: unadjusted and adjusted differences in GCI and IQ per 0.5 mg/L higher maternal creatinine-adjusted urinary fluoride (MUF_{cr}).

Estimate	GCI			IQ		
	<i>n</i>	β (95%CI)	<i>p</i> -Value	<i>n</i>	$\beta \pm S.E$ (95%CI)	<i>p</i> -Value
Unadjusted	287	−3.76 (−6.32, −1.19)	<0.01	211	−2.37 (−4.45, −0.29)	0.03
model A ^a	287	−3.15 (−5.42, −0.87)	0.01	211	−2.50 (−4.12, −0.59)	0.01
Model A −HOME	138	−3.63 (−6.48, −0.78)	<0.01	124	−2.36 (−4.48, −0.24)	0.03
Model A + HOME	138	−3.76 (−7.08, −0.45)	0.03	124	−2.49 (−4.65, −0.33)	0.02
Model A −CUF _{sg}				189	−1.79 (−3.80, 0.22)	0.08
Model A + CUF _{sg}				189	−1.73 (−3.75, 0.29)	0.09
Model A −SES	188	−4.55 (−7.23, −1.88)	0.01	199	−2.10 (−4.02, −0.18)	0.03
Model A + SES	188	−4.45 (−7.08, −1.81)	0.01	199	−2.10 (−4.06, −0.15)	0.04
Model A −Pb	167	−5.57 (−8.48, −2.66)	<0.01	177	−3.21 (−5.17, −1.24)	<0.01
Model A + Pb	167	−5.63 (−8.53, −2.72)	<0.01	177	−3.22 (−5.18, −1.25)	<0.01
Model A −Hg	141	−7.13 (−10.26, −4.01)	<0.01	149	−4.59 (−7.00, −2.17)	<0.01
Model A + Hg	141	−7.03 (−10.19, −3.88)	<0.01	149	−4.58 (−6.99, −2.16)	<0.01
Model A −Ca	194	−3.67 (−6.57, −0.77)	0.01	136	−3.23 (−5.88, −0.57)	0.02

^aCoefficients from linear regression models adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked during the pregnancy vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Model A−HOME, model A for subset of cases who have data on Home Observation for the Measurement of the Environment (HOME) scores (but the model did not include HOME score). Model A + HOME, model A for subset of cases with HOME score, adjusted for HOME score. Model A −CUF_{sg}, model A for subset of cases who have data on child contemporaneous specific gravity-adjusted urinary fluoride CUF_{sg} (but the model did not include CUF_{sg}). Model A + CUF_{sg}, model A for subset of cases with CUF_{sg}, adjusted for CUF_{sg}. Model A −SES, model A for subset of cases who have data on socioeconomic status (family possession measured by questionnaire of family possessions) (but the model did not include SES). Model A + SES, model A for subset of cases with SES data, adjusted for SES. Model A−Pb, model A for subset of cases who have data on maternal bone lead (but the model did not include maternal bone lead). Model A + Pb, model A for subset of cases with data on maternal bone lead, adjusted for maternal bone lead. Model A −Hg, model A for subset of cases who have data on maternal blood mercury (but the model did not include maternal blood mercury). Model A + Hg, model A for subset of cases who have data on maternal blood mercury, adjusted for maternal blood mercury. Model A −Ca, model A for subset of cases who did not receive the Ca supplement (they received the placebo).

values of creatinine-corrected urinary fluoride for the mothers was 0.90 (0.36) mg/L. The distributions of the urinary fluoride, outcomes (GCI and IQ), and additional exposure variables examined in our sensitivity analyses (maternal bone lead, maternal blood mercury, and children's contemporaneous urinary fluoride) across the three cohort strata (Cohort 3-Calcium, Cohort 3-placebo, and Cohort 2A) and all strata combined are shown in Table 1 for the mother-child pairs who had data for the GCI outcome ($n=287$) and the IQ outcome ($n=211$). The distributions showed little variation across the cohort strata except for bone lead and possibly blood mercury, for which, in comparison with Cohort 3, Cohort 2A clearly had higher mean bone lead levels ($p < 0.001$) and possibly higher blood mercury levels ($p = 0.067$). The mean (SD) values of specific gravity-corrected urinary fluoride for the children who had these measures (only available for those children who had IQ; $n = 189$) were 0.82 (0.38) mg/L.

In terms of the comparability of the participants across Cohort 2A and Cohort 3 with respect to our covariates, the distribution of the covariates was very similar with the exception of age of the offspring when IQ was measured, for which the mean ages were 7.6 and 10.0 y, respectively; and birth weight in the GCI analysis, for which Cohort 3 participants were slightly heavier than Cohort 2 participants (see Table S1).

GCI versus IQ Scores

There was a significant correlation between GCI at 4 y and IQ at 6–12 y old (Spearman $r = 0.55$; $p < 0.01$). There was no significant correlation between prenatal MUF_{cr} and offspring CUF_{sg} (Spearman $r = 0.54$, $p = 0.44$).

Comparisons of Participants in Relation to Missing Data

In comparing the participants who were included for the GCI and IQ analyses with the participants who were not included (based on data missing on GCI, IQ or other covariates), the distribution of covariates were similar except for sex, for which the proportion of females was somewhat higher in the included versus excluded group for both the GCI and IQ analyses (Table 2).

In terms of the sensitivity analyses, for each sensitivity variable of interest, we compared participants who had data on our exposures, outcomes, covariates, and the sensitivity variable of interest (and were thus included in the sensitivity analysis) versus participants who had data on the sensitivity variable of interest but were missing data on the exposure, outcomes, and/or covariates of interest (and were thus excluded from the sensitivity analysis; Table 2). It can be seen that for each sensitivity analysis, most of the participants with data on the sensitivity variable of interest also had data on the exposures, outcomes, and covariates and were therefore included in the sensitivity analysis. In addition, the distributions appeared to be similar comparing those included with those excluded in each sensitivity analysis (means were within 10% of each other), with the exception of maternal blood Hg, for which the mean levels for those included were 28.5% and 24.9% higher than the mean levels for those excluded in the GCI and IQ analyses, respectively.

Comparisons of GCI and IQ across Covariates

Table 3 shows mean and SD values for MUF_{cr} and offspring cognitive scores across categories of the covariates. In the participants with GCI data, the offspring cognitive scores were higher among mothers with higher levels of education, measured IQ, and HOME scores for both analyses; and scores were higher among first children and girls. In the IQ analysis a statistically significant difference was observed in MUF_{cr} as a function of child sex. No significant differences in MUF_{cr} values across levels of other covariates were observed. A modest difference (not statistically significant), was observed in MUF_{cr} as a function of maternal IQ ($p = 0.09$), and MUF_{cr} as a function of child sex ($p = 0.09$). Among other co-variables there were significant differences in age ($p < 0.01$) in both analyses.

Regression Models of GCI

Before adjustment, a 0.5 mg/L increase in MUF_{cr} was negatively associated with GCI at 4 y old [mean score −3.76; 95% confidence interval (CI): −6.32, −1.19] (Table 4). The association was somewhat attenuated after adjusting for the main covariates

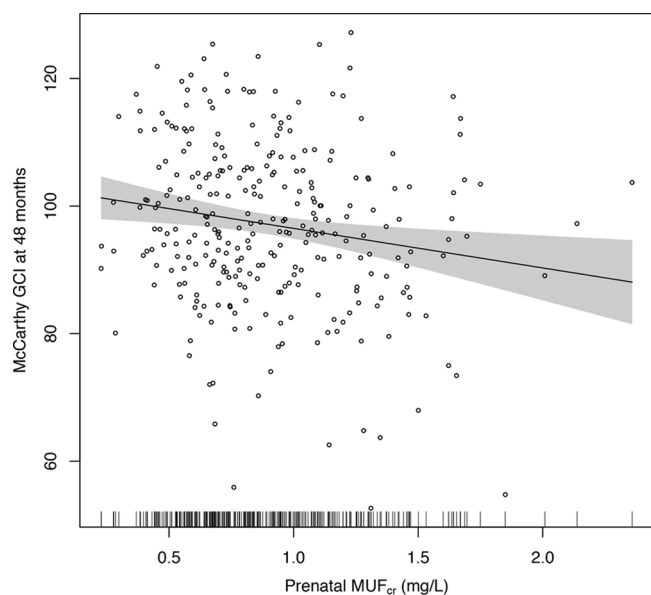


Figure 2. Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and General Cognitive Index (GCI) scores in children at age 4 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Shaded area is 95% confidence interval. Short vertical bars on the x-axis reflect the density of the urinary fluoride measures. Individual data points are individual observations, $n = 287$.

(model A, -3.15 ; 95% CI: -5.42 , -0.87). The smooth plot of the association between GCI and maternal prenatal urinary fluoride from an adjusted GAM model suggested a linear relation over the exposure distribution (Figure 2).

Regression Models of IQ

A 0.5 mg/L increase in prenatal fluoride was also negatively associated with IQ at age 6–12 y based on both unadjusted (-2.37 ; 95% CI: -4.45 , -0.29) and adjusted models (-2.50 ; 95% CI: -4.12 , -0.59) (Table 4). However, estimates from the adjusted GAM model suggest a nonlinear relation, with no clear association between IQ scores and values below approximately 0.8 mg/L, and a negative association above this value (Figure 3A). There was a nonsignificant improvement in the fit of the model when a quadratic term was added to the linear model ($p = 0.10$).

Sensitivity Analyses

In sensitivity analyses, adjustment for HOME score increased the magnitude of the association between MUF_{cr} and GCI, though the difference was less pronounced when associations with and without adjustment for HOME score were both estimated after restricting the model to the subset of 138 children with HOME score data (Table 4). The association of IQ scores with MUF_{cr} did not substantially change after adding HOME score to the model (Table 4).

The association between MUF_{cr} and IQ was attenuated slightly after adjusting for contemporaneous children's urinary fluoride (CUF_{sg}) and comparing estimates with $[-1.73$ (95% CI: -3.75 , 0.29)] and without $[-1.94$ (95% CI: -4.15 , 0.26)] adjustment for CUF_{sg} among the 189 children with this data (Table 4). In addition, the evidence of nonlinearity was more pronounced, with no clear evidence of an association for $MUF_{cr} < 1.0$ mg/L

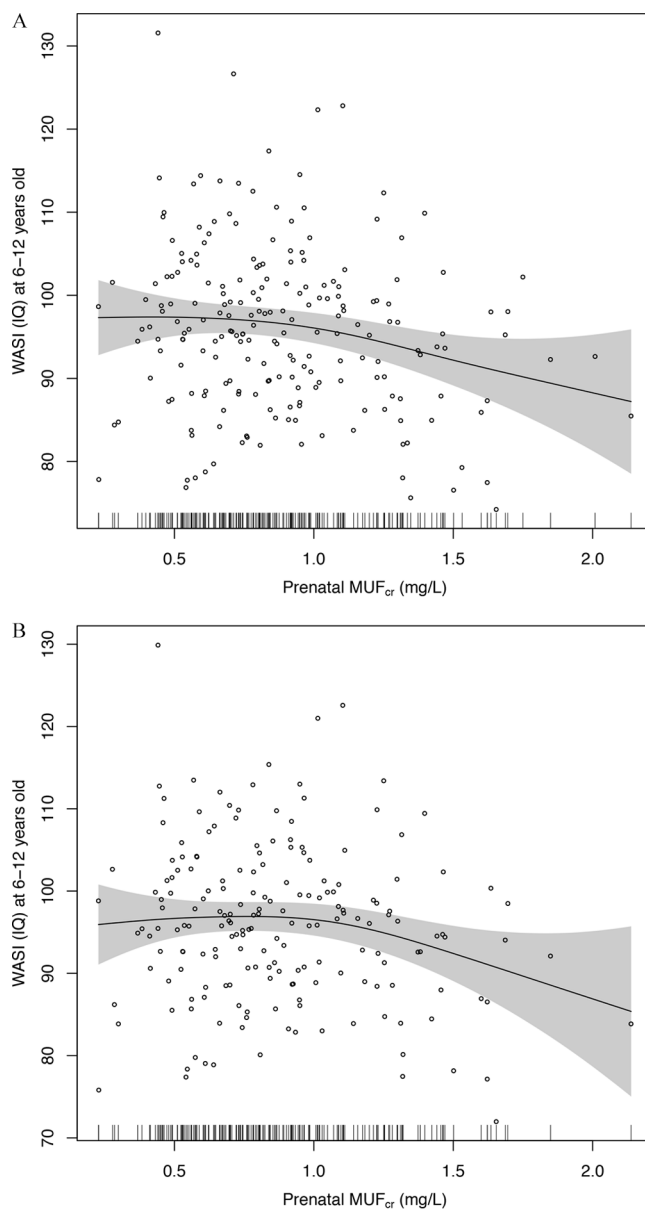


Figure 3. (A) Adjusted association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and children's IQ at age 6–12 y. Adjusted for gestational age, weight at birth, sex, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Short vertical bars on the x-axis reflect the density of the urinary fluoride measures. Individual data points are individual observation, $n = 211$. (B) Association of maternal creatinine-adjusted urinary fluoride (MUF_{cr}) and children's IQ at age 6–12 y, adjusted for specific gravity-adjusted child urinary fluoride (CUF_{sg}). Adjusted for gestational age, weight at birth, sex, parity (being the first child), age and CUF_{sg} at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. others), age at delivery, IQ, education, and cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A). Shaded area is 95% confidence interval. Short vertical bars on the x-axis reflect the density of the urinary fluoride measures. Individual data points are individual observation, $n = 189$.

based on the GAM model (Figure 3B), and a significant improvement in model fit when a quadratic term was added to the linear regression model ($p = 0.01$).

When we restricted models to subsets of children with available data for each additional covariate, there was little difference

between adjusted and unadjusted associations between MUF_{cr} and GCI or IQ when socioeconomic status (family possession), maternal bone lead, and blood mercury, were added to models (Table 4). However, the effect estimates associated with MUF_{cr} for these analyses appear to be higher in the subsets with available data for these variables.

Adding tester (psychologist who performed WASI) in the model did not substantially change the results (data not shown). In the sensitivity analyses in which we excluded Cohort 3 participants who received the calcium supplement, we continued to observe a negative association between MUF_{cr} and GCI [0.5 mg/L increase in MUF_{cr} associated with 3.67 lower GCI (95% CI: -6.57, -0.77), *n* = 194]; and between MUF_{cr} and IQ [0.5 mg/L increase in MUF_{cr} associated with 3.23-lower IQ (95% CI: -5.88, -0.57), *n* = 136].

In sensitivity analyses in which we re-ran models that included the 10 outliers with respect to fluoride exposure (for each of seven participants already in our models, an additional value of MUF_{cr} [from a different trimester]; for three participants, a value of MUF_{cr} that then allowed the participants to be added to our models), the results did not change in any meaningful way (data not shown). There were no outliers with respect to cognitive outcomes.

Independent Influence of Child Fluoride Exposure

Finally, in models that focused on the cross-sectional relationship between children's exposure to fluoride (reflected by their specific gravity-adjusted urinary fluoride levels) and IQ score and that contained the main covariates of interest, there was not a clear, statistically significant association between contemporaneous children's urinary fluoride (CUF_{sg}) and IQ either unadjusted or adjusting for MUF_{cr}. A 0.5 mg/L increase in CUF_{sg} was associated with a 0.89 lower IQ (95% CI: -2.63, 0.85) when not adjusting for MUF_{cr}; and 0.77-lower IQ (95% CI: -2.53, 0.99), adjusting for MUF_{cr} (*n* = 189).

Discussion

In our study population of Mexican women and children, which accounted for two of the three cohorts included in the ELEMENT study, higher prenatal exposure to fluoride (as indicated by average creatinine-adjusted maternal urinary fluoride concentrations during pregnancy) was associated with lower GCI scores in children at approximately 4 y old, and with lower Full-Scale IQ scores at 6–12 y old. Estimates from adjusted linear regression models suggest that mean GCI and IQ scores were about 3 and 2.5 points lower in association with a 0.5 mg/L increase in prenatal exposure, respectively. The associations with GCI appeared to be linear across the range of prenatal exposures, but there was some evidence that associations with IQ may have been limited to exposures above 0.8 mg/L. In general, the negative associations persisted in sensitivity analyses with further adjustment for other potential confounders, though the results of sensitivity analyses were based on subsets of the population with available data.

Overall, our results are somewhat consistent with the ecological studies suggesting children who live in areas with high fluoride exposure (ranging from 0.88 to 11.0 mg/L fluoride in water, when reported) have lower IQ scores than those who live in low-exposure or control areas (ranging from 0.20 to 1.0 mg/L fluoride in water) (Choi et al. 2012) and with results of a pilot study of 51 children (mean age 7 y) from southern Sichuan, China, that reported that children with moderate or severe dental fluorosis (60% of the study population) had lower WISC-IV digit span scores than other children (Choi et al. 2015). A distinction is that

our study, which was longitudinal with repeated measures of exposure beginning in the prenatal period, found associations with respect to prenatal fluoride exposures.

To our knowledge, the only other study that is similar to ours was only recently published. Valdez Jiménez et al. (2017) studied the association of prenatal maternal urinary fluoride levels (not corrected for dilution) and scores on the Bayley Scales of Infant Development II among 65 children evaluated at age 3–15 mo (average of 8 mo). The mothers in their study had urinary fluoride levels of which the means at each of the three trimesters of pregnancy (1.9, 2.0, 2.7 mg/L) were higher than the mean MUF_{cr} in our participants (0.88 mg/L) (Valdez Jiménez et al. 2017). These levels of exposure were found to be associated with statistically significantly lower scores on the Bayley Scales' Mental Development Index (MDI) score after adjusting for gestational age, age of child, a marginality index, and type of drinking water (Valdez Jiménez et al. 2017). By comparison, our study had much longer periods of follow-up and larger sample sizes, controlled for a much larger set of covariates and sensitivity variables, and used creatinine-corrected urinary fluoride measures (which, by adjusting for urinary dilution effects, provides a more reliable measure of internal fluoride exposure).

With respect to understanding the generalizability of our findings to other populations, there are very few studies that measured prenatal fluoride levels among women derived from population-based samples. Gedalia et al. (1959) measured urinary fluoride in multiple samples collected from each of 117 healthy pregnant women living in Jerusalem, where fluoride in the water was approximate 0.50 mg/L, and reported mean levels per person that ranged from 0.29 to 0.53 mg/L. However, these analysis were not conducted utilizing modern analytical techniques. In a study of 31 pregnant women living in Poland, Opydo-Szymaczek and Borysewicz-Lewicka (2005) measured urinary fluoride in healthy pregnant women patients of a maternity hospital in Poland, where fluoride in the water ranged from 0.4 to 0.8 mg/L, and found a mean level of 0.65 mg/L for women in their 28th week of pregnancy, 0.84 mg/L in their 33rd week, and 1.30 mg/L in healthy non-pregnant women of similar age. This would suggest that the mothers in our study, who had a mean MUF_{cr} value of 0.90 mg/L, had fluoride exposures slightly higher than prior-mentioned populations.

In terms of comparing our findings with other studies of fluoride (using urinary fluoride as a biomarkers of exposure) and intelligence (i.e., those not involving prenatal exposures), of the 27 epidemiologic studies on fluoride and IQ reviewed by Choi et al. in their 2012 meta-analysis, only 2 had measures of urinary fluoride. Both were of urinary fluoride measures in children (not pregnant mothers), and neither corrected for dilution (either by correcting for urinary creatinine or specific gravity). Of these two, in comparison with the urinary fluoride levels of both our mothers (0.88 mg/L) and our children (0.82 mg/L), the mean levels of children's urinary fluoride were higher in the non-fluorosis (1.02 mg/L) and high-fluorosis (2.69 mg/L) groups found by Li et al. (1995) as well as the control (1.5 mg/L) and high-fluorosis (5.1 mg/L) groups described by Wang et al. (2007).

Among the limitations of our study are that we measured fluoride in spot (second morning void) urine samples instead of 24-hr urine collections. However, others have noted a close relationship between the fluoride concentrations of early morning samples and 24-hr specimens (Watanabe et al. 1994; Zohouri et al. 2006). Another limitation relates to the potential differences in the distribution of covariates over our study cohorts, raising the issue of potential bias. In the analyses we conducted across cohorts, we saw that, in comparison with Cohort 3, Cohort 2A clearly had

higher mean bone lead levels ($p < 0.001$) and possibly higher blood mercury levels ($p = 0.067$). However, we saw no other differences and the differences in these measures have a clear likely explanation: Cohort 2A had bone lead levels measured in 1997–2001 and Cohort 3 had bone lead levels measured in 2001–2005. Given that environmental lead and mercury exposures were steadily decreasing during this time interval (due to the phase-out of lead from gasoline), this difference likely relates to an exposure–time–cohort effect. We do not anticipate that this phenomenon would have introduced a bias in our analyses of fluoride and cognition controlling for bone lead.

Another limitation relates to the missing data that pertain to our covariate and sensitivity variables. In the comparisons of participants in relation to missing data (Table 2A,B), the proportion of females was somewhat higher in the included versus excluded group for both the GCI and IQ analyses, and the mean levels of maternal blood Hg for those included were 28.5% and 24.9% higher than the mean levels for those excluded in the GCI and IQ analyses, respectively. We also note that the coefficients for the associations between fluoride on cognition varied substantially in some of the sensitivity analyses, particularly with respect to the subgroups of participants who have data on SES, lead exposure, and mercury exposure (of which, for the latter, the effect estimates almost doubled). We do not have a ready explanation for this phenomenon, given that there is no obvious way that each of the selection factors governing which mothers had these measurements (discussed above) could have influenced the fluoride–cognition relationship. Nevertheless, it is not possible to entirely rule out residual confounding or in the population as a whole (that might have been detected had we had full data on larger sample sizes) or bias (should the subpopulations that had the data for analysis have a different fluoride–cognition relationship than those participants who were excluded from the analyses).

Other limitations include the lack of information about iodine in salt, which could modify associations between fluoride and cognition; the lack of data on fluoride content in water given that determination of fluoride content is not reported as part of the water quality monitoring programs in Mexico; and the lack of information on other environmental neurotoxicants such as arsenic. We are not aware of evidence suggesting our populations are exposed to significant levels of arsenic or other known neurotoxicants; nevertheless, we cannot rule out the potential for uncontrolled confounding due to other factors, including diet, that may affect urinary fluoride excretion and that may be related to cognition.

Another potential limitation is that we adjusted maternal urinary fluoride levels based on urinary creatinine, whereas we adjusted children's urinary fluoride levels based on urinary specific gravity; however, these two methods are almost equivalent in their ability to account for urinary dilution. We also had no data to assess the inter-examiner reliability of the testers administering the WASI test; however, the excellent reliability of these same testers in administering the McCarthy tests provides some reassurance that the WASI tests were conducted in a consistent manner.

Finally, our ability to extrapolate our results to how exposures may impact on the general population is limited given the lack of data on fluoride pharmacokinetics during pregnancy. There are no reference values for urinary fluoride in pregnant women in the United States. The Centers for Disease Control and Prevention has not included fluoride as one of the population exposures measured in urine or blood samples in its nationally representative sampling. The WHO suggests a reference value of 1 mg/L for healthy adults when monitoring renal fluoride excretion in

community preventive programs (Marthaler 1999). As part of the NRC's review of the fluoride drinking-water standard, it was noted that healthy adults exposed to optimally fluoridated water had urinary fluoride concentrations ranging from 0.62 to 1.5 mg/L.

Conclusion

In this study, higher levels of maternal urinary fluoride during pregnancy (a proxy for prenatal fluoride exposure) that are in the range of levels of exposure in other general population samples of pregnant women as well as nonpregnant adults were associated with lower scores on tests of cognitive function in the offspring at 4 and 6–12 y old.

Community water and salt fluoridation, and fluoride toothpaste use, substantially reduces the prevalence and incidence of dental caries (Jones et al. 2005) and is acknowledged as a public health success story (Easley 1995). Our findings must be confirmed in other study populations, and additional research is needed to determine how the urine fluoride concentrations measured in our study population are related to fluoride exposures resulting from both intentional supplementation and environmental contamination. However, our findings, combined with evidence from existing animal and human studies, reinforce the need for additional research on potential adverse effects of fluoride, particularly in pregnant women and children, and to ensure that the benefits of population-level fluoride supplementation outweigh any potential risks.

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Letters

COMMENT & RESPONSE

In Reply We appreciate the widespread interest in our study and the opportunity to respond to the critiques and clarify some facts.

1. Fundamentals of epidemiology | We agree that our study reported an association, not causation. Still, observational studies are optimal for testing many important questions in public health, and they are often used to infer causality. Indeed, if we dismissed observational studies, we would have no evidence that water fluoridation prevents tooth decay in children.

Several commentators raised questions about the effect of residual confounding. Our results, as with all observational studies, are subject to confounding by unmeasured factors. Still, we considered many potential confounders. Unless unmeasured factors are identified and shown to be associated with both fluoride exposure and IQ, these criticisms are speculative.

Our conclusions did not “simply rely on *P* values.” We established our hypotheses *a priori*, carefully interpreted effect estimates and confidence intervals, conducted a comprehensive set of sensitivity analyses, acknowledged the limitations of our study, and considered the results of other studies before concluding that pregnant women should reduce their fluoride intake.

Others were concerned about imprecise results. Keep in mind that (1) the fitted regression line is covariate-adjusted, whereas individual data points in the figure are not, and (2) individual data points close to the regression line may represent numerous overlapping cases. Also, the outliers in our data set have low influence but good leverage because their inclusion improves the estimate’s precision. Nonetheless, we ran secondary analyses without the 2 very low IQ scores and the fluoride effect remained.

2. This is not a subtle finding | Is a 4.5 IQ decrement per 1 mg/L increase in urinary fluoride weak? A decrement of 4.5 IQ points among many boys can have a substantial effect on the population distribution of IQ scores.¹ With 14% of Canadian women living in fluoridated regions having urinary fluoride of at least 1 mg/L, we would expect even larger IQ decrements for some children.

Our study is consistent with other high-quality research; it is not a standalone study. More than 50 studies have shown an association between higher fluoride exposure and lower IQ. All 3 prospective birth cohort studies^{2,3} reported that higher prenatal fluoride exposure led to lower IQ scores in children.

3. Clarifying misconceptions | We did not set out to compare IQ scores in children who lived in fluoridated vs nonfluoridated communities. We used a biomarker of fluoride exposure that

accounts for all sources. However, we did find consistent IQ decrements associated with fluoride intake and water fluoride concentrations.

Some commentators were troubled by the reported sex differences. Male individuals are often more susceptible to toxicants, including prenatal fluoride exposure in some animal studies.⁴ Moreover, the National Toxicology Program (2016) called for sex-based analyses for fluoride.⁵ Thus, we planned to test sex differences. We thank Waugh for his suggestion that male mitochondria may be more sensitive to fluoride.

Blendoe et al suggest that the IQ differences are explained by sex differences. Sex differences in IQ scores do not explain the exposure-response association that we observed in boys using urinary fluoride concentrations.

We collected 3 urine samples (1 for each trimester) and adjusted them for urinary dilution, an improvement over other population-based studies on fluoride neurotoxicity. Urinary fluoride is not a perfect measure of fluoride intake, but it is reliable, and it is the optimal biomarker of concurrent fluoride exposure.⁶

We cited a dental fluorosis prevalence rate of 68% in adolescents based on a prior study using National Health and Nutrition Examination Survey data. As noted by Gehani et al, the quality of these data was assessed in an April 2019 report. The prevalence of fluorosis, which is now estimated to be 41%,⁷ is still considerably higher than when water fluoridation was introduced.

We acknowledge that IQ tests have been criticized as having cultural biases. However, our analyses did not compare groups that differed by culture. Moreover, we controlled for ethnicity and city.

Finally, several commentators requested results that we did not report in our manuscript. We endeavor to make our analyses as transparent as possible and have posted supplemental material on the Open Science Framework (<https://osf.io/7vfu5>). Access to the data to validate our findings is available to independent researchers who adhere to the MIREC Biobank policies outlined here: <http://www.mirec-canada.ca/en/research/>.

We agree with Howard et al. Ten years ago, many of the same criticisms, such as bias, imprecision, unmeasured confounding and subtle effects, were raised about studies of low-level lead toxicity.

To conclude, some commentators argued that studies that showed fluoride diminishes children’s intellectual abilities should be interpreted cautiously. We agree. We should also take precautions to protect children’s brains from a potential toxicant, especially when there is no benefit of fluoride for preerupted teeth.

Christine Till, PhD
Rivka Green, MA
Bruce Lanphear, MPH, MD

Author Affiliations: Faculty of Health, York University, Toronto, Ontario, Canada (Till, Green); Faculty of Health Sciences, Simon Fraser University, Vancouver, British Columbia, Canada (Lanphear).

Corresponding Author: Christine Till, PhD, Faculty of Health, York University, 4700 Keele St, Toronto, ON M3J 1P3, Canada (ctill@yorku.ca).

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WI Utilities Discontinued Fluoridation of Public Water Supplies Since 2016.
1. Potosi Waterworks
2. Fond Du Lac Waterworks
3. Coloma Waterworks
4. Blue Mounds Waterworks
5. South Wayne Waterworks
6. Luck Waterworks
7. Windsor Water utility North
8. Plymouth Utilities
9. Saukville Waterworks
10. Lake Delton Waterworks
11. St Croix Falls Waterworks
12. Mellen Water Utility
13. Bonduel Waterworks
14. Berlin Waterworks
15. Oconto Falls Waterworks
16. Rock Springs Waterworks
Source: WI DNR June 2020

A critique of recent economic evaluations of community water fluoridation

Lee Ko¹, Kathleen M. Thiessen²

¹Oakland, CA, USA, ²Oak Ridge Center for Risk Analysis, Oak Ridge, TN, USA

Background: Although community water fluoridation (CWF) results in a range of potential contaminant exposures, little attention has been given to many of the possible impacts. A central argument for CWF is its cost-effectiveness. The U.S. Government states that \$1 spent on CWF saves \$38 in dental treatment costs.

Objective: To examine the reported cost-effectiveness of CWF.

Methods: Methods and underlying data from the primary U.S. economic evaluation of CWF are analyzed and corrected calculations are described. Other recent economic evaluations are also examined.

Results: Recent economic evaluations of CWF contain defective estimations of both costs and benefits. Incorrect handling of dental treatment costs and flawed estimates of effectiveness lead to overestimated benefits. The real-world costs to water treatment plants and communities are not reflected.

Conclusions: Minimal correction reduced the savings to \$3 per person per year (PPPY) for a best-case scenario, but this savings is eliminated by the estimated cost of treating dental fluorosis.

Keywords: Water fluoridation, Economic evaluation, Cost of water fluoridation, Caries prevention, Cost benefit, Cost effectiveness, Effectiveness in adults, Dental fluorosis

Introduction

The USA and several other countries practice community water fluoridation (CWF), which has been promoted as the preferred solution to reduce caries for over half a century.¹ Approximately two-thirds of the U.S. population is treated in this manner according to the Centers for Disease Control and Prevention (CDC).² Community water fluoridation programs have increased water fluoride concentrations to 0.7–1.2 mg/l [0.7–1.2 parts per million (ppm)], although a 2011 proposed recommendation, if finalized, would decrease this to 0.7 mg/l.³

Community water fluoridation is a unique delivery mode of public health care in that fluoride is administered to everyone who drinks the water, regardless of dental status or needs, and at an amount proportional to the water consumed from the fluoridated source, which can range from zero to several liters per day.⁴ At the same time, because most community water is not consumed by people, CWF results in dispersion of a regulated contaminant, fluoride, to the greater environment via wastewater treatment plants, storm sewer systems, and use on lawns and gardens. Fluoridation chemicals typically contain other regulated contaminants (e.g. arsenic),

extending the possibility of human exposures and environmental dispersal.^{5–8}

A central argument for using CWF to reduce tooth decay is the cost savings claimed by the CDC:⁹ Every \$1 invested in this preventive measure yields approximately \$38 savings in dental treatment costs. This argument is repeated by the majority of state governments (Appendix 1) and is frequently cited by proponents to argue for initiating or maintaining CWF.

All \$ signs in this paper refer to US\$ unless otherwise indicated. However, statements such as \$1 saves \$38 are currency neutral.

The CDC's estimate is calculated from the per person per year (PPPY) savings reported by Griffin *et al.*¹⁰ With base-case assumptions, the annual per person cost savings resulting from fluoridation ranged from \$15.95 in very small communities to \$18.62 in large communities.¹⁰ⁱ Table 1 summarizes Griffin *et al.*'s results by population size. The CDC derived the \$1-saves-\$38 claim by scaling the \$0.50 cost and the \$18.62 savings estimate for large systems (>20,000 people) to get \$0.50 : \$18.62 ≈ \$1 : \$38. However, this derivation is not valid because it implies

Correspondence to: Kathleen M. Thiessen, Oak Ridge Center for Risk Analysis, 102 Donner Drive, Oak Ridge, TN 37830, USA. Email: kmt@orrisk.com

ⁱ CDC focused on the smallest and largest systems:⁹ for a population <5,000 people, the net savings is \$19.12 – \$3.17 = \$15.95; for a population >20,000 people, the net savings is \$19.12 – \$0.50 = \$18.62.

Table 1 Estimated costs and savings of community water fluoridation (CWF) for communities of various sizes from Griffin *et al.*¹⁰

Population size	Estimated cost* (\$, PPPY) [‡]	Estimated savings** (\$, PPPY) [‡]
<5,000	3.17	15.95
5,000–9,999	1.64	17.48
10,000–20,000	1.06	18.06
>20,000	0.50	18.62

*Based on a 4% discount rate.

†Calculated with the base-case gross savings of \$19.12.

‡Per person per year.

Table 2 Stated assumptions of Griffin *et al.*¹⁰ and key inputs of the calculation of benefits

Stated assumptions	Key inputs
(1) The benefit is decay prevented and begins at age 6 years	(a) Benefit is the number of decayed tooth surfaces that would otherwise have been treated
(2) The benefit is constant over time	(b) Benefit in dollar amounts, or gross savings, is quantified in terms of averted dental fees for amalgam fillings and averted productivity losses due to a visit to a restorative dentist
(3) All decay is eventually treated	(c) Every decayed surface results in a 1-hour dental visit for a single-surface restoration in the same year it occurs
(4) The adverse effects are negligible	(d) The dental fee for a single-surface filling is \$54, and the productivity loss from the visit is \$18 (the U.S. average hourly wage)
(5) Dental fees equal the cost of dental resources	(e) A single-surface filling is replaced every 12 years with another single-surface filling, up to age 65 years
(6) A decayed tooth surface will always receive a one-surface restoration	(f) It takes one year of exposure for CWF to begin to prevent tooth decay
	(g) CWF averts 0.19 decayed tooth surfaces per person per year (PPPY) on average
	(h) The same rate of caries aversion applies from age 6 to 64 years

CWF: community water fluoridation.

scalability where scalability does not apply: spending more on CWF does not increase caries aversion or caries to be averted.

Griffin *et al.*¹⁰ is the prime example of a body of work that attempts to evaluate the economics of CWF. As the most comprehensive and most cited work, it will be our focus. We limit our analysis to the smallest and largest systems in keeping with the CDC's report.⁹ We also examined and comment on additional CWF cost-benefit analyses (Appendix 2).ⁱⁱ

Key steps in Griffin *et al.*¹⁰

A 1989 workshop¹² at the University of Michigan discussed the cost-effectiveness of CWF and other caries prevention programs, with cost estimates based primarily on data from Garcia.¹³ A 1992 paper by Ringelberg *et al.*¹⁴ improved upon Garcia's cost estimates, and Griffin *et al.*¹⁰ produced their cost estimates (Table 1) by applying minor adjustments to the results of Ringelberg *et al.*,¹⁴ as described later in this paper.

Griffin *et al.*¹⁰ adopted a “societal perspective” and defined benefit as the cost of averted dental fees and associated productivity losses. They used a 4%

discount rate for the main result of \$19.12 gross savings. Griffin *et al.*'s stated assumptions and key intermediate results, organized into a set of key inputs, are provided in Table 2. Note that Input (c) differs from Assumption (3) in the timing of treatment — the authors' calculation was consistent with treatment in the same year. The following steps explain how Griffin *et al.* obtained their value:

Step 1: From Input (d), restoring one decayed tooth surface costs \$54 + \$18 = \$72.

Step 2: As described by Input (e) the lifetime costs of a decayed surface include future replacement fillings; the number of replacements depends on when the decay occurs. Future replacement costs are discounted to arrive at a present value. The first avertable filling is discounted 1 year because of Input (f) in Table 2; replacements take place every 12 years up to age 65 years, based on Input (e).ⁱⁱⁱ For example, for a child age 12.5 years, the lifetime cost at a 4% discount rate was estimated to be \$159.61 as shown in the following equation:

ⁱⁱⁱ While cutting off replacement at age 65 years may appear to underestimate the benefit (cost of fillings), Griffin *et al.* appear to have overestimated by incorrectly or inconsistently applying the factors in the numerator, e.g. the expected lifetime costs of a decayed surface for age groups 55–59 and 60–64 years are both \$69.23 = \$72/1.04 (Table 3), without the factor (which should be around 0.79) to account for fewer teeth at older ages. (Since Griffin *et al.* did not present these factors, except for the few that appear in the Equation (1) example, we are not able to recalculate and correct the numbers in Table 3.)

ⁱⁱ These papers are technically cost-benefit analyses,¹¹ although the term cost-effectiveness is frequently used to refer to the degree that the value of benefit exceeds cost.

$$\$72 \left(\frac{1}{1.04} + \frac{1}{1.04^{13}} + \frac{0.90}{1.04^{25}} + \frac{0.86}{1.04^{37}} + \frac{0.79}{1.04^{49}} \right) = \$159.61 \quad (1)$$

Thus the last replacement takes place at age $12.5 + 1 + (4 \times 12) = 61.5$ in this example. The cost for each filling or replacement filling is adjusted by a factor (the numerator of the term) representing the probability that the tooth remains at the replacement age.

- Step 3: Calculate the national average, using the population distribution in Table 3. Use the midpoint to represent the group in each bracket, e.g. Equation (1) gives the lifetime benefit of an averted decay surface for the 6–19 age group, based on the midpoint, age 12.5 years.
- Step 4: The calculation is repeated for each age bracket, except the first and the last age brackets as described by Input (h) in Table 2. Summing the weighted costs gives \$100.62 as the national average lifetime cost averted per decayed surface.
- Step 5: As CWF averts 0.19 decayed surfaces PPPY, as described by Input (g), the benefit of CWF is thus

$$\text{Gross saving} = \$100.62 \times 0.19 = \$19.12 \text{ PPPY}$$

Costs

Griffin *et al.*¹⁰ based their cost estimates for CWF on Ringelberg *et al.*,¹⁴ except that the numbers were adjusted to 1995 dollars, and a different grouping of community sizes was used. Griffin *et al.* devote one paragraph to their cost estimates.¹⁰

Ringelberg *et al.*¹⁴

Ringelberg *et al.* used data for 44 Florida communities to estimate CWF costs. (Florida's phosphate industry is the largest U.S. producer of fluoridation chemicals.)^{15,16} Ringelberg *et al.*'s improved estimates included costs for bulk storage and containment, labor, and opportunity costs of capital investment, and were based on a larger number of communities than previous estimates.¹³ The estimated average cost increased from \$0.49 PPPY¹³ to \$1.25 PPPY.¹⁴ With phrases such as “allowable initial one-time costs ... were documented by copies of actual invoices for equipment and services”

Ringelberg *et al.*¹⁴ appears detailed and based on actual data. However, these invoices were obtained from the Florida public health dental program, which has the authority to approve costs for communities seeking state grants to implement CWF,¹⁷ and thus reflect costs allowed by the state dental program rather than actual costs.

Ringelberg *et al.*¹⁴ used a 15-year life, with no remaining value, for initial implementation costs, and used 2.4% of the initial costs to calculate the maintenance and repair costs. Labor costs provided by CDC's fluoridation engineer were based on 1 hour per day for all systems and rates of \$7 per hour for small systems and \$9 per hour for medium and large systems. (Note that, in contrast, Input (d) in Table 2 uses \$18 per hour to calculate CWF benefit.) We will show that this is a simplistic and unrealistic view of what is involved in CWF operations.

Reality on the ground

In 2010, amid a budget crisis, the City of Sacramento, CA, instructed all departments to review programs and services. Mr. Marty Hanneman, then Director of the Department of Utilities, wrote in a memo to the City Council:¹⁸

The City of Sacramento has been fluoridating its water supplies just over 10 years. Within that time, the actual cost of operating and maintaining the fluoridation systems has proven to be considerably more than the initial estimate. ... The fluoridation infrastructure at the E.A. Fairbairn Water Treatment Plant is overdue for replacement and will be very expensive to replace. ... Fluoridating water is a very costly and labor intensive process and requires constant monitoring of fluoride concentrations to ensure proper dosages. ... The chemical is very corrosive, so all equipment that is used in the fluoridation process has a very short life expectancy and needs to be replaced frequently. ... but also causes frequent and complex system failures.

This was echoed by Mr. René Fonseca of Carroll-Boone Water District in Eureka Springs, AR, which was required by a 2011 State mandate to begin CWF (Fonseca, 2012, private communication):

Table 3 Griffin *et al.*¹⁰ weighted per person discounted lifetime cost of carious surface initially occurring at various ages

Age (years)	Discounted expected lifetime cost of decayed surface (\$)	1996 U.S. population (%)	Weighted cost (\$)
0–5		8.4	
6–19	159.61	20.4	32.56
20–24	146.95	6.8	9.99
25–29	144.86	7.2	10.43
30–34	128.24	8.3	10.64
35–39	127.76	8.5	10.86
40–44	105.12	7.7	8.09
45–49	105.55	6.6	6.97
50–54	106.42	5.2	5.53
55–59	69.23	4.2	2.91
60–64	69.23	3.8	2.63
65+		12.8	
Total		100	100.62

All of our chemical feed systems require regular maintenance which is routine but fluoride feed equipment often requires replacement and more frequent attention. ... I have toured plants and seen in trade publications deteriorating pipes, steel doors and casing, electrical components, etc. There are millions of dollars spent yearly on infrastructure damage caused by fluoride in our industry.

The realities expressed in these two quotes are not the exceptions. A water plant manager in Alberta, Canada, complained that the fumes from the acid etched the glass, paint, and computer screens of the water treatment plant.¹⁹ Seven years after CWF began in 2001, Riverton, Utah, spent nearly \$1.2 million for two new buildings “to get fluoride out of electrical and pump area.”²⁰

Several incidents of fluoride overfeeds at water-treatment plants have been investigated. Gessner *et al.*²¹ described an accident that occurred in Hooper Bay, Alaska, in 1992, in which 296 residents suffered acute poisoning and a 41-year-old man died. Petersen *et al.*²² reported on an overfeed incident in a residential Connecticut community in 1986. The fluoride caused gastroenteritis in 33% of those who drank the water and itching and skin rashes in those with dermal contact; the acidity leached copper from domestic plumbing. Penman *et al.*²³ investigated an outbreak of acute poisoning caused by a fluoride overfeed in a small rural community in Mississippi in 1993. Several people became ill and connected the onset of their illness to drinking tap water at the same restaurant. A community survey was performed, and the authors concluded that approximately one third of households in the town may have been affected, though the extent remains unknown.

Akiniwa²⁴ examined seven events of acute fluoride poisoning related to the fluoridation of drinking water that have been reported in the U.S. He estimated from these reports that acute fluoride poisonings have occurred at doses of 0.1–0.8 mg fluoride per kg of body weight. One fatal fluoride intoxication caused serious illness in 12 patients, 3 of whom died, in a hospital hemodialysis unit in Chicago in 1993.²⁵ Caused by failure of a widely used deionization system, this event would not have been catastrophic had the water not been fluoridated.

Other incidents reported in local media have included injuries to water plant workers, massive evacuation around an interstate highway, damages to water pipes or concrete floors, and environmental hazards to fish and ground. A number of these incidents are cited in Appendix 3.

An economic evaluation taking a societal perspective should have considered the societal costs from these inevitable consequences of CWF. However, comprehensive data needed to estimate such costs

are lacking, because the government agencies that should track these incidents appear to have a conflict of interest in protecting and defending the CWF policy (e.g. Florida;²⁶ Layton;^{27iv} Appendix 1). Nevertheless, evidence presented here demonstrates that Ringelberg *et al.*¹⁴ were unrealistic even considering only the direct costs of CWF to a water system.

Real-world estimates

In late 2010, Black and Veatch Corporation (Overland Park, KS USA) was retained through a competitive bid process to perform an objective evaluation of the fluoride program of the city of Sacramento, CA. After a comprehensive and detailed review, the study²⁸ observed that immediate and future upgrades would be needed to continue fluoridating and to achieve modest operational efficiency improvements. Noting that Sacramento's operational costs were within industry practice, the report developed detailed cost estimates and gave a different picture from Ringelberg *et al.*,¹⁴ e.g. the labor cost was set at a rate of \$100 per hour, in contrast to the \$7/\$9 per hour labor rate from the CDC. The city's engineer, Mr. Brett Ewart, explained (Ewart, 2012, private communication):

The 100/hr. is a hybrid rate used to represent the large variety of machinists, electrical staff, water quality staff, management, etc., that work on the program. The amount of staff time (and type of staff) dedicated to the fluoride program is flexible. Some maintenance activities are generally fixed, others are reactionary and difficult to predict in advance. The rate would include the employees' salary, benefits, and overhead to perform the work.

Sacramento's water system consisted of the following: One large treatment plant supplying 44% of the water, whose fluoridation system had already been updated in 2007; a second large treatment plant (Fairbairn WTP) supplying 42% of the water, whose fluoridation system was in need of replacement; and 27 wells supplying 14% of the water, and whose fluoridation systems also required updates.²⁹ The overall cost estimates provided by Black and Veatch for the needed replacement and updates, annualized using a 2.5% discount rate over a 20-year planning horizon,^v were \$1 million for the 27 wells and \$464,000 for the Fairbairn WTP.²⁹ The cost projection for the Fairbairn WTP is applicable for large water treatment plants, while the cost projections for the well upgrades are applicable for small systems.

^{iv} In a letter to Davis County Health Department and others, the Mayor of Layton, Utah strongly protested that the costs of fluoridation to the citizens of Layton and Davis County were far greater than the costs portrayed by the Department when it “clearly knew better”.²⁷

^v First 5 Sacramento, the organization that funded the study, may fund the capital update cost with a condition that requires the city to commit to CWF for 20 years, regardless of the city's future fiscal conditions.¹⁸ In July 2012, the city accepted a grant from First 5 Sacramento to continue fluoridation until June 30, 2015, even though the grant will provide less than 10% of the system costs over the next 3 years.³⁰

Table 4 Examples of fluoridation cost estimates

Water districts	Year Est	Pop (in thousands)	Reported implementation (I) and annual operation and maintenance (O) costs	PPPY (\$) 15 years, 4% (I)
Napa, CA ³⁴	2003	77	I: \$1M; O: \$150,000	3.07
New York, NY ³⁵	2008	8,350	I: \$12.57M (2 plants); O: \$11.14M (chemicals)	1.45
San Jose, CA ³⁶	2011	1,000	I: \$23M; O: \$1.732M (Wells only)	3.72
Watsonville, CA ³²	2011	51	I: \$50/person; O: \$4/person	8.33
Portland, OR ³⁷	2012	900	I: \$3.5M–\$7.6M, O: \$575,000	0.98–1.37
Carroll-Boone, AR ^{33,38}	2012	25	I: \$894,000–\$1.23M	3.09–4.26†
Davis, CA ³⁹	2013	67	I: \$1.1M–\$2.4M; O: \$228,800–\$240,700	4.84–6.69
Riverton, UT ²⁰	2000	35	I: \$90,000 (estimate)	0.22†
	2001		I: \$200,000 (actual)	0.49†
	2008		I: \$1,174,278 (actual w/2 new buildings)	2.90†
Jordan Valley, UT ⁴⁰	2000	82	I: \$56,000–\$2.1M (estimates)	0.06–2.22†
	2004		I: \$2.45M; O: \$297,000 (actual)	6.21

†Estimates do not include operation and maintenance costs.

To calculate the PPPY costs, we allocated the total population of Sacramento, 466,000 people (2010 U.S. Census), to the 27 wells and to the Fairbairn WTP using the percentages of total water supplied of 14% and 42%, respectively. The allocated populations are 65,000 and 196,000, respectively. Dividing the total costs by population and number of injection sites, we obtain a cost estimate of \$15.38 and \$2.37 PPPY for a single-injection point water system serving 2,400 and 196,000 people, respectively. (Systems serving 2,400 people are not rare. Of the 44 systems in Ringelberg *et al.*¹⁴ three systems had smaller populations and seven systems had smaller populations per injection site.)

We considered whether to adjust for the cost of living in Sacramento and determined that there was no need. The cost of living for Sacramento is 8% higher than the U.S. average.³¹ This differential, however, is easily offset by other considerations, e.g. the use of a 2.5% instead of 4% discount rate. The cost projection also assumes that the Health Department continues to waive a requirement for certain standard equipment. In addition, actual bids for construction may turn out to be much higher than the engineer's estimates.^{32,33} Finally, it was unknown whether implementing the recommendations would solve the city's fluoridation issues.²⁹

A small water system serving more than 2,400 people is expected to cost less than \$15.38 PPPY. Similarly, many large systems serve less than 196,000 people and are expected to cost more than \$2.37 PPPY. (Note that large water districts serving more than 196,000 people will not necessarily cost much less than \$2.37 PPPY, because such water districts often have multiple treatment plants and/or auxiliary wells, which make them equivalent to a smaller single-injection point system). Therefore, reasonable cost estimates for the smallest (<5,000 people) and largest (>20,000) systems in Table 1 would be about \$10 and \$3 PPPY, respectively.

Strictly speaking the annual cost projections provided by Black and Veatch are 20-year financing costs.

At the end of the 20-year period, components such as new buildings may still have value. However, given the ability of the chemicals to degrade concrete (Appendix 3 items 17 and 19), significant annual maintenance and repair costs after the financing period are expected. In addition, circumstances could require a water system to implement major infrastructure changes to their fluoridation facilities. Sacramento is such an example. Despite implementing fluoridation comparatively late (around 2000), the city has already endured major infrastructure adjustments and is considering more, long before the 20-years projection period. Finally, it is possible that a system may discontinue CWF; in that case, buildings constructed specifically for CWF may hold little value.

Other estimates

The Black and Veatch report cited above is valuable in that it is recent, comprehensive, detailed, and authored by a firm that has consulted on other fluoridation programs. In general, reliable cost information for CWF programs is difficult to obtain, and information provided in response to a request is often limited to the cost of the fluoride chemicals. In Table 4, we present additional cost information and estimates collected from various sources.^{20,32–40} The majority of these are cost estimates prior to implementation; New York and some Utah figures show actual costs. Costs are reported either for implementation (*I*) or for annual operation and maintenance (*O*). For convenience, we calculate a PPPY cost by annualizing the implementation cost (*I*) using a 4% discount rate over 15 years^{vi} (meaning \$100 annualizes to \$8.65) and normalizing the total, i.e., dividing the annualized *I* plus *O*, if available, by

^{vi} The service life of fluoridation equipment depends very much on the component and on the service conditions. According to Black and Veatch,²⁹ only a few components in indoor setups can expect a service life of 15 years or more, and some components have a service life of only 5–10 years in an outdoor setup.

population. (Population figures are taken from the CDC website or the U.S. Census Bureau if they are not reported in the source article.)

Many of the cost estimates shown in Table 4 are incomplete or partial, or the values are underestimated. Several (denoted with †) do not include operation and maintenance (O&M) costs. The New York numbers consist of costs to rehabilitate CWF facilities in two plants, and only chemicals are included in O&M. The San Jose numbers provided in a Black and Veatch study were for wells that provide only half of the water for the city, which imports the other half. The preliminary estimates for Napa, CA are from about the time that Sacramento began its fluoridation program and probably suffer from similar underestimates of costs.¹⁸ The estimates for Portland, OR were provided by the Water Bureau after a meeting with representatives from the CDC and the organizations pushing to fluoridate the city. The \$575,000 O&M figure appears unrealistic — Sacramento already paid over \$400,000 back in fiscal year 2008/2009 for hydrofluorosilicic acid (HFSA) to fluoridate 86% of their water; this translates to about \$1 PPPY for the cost of HFSA alone. In addition, the O&M estimate excluded costs of additional caustic or other corrosion control chemicals to bring the pH back to an appropriate level, and the cost of additional capital improvements needed to mitigate water quality impacts were not included in the estimated capital costs.³⁷

Community water fluoridation proponents have a poor track record for cost estimates. For example, the county health board of Davis County, UT, provided a cost estimate of \$1.38–\$2 PPPY prior to a vote in 2000, but the true implementation cost was \$4.29 PPPY.⁴¹ This is also seen in the estimates/observed figures for the two Utah systems in Table 4. In 2001, Arkansas state legislators passed a state mandate to fluoridate community drinking water. They were partially motivated by an offer from Delta Dental of Arkansas to donate \$500,000 total toward startup costs for the 32 water systems affected.⁴² Later Delta Dental pledged \$2 million for 34 systems and soon found itself needing to raise another \$6–\$10 million.⁴³ (State mandates in California and Arkansas both require the initial implementation costs be funded by outside sources.)

Overall, reported costs of CWF are consistent with our real-world estimates and not with those estimates^{10,14} commonly cited by fluoridation proponents.

Costs of dental fluorosis

Griffin *et al.*'s Assumption (4) in Table 2, that the adverse effects of CWF are negligible,¹⁰ is common to most cost-benefit analyses of CWF. It is inexplicable that neither Griffin *et al.*¹⁰ nor other similar studies

(Appendix 2) mention dental fluorosis, defective enamel in permanent teeth due to childhood over-exposure to fluoride.^{44,45} Community water fluoridation, in the absence of other fluoride sources, was expected to result in a prevalence of mild-to-very-mild (cosmetic) dental fluorosis in about 10% of the population and almost no cases of moderate or severe dental fluorosis.⁴⁶ However, in the 1999–2004 NHANES survey, 41% of U.S. children ages 12–15 years were found to have dental fluorosis, including 3.6% with moderate or severe fluorosis.⁴⁷

As an increased prevalence of dental fluorosis became evident, there were attempts to shift attention to other sources of swallowed fluoride, such as toothpaste.⁴⁸ However, 1/4 liter (or about 8 oz) of fluoridated water at the “optimal” concentration of 1 mg/l contains the same amount of fluoride as a bead of toothpaste (0.15% w/v fluoride ion) 0.68 cm in diameter. Regarding other sources of ingested fluoride, Szpunar and Burt⁴⁹ state that the factor that differentiates the studied communities with respect to the prevalence of caries and fluorosis is the fluoride concentration in the community water supply.

Dental fluorosis had been dismissed as cosmetic by CWF promoters and government agencies in the U.S. until the National Research Council (NRC) concluded that “severe dental fluorosis” qualified as an adverse health effect due to increased risk of caries and loss of dental function.⁴⁴ When an economic evaluation is framed as having a societal perspective, it should include effects that result in social costs, regardless of whether the effects are cosmetic or systemically harmful. In a later paper, Griffin *et al.* indicated that some people may want “esthetic restorative procedures” to treat fluorosis, but treatment costs were not estimated.⁵⁰ We next provide a high level estimate of the minimal costs of treating dental fluorosis.

Dental fluorosis is classified by the severity of the discoloration, the presence of pitting, and the extent of the tooth surfaces affected.^{44,45vii} Although bleaching and microabrasion can be used to improve the appearance of milder cases of fluorosis, moderate and severe dental fluorosis can require extensive treatment to improve the cosmetic appearance and prevent further loss of enamel.^{44,45} Treatment options include applications of veneers or crowns. Porcelain veneers may cost more than composite resin veneers (\$800–\$2,500 vs. \$250–\$1,500), but they require less frequent replacement (10–15 vs. 5–7 years).^{52,53}

vii Dean's classification for very mild, mild, moderate, severe and very severe dental fluorosis: at least two teeth contain mottled surface area covering less than 25%, between 25 and 50%, between 50 and 100%, 100% (with discrete pitting), and 100% (with confluent pitting) of the tooth surface, respectively.⁵¹

Crowns are “usually used as a last resort because they can be a threat to tooth vitality.”⁴⁴

For this analysis, we assume that each moderate or severe fluorosis tooth receives a porcelain veneer treatment. We further assume that a child with the condition gets the first treatment at age 13.5 years, and the veneers are replaced every 12 years. The lifetime cost of a veneer is calculated using equation (1), except the \$72 is replaced by the cost of a veneer, for which we use a lower-end number of \$1,000. This gives a lifetime cost of \$2,217. Dean’s Enamel Fluorosis Index, the most widely used classification of dental fluorosis, is assigned on the basis of the two most-affected teeth.⁴⁴ Thus, the lifetime cost of veneers for a child with moderate or severe fluorosis would be at least \$4,434.

Beltrán-Aguilar *et al.*⁴⁷ reported that 3.6% of U.S. children ages 12–15 years in 1999–2004 had moderate or severe dental fluorosis, but did not provide information on the fluoridation status of the affected children. At most about 60% of the U.S. population received fluoridated water during the time period when these children were susceptible to development of fluorosis.^{viii} Both the prevalence and the severity of dental fluorosis are correlated with the fluoride concentration in drinking water.^{45,49,55} If all of the cases of moderate and severe dental fluorosis occurred in fluoridated rather than nonfluoridated areas, then at least 6% of children in fluoridated areas would have moderate or severe fluorosis.^{ix} For our calculations, we have assumed that 5% of children in fluoridated areas have moderate or severe fluorosis. From Table 3, the percentage of children at age 13.5 years is about 20.4%/14 = 1.46%. Thus the minimum cost of treating dental fluorosis is estimated to be $\$4,434 \times 1.46\% \times 5\% = \3.24 PPPY.

Other costs

There are other costs missing from the conventional cost-benefit analyses of CWF (Appendix 2). The NRC’s 2006 report on fluoride exposures and toxicity found that the U.S. Environmental Protection Agency’s (EPA) drinking water standard for fluoride was not protective of human health.⁴⁴ The NRC did not evaluate CWF for safety or efficacy, but the report showed that the average fluoride exposures associated with adverse health effects are within the expected range of fluoride intake for populations with fluoridated water, especially for infants, young

children, and people with high water intake.^{44,56x} Peckham and Awofeso’s recent review specifically concluded that fluoridation has “significant costs” in relation to adverse effects on human health, although these costs were not quantified.⁵⁷

Health risks to water plant operators are not included in most discussions of CWF, but these individuals may receive substantial occupational exposures to fluoride if the safety infrastructure or training is not adequate or if equipment malfunctions.^{58,59}

Most of the fluoridation chemicals used in the U.S. are byproducts of the phosphate fertilizer industry in North America or Asia.^{15,16,60} Since only a small percentage of municipal water is actually consumed by people, the practice results in wide dispersion of a regulated pollutant into the environment via local water districts. Fluoride pollution may result in serious ecological risks to aquatic organisms.⁶¹

Fluoride is regulated by the U.S. EPA as a contaminant in drinking water⁶² and as an air pollutant.⁶³ A number of fluoride compounds are considered hazardous substances with assigned Reportable Quantities.⁶⁴ In addition, fluoridation chemicals often contain other regulated contaminants.^{5–8} Hirzy *et al.*⁶⁵ estimated that the typical concentration of arsenic in the major fluoridation chemical (HFSA) could be responsible for several excess lung and bladder cancers per year in the U.S. and the consequent costs of treatment.

Political costs have at times been acknowledged but not included in CWF analysis.¹⁰ This category goes beyond costs associated with fluoridation referenda to include government expenditures for promoting fluoridation programs, costs associated with lobbying elected officials on this issue, legal challenges to fluoridation programs, and possible personal injury litigation involving workers or members of the public.^{66–70}

There are also costs associated with avoiding fluoridated tap water, either by need or by choice. These are all societal costs of CWF that should not simply be excluded or assumed negligible without examination.

Benefits

The primary benefit attributed to CWF is prevention of caries, although a major review in the United Kingdom reported no relevant studies of “evidence level A (high quality, bias unlikely)” and expressed surprise that little high quality research had been undertaken.⁷¹ Caries prevention is commonly assessed in terms of a reduction of decayed, missing, or filled

^{viii} Infants and young children are most at risk for exposures leading to dental fluorosis.⁴⁵ Children ages 12–15 years when surveyed between 1999 and 2004 were born between 1984 and 1992. Centers for Disease Control and Prevention’s data indicate that 53–60% of the U.S. population between 1984 and 2002 received fluoridated water.⁵⁴

^{ix} $3.6 / 53\% = 6.8\%$ and $3.6 / 60\% = 6\%$.

^x People with high water intake include athletes, outdoor workers, military personnel, and people with medical conditions such as diabetes insipidus or diabetes mellitus.⁴⁴ People with impaired kidney function may have high water intake and might also have reduced urinary excretion of fluoride.⁴⁴

teeth (DMFT), DMF tooth surfaces (DMFS), or their variations.^{xi} Estimation of averted caries is obviously central to a cost-benefit analysis.

Griffin *et al.*¹⁰ relied on the theory that caries averted by CWF can be considered in terms of two factors as shown in the following equation

$$\text{Averted caries} = \text{Incidence} \times \text{Effectiveness} \quad (2)$$

where Incidence is the per person annual caries increment without CWF, and Effectiveness is the percentage reduction in caries due to CWF.

Before we explain and critique how Griffin *et al.*¹⁰ derived their values for Incidence and Effectiveness, it is worthwhile to examine the concepts of incidence and effectiveness in the context of CWF.

Incidence

Griffin *et al.*¹⁰ treat the reported caries incidence in selected nonfluoridated areas as the caries incidence in the absence of CWF. However, they have not accounted for the decline in caries rates over time apart from CWF or the variability in caries rates among various areas, independent of CWF.

It has been known for decades that tooth decay prevalence has been declining in developed countries regardless of CWF status, i.e., the “secular decline”.¹¹ Diesendorf⁷² listed over 20 studies which reported substantial temporal reductions in caries in unfluoridated areas. In many cases, the magnitudes of the reduction were comparable to those attributed to fluoridation in some fluoridated areas; it was also pointed out that fluoride toothpaste or supplement could not have accounted for many of the reductions.

That fluoride is not needed for dental health is not surprising. A 1952 NRC report⁷³ described studies reporting that the teeth of ancient peoples and modern primitive peoples were relatively free from dental caries, in a striking contrast to the teeth of modern people. However, primitive peoples had increased rates of caries when brought into contact with a modern diet. This is consistent with the fact that caries are rare in animals in the wild. Finn⁷³ also described the significant geographic and temporal variability of caries prevalence, citing Hagan⁷⁴ for demonstrating how caries prevalence may vary within narrow geographic limits, as well as fluctuating within the same area from time to time.

Hagan⁷⁴ studied 12 communities in Georgia, including 24,092 children, and reported the following by community: The average annual caries increments were 0.18–0.90 for children up to 16 years old; the

DMFT ranged from 0.40–2.44 at age 7 years to 1.41–10.64 at age 16 years; the percentage of children with at least 1 DMFT ranged from 23–77% at age 7 years to 58–100% at age 16 years. The ranges of DMFT for a given age in these pre-CWF situations approach or exceed the differences reported between fluoridated and nonfluoridated locations in more recent years. For example, Heller *et al.*⁵⁵ reported mean DMFS values ranging from 2.53 (0.7–1.2 ppm F) to 3.08 (<0.3 ppm F), with a mean DMFS of 2.75 for the entire sample (18,755 U.S. schoolchildren ages 5–17 years with a history of a single residence). The percentage of caries-free children ranged from 52.5% (>1.2 ppm F) to 57.1% (0.3–0.7 ppm F), averaging 54.6% for the entire sample. McDonagh *et al.*⁷¹ reported that, among 15 studies analyzed, the mean differences in dmft or DMFT ranged from 0.5 to 4.4 (median 2.25).

Other historical data contradicting the idea that fluoride is needed for dental health have been reported. Using data from New Zealand Health Department records of 5-year-olds’ tooth decay from 1930 to 1990, fluoridation coverage, and fluoride toothpaste sales, Colquhoun⁷⁵ showed that the dramatic decline in tooth decay started long before water fluoridation, fluoride toothpaste, or application of fluoride. Another paper noted that the DMF rate in children ages 12–15 years in Taiwan was as low as 1/3 to 1/6 of that in children of the Western countries where water fluoridation had been in effect for 8–11 years.⁷⁶

Studies that attributed differences in tooth decay rates between selected communities to CWF may have only observed these geographic or temporal variabilities, independent of any effect of CWF. Other studies (see Appendix 5) found that non-fluoridated cities also experienced rapid reductions in tooth decay rates without installing CWF, even though these cities had previously been compared with fluoridated cities as evidence that CWF reduces caries. Hence the concept of a no-fluoridation caries incidence rate has little meaning.

Effectiveness

Griffin *et al.*¹⁰ derived their estimate of effectiveness from Brunelle and Carlos,⁷⁷ who reported on the second of two large-scale National Institute of Dental Research (NIDR) surveys, completed in 1980 and in 1987, respectively. Each survey sampled and examined approximately 40,000 U.S. school children aged 5–17 years.

Community water fluoridation effectiveness has been variously reported in the literature. The unit of measure can be variations of DMFT, DMFS for permanent teeth, the corresponding measures for deciduous teeth, or the percentage of children with no caries. They could be for a single age or for an age range. Information about length of exposure to CWF

^{xi} DMFS counts the number of decayed (untreated), missing, filled tooth surfaces and DMFT counts teeth instead of surfaces. (An adult without wisdom teeth has 28 permanent teeth and 128 tooth surfaces.) Capital letters refer to permanent teeth and lower case letters (dmfs, dmft) to deciduous teeth.

may or may not be included. Study parameters are often poorly defined and confounding factors not typically examined.

Often a percentage value is produced from some relative differentials and referred to as CWF effectiveness, despite that the percentages come from different situations. Some may argue that since all the different kinds of studies point to similar ranges of effectiveness, it is proof that the effectiveness estimates are robust. However, the premise of this argument is false.

First: Units. Units of measures do affect the results. An independent investigation of the 1987 NIDR data using DMFT instead of DMFS led to the conclusion of no effectiveness.⁷⁸ When asked about results for teeth, Brunelle was quoted to have said that they “are in a box somewhere” and she “could not remember what exactly the results were” and that the decay rate for teeth “is rather low so that there is very little difference in most anything.”⁷⁹ Truman *et al.*⁸⁰ estimated effectiveness in units of teeth from data reported in a number of studies (Table 5) even if a study reported data in both teeth and surfaces.

Studies reporting results in teeth were more common in the past. The focus shifted toward surfaces as the prevalence of caries dropped and caries became concentrated in a small subset of the population.⁸¹ Measuring caries in units of surfaces gives heavy weight to the small percentage of people with high levels of decay.^{xii}

Second: Lengths of exposure. There are two relevant exposures: exposure to carious influence and exposure to CWF.

Exposure to caries is determined in part by the time a tooth erupts. Usually age is used as a surrogate for the length of this exposure. If a study examines subjects of a range of ages and one effectiveness number is to be presented, which age is selected or how different age groups are weighted to calculate an average can produce different results. Appendix 4 provides examples of studies showing differences in caries experience that were attributed to CWF exposures, when the results may be better explained by differences in age distributions of the populations being compared.

Exposure to CWF is often handled by comparing only those with lifetime exposure to those with no exposure. However, if a result is contingent on excluding partial exposure it weakens the argument for CWF as a public policy. More importantly, this approach introduces a probable bias if the two exposures (to caries and to CWF) are not independent.

Evidence indicates that ingested fluoride may delay tooth eruption,^{44,45,85} which would affect caries scoring by giving the appearance of less decay for a given age.^{44,45} Komárek *et al.*⁸⁶ used data for actual tooth eruption time and found no convincing effect of fluoride intake on caries development. Weaver⁸⁷ indicated that “the caries inhibitory property of fluorine seems to be of rather short duration,” consistent with a delay in the exposure of permanent teeth to a cariogenic environment.

Third: Methods. The methods of determining an effectiveness value are even more problematic, especially in regard to policy references. This is best demonstrated by an examination of Truman *et al.*,⁸⁰ which was co-authored by Griffin, other CDC personnel, and a Task Force appointed by the Director of the CDC. The Task Force was established by the U.S. Department of Health and Human Services (HHS) in 1996 to provide recommendations for community preventive services, programs, and policies. Reported in 2000, the findings of the Task Force’s systematic review⁸⁸ became the main results of Truman *et al.*⁸⁰ on CWF effectiveness, as well as the basis for Healthy People^{xiii}2010’s goal of increasing CWF in the U.S. to cover 75% of the population.⁹¹ Healthy People 2020⁹² continues with a goal of increasing coverage to 79.6%.

Truman *et al.*⁸⁰ based their conclusion on 14 studies in three groups (Table 5):^{76,93–105}

- Studies starting or continuing CWF with before and after measurements (Group A-On)
- Studies stopping CWF with before and after measurements (Group A-Off)
- Studies starting or continuing CWF with only post measurements (Group B-On)

They calculated a number of “estimates of effectiveness” from the studies using two formulas, one for Group A (before-and-after) and one for Group B (post measurements only). The measures were mostly DMFT or dft.

The median of estimates was taken to represent the CWF effectiveness for each study type; the results were 29.1% for Group A-On, 50.7% for Group B-On, and 17.9% for Group A-Off. (The 29.1% and 50.7% figures were presented by the Task Force.)⁸⁸ With these numbers the authors concluded “strong evidence shows that CWF is effective.” This conclusion is not valid. We describe three areas of problems below (details provided in Appendix 5).

^{xii} Proponents often appeal to sympathy for young children with high levels of tooth decay to argue for CWF.⁸² However, early childhood caries (ECC) is not prevented by fluoride.^{83,84}

^{xiii} CDC’s “Healthy People” series “provides science-based, national goals and objectives with 10-year targets designed to guide national health promotion and disease prevention efforts to improve the health of all people in the United States.”⁸⁹ One goal of Healthy People 2000, 2010, and 2020 has been to “increase the proportion of the U.S. population served by community water systems with optimally fluoridated water.”^{90–92}

Selection of studies: Studies of higher quality and relevance such as the NIDR surveys or other U.S. studies were not included. Many studies on the effect of cessation of CWF (Group A-Off) were omitted even though this group had only three studies. Not all included studies are relevant for CWF or meet the stated criteria.

Selection of estimates: The number of estimates selected from each study appears arbitrary. Fewer estimates were selected from large-scale studies reporting findings in detail than from small studies reporting few findings. Sometimes the selected estimate did not fit the group it was placed in. Selection of arbitrary numbers of estimates from an arbitrary set of studies does not lead to confidence in the reported median.

Selection of formula: Within the limited set of studies and estimates selected, the authors failed to apply their formula consistently. In addition, the results from the application of the formula can be misleading. Upon examination of the data, some purported positive outcomes are revealed as purely an artifact of the formula — the never-fluoridated communities had a dramatic reduction in caries without the help of CWF.

The incidence and effectiveness in Griffin et al.¹⁰ Three estimates for Incidence were compiled from several unrelated sources while three estimates for Effectiveness were derived from a single source. They are paired by magnitude and substituted in Equation (2) to arrive at three cases of averted DMFS as shown in Equation (3).

$$\begin{aligned} \text{best case : } 1.16 \times 29\% &= 0.34 \\ \text{base case : } 0.76 \times 25\% &= 0.19 \\ \text{worst case : } 0.33 \times 12\% &= 0.04 \end{aligned} \quad (3)$$

The base-case averted DMFS of 0.19 is the key input (g) in Table 2. (Note that not all studies cited

Table 5 The studies, the age of children examined, group placed, and number of estimates calculated by Truman et al.⁸⁰ to evaluate CWF effectiveness

Study	Age	Group/no. Est.
Arnold and Dean ⁹³	4–15	A-On/4
Beal and James ⁹⁴	5	A-On/2
Beal and Clayton ⁹⁵	5,8,12	A-On/4
Loh ⁹⁶	7–9	A-On/2
Evans et al. ⁹⁷	5	A-On/3, B-On/1
Guo et al. ⁷⁶	4–15	A-On/2, B-On/3
Künzel and Fischer ⁹⁸	6–15	A-On/4, A-Off/2
Attwood and Blinkhorn ⁹⁹	10	A-Off/1
Kalsbeek et al. ¹⁰⁰	15	A-Off/2
Brown and Poplove ¹⁰¹	14–17	B-On/4
Fanning et al. ¹⁰²	3–6	B-On/3
Hawew et al. ¹⁰³	6,12	B-On/4
Provar and Carmichael ¹⁰⁴	5	B-On/2
Rugg-Gunn and Nicholas ¹⁰⁵	5	B-On/3

by the authors measured DMFS, and the differences were not always pointed out.) We next examine how the numbers on the left-hand side were derived.

The Incidence

Griffin et al.¹⁰ obtained three sets of annual caries increments in nonfluoridated communities as Incidence; they are reproduced in Table 6. The sources were, respectively, published studies cited in Garcia,¹³ the National Survey of Oral Health (NSOH) in U.S. Schoolchildren and a separate NSOH in Employed Adults and Seniors, and the First and Third National Health and Nutrition Examination Survey (NHANES I, 1971–1974 and NHANES III, 1989–1994).

For the best case, the authors used the controls in Garcia's review¹³ of published studies of clinical and community trials. For the base case, the incidence for children was imputed by dividing the difference in mean DMFS for 6-year-olds and 17-year-olds living in communities without fluoridation by 11. Unrelated to the children's survey, the adult NSOH survey was measured in DFS (without M, missing surface) and was not stratified by community fluoridation status. Hence, they imputed the incidences by using the least fluoridated region (Pacific). They scaled the mean DFS by the ratio of average numbers of teeth in the two age points to adjust for missing teeth. They also added root caries incidences from other studies. For the worst case, the authors imputed the incidence using data from two NHANES surveys, which did not report fluoridation status. A major difference from the base case was that they tried to use data on the same birth cohort over time. Additional adjustment was applied because earlier NHANES data measured DFT instead of DFS.

The source of the best case, Garcia,¹³ was the basis for discussion of CWF in the 1989 Michigan Workshop. Workshop participants were critical of the numbers. "Most work groups felt that the estimates of caries incidence in Garcia's report were generally too high and reduced them by several decimal points, though some reduced them further."¹² Griffin et al.¹⁰ also stated in their discussion that the samples were probably not representative of the general population. Thus, the best case is invalid.

Griffin et al.¹⁰ also admitted that the base case was overestimated. They remarked that, given the secular decline in caries, using cross-sectional data to impute

Table 6 Griffin et al.'s estimates of annual caries increment (tooth surfaces) from selected studies, by age¹⁰

Source	Age (year)			
	6–17	18–44	45–65	Avg.
Published studies (best case)	1.40	0.83	1.24	1.16
NSOH (base case)	0.77	1.09	0.43	0.76
NHANES (worst case)	0.49	0.49	0.00	0.33

caries increment from the NSOH would overestimate current increment. Secular decline^{11,72} refers to the widespread decline in caries observed in nonfluoridated areas. It means that when a 6-year old living in a nonfluoridated area today grows up to be 17 years old, he will likely have fewer caries than his 17-year old neighbor has today. Thus using the latter to represent the former (cross-sectional data) overstates the incidence of caries.

The Effectiveness

As with the Incidence, Griffin *et al.*¹⁰ presented three cases for Effectiveness, all essentially from Brunelle and Carlos.⁷⁷ The 1987 NIDR Survey examined 39,206 children, of whom about 92% had complete residence histories. Brunelle and Carlos⁷⁷ analyzed data from 16,398 children with either lifelong exposure or no exposure to CWF and presented mean DMFS by age (see Table 12) and by region (Table 7). The national averages from this subset of data showed a difference of 0.6 DMFS, or 18%, between the two exposure groups. By further restricting their sample to a subset of 5,954 children (reportedly by removing all data points with any supplemental fluoride exposure), the 18% difference was raised to 25%. No age or regional distribution was shown for this restricted set of data. Griffin *et al.*¹⁰ took this 25% as the base-case Effectiveness.

Brunelle and Carlos⁷⁷ ignored 58% of the total data (or 55% of those with complete residence histories), despite that partial exposure data from this national survey can be analyzed and are informative.⁷⁸ It is therefore questionable if the 18% reduction in DMFS represents the findings of the survey. Even more troublesome is the 25% adopted as the base-case Effectiveness, as it ignores 85% of the survey data.

The best- and worst-case Effectiveness, 29% and 12%, respectively, were supposed to be calculated from the best three and the worst four effective regions. However, the worst four regions (I, II, III, and V in Table 7) would average closer to 6% than 12% using regional population data found elsewhere.¹⁰⁶ It appears that Griffin *et al.*¹⁰ may have removed Region III (Midwest) from the calculation given the

comment: “The negative effectiveness value in the Midwest may have been due to small sample size because few children living in this region actually received nonfluoridated water.” This criticism would equally apply to the highest-effectiveness Region VII (Pacific), as few children in this region received fluoridated water, but it was not considered a problem.

Lack of evidence for adults

Assumption (2) and Input (h) in Table 2 assume the same CWF benefit to age 64 years, despite that estimates of Effectiveness were derived from a children’s survey. Two adult studies^{51,107} were cited to support this extrapolation. However, the data presented in Grembowski *et al.*¹⁰⁷ do not support its conclusion, and Eklund *et al.*⁵¹ appear to be mis-cited in addition to the fact that the concentrations involved, 3.5 versus 0.7 mg/l, are irrelevant to an evaluation of CWF. We examine each of these studies below.

That few adult studies are available has been noted elsewhere. Garcia¹³ stated that very limited information exists in the literature about caries incidence in adults, and Newbrun¹⁰⁸ identified only seven adult studies; he commented that very few acceptable data exist and that the comparison was either between those living in low-fluoridated and high-fluoridated (greater than optimal) communities or between those living in optimally fluoridated and high-fluoridated communities. Thus, it is not surprising that Truman *et al.*⁸⁰ included “What is the effectiveness of CWF among adults aged ≥ 18 years?” among important unanswered questions.

More recently Slade *et al.*¹⁰⁹ presented an analysis of Australian data from a 2004–2006 survey, and Griffin *et al.*¹¹⁰ did a meta-analysis of several earlier studies. We examine these papers in detail in Appendix 4. Among other problems, both articles (and several studies included in the latter) failed to properly account for different age distributions.

Grembowski *et al.*¹⁰⁷

This study examined Washington state employees and spouse-dependents aged 20–34 years living in Olympia, Seattle, or the Pullman, WA/Moscow,

Table 7 Mean DMFS of each U.S. region by CWF status (1986–1987) from Brunelle and Carlos⁷⁷

Region	Lifelong exposure	No CWF exposure	Population with CWF (%)	Relative Diff (%)
I	3.11	3.45	55	9.9
II	3.08	3.42	49	9.9
III	2.86	2.69	74	–6.3
IV	2.75	3.60	54	23.6
V	2.49	2.71	59	8.1
VI	2.36	3.07	34	23.1
VII	1.42	3.61	19	60.7
U.S.	2.79	3.39	53	17.7

DMFS: decayed, missing, or filled tooth surfaces; CWF: community water fluoridation.

Table 8 Average number of decayed and filled surfaces by period of fluoridated exposure in lifetime from Grembowski *et al.*¹⁰⁷

Period of fluoridation exposure in lifetime	No. of adults	Average age	College degree (%) [*]	Average DFS
No exposure in lifetime	226	30.4	35	27.9
Pre-eruptive exposure patterns (ages 0–5 only or ages 0–14 only)	40	30.1	40	20.0
Post-eruption exposure patterns (ages 15–34 only)	266	30.7	78	22.2
Exposed most of life	63	31.0	72	15.7

^{*}Includes those with a college degree and those with graduate work or a graduate degree.

Idaho area. The data presented in this study are reproduced in Table 8.

Griffin *et al.*¹⁰ paraphrased Grembowski *et al.*¹⁰⁷ claiming that the average 30-year-old adult with continuous lifetime exposure to fluoridated water had 8.7 fewer decayed or filled surfaces, or a 31% reduction compared with 30-year-old adults with no CWF exposure. However, based on the data (Table 8), it is unclear how these figures were estimated.

There are additional problems with Grembowski *et al.*¹⁰⁷ For example, it was stated that “1,066 ... formed the data base for this analysis”; but the paper shows results for only 595 participants, and makes no mention of the other 471 participants. In other words, 44% of the data are unaccounted for.

Grembowski *et al.* described calculating the years of fluoridation exposure for the age ranges: 0–5, 6–14, 15–19, and 20–34 years, to “explore systemic and topical effects.” However, Table 8 has a group described as having an exposure pattern, meaning exposure to CWF for the majority of time during the period of “ages 0–5 only or ages 0–14 only” — it appears to be a hastily created grouping to avoid showing results from the original design. Indeed only 40 adults were in this group, so that they had to qualify their conclusion that “exposure to fluoridated water during childhood has lifetime benefits” with “These results are tentative, however, because the pre-eruptive sample size was small.”

The four groups differed in their education levels as well as their fluoride exposure (Table 8), with the no-exposure group having the lowest percentage with a college degree. The CDC has reported that oral health disparities are associated with lower education level.^{111xiv} Although Grembowski *et al.* pointed out the difference in education level, they did not evaluate the possible impact of this difference on their findings.¹⁰⁷

Grembowski *et al.* revealed that people in the nonfluoridated sites had less untreated decay than in the fluoridated sites. They also pointed out that the

filled component of DFS is influenced by dentists’ treatment decisions. They noted that dentists in nonfluoridated areas may restore teeth in adults more frequently, and that use of identical treatment criteria would “slightly reduce” their estimates of fluoridation’s benefits.

They claimed to offer evidence that exposure to fluoridated water during childhood has a lifetime benefit and concluded that their findings provide support for health officials to continue and expand this public health program. Their data do not support the conclusion.

Eklund *et al.*⁵¹

This study examined the communities of Lordsburg and Deming, New Mexico, with fluoride concentrations of 3.5 and 0.7 mg/l in the drinking water supply, respectively. Subjects were approximately 30–60 years of age, had been born and lived at least the first 6 years of life in the city, and had an unequivocal water history. The main results were summarized in two tables, one for dental fluorosis and one for caries, reproduced in Tables 9 and 10, respectively.

Griffin *et al.*¹⁰ wrote that this work found adults who received a high fluoride concentration experienced 20% fewer carious surfaces. The 20% number was an interpretation from two numbers, 7.0 and 8.7, found at the upper right corner of Table 10. (Note: the unit of measure was teeth, not surfaces.) The authors, however, were less inclined to draw the kind of conclusion that Griffin *et al.*¹⁰ did. They wrote:

The picture is less obvious for dental caries. ... The assessment of dental caries in an adult population is difficult. ... First, it is often difficult to determine why missing teeth were removed. ... Second, it is not

Table 9 Number and percent of subjects by city and fluorosis classification from Eklund *et al.*⁵¹

Fluorosis	Lordsburg (n=164)		Deming (n=151)	
Normal			104	(68.9%)
Questionable			23	(15.2%)
Very mild	1	(0.6%)	17	(11.3%)
Mild	1	(0.6%)	2	(1.3%)
Moderate	37	(22.6%)	5	(3.3%)
Severe	63	(38.4%)		
Very severe	62	(37.8%)		

^{xiv} “Disparities [in dental health] were noticed across all age groups, among racial/ethnic groups, persons with lower education and income, and by smoking status.”¹¹¹

Table 10 Comparison of mean decayed, missing, or filled teeth (DMFT) and selected components by city and age of lifelong resident adults from Eklund *et al.*⁵¹

Age group	Decayed		Missing		Filled		DMFT	
	L	D	L	D	L	D	L	D
All	0.8	0.6	2.8	2.4	2.9	5.4	7.0	8.7
27–40	0.4	0.7	1.3	1.6	3.6	4.4	5.9	6.9
41–50	1.5	0.5	2.4	3.7	2.4	6.6	7.1	11.1
51–65	0.6	0.2	5.6	3.3	2.2	7.3	8.8	11.1

L: Lordsburg; D: Deming

possible to determine whether all filled teeth had a carious lesion as defined by the diagnostic criteria.

In contrast, they concluded that differences between the communities are “obvious and unequivocal” for dental fluorosis. Indeed, no one from Lordsburg escaped dental fluorosis and 76% of them were severe or very severe. At the lower concentration of 0.7 mg/l, Deming had 16% dental fluorosis, including some moderate cases.

Table 10 shows that the higher DMFT in Deming was due to a much higher filled component across all age groups. As with Grembowski *et al.*,¹⁰⁷ Eklund *et al.*⁵¹ noted that the filled component is influenced by dentists’ treatment decisions. On the other hand, the oldest age group in Lordsburg had many more missing teeth, similar to other studies that found a relationship between high fluoride exposure and tooth loss.^{112,113}

Costs of dental treatments

Costs of dental treatments consist of dental fees and lost productivity. Griffin *et al.*¹⁰ used survey data for the dental charge,¹¹⁴ which may differ from the charge in a competitive market, and therefore not be representative of the resource costs. Assumption (6) holds that all fillings are single-surface fillings. This overestimates dental costs, since a three-surface cavity does not require three times more resources than a one-surface cavity requires, in terms of either time lost or dentist’s effort. In fact, the fees in the survey were \$53.60 and \$83.27 for one- and three-surface amalgam fillings, respectively.¹¹⁴ Griffin *et al.* used the U.S. average hourly wage for the productivity cost. Average hourly wage overestimates productivity cost, since another central argument for CWF is equity, i.e. it is supposed to be particularly beneficial to low-income people.

Minimal corrections

In this section, we show how the defects in the derivation of CWF benefits, or gross savings, discussed above can be corrected.

Costs of dental treatments

The resource value of a treatment is best represented by the allowable charge from a widely accepted insurance fee schedule. Fee schedules may vary for a number of reasons, but the relative values among closely related procedures tend to be stable.

Table 11 shows the allowable charges for amalgam fillings from two large payers, one from a public payer¹¹⁵ and one from the largest commercial payer (private communication). The payments are not proportional to the number of surfaces involved, and Assumption (6) in Table 2 clearly overestimates the dental charges. Using these relativities and two assumptions a new gross savings estimate will be provided.

Our first assumption is that the average number of decayed surfaces per filling is two and the average dental fee is about that of a two-surface filling. For example, a 40% : 30% : 20% : 10% distribution of one-, two-, three-, and four-or-more-surface fillings, respectively, produces such averages using the relativities in Table 11. Our second assumption is that each equivalent two-surface filling costs 1 hour in lost wages.

Brown and Lazar¹¹⁴ reported that there were more two-surface fillings than one-surface fillings in the 1990 survey and that the number of one-surface fillings has been dropping faster despite a vastly increased number of examinations. Since the more the distribution is weighted toward more-surface decays the less gross savings there are, our first assumption likely overestimates gross savings.

Table 11 Allowed charges and their relativities for amalgam fillings from two insurance fee schedules

Surfaces	Denti-Cal (CA Medicaid, \$)	Delta Dental (San Diego area, \$)
One	39 (1)	72 (1)
Two	48 (1.23)	87 (1.21)
Three	57 (1.46)	108 (1.50)
Four or more	60 (1.54)	118 (1.64)

Using the more generous 1.23 factor from Denti-Cal to calculate a correction, the average cost per carious surface, \$54+\$18, in Step 1 is changed to

$$(1.23 \times \$54 + \$18)/2 = \$42.21 \quad (4)$$

The \$54 fee for a one-surface amalgam filling was based on a survey of about 5% of U.S. dentists in private practice.¹¹⁴ We argue that the allowed charge from a major commercial dental insurer better represents the true cost of resources, and we have an actual allowable charge of \$72 from the San Diego area (Table 11). The cost of living in San Diego is 1.43 relative to the U.S. average.³¹ Using that index would give a one-surface amalgam cost of \$72/1.43=\$50.35 today. It is reasonable then to keep the national average assumption at \$54, which is 38% higher than the current California Medicaid payment rate.

The \$18 opportunity cost was a U.S. average hourly wage. The 2010 U.S. median and mean hourly wages are reported to be \$12.68 and \$19.21, respectively.¹¹⁶ As equity is the other strongest appeal of CWF, the median wage is more appropriate than the mean wage for representing productivity loss. Substituting the \$12.68 for the \$18 in equation (4) to obtain an updated average cost per carious surface gives

$$(1.23 \times \$54 + \$12.68)/2 = \$39.55 \quad (5)$$

This value replaces the \$72 in equation (1) in Step 2. The final result is that the \$19.12 PPPY gross savings in Step 5 changes to

$$\$19.12 \times (\$39.55/\$72) = \$10.50 \text{ PPPY} \quad (6)$$

Averted caries — a consistent approach

Calculating averted caries as a product of no-CWF Incidence and CWF Effectiveness is fundamentally unsound. Griffin *et al.*¹⁰ could have derived a self-consistent averted caries directly from Brunelle and Carlos,⁷⁷ the results from which are summarized in the first six columns in Table 12.

As it was assumed that CWF benefit begins at age 6 years and the caries aversion begins after 1 year of exposure [Inputs (f) and (h) in Table 2], the first annualized data point (difference in DMFS) is at age 7 years with 1 year of exposure. This procedure provides 11 data points, as illustrated in the last three columns in Table 12. Taking the mean of the 11 data points gives the average annual DMFS difference (0.11), which can be used as the averted tooth decay surfaces PPPY.

Thus a self-consistent derivation yields an averted DMFS PPPY of 0.11, not 0.19. Applying this correction to the previous adjustment, the gross savings is further reduced to

$$\$10.50 \times (0.11/0.19) = \$6.08 \text{ PPPY} \quad (7)$$

Lack of evidence for adults

Since there is no real evidence that CWF prevents caries in adults, we present hypothetical scenarios; each scenario assumes that the caries aversion rate extends to a given age.

To calculate the estimate for each scenario, Step 4 is modified by summing the weighted costs to the cut-off age. Thus, if CWF is effective to age 19, 29, 39, or 64 years, the national average lifetime cost averted per decayed surface becomes \$32.56, \$52.98, \$74.48, or \$100.62, respectively, prior to the corrections. The ratio of each of the lifetime costs to \$100.62 is how the gross savings is reduced in each age scenario.

Table 12 Summary data from Brunelle and Carlos,⁷⁷ differences between no exposure and lifelong exposure groups, and estimate of averted caries based on the data

Age	Lifelong exposure			No exposure		Years after age 6	Difference in mean DMFS	
	U.S. population	Children examined	Mean DMFS	Children examined	Mean DMFS		Cumulative	Annual
5	2,552,751	227	0.03	229	0.10			
6	3,980,732	705	0.14	645	0.14			
7	3,578,063	764	0.36	780	0.53	1	0.17	0.17
8	3,211,415	782	0.64	757	0.79	2	0.15	0.08
9	3,332,326	766	1.05	811	1.33	3	0.28	0.09
10	3,357,708	802	1.64	710	1.85	4	0.21	0.05
11	3,179,166	716	2.12	756	2.63	5	0.51	0.10
12	3,206,386	649	2.46	687	2.97	6	0.51	0.08
13	3,229,289	616	3.43	613	4.41	7	0.98	0.14
14	3,473,894	590	4.05	600	5.18	8	1.13	0.14
15	3,552,049	504	5.53	559	6.03	9	0.50	0.06
16	3,581,737	529	6.02	551	7.41	10	1.39	0.14
17	3,045,456	515	7.01	535	8.59	11	1.58	0.14
Total	43,280,972	8,165	2.66	8,233	3.24		Average =	0.11

DMFS: decayed, missing, or filled tooth surfaces.

Thus the gross savings of \$6.08 PPPY becomes \$1.97, \$3.20, \$4.50, or \$6.08 PPPY if the CWF benefit extends to age 19, 29, 39, or 64 years, respectively.

Discussion

Corrected net savings

In the previous section, we showed how several defects in the derivation of the \$19.12 PPPY estimate of CWF benefit can be corrected. The corrected gross savings estimate is \$1.97, \$3.20, \$4.50, or \$6.08, if the CWF benefit extends to age 19, 29, 39, or 64 years, respectively.

As described earlier, the cost estimates of \$0.50 for large water systems and \$3.17 for small systems¹⁰ were not based on reality. We used a detailed engineering projection report prepared for a system that has a decade of CWF experience and has characteristics of both large and small systems to obtain a more reasonable estimate of \$3 and \$10 PPPY, respectively.

The net savings are summarized in Table 13. In short, there is minor savings only if the caries aversion attributed to CWF extends to old ages and only in large systems. Thus minimal correction to several methodological problems eliminates most of the savings. When we include the estimated cost of treatment of dental fluorosis of at least \$3.24 PPPY, there are no savings left in any scenario in Table 13.

Topical effect

There is a question whether any savings for averted caries are real, because the mechanism by which fluoride is thought to help prevent caries is topical. Griffin *et al.*¹⁰ explained that Assumption (1) in Table 2 was due to the benefit from water fluoridation being primarily “topical and post-eruptive.” The CDC¹ states that fluoride prevents dental caries predominantly after eruption of the tooth into the mouth, and its actions are primarily topical. Both articles referenced Featherstone,¹¹⁷ who stated that the effect of ingested fluoride on caries is minimal.

Current official justification for continuing promotion of CWF is that fluoride in tap water provides teeth with continuous exposure from water, beverages, and foods prepared with tap water, and that a constant low concentration of fluoride is maintained in the dental plaque and saliva all day.¹¹⁸ The first point can be left to common sense. The second point contradicts current oral hygiene recommendations concerning plaque and has been refuted concerning

saliva. The concentrations of fluoride in ductal saliva, approximately 0.016 ppm in fluoridated areas and 0.006 ppm in nonfluoridated areas, are “not likely to affect cariogenic activity.”¹¹⁹

In addition, fluoride, by ingestion or by contact, negatively affects enamel remineralization in individuals with low calcium and magnesium in teeth enamel (usually due to undernutrition).⁵⁷ Hence, CWF may increase caries in people with poor nutritional status.

Equitable?

That CWF particularly helps the poor at a very low average cost to all has been an integral argument for CWF. We briefly examine the equity aspect.

A major review of the effectiveness of CWF states “There is some evidence [strength of evidence=C] that water fluoridation reduces inequality in dental health across social classes in 5- and 12-year-olds [in England] ... The small quantity of studies, differences between these studies, and their low quality rating, suggest caution in interpreting these results.”⁷¹

In Appendix 5, we point out two studies missing from the review of Truman *et al.*⁸⁰ In the first study Szpunar and Burt⁴⁹ reported that a fluoride concentration of 1.0 or 1.2 mg/l prevented caries, but 0.8 mg/l did not. (The current CWF range is 0.7–1.2 mg/l, and HHS proposed to decrease it to 0.7 mg/l.)³ This study chose a predominately white township bordering Detroit, instead of the largely black and long fluoridated Detroit, to represent a fluoridated community. Burt *et al.*¹²⁰ reported that only 0.2% of low-income adults in Detroit in the 14–35 age group (born after CWF started in 1967) were caries free (compared to 55% of children up to age 12+ in the unfluoridated community in Szpunar and Burt).⁴⁹

In the second study, Shiboski *et al.*¹²¹ found that the prevalence of early childhood caries was not affected by fluoridation status. Among Head Start (low income) children, the most fluoridated ethnic group (Asians, with 69% in fluoridated areas) had the worst tooth decay status. Among non-Head Start children, the most fluoridated ethnic group (Asians, with 81% in fluoridated areas) had tooth decay rates similar to those of white Head Start children, with 12% in fluoridated areas.

Truman *et al.*⁸⁰ stated: “The current burden of poor oral health continues to disproportionately

Table 13 Present-day, corrected estimates of net savings (\$) per person per year from water fluoridation

System size	Cost (\$)	Benefit (\$) ⇒	CWF benefit extends to age			
			19	29	39	64
			1.97	3.20	4.50	6.08
Large	3		–1.03	0.20	1.50	3.08
Small	10		–8.03	–6.80	–5.50	–3.92

affect communities with large numbers of African Americans, American Indians, Hispanics, the poor, and the disabled of any race or ethnic group.” (See also CDC.)¹¹¹ This was not the case historically. Citing many studies published between 1933 and 1947, Finn⁷³ stated that blacks had less caries than whites. On the other hand, recent data indicate that dental fluorosis is more prevalent among blacks and Hispanics,^{47,111} suggesting that lack of fluoride is not an explanation for their poorer oral health.

Conclusion

For decades, the U.S. federal and state governments have promoted CWF to improve dental health of residents at low costs. Yet, in spite of the presumed savings in dental costs to Americans due to widespread use of CWF, employment of dentists is projected to grow by 16% between 2012 and 2022 (vs. 11% for all occupations),¹²² and cosmetic dentistry in the U.S. has grown to be a multi-billion dollar industry.¹²³ We have shown that the promise of reduced dental costs was based on flawed analyses. In particular, the primary cost-benefit analysis used to support CWF in the U.S. assumes negligible adverse effects from CWF and omits the costs of treating dental fluorosis, of accidents and overfeeds, of occupational exposures to fluoride, of promoting CWF, and of avoiding fluoridated water. In assessing the benefits, it ignores important large data sets and assumes benefits to adults that are unsupported by data. Thus this analysis, as well as other economic analyses of CWF (Appendix 2), falls short of reasonable expectations for a cost-benefit analysis from a societal perspective. Minimal correction of methodological problems in this primary analysis of CWF gives results showing substantially lower benefits than typically claimed. Accounting for the expense of treating dental fluorosis eliminates any remaining benefit.

Disclaimer Statements

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Appendix 1: State governments repeating the \$1 saves \$38 claim

This appendix gives a list of U.S. State governments, other U.S. government agencies, and Canadian sources that repeat the claim that \$1 saves \$38. Mississippi and Oregon did not repeat CDC's claim of \$1 saves \$38. We include them in the list because they repeat the net savings PPPY estimated by Griffin *et al.*¹⁰ Mississippi provided its own cost estimate (\$1 to \$2 PPPY), but the estimated net savings are from Griffin *et al.*¹⁰ All URLs were last accessed on August 13–15, 2013, except Canadian sources, which were last accessed on October 15, 2013. † indicates state legislative records. The list may not be exhaustive.

1. *Alabama*: “For most cities, every \$1 invested in fluoridation saves \$38 in dental treatment costs.” http://medicaid.alabama.gov/documents/2.0_Newsroom/2.5_Presentations/2.5_Medical_Services_Presentations/2.5_OHCA_Goode_Fluoridation_9-23-10.pdf
2. *Alaska*†: “It is one of the most efficient ways of providing cost effective preventative health care; every \$1 spent on fluoridation saves \$37 in future dental expenses.” http://www.legis.state.ak.us/basis/get_single_minute.asp?session=24&beg_line=00787&end_line=00956&time=1605&date=20060228&commHES&house=H
3. *Arizona*: “Research shows that every \$1 invested in water fluoridation saves \$38 in unnecessary costs for dental treatment.” <http://directorsblog.health.azdhs.gov/?p=1072>
4. *Arkansas*: “Fluoridation saves money. According to the the Centers for Disease Control and Prevention (CDC), every \$1.00 spent on fluoridation prevents \$38 in dental treatment.” <http://www.healthy.arkansas.gov/programsServices/oralhealth/Documents/FactSheetFluoridation.pdf>
5. *California*: “Every \$1 spent on fluoridation saves \$38 in dental treatment costs.” <http://www.cdph.ca.gov/programs/Pages/FluoridationInformation.aspx>
6. *Colorado*: “Fluoridation is proven to reduce tooth decay over a person's lifetime, and is a cost-effective prevention strategy, saving \$38 for every \$1 invested and preventing up to 40 percent of tooth decay.” Select “The State of Health – Full report” on <http://www.colorado.gov/cs/Satellite/HealthCareReform/CBON/1251641417543>
7. *Connecticut*: “Every dollar spent on fluoridation saves \$38 in avoided dental bills.” http://www.ct.gov/dph/lib/dph/drinking_water/pdf/Water_Fluoridation_Fact_Sheet.pdf
8. *Delaware*: “In fact, every \$1 invested in fluoridation saves at least \$38 in costs for dental treatment.” <http://www.dhss.delaware.gov/dhss/pressreleases/2013/cdcfluoridationaward-021313.html>
9. *Florida*: “The return on investment is tremendous — with various studies reporting \$38–\$80 in dental treatment cost savings for each dollar invested in community water fluoridation.” <http://www.doh.state.fl.us/family/dental/perspectives.pdf>
10. *Georgia*: “Water fluoridation has been shown to reduce dental decay by 20–40% in fluoridated communities, and results in a savings of \$38 in future

- dental expenditures for each \$1 invested in fluoridation.” <http://www.dph.ga.gov/programs/oral/index.asp>
11. *Illinois*: “Studies have shown that for every dollar invested in fluoridation, as much as \$38 is saved in dental treatment costs.” <http://www3.illinois.gov/PressReleases/PrintPressRelease.cfm?RecNum=2846>
 12. *Indiana*: “CDC data shows that for every dollar spent on water fluoridation, \$38 are saved in reduced costs for dental care.” <http://www.in.gov/isdh/23287.htm>
 13. *Iowa*: “In fact, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” http://publications.iowa.gov/6430/1/may_jun2008%5B1%5D.pdf
 14. *Kansas*: “For most cities, on average, every \$1 spent toward community water fluoridation saves \$38 in dental treatment costs.” http://www.kdheks.gov/ohi/download/Burden_of_oral_disease_in_Kansas.pdf
 15. *Louisiana*: “Each \$1 spent saves \$38 in future dental treatment costs.” http://new.dhh.louisiana.gov/assets/oph/Center-EH/operator/04-FlouridePresentation_Exercise.pdf
 16. *Maine*: “In fact, for every dollar spent on community water fluoridation up to \$42 is saved in treatment costs for tooth decay.” <http://www.maine.gov/dhhs/mecdc/population-health/odh/water-fluoridation.shtml>
 17. *Maryland*: “For most cities, every \$1 invested in community water fluoridation saves \$38 in dental treatment costs.” <http://phpa.dhmdh.maryland.gov/oralhealth/docs1/community-water-fluoridation.pdf>
 18. *Massachusetts*: “In fact, for every dollar spent on community water fluoridation, up to \$38 is saved in treatment costs for tooth decay.” <http://www.mass.gov/eohhs/docs/dph/com-health/oral-fluoride-community-water-factsheet.pdf>
 19. *Michigan*: “For most cities, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” http://www.michigan.gov/documents/mdch/2012_MOHC_CWF_Tool_Kit_395210_7.pdf
 20. *Minnesota*: “Recently published CDC studies have indicated that, for most cities, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” <http://mn.gov/health-reform/images/WG-PPH-2012-04-Public-Comments-Minnesota-Fluoridation-Plan.pdf>
 21. *Mississippi*: “In Mississippi, the cost of water fluoridation is usually between one and two dollars per person per year and saves \$16 – \$19 per person per year in dental treatment costs.” http://www.msdc.state.ms.us/msdcsite/_static/resources/1067.pdf
 22. *Missouri*: “For most cities, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” <http://health.mo.gov/living/families/oralhealth/pdf/oralhealthbrochure.pdf>
 23. *Nevada*: “It has been estimated that for every one dollar invested in community water fluoridation there is a savings of approximately \$38 or more in averted dental treatment costs.” <http://health.nv.gov/PDFs/OH/BurdenOfOralDisease2012.pdf>
 24. *New Jersey*[†]: “An analysis by the CDC has found that, in communities of more than 20,000 people where it costs about 50 cents per person to fluoridate the water, every one dollar invested yields \$38 savings in dental treatment costs.” ftp://www.njleg.state.nj.us/20082009/A4000/3709_I1.DOC
 25. *New York*: “Every dollar spent on fluoridation on average saves \$38 in avoided dental bills.” <http://www.health.ny.gov/prevention/dental/fluoridation/cost.htm>
 26. *North Carolina*: “For every dollar spent on community water fluoridation, approximately \$38 is saved in treatment costs for tooth decay.” <http://www.ncdhhs.gov/dph/oralhealth/services/fluoride.htm>
 27. *North Dakota*: “According to the U.S. Centers for Disease Control and Prevention, for every dollar spent on community water fluoridation, up to \$38 is saved in treatment costs for tooth decay.” http://www.ndhealth.gov/oralhealth/Publications/2012-2017_Oral_Health_State_Plan.pdf
 28. *Ohio*: “Every dollar spent on fluoridation saves more than \$40 in dental care.” <http://www.odh.ohio.gov/features/odhfeatures/PublicHealthWeek/Friday.aspx>
 29. *Oklahoma*: “For most cities, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” http://www.ok.gov/health/Child_and_Family_Health/Dental_Health_Service/Community_Water_Fluoridation_Program/
 30. *Oregon*: “Saves per person per year: \$15.95 in small communities; \$18.62 in large communities.” <http://public.health.oregon.gov/PreventionWellness/oralhealth/Documents/fluoride-program-module1.pdf>
 31. *Pennsylvania*[†]: “However, for most cities, every \$1.00 invested in water fluoridation saves \$38.00 in dental treatment costs.” http://www.legis.state.pa.us/WU01/LI/CSM/2009/0/25_X.pdf
 32. *Rhode Island*: “For every dollar spent on community water fluoridation, up to \$38 is saved in treatment costs for tooth decay.” <http://www.health.ri.gov/healthyliving/oralhealth/about/fluoridation/>
 33. *South Carolina*: “For most cities, every \$1 invested in community water fluoridation saves \$38 in dental treatment costs.” http://www.scdhec.gov/health/mch/oral/docs/water_fluoridation_flyer.pdf
 34. *Tennessee*: “Every dollar spent on fluoridation saves \$38 in avoided dental bills.” <http://health.tn.gov/oralhealth/communityBenefits.html>
 35. *Texas*: “A CDC study found that for communities with 20,000+ residents, every \$1 invested in community water systems with fluoridation yields \$38 in savings from fewer cavities treated.” <http://www.dsds.state.tx.us/dental/Oral-Health-in-Texas-2008-Report.doc>
 36. *Utah*: “... in most communities, every \$1 invested in fluoridation saves \$38 or more in treatment costs.” http://health.utah.gov/oralhealth/resources/oralHealthReport_2011webFinal.pdf
 37. *Vermont*: “For every dollar spent on fluoridation, up to \$38 is saved in costs associated with dental care.” <http://healthvermont.gov/family/dental/fluoride/>
 38. *Virginia*: “CDC recommends water fluoridation as a safe, effective, and inexpensive method of preventing decay; every \$1 invested in fluoridation saves approximately \$38 in costs for dental treatment.” <https://www.vdh.virginia.gov/news/PressReleases/2011/110411FlouridationAward.htm>
 39. *Washington*: “For most communities, every \$1 invested in water fluoridation saves \$38 in dental

- treatment costs.” http://www.doh.wa.gov/Portals/1/Documents/Pubs/160-021_Fluoridate_Facts.pdf
40. *West Virginia*: “For every one dollar invested in community water fluoridation, \$38 in dental treatment costs are saved.” http://www.wvdhhr.org/mcfh/ica/wv_oral_health_plan_2010.pdf
 41. *Wisconsin*: “For most cities, every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” <http://www.dhs.wisconsin.gov/publications/P0/p00457.pdf>
 42. *Indian Health Service*: “Cost savings — for every \$1 spent, \$38 saved.” <http://www.ihs.gov/doh/clinicmanagement/ohpgdocs/chapter4/community%20water%20fluoridation.doc>
 43. *National Institute of Dental and Craniofacial Research*: “An economic analysis has determined that in most communities, every \$1 invested in fluoridation saves \$38 or more in treatment costs.” <http://www.nidcr.nih.gov/OralHealth/Topics/Fluoride/StatementWaterFluoridation.htm>
 44. *Chief Dental Officer of Canada*: “Cooney said the Center for Disease Control estimates every \$1 invested in fluoridation saves \$38 of dental treatment.” <http://www.insidehalton.com/news-story/2895950-fluoride-to-stay/>
 45. *New Brunswick*: “A study from the Centre for Disease Control in the United States estimated that for every \$1 invested in community water fluoridation saves \$38 in costs for dental treatment.” <http://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/HealthyEnvironments/FluorideStatement.pdf>
 46. *Ontario*: “The CDC estimates \$38 in avoided costs for dental treatment for every \$1 invested in community water fluoridation.” http://www.health.gov.on.ca/en/news/bulletin/2011/hb_20110404_2.aspx
 47. *Quebec*: Institut national de santé publique du Québec. “According to the CDC, US\$38 could be saved for every dollar invested in fluoridation in a community of 20,000 inhabitants.” <http://www.inspq.qc.ca/pdf/publications/705-WaterFluoridation.pdf>
 48. *Saskatchewan*: “Every \$1 invested in water fluoridation saves \$38 in dental treatment costs.” <http://www.health.gov.sk.ca/Default.aspx?DN=7d4df43c-3e21-49cf-9ef2-4b1feca2b4fd>
 49. *Winnipeg*: “It is also the most cost-effective means of fluoride delivery, with every dollar spent on water fluoridation saving an estimated \$38 in treatment costs for tooth decay.” <http://www.wrha.mb.ca/wave/2011/11/fluoride-facts.php>

Appendix 2: Other cost-benefit studies

Earlier economic evaluations of CWF have been reviewed by White *et al.*¹¹ Mariño *et al.*¹²⁴ summarize a number of studies for caries prevention programs but do not discuss those studies in detail. Griffin and Jones¹²⁵ reviewed Mariño *et al.* Other studies examined dental insurance data and did not find CWF to be associated with lower utilization or costs of dental services.^{126,127}

In this appendix, we comment on several additional recent CWF cost-benefit studies: Campain *et al.*¹²⁸ assessed the impact of changing dental needs over time on the cost savings from CWF in Australia. O’Connell

*et al.*¹²⁹ estimated the cost savings associated with CWF in Colorado and potential savings if the unfluoridated communities were to implement CWF. Wright *et al.*¹³⁰ investigated whether it would be cost-effective to fluoridate water supplies that were not fluoridated in New Zealand. Kroon and van Wyk¹³¹ examined whether water fluoridation is still a viable option to reduce dental caries in South Africa by addressing concerns about cost and effectiveness. Tchouaket *et al.*¹³² estimate the cost savings in Quebec resulting from CWF; since this is a 2013 paper claiming to use an “innovative approach” we will comment on it separately.

Costs

As with Griffin *et al.*,¹⁰ both O’Connell *et al.*¹²⁹ and Kroon and van Wyk¹³¹ based their cost estimates on Ringelberg *et al.*¹⁴ Wright *et al.*¹³⁰ hypothetically estimated capital and annual operating costs “by consulting equipment providers and operators of fluoridation systems.” These studies all adopt the assumption of a 15-year replacement schedule except Kroon and van Wyk,¹³¹ who are more detailed in the cost aspect and have a separate replacement schedule of 8 years for mechanical and electrical plant. On the other hand, Campain *et al.*¹²⁸ used a simple A\$0.27 PPPY but provided no details.

Estimates of averted caries

O’Connell *et al.*¹²⁹ essentially used the base case from Griffin *et al.*¹⁰ They used the 25% value for Effectiveness. For Incidence, they used the base case (middle row in Table 6 in the main text) with minor changes: They reduced the 0.77 and 1.09 values by 20.9% for the secular trend, but decided that the 0.43 value for age 45–65 years was too low; instead they used 1.08 and 1.31 for ages 45–64 years and ages 65 years and older, respectively, through consultation with Griffin. The resulting average averted caries is 0.2 DMFS, almost the same value (0.19 DMFS) as in Griffin *et al.*,¹⁰ but O’Connell *et al.* applied it to all ages from age 5 years.

Campain *et al.*¹²⁸ assumed uniform but changing effectiveness for all ages from age 6 years. They picked a value within the range of numbers reported from a set of references, including several discussed in this article.^{77,107,108,133} Thus they assumed that CWF effectiveness was 50% in the 1970s, 30% in the 1980s, and 25% in the 1990s. For Incidence they constructed a matrix of year versus age range from their literature search and imputed values where information was missing.

Kroon and van Wyk¹³¹ cited the 15% Effectiveness from Petersen *et al.*,¹³⁴ and also modeled the benefit using 30% and 50%. This Effectiveness is applied to teeth, not surfaces as in the other studies. For Incidence they used local survey data by city. The

method, according to Kroon and van Wyk,¹³⁵ is to divide the DMFT survey of, say, 15-year-olds by $15 - 6 = 9$ and assume it is the same for people of all ages, including those age 6 years and less. The authors noted that the mean DMFT for 12-year-old South African children decreased from 1.73 in 1988–1989 to 1.05 in 1999–2002 in this unfluoridated country.

Wright *et al.*¹³⁰ did not try to estimate a value for Effectiveness. For children aged 4–13 years, they compared treatment data for restorations and extractions for both deciduous and permanent teeth to calculate savings on dental fees. They used 1996 Wellington and Canterbury data without supporting the selection, since such data are available for all New Zealand and for all years. For ages 14–34 years, they used a 0.29 averted DFS number from Grembowski *et al.*¹⁰⁷ (but increased it to 0.59 surfaces for Maori) and assumed no effectiveness after age 34 years.

Costs of dental treatments

On productivity loss, Campain *et al.*¹²⁸ and O'Connell *et al.*¹²⁹ used approaches similar to Griffin *et al.*¹⁰ Wright *et al.*¹³⁰ and Kroon and van Wyk¹³¹ did not include productivity cost. Below, we note the variations in the methods of estimating dental fees in these studies.

Kroon and van Wyk¹³¹ estimated caries in DMFT and used the average cost of two-surface fillings for the dental charge for each DMFT. Wright *et al.*¹³⁰ used the treatment database from Wellington and Canterbury for children ages 4–13 years and included both deciduous and permanent teeth. For those ages 14–34 years, they calculated the cost of a single-surface filling using an average dentist hourly rate (with inflation) and the 15 minutes time needed to put in the filling. They assumed that fillings are replaced every 8 years.

Campain *et al.*¹²⁸ and O'Connell *et al.*¹²⁹ attempted to include more-surface fillings, composite fillings, and crown or extraction costs. However, the calculations lack transparency, and there are questions as to whether the interaction between extractions and restorations is handled properly in the latter. The most serious problem with the two studies is that they calculated the dental fees plus productivity cost on a *per visit* or *per service* basis, rather than normalizing that cost to a *per surface* basis, because one visit or service may treat more than one surface. By multiplying the estimated averted DMFS by a cost per visit or service rather than a cost per surface, they overestimated the averted costs of dental services. In addition, crowns or extractions are not always due to caries, but may have other causes. Thus these approaches lead to a far worse overestimation than Assumption (6) in Griffin *et al.*'s analysis.¹⁰

Tchouaket *et al.*¹³²

A paper by Tchouaket *et al.* claims to use an “innovative approach” to assess the economic value of water fluoridation for Quebec, in which only 2.7% of the population is fluoridated.¹³² The presentation lacks critical information and contains fundamental errors. The authors claim that their analysis “adopted a societal perspective that allowed us to track all the costs and effects of the intervention.” However, they did not include or mention the costs of treating dental fluorosis or any of the costs we discussed under “Other costs.” All \$ signs in this section are Canadian dollar, C\$.

Tchouaket *et al.* produced \$1.93, \$2.05, or \$2.25 PPPY as the costs of CWF, using information from the few fluoridated municipalities in Quebec. Supposedly, the three values correspond to using 3%, 5%, or 8% to amortize the subsidies received by these municipalities over 20 years. They listed several salary rates but provided no other quantitative information, thus readers are not able to repeat any calculations or confirm the numbers.

For CWF benefits, Tchouaket *et al.* did not try to estimate averted caries. Instead, they estimated the yearly costs associated with restorative dental treatments in Quebec to be \$532.08, \$532.87, or \$534.05 PPPY, depending on discount rates. They compared these with the cost values above at various hypothetical values of CWF effectiveness, and claimed that CWF is cost-effective even at 1% effectiveness and that Quebec saves more than \$560 million a year at an “expected average effectiveness of 30%.”

It should be noted that the \$532–\$534 PPPY *restorative* expense exceeds the actual per capita spending on *all* dental services in Canada, which was reported to be \$380.83 in 2009 and \$399.10 in 2011.^{136,137} Tchouaket *et al.* confused untreated tooth decay and dmft/DMFT (decayed, missing, or filled teeth) — only untreated decay (“d” or “D” in dmft/DMFT) requires a restoration service. A filled tooth might need a replacement at some point in the future, but definitely not every year.

The authors calculated the number of teeth restored in a year by multiplying the number of persons who used dental services within the past year, by age group, times the dmft/DMFT index for that age group. First, the average dmft/DMFT values given in the paper are clearly cumulative, not an annual increment. Only a small percentage of these would correspond to untreated decay that requires a restoration service.^{xv} Second, Tchouaket *et al.*

^{xv} While the level of caries experience is very high in Quebec adults aged 35–44 years, only 1.8 out of 148 surfaces are decayed (in need of treatment), on the average, and more than half of the people (55.5%) have no decayed surfaces.¹³⁸

apparently failed to recognize that routine dental cleaning and examinations are common in developed countries, thus having used dental services does not equate to having had a tooth restored.

Data in the paper indicate that 25–61% of children (depending on age) were caries free, while 78–91% had visited a dentist in the past year; thus many of the children utilizing dental services had not had any restorations, that year or previously. The 35–44 age group had an average 20 DMFT, and 69% used dental services in the past year. Tchouaket *et al.*'s calculations assumed that each of the 69% (724,000 people) had 20 restorations in 1 year. The correct interpretation of the data is that the average Quebecer 35–44 years old had accumulated 20 DMFT between the age of about 6 and the time of the survey, about 29–38 years, or approximately 0.5–0.7 new DMFT on average per year. This is consistent with the increments of 0.2–0.6 dmft/DMFT for children that can be derived from other information in the paper.

Tchouaket *et al.* summarized fees for treatment of one cavity, including transportation costs and lost wages. A total fee for each of three categories (by type of tooth and age group) was not provided. The text and table in the paper disagree on the calculation of transportation costs, and some information in the summary table is not explained. The text indicates that those age 14 years or older require two separate trips, one for a complete examination and one for the restoration to treat one cavity. However, fees for routine dental exams should not be counted toward costs that can be saved by CWF.

The authors appear to have taken their calculated number of teeth restored for a given age group times the cost per restoration for that age group to obtain the total cost of restorations in one year for that age group. The combined total cost for the three age groups included in the analysis (5–8, 11–14, 35–44;

1.7 million people total) appears to have been averaged over the entire population of Quebec (7.9 million people) to obtain their final average of \$532–\$534 PPPY. This brings up the question of whether other age groups (9–10, 15–34, and 45+) were assumed to have no restorations. However, averaging (incorrectly) over the entire population rather than over the relevant age groups compensates partly for the great overestimation in the number of restorations per year.

The three values \$532.08, \$532.87, or \$534.05 supposedly differ in the different discount rates (3%, 5% and 8%) used to calculate repeat treatment. Estimating the dental cost for replacement services is not new, but the scant description provided in two sentences does not show what the authors have done or allow readers to understand why the three results are so close.

Tchouaket *et al.* admitted that basing the 2010 economic value on caries prevalence data more than a decade old is a limitation. This is a legitimate concern due to the well known “secular decline” of caries in developed countries.⁷² However, the authors argued that because the percentage of the Canadian population with at least one dental cavity has remained stable at 96%, the average DMFT in Quebec likely has remained the same or even increased. Actually, the 96% figure applies only to dentate adults aged 20–79 years. For children aged 6–11 years and adolescents aged 12–19 years, the corresponding national figures are less than 60%.¹³⁶ Factual error aside, this argument reflects their confusion with the differences between cumulative DMFT and new caries and with properly defined populations.

Appendix 3: Accidents, overfeeds and damages

A number of accidents, overfeeds, and damages caused by CWF are summarized in Table 14.

Table 14 Examples of accidents, overfeeds and damages from CWF

Location and date	Description
1. Deltona, FL September, 1994	“A tanker truck cracked open on I-4 near Deltona ... and released 4,500 gallons of fluorosilicic acid in one big whoosh.” It was “one of the worst chemical spills in Volusia county’s history.” 2,300 people were evacuated, and more than 50 people were sent to hospitals with complaints of skin and respiratory irritations, including some hours after the spill. Motorists were instructed not to wash off the chemical film with water as that could cause respiratory problems to anyone nearby. EPA officials felt it was “a significant health hazard as far as ground water.” The agency ordered around-the-clock cleanup on I-4 that lasted days.
2. Lowell, AR December, 1996	Beaver Water District fluoridated Fayetteville with fluorosilicic acid and Springdale with sodium fluorosilicate powder prior to 1992. When CWF was resumed in 1996, adding Rogers and Bentonville, the decision was made to use the powder, as fumes from the liquid had severely damaged the injection facility in the past.
3. Malvern, AR March, 1997	A water plant operator at the Kimzey Regional water plant was sprayed by fluorosilicic acid at work. According to his 2012 personal account, he became 100% disabled for almost 14 years and still requires large amounts of pain medicine. He suffered permanent health damage, including losing all his teeth.
4. Charleston, SC August, 2000	A worker accidentally put the wrong chemical in the fluoride tank in the Hanahan Water Treatment Plant. The chemical “reacted; it released a large amount of heat; the fiberglass essentially melted; the gas flowed; it just burst.” This resulted in a 20,000-gallon acidic mess. The total bill for cleanup and repairs was about \$250,000.

Table 14 Continued

Location and date	Description
5. Wakefield, MA August, 2000	An overdose of fluoride seeped into the town water supply. Officials made door-to-door warnings around the pumping station. The public became aware only after a local news station called the town. Authorities said there were no reports of illness; but Linda Collins disagreed, "I was crazy dizzy and I had the runs. I think it was woefully inadequate the way they notified us," she said. "Because they didn't."
6. Coos Bay, OR October, 2000	At least 3.5 million gallons of partially treated sewage has spewed into the Coos Bay after 400 gallons of fluorosilicic acid flowed into a sewage treatment plant, killing its bacteria-munching organisms.
7. Fort Wayne, IN February, 2001	About 6,000 gallons of fluorosilicic acid drained from the lower level of the filtration plant into the sewer. The fluoride tank overflowed, and caustic fumes filled the area causing difficulty breathing, chest pains, severe headache and sore eyes in plant workers. Four workers were treated in the hospital.
8. Marlboro, MA October, 2003	A valve malfunction allowed a concentrated level of fluoride to flow into the water system. Workers went door to door to alert nearby customers, flushed water mains, and shut down the plant for some time. Residents and businesses were advised to take extreme care when flushing their pipes, and not to come into contact with the water, which could cause burning, skin irritation, or both.
9. Westminster, MA November, 2005	Emergency crews responded to a chemical spill at the Regional Water Treatment Facility after one of the storage tanks leaked about 750 gallons of fluorosilicic acid. An operator and two colleagues were transported to the hospital.
10. Moncks Corner, SC April, 2006	In the Santee Cooper water treatment plant, a water plant security guard became sick after she walked through a cloud of sodium fluorosilicate. The complaints included having trouble breathing, feeling like something was constantly caught in her throat, and "in the following weeks, Morris's hair started falling out, she developed a rash on her arms and back, and she continued to be wracked with convulsive fits of coughing."
11. Nashville, TN March, 2007	Valve malfunctions caused a fluoride overfeed in Harpeth Valley Utilities District. The Incident Event Log showed that an operator noted abnormal measurements starting at 12:40 a.m. 9 March 2007. Plant workers went through the facility shutting off equipment, conducted frequent water samplings and measurements, performed aggressive and continuous flushing, and contacted authorities. They also prepared for door to door public notifications, fielded incoming calls, responded to media requests, and continued sampling throughout the distribution systems until 17 March 2007. They also retained an outside engineering service to review and provide recommendations for the chemical feed systems.
12. Salt Lake City, UT August, 2007	A fluoride tank overflowed at a water treatment plant. Fluoride (1,500 gallons) spilled into a pond, resulting in an advisory to avoid Parleys Creek for several days. Utility workers used sandbags and a makeshift earthen dam to contain the chemical. Four hazmat teams worked to keep the fluoride from flowing beyond a park at the base of Parleys Canyon. Water was released from a reservoir to flush the chemical from the creek.
13. Conway, AR July, 2008	A 42-inch water pipe corroded to the point of failure, due to the fluoride injection port being mounted too close to a chlorine injection port, necessitating the shutdown of a portion of the plant that was completed only in 2005.
14. Chesterfield, MO February, 2009	Approximately 200 gallons of fluoride spilled from a ruptured tanker truck, which was carrying 4,000 gallons of the chemical at Missouri American Water's central plant. The truck's driver and two employees from the plant were taken to an area hospital.
15. Anchorage, AK April, 2010	A system malfunction at Fort Richardson Water Treatment Plant caused excess fluoride in the drinking water supply. Officials warned "anyone who lives, works on or visits the two posts in Anchorage not to drink the water ... The water also should not be used to brush teeth and wash or cook food. Any ice cubes ... should be thrown out."
16. Asheboro, NC June, 2010	Tank malfunction caused approximately 60 gallons of fluoride to be dispersed into the water system. The news release said: "Residents who consumed a large quantity of water during this period may possibly experience short-term effects such as an upset stomach, vomiting, or diarrhea. The temporary effect from skin contact, such as showering, might include slightly irritated skin."
17. Rock Island, IL March, 2011	Hazmat crews were called to the Rock Island water treatment plant for a spill of hydrofluorosilicic acid from a tanker truck. As plant employees evacuated, crews began suiting up, working quickly to stop the leak that had begun eating through concrete.
18. England, AR April, 2011	A worker mistakenly poured about 10 to 20 gallons of fluoride into a container holding around 150 gallons of bleach. It created a dangerous gas and led to an evacuation of several businesses near the water treatment plant. The worker and an employee from a nearby business were treated for breathing problems. The county Hazmat team cleaned up the area 3 hours later.
19. Hickory, NC August, 2011	The City transferred \$106,713 from capital reserve to maintenance and repair to pay for refurbishing the chemical room and to replace two fluoride tanks. The tanks leaked enough fluoride to degrade the concrete around the containment area and floor.
20. Martinsville, VA February, 2012	The city had to pay \$16,450 in penalties after about 1,000 gallons of fluorosilicic acid leaked from a tank at the city water treatment plant. The spill caused the deaths of an estimated 4,445 fish. Officials said that the ground near the spill absorbed quite a bit of the acid, and how much went into the creek was unknown. "Fluorosilicic acid is 'a very strong acid ... with a very corrosive effect on any metals it touches,' and corrosion caused the pump to fail."
21. Memphis, TN July, 2012	Fluorosilicic acid tank failure along with containment failure caused approximately 1,500 gallons of the acid to be released onto ground at the public utility. Approximately 1.5 acres were impacted. Workers cordoned off the area and placed berm along the west property line to prevent further runoff. The impacted area was to be excavated and soil properly disposed of.

CWF: community water fluoridation.

Additional incidents of acute poisoning have been described elsewhere.^{139,140}

Below are the sources, which are mostly media reports, often reproduced in secondary sources, except for the following: Item 3 is a first-person account; Item 11 is an internal log of the water district obtained by request; Item 19 is a city council record; and Item 21 is a report in the National Response Center database. A compilation of other reports in this database up to February 2005 can be found in ActionPA.¹⁴¹ All URLs for the sources were last accessed on August 20, 2013, except those in Item 4 that were accessed on April 10, 2014.

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2. Lowell, AR. 1996. Adding fluoride costly. Carroll County News. <http://www.carrollconews.com/story/print/1778486.html> and phone conversation with Beaver Water District personnel.
3. Malvern, AR. 1997. The Joe Walls Story by Joe and Jodee Walls, 2012. http://arkansas.securetherepublic.com/www/archiveviewer.php?post_id=1464&post_year=2012
4. Charleston, SC. 2000. Water plant loses fluoride. The Post & Courier. http://nl.newsbank.com/nl-search/we/Archives?p_action=doc&p_docid=111F18B49B49D318&p_docnum=35 and CPW officials treated to plate of headaches. The Post & Courier. http://nl.newsbank.com/nl-search/we/Archives?p_action=doc&p_docid=111F1DB9C2FE DC68&p_docnum=33
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6. Coos Bay, OR. 2000. Fluoride Spill in Oregon. The Oregonian. <http://www.fluoridealert.org/news/fluoride-spill-in-oregon/>
7. Fort Wayne, IN. 2001. Fluoride Spill in Fort Wayne, Indiana. The Journal Gazette. <http://www.fluoridealert.org/news/fluoride-spill-in-fort-wayne-indiana/>
8. Marlboro, MA. 2003. Marlboro water flooded with fluoride — Stuck valve in treatment plant caused toxic release. Worcester Telegram & Gazette. See Item 5 for URL.
9. Westminster, MA. 2005. Two water-treatment workers in hospital after fluorosilicic acid spill. Sentinel & Enterprise. <http://www.fluoridealert.org/news/2-water-treatment-workers-in-hospital-after-fluorosilicic-acid-spill/>
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11. Nashville, TN. 2007. Fluoride overfeed incident event log (March 9–17) and water advisory. Harpeth Valley Utilities District.
12. Salt Lake City, UT. 2007. Fluoride spill taints Parleys Creek. People, dogs warned to avoid stream. The Salt Lake Tribune. <http://archive.sltrib.com/printfriendly.php?id=6773022&itype=NGPSID>
13. Conway, AR. 2008. Conway Corp. approves funds for fluoridation. The Cabin. http://thecabin.net/stories/071608/loc_0716080001.shtml
14. Chesterfield, MO. 2009. Chesterfield: workers contain spill of approximately 200 gallons of fluoride. St. Louis Post-Dispatch. <http://www.fluoridealert.org/news/workers-contain-chemical-spill-of-estimated-200-gallons-of-fluoride-in-chesterfield/>
15. Anchorage, AK. 2010. Excess fluoride taints water at Anchorage military bases — Poisonous: High levels can lead to stomach ailments and even death. Anchorage Daily News. <http://www.adn.com/2010/04/28/1254268/military-bases-water-supply-overloaded.html>
16. Asheboro, NC. 2010. City reports over-release of fluoride. Courier-Tribune. See Item 5 for URL.
17. Rock Island, IL. 2011. Rock Island: hydrofluorosilicic acid spill at Rock Island water-treatment plant. WQAD TV. <http://www.fluoridealert.org/news/hazmat-crews-respond-to-chemical-spill-at-rock-island-water-treatment-plant/>. Also available in a video at <http://www.youtube.com/watch?v=Hvttwsc5lh8>.
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21. Memphis, TN. 2012. Spill of 1500 gallons FSA in Memphis, TN. National Response Center Incident Report. Incident Report # 1017173 http://www.nrc.uscg.mil/reports/rwervlet?standard_web+inc_seq=1017173

Appendix 4: More on CWF effectiveness in adults

We examine two recent articles claiming to show effectiveness of CWF for adults: Slade *et al.*¹⁰⁹ applied SAS procedures on data from a 2004–2006 Australian survey of adults. Griffin *et al.*¹¹⁰ performed a meta-analysis of 20 studies that sought to “examine the effectiveness of self- and professionally applied fluoride and water fluoridation among adults.”

Slade *et al.*¹⁰⁹ concluded that high lifetime fluoridation exposure was associated with 11% and 10% lower DMFT (or 30% and 21% DFS) among pre-1960 and 1960–1990 birth cohorts. We show that what is attributed to CWF is better explained by differences in age distributions.

Griffin *et al.*¹¹⁰ combined CWF with self- and professionally applied fluoride, which are topical treatments

and very different from CWF in many respects, e.g. the applications or dosages are controllable; it does not appear reasonable to combine them in a meta-analysis. They “used a random-effects model, which assumes that each study was randomly selected from a hypothetical population of studies,” without discussing the applicability of the model. We focus on the CWF-related studies. These authors concluded that the CWF effectiveness was a 27.2% reduction in caries. We are not able to reproduce this result, which was based on four studies reporting DMFT and one study reporting DMFS; there was no explanation how the different units were handled. As with Slade *et al.*,¹⁰⁹ Griffin *et al.*¹¹⁰ failed to adequately account for different age distributions.

Slade *et al.*¹⁰⁹

Thirty dentist-examiners conducted the oral examination in this national survey. For participants aged <45 years, only teeth extracted because of dental caries or periodontitis were counted as missing, but all absent teeth for older people were counted. Fluoridation exposure was determined by residential history, and a value of 0, 0.5, or 1 was assigned if the fluoride concentration at the location was less than 0.3, between 0.3 and 0.7, or greater than 0.7 mg/l, respectively. A value of 0.5 was assigned to all localities in New Zealand, Canada, or the U.S. and 0 to all other foreign localities, without regard to the actual CWF status of the locality.

A significant portion of CWF exposure status was imputed: 3,779 people were considered to have valid exposure data (Complete case), meaning less than 50% of the person’s residential data were missing; the missing years were assumed to be their average observed fluoridation exposure. The exposure status of the remaining 1,726 people with more than 50% missing residential data was imputed by substituting with the status of a random sample from the 3,779 people who belonged to the same geographical stratum and 10-year age group.

Samples were divided into four levels of CWF exposure, i.e. <25% (negligible), 25 to <50%, 50 to <75%, and ≥75% (prolonged) of lifetime. Given the way CWF exposure was determined, the accuracy of this classification is questionable.

Slade *et al.* use unspecified linear regression models to “age-adjust” caries experience and fluoridation exposure. They draw the main conclusion of effectiveness by comparing the “age-adjusted” DMFT/DFS scores of the “prolonged” and “negligible” groups for the cohorts born before 1960 and those born between 1960 and 1990, respectively. The observed DMFT/DFS scores are not provided. The “age-adjusted” DMFT/DFS scores are given by birth cohort and exposure group (Table 15).

Table 15 “Age-adjusted” DMFT and DFS from Slade *et al.*¹⁰⁹

	% of Lifetime exposed to CWF			
	<25%	25–50%	50–75%	≥75%
Pre-1960 birth cohort				
DMFT	21.75	20.90	21.62	19.21
DFS	37.90	35.83	37.00	29.97
1960–1990 birth cohort				
DMFT	8.91	9.53	8.88	7.61
DFS	15.89	18.01	15.65	12.41

CWF: community water fluoridation; DMFT: decayed, missing, or filled teeth.

The scores reported in Table 15 are not consistent with the conclusion that CWF exposure is effective. The scores for the two middle exposure levels were interpreted as “suggested a dose-response relationship.” This is an unreasonable explanation, as an apparent difference in DMFT/DFS is lacking among the first three exposure categories. In addition, exposure levels were defined by cumulative residential status relative to age. For example, a person who lived in places with a fluoride concentration of 1 mg/l for 50 years and 0.25 mg/l for 20 years (treated as 0 mg/l, as 0.25 is less than 0.3) would have been assigned to the 50 to <75% exposure group, which, according to their results, gets no benefit relative to someone living all 70 years in nonfluoridated areas.

There are also questions regarding the validity of their use of linear regression models to “age-adjust.” Calculation from data provided by Slade *et al.* (shown in Table 16) reveals that some cells have few or no people. In particular, the category of ≥75% exposure level is clearly much younger than the other three exposure categories. Given the large difference in DMFT/DFS between the pre-1960 and 1960–1990 birth cohorts (Table 15), and the large difference in age distributions between the first three exposure categories and the fourth category (Table 16), it is not surprising that the ≥75% exposure category would have lower DMFT/DFS scores than the other exposure categories. Hence the differences in caries attributed to CWF between the <25% and

Table 16 Number of people and age distributions in the 2004–2006 Australian National Survey (calculated from information in Slade *et al.*¹⁰⁹)

	% of lifetime exposed to CWF				
	<25	25–50	50–75	≥75	All categories
15–24	65	10	17	154	246
25–34	91	19	39	268	416
35–44	174	103	187	301	765
45–54	177	143	365	108	792
55–64	212	236	394	0	842
≥65	192	393	134	0	718
Total	910	903	1,135	831	3,779

CWF: community water fluoridation.

$\geq 75\%$ exposure groups are probably due to inappropriate handling of age distributions.

There are other unexplained discrepancies. For example, the differences in DMFT or DFS between the $<25\%$ and $\geq 75\%$ exposure groups given in the text are not consistent with the numbers reproduced in Table 15. In particular, the DFS difference in the pre-1960 cohort was said to be 11.10 or 30%, but the numbers indicate 7.93 or 21%.

Griffin *et al.*¹¹⁰

This 2007 article included nine CWF studies (Table 17).^{51,107,133,142–147} Few, if any, of the studies can be considered high quality studies appropriate for examining the effects of CWF. Four studies involved concentrations greater than those used for CWF (0.7–1.2 mg/l).^{51,133,143,145} In all, but one study,¹⁴⁶ the examiners were probably not blind to the location of a subject's residence. Eight studies were cross-sectional, and the towns compared may have simply differed for reasons having nothing to do with CWF. The one study categorized as "prospective" is in essence a cross-sectional study that compares caries increment over an 18-month period, since no "intervention" was started or changed at the onset of the period.¹⁴³

Only four of the nine studies were conducted in the U.S. Of these, two were examined earlier in this paper.^{51,107} Below we offer a few general remarks, followed by comments on the remaining studies, especially the other two U.S. studies.^{142,143}

As we discussed earlier, assessment of dental caries in adults is difficult. Wiktorsson *et al.*¹⁴⁴ described difficulties in judging caries prevalence based on fillings (due to practices such as preventive fillings for discolored fissures on occlusal surfaces) and in defining new caries incidence, since the majority of the primary caries lesions are only enamel lesions, possibly arrested caries in many cases.

In some studies,^{133,145,146} the reported age distributions suggest that the low fluoride groups were older than the fluoride groups. Griffin *et al.*¹¹⁰ do not seem to have considered this difference in the age distributions in their analysis.

In the context of testing the hypothesis that adults benefit by continuing to drink fluoridated waters, the

progression of the differences in caries is important. Englander and Wallace,¹⁴² Murray,¹³³ and Stamm *et al.*¹⁴⁵ each reported narrowing of the differences in mean DMFT between the low fluoride and fluoride groups with increasing ages for lifetime residents. The logical conclusion is that drinking fluoridated water is not helpful beyond a certain age.

Englander and Wallace¹⁴² examined 896 and 935 adults aged 18–59 years from two Illinois towns, Aurora (1.2 mg/l) and Rockford (0.1 mg/l, referred to as "fluoride deficient"). All subjects were examined by the first author. The caries experience was found to be significantly less in the subjects from Aurora, which was attributed to the different fluoride levels in their drinking water. We offer some observations that disagree with that conclusion.

The differences in mean DMFT presented for the two towns were 5.22, 8.14, 6.62, 5.59, and 5.76 for the 18–19, 20–29, 30–39, 40–49, and 50–59 years old age groups, respectively. The mean years of consuming the respective waters in either city were increased by about 10 years for each additional 10 years age group. However, the difference in mean DMFT decreased for age groups above 29 years (for DMFS, the corresponding differences in the means decreased slightly for ages 30–39 years, but decreased substantially for ages >39 years). If the caries difference is to be attributed to fluoride, are we to conclude that after age 29 years, consuming water with 1.2 mg/l fluoride increases caries?

The study groups from the two cities were said to have similar socioeconomic structures, but there are questions as to how similar the two groups really were. Almost everyone in Aurora (pop. 65,000) and more than half the population of Rockford (pop. 130,000) were contacted. It was found that 2% of those in Aurora over 20 years old were toothless, yet the figure was 14% for Rockford. (Anyone with less than 10 teeth was not invited to participate. The percentages of people contacted who had 1–9 teeth were not given.) A sevenfold difference in the toothless population may indicate an economic difference. Even though the edentulous people were not included in the study, the authors appeared to consider the figures representative, as they tried to adjust the measurements by adding the

Table 17 Summary of community water fluoridation (CWF) studies included in Griffin *et al.*¹¹⁰

Study	Study location	Type of study	High fluoride (>1.2 mg/l)
Eklund <i>et al.</i> ⁵¹	USA	Cross-sectional	3.5 mg/l
Grembowski <i>et al.</i> ¹⁰⁷	USA	Cross-sectional	
Murray ¹³³	Great Britain	Cross-sectional	1.5–2.0 mg/l
Englander and Wallace ¹⁴²	USA	Cross-sectional	
Hunt <i>et al.</i> ¹⁴³	USA	"Prospective"	0.7–1.5 mg/l
Wiktorsson <i>et al.</i> ¹⁴⁴	Sweden	Cross-sectional	
Stamm <i>et al.</i> ¹⁴⁵	Canada	Cross-sectional	1.6 mg/l
Thomas and Kassab ¹⁴⁶	Great Britain	Cross-sectional	
Morgan <i>et al.</i> ¹⁴⁷	Australia	Cross-sectional	

2% and 14% toothless figures into the DMFT figures to raise the total percentage difference.

Englander and Wallace¹⁴² reported their results in DMFT as well as in DMFS. (They wrote that differences in dental caries experience were more striking when evaluated by means of DMF tooth surfaces.) Griffin *et al.*¹¹⁰ chose to use the numbers in DMFS. (The ratio of DMFT between the two towns appears to be similar to the ratio of DMFS according to Griffin *et al.*,¹¹⁰ but that is because they incorrectly listed the value for the filled component instead of the DMF for Aurora.)

Hunt *et al.*¹⁴³ reported new caries incidence over an 18-month period for 424 adults aged 65 years and older from a “narrowly defined geographical area” in two rural Iowa counties. Of these subjects, 174 were lifelong residents of “fluoride deficient” nonfluoridated communities, and 250 had lived in fluoridated communities (0.7–1.5 mg/l) for various lengths of time. Those who had 5–30 years of residence in fluoridated communities had comparable or worse new caries incidence compared to the lifelong nonfluoridated subjects. The authors thus focused on the remaining 101 persons with more than 30 years of residency in fluoridated communities (40% of the fluoridated sample) to draw the conclusion of effectiveness. Griffin *et al.*¹¹⁰ used only the 77 persons with more than 40 years of residency in fluoridated communities (31% of the fluoridated sample). As mentioned above, one would be tempted to conclude from Englander and Wallace¹⁴² that drinking fluoridated water after age 29 years does not work. Here, we learn that drinking it for less than 30 or 40 years does not work.

Hunt *et al.*¹⁴³ used a cross-sectional approach to compare baseline characteristics of the two groups for those with more than 30 years of residence. After at least 30 years of exposure to fluoridated water, no statistically significant difference in DFS (coronal or root caries) was noticed. In fact, Hamasha *et al.*, describing the same study population, did not even mention fluoride as a possible factor in the long-term caries experience.¹⁴⁸ Apparently, only in this 18-month period was a difference observed and attributed to fluoride. In a companion paper from the same study, Hunt *et al.* indicated no significant correlation between tooth loss and residence in a nonfluoridated community.¹⁴⁹

Murray¹³³ reported on two towns in Great Britain, one with high fluoride (1.5–2 mg/l) and one with low fluoride (0.2 mg/l). Data were reported in 5-year age groups for general samples and for dentate samples. One interesting finding was that the prevalence of edentulous persons by age was strikingly similar between the two towns, reaching about two-thirds by age 60–65 years. In the author’s terms, the “M”

component of the DMFT score was similar in both groups. However, one way to look at this is that fluoride ingestion had little or no effect on the likelihood that a person would have a full set of dentures by age 60–65 years. The difference in mean DMFT was fairly constant in the earlier age groups and significantly narrowed from around age 40 years in the general sample. (The pattern of narrowing difference in DMFT persists after removing edentulous samples.) Murray’s samples differed greatly in their age distributions, with the high fluoride group having approximately twice the fraction (33.2% vs. 16.5%) of people in the 20–24 age group and a substantially smaller fraction (27.1% vs. 44.3%) in the 40–65 age groups. Griffin *et al.*¹¹⁰ apparently included these samples without considering that it might not be appropriate.

Wiktorsson *et al.*¹⁴⁴ compared adults 30–40 years old in Swedish towns with 1 or 0.3 mg/l fluoride. Griffin *et al.*¹⁰⁷ indicate blinded examiners and unspecified fluoride concentrations, but these descriptions do not fit the actual paper — a single examiner performed examinations in the respective communities and was unlikely to have been blind to subjects’ geography. Persons with non-representative water sources were not examined. After discussing difficulties in scoring caries in adults, Wiktorsson *et al.*¹⁴⁴ report that the community with “optimal” fluoride had “significantly better” dental health status. However, without summary data for age subgroups, the picture is not entirely clear — the presented scatter plots for filled surfaces and for decayed surfaces (for ages 31–43 years) do not appear to suggest a benefit for continuing consumption of fluoridated water. (This study reports in tooth surfaces only and uses linear regression analysis.)

Stamm *et al.*¹⁴⁵ deal with 1.6 and 0.2 mg/l fluoride in Canada, and the examiners were not blind to their subjects’ place of residence. The study excluded people with fewer than eight teeth. Griffin *et al.*¹¹⁰ included the 17–19 year old group in the total sample from Stamm *et al.*,¹⁴⁰ although the 15–19 year olds in Murray¹³³ were excluded. The low fluoride group included only 1.5% in that age group, versus 6% in the fluoride group. Ages 60+ years made up nearly 18% of the low fluoride group but only 12% of the fluoride group. With respect to progression, the differences in mean DMFT between the high and low fluoride groups decreased with the older age groups, from 5.1 at ages 30–39 years to 1.7 for ages 60+ years.

Thomas and Kassab¹⁴⁶ included only females up to 32 years old, while they were hospitalized to give birth. A single hospital was used by women from a fluoridated island community (Anglesey) and several nonfluoridated mainland communities in Wales (United Kingdom); lifelong residents were included in the study. Although the authors indicate no

significant differences in age group structure of the samples from the two areas, the data show that Anglesey had more in the youngest (<20) age group, 24.1% versus 12.9% and fewer in the oldest (25–29 and 30–32) age groups, 30.0% and 5.9% versus 36.5% and 9.6%. The island of Anglesey was chosen for a demonstration fluoridation study in the 1950s. The experiment was terminated after only 5 years and the whole island was fluoridated based on the mean dmft index for 5-year-old children.

Morgan *et al.*¹⁴⁷ analyzed data for a group of Royal Australian Navy recruits, mostly males, ages 15–24 years, and with limited education. Griffin *et al.*¹¹⁰ used only the results (mean DMFT scores by fluoride history) for 20–24 year olds (208 recruits). Morgan *et al.* indicated only that approximately 20% and 30% of the total sample (1,100 recruits) were considered “fluoridated” and “nonfluoridated” (determined by residential history), respectively, and included in the calculation of the mean DMFT scores. Griffin *et al.* used the percentages to impute the sizes of the “fluoridated” and “nonfluoridated” groups to be 42 and 62, respectively.

Appendix 5: More on the CWF effectiveness in Truman *et al.*⁸⁰

Despite a reference to 21 papers, Truman *et al.*⁸⁰ based their conclusion of CWF effectiveness on 14 studies grouped into three groups:

- Studies starting or continuing CWF with before and after measurements (Group A-On)
- Studies stopping CWF with before and after measurements (Group A-Off)
- Studies starting or continuing CWF with only post measurements (Group B-On)

They calculated a number of “estimates of effectiveness” using two formulas:

Group A (before-and-after):

$$\{(NoF_{pre} - NoF_{post}) - (F_{pre} - F_{post})\} / NoF_{pre}$$

Group B (post measurements only):

$$(F_{post} - NoF_{post}) / NoF_{post}$$

The measures were mostly DMFT or dft. See Table 5 for summaries.

The median of the estimates thus calculated for each group was taken to represent the CWF effectiveness for each type of studies, even though median can be sensitive to the studies or estimates included in the set. The results were 29.1% for Group A-On (based on 21 estimates from 7 studies), 50.7% for Group B-On (based on 20 estimates from 7 studies), and 17.9% for Group A-Off (based on 5 estimates from 3 studies). With these numbers the authors concluded that “strong evidence shows that CWF is effective.” Below, we discuss a number of problems.

Selection of studies: Of the 14 studies, only one 1956 article is a U.S. study.⁹³ The two large-scale,

multimillion dollar NIDR surveys were not included, peculiar as this review was to be the basis for setting goals for U.S. public policies. Szpunar and Burt,⁴⁹ a study co-authored by the organizer of the 1989 Michigan Workshop, was not included, nor was Shiboski *et al.*,¹²¹ a CDC-funded study examining caries in California children by ethnicity and head-start (or low income) status. One would expect the authors of Truman *et al.*⁸⁰ to make particular efforts to include this study because (1) the Pacific Region was the least fluoridated region and hence the main target of a new push for CWF and (2) they posed “What is the effectiveness of CWF in reducing socioeconomic or racial and ethnic disparities in caries burden?” as an important unanswered question.

Among the included studies, Loh⁹⁶ is a review article providing partial information from a 1970 paper; it failed to meet the authors’ stated criteria for inclusion. Another inappropriate inclusion was Hawew *et al.*,¹⁰³ a Libyan study with the goals of demonstrating feasibility of collecting data and recording the caries prevalence in Benghazi (0.8 mg/l). The paper also reports data for a small rural area with 1.8 mg/l fluoride concentration, but the comparison of 0.8 (within the CWF range of 0.7–1.2 mg/l) versus 1.8 mg/l (above the CWF range) is not relevant to demonstrating the effectiveness of CWF.

Some authors of the included studies have published other CWF studies, e.g. Attwood co-authored Downer *et al.*,¹⁵⁰ which could be a B-On study. Künzel *et al.*¹⁵¹ and the many studies cited therein could be in group A-Off. These omissions are particularly surprising since group A-Off has only three studies and five estimates.

Selection of estimates: Group A-Off contains three studies and five imputed estimates: 17.9% from Attwood and Blinkhorn,⁹⁹ 29.1% and 31.7% from Kalsbeek *et al.*,¹⁰⁰ and –1.1% and –42.2% from Künzel and Fischer.⁹⁸ Thus the median is 17.9%.

Kalsbeek *et al.*¹⁰⁰ reported measurements for 15-year-olds taken in different years. Of the two before-and-after estimates imputed from this study, one was not a before-and-after comparison — the fluoridated town had stopped CWF about 6 or 7 years before the “before” point.

Künzel and Fischer⁹⁸ reported measurements for every age from 6 to 15 years. This was a large-scale multiyear study, and the sizes of each age group are significant. But instead of imputing multiple estimates from selected single-age data, as was done with some other studies, all single-age data were ignored, and only two age-range summaries were used to impute two estimates. Had Truman *et al.*⁸⁰ been consistent in the selection of estimates, the median for Group A-Off would have shifted to a negative value and changed the conclusion to no CWF effectiveness.

In contrast, four estimates were imputed from the much smaller Libyan study¹⁰³ — for each of the two ages reported, the public school data from the rural town were used twice to impute two estimates by comparing them with the public school data and, separately, with the private school data from Benghazi.

Selection of formula: Within the limited set of studies and estimates selected, the authors failed to apply their formula consistently. Two estimates for deciduous teeth from Guo *et al.*⁷⁶ were included in group A-On and two for permanent teeth in group B-On. The study clearly belongs to group A-On, as it reported before-and-after measurements for all ages and for both deciduous and permanent teeth. Instead of following their stated method and including the estimates of 300%, 211%, and 208% for the permanent teeth of the three selected age groups, they ignored the before measurements and treated them as if there were only post measurements for permanent teeth. Similarly, Evans *et al.*⁹⁷ reported measurements for 5-year-olds divided into three social classes. Truman *et al.*⁸⁰ included three Group A-On estimates, one for each social class; but the combined total for all social groups was treated as a post-only study and contributed another estimate in Group B-On.

The results from the application of the formula can be misleading. For example, the three positive estimates^{99,100} in group A-Off are presented as estimates of how much CWF prevents caries. In fact, the data in these two studies, as well as other studies involving cessation of CWF, showed that there were no increases in caries after stopping fluoridation, aside from possibly a temporary and small increase shortly afterward, which could simply be reflecting the removal of the delayed eruption effect. (Within the 6-year period in Attwood and Blinkhorn,⁹⁹ the mean DMFT decreased by 0.54 in the never-fluoridated town and increased by 0.06 in the town that stopped fluoridation at the midpoint of the period. In the 9-year period that sandwiched the cessation of CWF in Kalsbeek *et al.*,¹⁰⁰ the DMFT decreased by 3.7 in the never-fluoridated town and increased by 0.4 in the fluoridated town; 8 years later, it further decreased by 5.6 in the former and decreased by 2.3 in the latter town.) Thus the purported positive outcomes were purely an artifact of the formula — the never-fluoridated communities had a dramatic reduction in caries without the help of CWF.

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THE WORLD-WIDE MOVEMENT AGAINST WATER FLUORIDATION



In stark contrast to the Center for Disease Control's claim that fluoridation is one of the top ten public health achievements of the 20th century, it is **one of the most widely rejected health interventions in the world.**

Out of 196 nations, only 24 have any fluoridation, and only 10, like the U.S., for more than half their population. Over 95% of the world's population is fluoridation-free. The U.S. fluoridates as many people as the rest of the world combined.

None of the largest Asian nations, including China, India and Japan, fluoridate. Out of 54 countries in Africa, only one fluoridates – Libya, and only for a small percent of its population. In Europe, only four out of 48 countries fluoridate (less than 2% of the population). A few have fluoridated salt, but only as a consumer choice.

France, Germany, Belgium, the Netherlands, Denmark, Norway and Sweden have all prohibited fluoridation, many citing the ethical problem of putting any drug in drinking water.

For dozens of nations that haven't banned it, thousands of major cities and smaller towns don't fluoridate, including **Athens, Barcelona, Budapest, Geneva, Helsinki, London, Madrid, Prague, Rome, Vienna and Warsaw**. Ireland is the only European nation mandating fluoridation. But despite the mandate, 13 town and county councils, including Dublin and Cork, have voted for its immediate cessation.

Many organizations still support fluoridation, but **those opposing it grows year by year**. They include:

- American Academy of Environmental Medicine • Center for Health, Environment and Justice
- Children's Health Defense • Eau Secours (Canadian coalition of 234 groups promoting clean, safe water)
- Council of Canadians • Environmental Working Group • Food and Water Watch
- * Institute of Neurotoxicology & Neurological Disorders • International Academy of Biological Dentistry and Medicine
- International Academy of Oral Medicine and Toxicology • League of United Latin American Citizens
- Moms Against Fluoridation • Organic Consumers Association

In addition, **many organizations once endorsing fluoridation have pulled back**, no longer taking a position. They include the Alzheimer's Association, American Academy of Allergy, Asthma and Immunology, Center for Science in the Public Interest, Consumers Union (Consumer Reports), National Association of Social Workers, National Down Syndrome Congress, National Down Syndrome Society and National Kidney Foundation.

The trend is clear. And as the scientific data accumulate, more and more nations, cities and organizations are challenging the safety, efficacy, costs and ethics of fluoridation.



National Toxicology Program

U.S. Department of Health and Human Services

DRAFT NTP MONOGRAPH ON THE SYSTEMATIC REVIEW OF FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS*

Revised September 16, 2020

*The September 6, 2019 draft monograph was peer reviewed by a committee convened by the National Academy of Sciences, Engineering, and Medicine (NASEM). This current draft incorporates changes in response to that review and is being submitted to the same NASEM committee for an additional round of peer review.

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOREWORD

The National Toxicology Program (NTP), established in 1978, is an interagency program within the Public Health Service of the U.S. Department of Health and Human Services. Its activities are executed through a partnership of the National Institute for Occupational Safety and Health (part of the Centers for Disease Control and Prevention), the Food and Drug Administration (primarily at the National Center for Toxicological Research), and the National Institute of Environmental Health Sciences (part of the National Institutes of Health), where the program is administratively located. NTP offers a unique venue for the testing, research, and analysis of agents of concern to identify toxic and biological effects, provide information that strengthens the science base, and inform decisions by health regulatory and research agencies to safeguard public health. NTP also works to develop and apply new and improved methods and approaches that advance toxicology and better assess health effects from environmental exposures.

NTP conducts literature-based evaluations to determine whether exposure to environmental substances (e.g., chemicals, physical agents, and mixtures) may be associated with adverse health effects. These evaluations result in hazard conclusions or characterize the extent of the evidence and are published in the NTP Monograph series, which began in 2011. NTP Monographs serve as an environmental health resource to provide information that can be used to make informed decisions about whether exposure to a substance may be of concern for human health.

NTP conducts these health effects evaluations following pre-specified protocols that apply the general methods outlined in the [“Handbook for Conducting a Literature-Based Health Assessment Using the OHAT Approach for Systematic Review and Evidence Integration.”](#)¹ The protocol describes project-specific procedures tailored to each systematic review in a process that facilitates evaluation and integration of scientific evidence from published human, experimental animal, and mechanistic studies.

The key feature of the systematic review approach is the application of a transparent framework to document the evaluation methods and the basis for scientific judgements. This process includes steps to comprehensively search for studies, select relevant evidence, assess individual study quality, rate confidence in bodies of evidence across studies, and then integrate evidence to develop conclusions for the specific research question. Draft monographs undergo external peer review prior to being finalized and published.

NTP Monographs are available free of charge on the [NTP website](#) and cataloged in [PubMed](#), a free resource developed and maintained by the National Library of Medicine (part of the National Institutes of Health). Data for these evaluations are included in the [Health Assessment and Workspace Collaborative](#).

For questions about the monographs, please email [NTP](#) or call 984-287-3211.

¹ OHAT is the abbreviation for Office of Health Assessment and Translation, which is within the Division of the National Toxicology Program at the National Institute of Environmental Health Sciences.

TABLE OF CONTENTS

Foreword.....	ii
Table of Contents.....	iii
List of Tables and Figures	v
Abstract.....	1
Introduction	3
Objective and Specific Aims.....	4
Objective	4
Specific Aims	5
Methods.....	5
Problem Formulation and Protocol Development.....	5
NASEM Review	6
PECO Statements	6
Literature Search.....	8
Main Literature Search.....	8
Supplemental Chinese Database Literature Search	9
Databases Searched	10
Searching Other Resources	10
Unpublished Data.....	10
Study Selection.....	10
Evidence Selection Criteria.....	10
Screening Process.....	11
Screening of the May 2020 Literature Search Update	11
Data Extraction.....	11
Quality Assessment of Individual Studies	12
Key Risk-of-bias Questions	13
Organizing and Rating Confidence in Bodies of Evidence.....	15
Health Outcome Categories for Neurodevelopmental and Cognitive Effects	15
Considerations for Pursuing a Narrative or Quantitative Evidence Synthesis.....	15
Confidence Rating: Assessment of Body of Evidence	16
Preparation of Level of Evidence Conclusions	17
Integrate Evidence to Develop Hazard Identification Conclusions.....	18
Consideration of Human and Animal Data.....	18
Consideration of Mechanistic Data	19
Results and Evidence Synthesis	21
Literature Search Results	21
Literature Search Results Counts and Title and Abstract Screening	21
Full-text Review.....	21
Evaluation of SWIFT-Active Screener Results.....	22
Supplemental Chinese Database Searches and Human Epidemiology Studies	22
Neurodevelopmental and Cognitive Health Effects Results	23
Risk-of-bias Considerations	24
Human Neurodevelopmental and Cognitive Data	24
Animal Learning and Memory Data	57

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In Vitro/Mechanistic Data on Neurodevelopmental or Cognitive Effects.....	65
Evidence Synthesis for Neurodevelopmental or Cognitive Effects	65
Discussion.....	70
Generalizability to the U.S. Population	72
Limitations of the Evidence Base	78
Limitations of the Systematic Review	79
Conclusion	79
References.....	81
Data Figures.....	94
Neurodevelopmental or Cognitive Effects and Outcomes	94
About This Review	104
Sources of Support.....	104
Contributors	104
Peer Reviewers.....	105
Protocol Reviewers	105
Technical Review of Draft Monograph.....	106
Protocol History and Revisions	106
Appendices	107
Appendix 1. Literature Search Strategy	107
Appendix 2. List of Included Studies	109
Studies in Humans.....	109
Studies in Non-human Animals	121
In Vitro Experimental Studies.....	142
Appendix 3. Risk-of-bias Figures	146
Studies in Humans.....	146
Studies in Non-human Animals	149
Appendix 4. Details for Lower Risk-of-bias Studies.....	159
Appendix 5. Results of Fluoride Meta-analyses.....	231
Aim 1. To update existing meta-analyses with additional studies	231
Approach.....	231
Summary Results.....	232
Overall Effect (Main Analysis)	233
Subgroup Analyses	233
Aim 2. To conduct new meta-analyses using individual-level exposure data	246
Approach.....	246
Summary Results.....	247
Dose-response meta-analyses using mean-effect estimates	253
Approach.....	253
Summary Results.....	253
Dose-Response Meta-analysis Using Mean Effects—Model Selection	254
Attachment A. Subgroup and Sensitivity Analyses (Aim 1)	255
Attachment B. Subgroup and Sensitivity Analyses (Aim 2).....	295

LIST OF TABLES AND FIGURES

TABLES:

Table 1. Human PECO (Population, Exposure, Comparator and Outcome) Statement	7
Table 2. Animal PECO Statement.....	8
Table 3. In Vitro/Mechanistic PECO Statement	8
Table 4. OHAT Risk-of-bias Questions and Applicability by Study Design	14
Table 5. The Four Risk-of-bias Rating Options.....	15
Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans	28
Table 7. Neurodevelopmental and Cognitive Function Evidence Profile for Fluoride.....	69
Table 8. Human Studies with Lower Fluoride Exposure and Effects on IQ	75

FIGURES:

Figure 1. Assessing Confidence in the Body of Evidence	17
Figure 2. Translate Confidence Ratings into Evidence of Health Effect Conclusions.....	18
Figure 3. Hazard Identification Scheme for Neurodevelopmental or Cognitive Effects	19
Figure 4. Study Selection Diagram	23
Figure 5. Number of Epidemiological Studies by Outcome and Age Categories	27
Figure 6. Potential Confounders Considered in Lower Risk-of-bias Studies Conducted in Children	42
Figure 7. Number of Lower Risk-of-bias Studies that Evaluated Thyroid Hormones in Children and Adults by Endpoint and Direction of Effect	57
Figure 8. Number of Higher Risk-of-bias Studies that Evaluated Thyroid Hormones in Children by Endpoint and Direction of Effect.....	57
Figure 9. Number of Animal Mechanistic Studies for Fluoride by Mechanistic Category and Exposure Level	60
Figure 10. Number of Lower Risk-of-bias Animal Studies that Evaluated Biochemical, Neurotransmission, and Oxidative Stress Effects at or Below 20 ppm by Mechanism Subcategory and Direction of Effect.....	65

DATA FIGURES:

Figure D1. IQ Distribution in Children by Fluoride Exposure (lower risk-of-bias studies; presented as % in area or % of total group)	94
Figure D2. Mean IQ in Children by Fluoride Exposure (lower risk-of-bias studies)	95
Figure D3. Intelligence Grade in Children by Fluoride Exposure (lower risk-of-bias studies; presented as mean).....	96
Figure D4. Mean Change in IQ in Children by Fluoride Exposure (lower risk-of-bias studies)	96
Figure D5. IQ Score in Children by Fluoride Exposure (lower risk-of-bias studies; presented as adjusted OR)	97
Figure D6. Correlations between IQ Score and Fluoride Exposure in Children (lower risk-of-bias studies; presented as coefficient)	98
Figure D7. Correlations between IQ Score and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted beta)—(a) China; (b) all other areas.....	99
Figure D8. Mean Motor/Sensory Scores in Children by Fluoride Exposure (lower risk-of-bias studies).....	101
Figure D9. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk- of-bias studies; presented as coefficient).....	101
Figure D10. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted beta).....	102

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Figure D11. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted OR)	103
Figure D12. Cognitive Impairment in Adults by Fluoride Exposure (lower risk-of-bias studies; presented as % of total group)	103

RISK-OF-BIAS FIGURES:

Figure A3-1. Risk-of-bias Heatmap for Lower Risk-of-bias Human Neurodevelopmental or Cognitive Studies Following Fluoride Exposure	146
Figure A3-2. Risk-of-bias Bar Chart for Lower Risk-of-bias Human Neurodevelopmental or Cognitive Studies Following Fluoride Exposure	146
Figure A3-3. Risk-of-bias Heatmap for Higher Risk-of-bias Human Neurodevelopmental or Cognitive Studies Following Fluoride Exposure	146
Figure A3-4. Risk-of-bias Bar Chart for Higher Risk-of-bias Human Neurodevelopmental or Cognitive Studies Following Fluoride Exposure	147
Figure A3-5. Risk-of-bias Heatmap for Lower Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure	147
Figure A3-6. Risk-of-bias Bar Chart for Lower Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure	147
Figure A3-7. Risk-of-bias Heatmap for Higher Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure	148
Figure A3-8. Risk-of-bias Bar Chart for Higher Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure	148
Figure A3-9. Risk-of-bias Heatmap for New Developmental Animal Learning and Memory Studies Following Fluoride Exposure.....	149
Figure A3-10. Risk-of-bias Bar Chart for New Developmental Animal Learning and Memory Studies Following Fluoride Exposure.....	149
Figure A3-11. Risk-of-bias Heatmap for New Adult Animal Learning and Memory Studies Following Fluoride Exposure	150
Figure A3-12. Risk-of-bias Bar Chart for New Adult Animal Learning and Memory Studies Following Fluoride Exposure	150
Figure A3-13. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure	151
Figure A3-14. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure	151
Figure A3-15. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure	152
Figure A3-16. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure	152
Figure A3-17. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure	153
Figure A3-18. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure	153
Figure A3-19. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure	154
Figure A3-20. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure	154
Figure A3-21. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure	155

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Figure A3-22. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure	155
Figure A3-23. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure	156
Figure A3-24. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure	156
Figure A3-25. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure	157
Figure A3-26. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure	157
Figure A3-27. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure	158
Figure A3-28. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure	158

META-ANALYSES TABLES:

Table A5-1. Pooled SMDs and 95% CIs for Children’s IQ Score and Exposures to Fluoride	232
Table A5-2. Pooled Effect Estimates and 95% CIs for Children’s IQ Scores and Individual-level Exposures to Fluoride.....	247
Table A5-3. Model Comparison for Dose-response Meta-analysis for Children’s IQ Scores (SMDs) and Exposures to Fluoride: Parameter Estimates and Model Fit	254

Attachment A

Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis	255
Table A-2. Studies Excluded from Mean-effect Meta-analysis.....	264
Table A-3. Characteristics of Studies Included in the Individual-level Meta-analysis.....	265

Attachment B

Table B-1. Characteristics of Studies Included in the Individual-level Meta-analysis.....	295
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META-ANALYSES FIGURES:

Figure A5-1. Association Between Fluoride Exposure and IQ Scores in Children: Overall Analysis	235
Figure A5-2. Funnel Plot of Included Studies.....	236
Figure A5-3. Test for Publication Bias	236
Figure A5-4. Trim-and-fill Analysis	237
Figure A5-5. Filled-in Funnel Plots to Eliminate Publication Bias	237
Figure A5-6. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Risk of Bias.....	238
Figure A5-7. Funnel Plot by Risk-of-bias Evaluation	239
Figure A5-8. Test for Publication Bias by Risk of Bias	239
Figure A5-9. Trim-and-fill Analysis for Higher Risk-of-bias Studies.....	240
Figure A5-10. Filled-in Funnel Plots to Eliminate Publication Bias for Higher Risk-of-bias Studies	240
Figure A5-11. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Gender	241
Figure A5-12. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Age Group.....	242
Figure A5-13. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Country	243
Figure A5-14. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type	244

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Figure A5-15. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type	245
Figure A5-16. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Overall Analysis	248
Figure A5-17. Funnel Plot of Included Studies with Individual-level Exposures	248
Figure A5-18. Test for Publication Bias for Studies with Individual-level Exposures.....	249
Figure A5-19. Trim-and-fill Analysis for Studies with Individual-level Exposures.....	249
Figure A5-20. Filled-in Funnel Plots to Eliminate Publication Bias for Studies with Individual-level Exposures.....	249
Figure A5-21. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type	250
Figure A5-22. Funnel Plot of Included Studies.....	250
Figure A5-23. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Country	251
Figure A5-24. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type	251
Figure A5-25. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Gender	252

Attachment A

Figure A-1. Funnel Plot by Risk-of-bias Evaluation	267
Figure A-2. Test for Publication Bias by Risk of Bias	267
Figure A-3. Trim-and-fill Analysis for High Risk-of-bias Studies	268
Figure A-4. Filled-in Funnel Plots for High Risk-of-bias Studies	268
Figure A-5. Funnel Plots by Gender	269
Figure A-6. Test for Publication Bias by Gender	269
Figure A-7. Trim-and-fill Analysis for Studies in Boys Using Linear and Run Estimators	270
Figure A-8. Filled-in Funnel Plots for Studies in Boys	270
Figure A-9. Funnel Plot by Age Group	271
Figure A-10. Test for Publication Bias by Age Group	271
Figure A-11. Funnel Plot by Country.....	272
Figure A-12. Test for Publication Bias by Country	272
Figure A-13. Trim-and-fill Analysis for Studies in India.....	273
Figure A-14. Filled-in Funnel Plot for Studies in India.....	273
Figure A-15. Funnel Plot by CRT-RC-type Test.....	274
Figure A-16. Test for Publication Bias by Assessment Type	274
Figure A-17. Trim-and-fill Analysis in Non-CRT-RC Tests	275
Figure A-18. Filled-in Funnel Plot to Eliminate Publication Bias in Non-CRT-RC Tests	275
Figure A-19. Trim-and-fill Analysis for Raven-type Tests.....	276
Figure A-20. Filled-in Funnel Plot to Eliminate Publication Bias for Raven-type Tests.....	276
Figure A-21. Funnel Plot by Exposure Type	277
Figure A-22. Test for Publication Bias by Exposure Type.....	277
Figure A-23. Trim-and-fill Analysis for Water Fluoride and Dental Fluorosis Exposures	278
Figure A-24. Filled-in Funnel Plots to Eliminate Publication Bias for Water Fluoride (Left Panel) and Dental Fluorosis (Right Panel) Studies	279
Figure A-25. Association Between Fluoride Exposure and IQ Scores in Children Using Any Exposure Versus Reference.....	280

Figure A-26. Funnel Plot in Sensitivity Analysis Using Any Exposure Versus Reference.....	281
Figure A-27. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference	281
Figure A-28. Trim-and-fill Analysis in Sensitivity Analysis Using Any Exposure Versus Reference	281
Figure A-29. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference	282
Figure A-30. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Any Exposure Group Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)].....	283
Figure A-31. Funnel Plot in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)]	284
Figure A-32. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)].....	284
Figure A-33. Trim-and-fill Analysis in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)]	284
Figure A-34. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference	285
Figure A-35. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)]	286
Figure A-36. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)]	287
Figure A-37. Test for Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)].....	287
Figure A-38. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)].....	287
Figure A-39. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), and Razdan <i>et al.</i> (2017)]	288
Figure A-40. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Excluding Lin <i>et al.</i> (1991)].....	289
Figure A-41. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin <i>et al.</i> (1991)]	290
Figure A-42. Test for Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin <i>et al.</i> (1991)]	290
Figure A-43. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin <i>et al.</i> (1991)]	290
Figure A-44. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin <i>et al.</i> (1991)].....	291
Figure A-45. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Excluding Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), Razdan <i>et al.</i> (2017), and Khan <i>et al.</i> (2015)]	292
Figure A-46. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), Razdan <i>et al.</i> (2017), and Khan <i>et al.</i> (2015)]	293
Figure A-47. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference [Excluding Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), Razdan <i>et al.</i> (2017), and Khan <i>et al.</i> (2015)]	293
Figure A-48. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), Razdan <i>et al.</i> (2017), and Khan <i>et al.</i> (2015)]	293

Figure A-49. Filled-in Funnel Plot to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind <i>et al.</i> (2016), Kundu <i>et al.</i> (2015), Razdan <i>et al.</i> (2017), and Khan <i>et al.</i> (2015)]	294
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Attachment B

Figure B-1. Association Between Individual-level Fluoride Exposure and IQ Scores in Children [No Pooling for Yu <i>et al.</i> (2018)]	297
Figure B-2. Funnel Plots of Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [No Pooling for Yu <i>et al.</i> (2018)]	297
Figure B-3. Test for Publication Bias for Studies with Individual-level Exposures	297
Figure B-4. Trim-and-fill Analysis for Studies with Individual-level Exposures	298
Figure B-5. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [No Pooling for Yu <i>et al.</i> (2018)]	299
Figure B-6. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [Using Wang <i>et al.</i> (2020b) Estimates in Place of Yu <i>et al.</i> (2018) Estimates]	300
Figure B-7. Funnel Plot of Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Wang <i>et al.</i> (2020b) Estimates in Place of Yu <i>et al.</i> (2018) Estimates]	300
Figure B-8. Test for Publication Bias for Studies with Individual-level Exposures [Using Wang <i>et al.</i> (2020b) Estimates in Place of Yu <i>et al.</i> (2018) Estimates]	300
Figure B-9. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Wang <i>et al.</i> (2020b) Estimates in Place of Yu <i>et al.</i> (2018) Estimates]	301
Figure B-10. Association Between Fluoride Exposure and IQ Scores in Children by Exposure for Individual-level Exposures [Using Wang <i>et al.</i> (2020b) Estimates in Place of Yu <i>et al.</i> (2018) Estimates]	301
Figure B-11. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [Using Till <i>et al.</i> (2020) Estimates in Place of Green <i>et al.</i> (2019) Estimates]	302
Figure B-12. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Till <i>et al.</i> (2020) Estimates in Place of Green <i>et al.</i> (2019) Estimates]	302
Figure B-13. Test for Publication Bias for Studies with Individual-level Exposures [Using Till <i>et al.</i> (2020) Estimates in Place of Green <i>et al.</i> (2019) Estimates]	302
Figure B-14. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Till <i>et al.</i> (2020) Estimates in Place of Green <i>et al.</i> (2019) Estimates]	303
Figure B-15. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type for Individual-level Exposures [Using Till <i>et al.</i> (2020) Estimates in Place of Green <i>et al.</i> (2019) Estimates]	303
Figure B-16. Association between Fluoride Exposure and IQ Scores in Children Using Verbal IQ Score for Green <i>et al.</i> (2019)	304
Figure B-17. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Verbal IQ Score for Green <i>et al.</i> (2019)]	304
Figure B-18. Test for Publication Bias for Studies with Individual-level Exposures [Using Verbal IQ Score for Green <i>et al.</i> (2019)]	304
Figure B-19. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Verbal IQ Score for Green <i>et al.</i> (2019)]	305
Figure B-20. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type Using Verbal IQ Score for Green <i>et al.</i> (2019)	305
Figure B-21. Association Between Fluoride Exposure and IQ Scores in Children Using Performance IQ Score for Green <i>et al.</i> (2019)	306
Figure B-22. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Performance IQ Score for Green <i>et al.</i> (2019)]	306

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Figure B-23. Test for Publication Bias for Studies with Individual-level Exposures [Using Performance IQ Score for Green <i>et al.</i> (2019)]	306
Figure B-24. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Performance IQ Score for Green <i>et al.</i> (2019)]	307
Figure B-25. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type Using Performance IQ Score for Green <i>et al.</i> (2019)	307
Figure B-26. Association Between Fluoride Exposure and IQ Scores in Children [Excluding Cui <i>et al.</i> (2018)]	308
Figure B-27. Funnel Plot and Filled-in Funnel Plot to Eliminate Publication Bias of Included Studies with Individual-level Exposures [Excluding Cui <i>et al.</i> (2018)]	308
Figure B-28. Test for Publication Bias for Studies with Individual-level Exposures [Excluding Cui <i>et al.</i> (2018)]	308
Figure B-29. Trim-and-fill Analysis for Studies with Individual-level Exposures [Excluding Cui <i>et al.</i> (2018)]	309

ABSTRACT

Background: The overall objective of this evaluation was to undertake a systematic review of published literature to reach conclusions concerning the potential for exposure to fluoride to affect neurodevelopment and cognition. The review only addresses whether exposure to fluoride could present a potential hazard (i.e., has the potential to cause harm, at any exposure level, including exposures that are higher than those typically encountered from consuming fluoridated drinking water in the United States). Benefits of fluoride with respect to oral health are not addressed in this monograph.

Previous reviews of epidemiological studies, including a 2006 evaluation by the National Research Council (NRC), found support for an association between consumption of high levels of naturally occurring fluoride in drinking water and adverse neurological effects in humans and recommended further investigation (NRC 2006). Most of the evidence reviewed was from dental and skeletal fluorosis-endemic regions that have higher levels of naturally occurring fluoride than the fluoride concentrations historically added to water in community water fluoridation programs (0.8–1.2 mg/L). For community water systems that add fluoride, the Public Health Service now recommends a fluoride concentration of 0.7 mg/L.

NTP previously published a systematic review of the evidence from experimental animal studies of the effects of fluoride on learning and memory (NTP 2016). The systematic review found a low-to-moderate level of evidence that learning and memory deficits occur in non-human mammals exposed to fluoride. Studies in animals generally used fluoride drinking water concentrations that far exceeded the levels used in water fluoridation, and the lack of studies at lower fluoride concentrations was identified as a data gap. The evidence for effects on learning and memory was strongest (moderate) in animals exposed as adults, and evidence was weaker (low) in animals exposed during development. Since the publication of the NTP (2016) systematic review of the animal evidence, additional animal studies have been published, many examining the effects of perinatal exposures. In addition, the number of studies examining cognitive and neurobehavioral effects of fluoride in humans has grown considerably since the NRC (2006) review, including several recent prospective cohort studies evaluating prenatal fluoride exposures.

Objective: To conduct a systematic review of the human, experimental animal [extending (NTP 2016) report], and mechanistic literature to evaluate the evidence and develop hazard conclusions about whether fluoride exposure is associated with neurodevelopmental and cognitive effects.

Method: A systematic review protocol was developed and utilized following the Office of Health Assessment and Translation (OHAT) approach for conducting literature-based health assessments.

Results: The literature search and screening process identified 159 published human studies, 339 published experimental animal studies, and 60 in vitro/mechanistic studies relevant to the objective. Ninety-two of the 159 human studies evaluated the association between fluoride exposure and neurodevelopmental or cognitive effects, and the remaining human studies evaluated thyroid effects or other potential mechanistic data. The majority of the experimental animal studies were mechanistic studies, which were not assessed in the NTP (2016) report. Since the NTP (2016) systematic review (through April 2019), 35 experimental animal studies evaluating effects on learning and memory and/or motor activity and sensory effects of fluoride were identified.

Supported by a meta-analysis, the human body of evidence provides a consistent and robust pattern of findings that higher fluoride exposure (e.g., >1.5 mg/L in drinking water) is associated with adverse effects on neurocognitive development, including lower intelligence quotient (IQ) in children. There is a moderate level of evidence from cognitive neurodevelopmental studies in children based on five prospective cohort studies and 14 cross-sectional studies where exposure was identified as occurring prior to outcome. The evidence for cognitive effects in adults is limited, coming from two cross-sectional studies, and is inadequate to evaluate whether fluoride exposure in adults is associated with cognitive effects. The assessment of the new animal data focuses on evaluating a deficiency identified during the prior NTP (2016) review concerning the difficulty in distinguishing potential effects of fluoride on motor and sensory functions from effects specifically on learning and memory functions. Further examination of the animal data, including studies carried out at the NTP, has not resolved this issue. Because of this and other deficiencies related to overall study quality, the animal body of evidence is now considered inadequate to inform conclusions on whether fluoride exposure is associated with cognitive effects (including cognitive neurodevelopmental effects) in humans. While the animal data provide evidence of effects of fluoride on neurodevelopment, the human evidence base is primarily focused on cognitive neurodevelopmental effects, and these human data are the primary basis of conclusions.

Conclusions: Because the majority of available studies evaluated cognitive neurodevelopmental effects in children, the focus of the hazard conclusions is on cognitive neurodevelopmental effects, primarily IQ. When focusing on findings from studies with exposures in ranges typically found in drinking water in the United States (0.7 mg/L for optimally fluoridated community water systems)² that can be evaluated for dose response, effects on cognitive neurodevelopment are inconsistent, and therefore unclear. However, when considering all the evidence, including studies with exposures to fluoride levels higher than 1.5 mg/L in water, NTP concludes that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans*. This conclusion is based on a moderate level of evidence that shows a consistent and robust pattern of findings in human studies across several different populations demonstrating that higher fluoride exposure (e.g., >1.5 mg/L in drinking water) is associated with lower IQ and other cognitive effects in children. Limited and weaker evidence is considered to provide an inadequate level of evidence that fluoride is associated with cognitive effects in adults. The evidence from animal studies is inadequate to inform conclusions on cognitive effects, and the mechanisms underlying fluoride-associated cognitive neurodevelopmental effects are not well characterized.

²As of April 2020, 1.08% of persons living in the United States (~ 3.5 million people) were served by community water systems (CWS) containing ≥ 1.1 mg/L naturally occurring fluoride. CWS supplying water with ≥ 1.5 mg/L naturally occurring fluoride served 0.59% of the U.S. population (~ 1.9 million people), and systems supplying water with ≥ 2 mg/L naturally occurring fluoride served 0.31% of the U.S. population (~1 million people) (<https://www.cdc.gov/fluoridation/data-tools/reporting-system.html>).

INTRODUCTION

The NTP's Office of Health Assessment and Translation (OHAT) conducted a systematic review to evaluate the evidence that exposure to fluoride is associated with neurodevelopmental or cognitive effects. This review was initiated in response to a nomination from the Fluoride Action Network. There are numerous human and animal studies reporting neurodevelopmental and cognitive health effects of exposure to excess fluoride. As noted by the National Research Council (NRC) in their 2006 report, although the studies lacked sufficient detail to fully assess their quality and relevance to the U.S. populations, the consistency of the results suggesting that fluoride may be neurotoxic warrants additional research (NRC 2006).

Fluoride salts are added to community water systems and dental products in the United States (e.g., toothpaste, mouth rinses, and supplements) for the prevention of dental caries. Approximately 67% of the U.S. population receives fluoridated water through a community drinking water system (CDC 2013). In other countries fluoride supplementation has been achieved by fluoridating food products such as salt, or milk. Fluoride supplementation has been recommended to prevent bone fractures (Jones *et al.* 2005). Fluoride also can occur naturally in drinking water. Other sources of human exposure include other foods and beverages, industrial emissions, pharmaceuticals, and pesticides (e.g., cryolite, sulfuryl fluoride). Soil ingestion is another source of fluoride exposure in young children (US EPA 2010).

The U.S. Public Health Service (PHS) first recommended communities add fluoride to drinking water in 1962. PHS guidance is advisory, not regulatory, which means that while PHS recommends community water fluoridation as a public health intervention, the decision to fluoridate water systems is made by state and local governments.³ For community water systems that add fluoride, PHS now recommends a fluoride concentration of 0.7 milligrams/liter (mg/L) (equal to 0.7 parts per million [ppm]). Under the Safe Drinking Water Act, the U.S. Environmental Protection Agency (EPA) sets maximum exposure level standards for drinking water quality. The current enforceable drinking water standard for fluoride, or the maximum contaminant level goal (MCLG, a concentration at which no adverse health effects are expected), is 4.0 mg/L. This is the maximum amount of fluoride contamination (naturally occurring not from water fluoridation) that is allowed in water from public water systems; it is set to protect against increased risk of skeletal fluorosis, a condition characterized by pain and tenderness of the major joints. EPA also has a non-enforceable secondary drinking water standard of 2.0 mg/L, which is recommended to protect children against the tooth discoloration and/or pitting that can be caused by severe dental fluorosis during the formative period prior to eruption of the teeth. Although the secondary standard is not enforceable, EPA does require that public water systems notify the public if the average levels exceed it (NRC 2006). As of April 2020, 1.08% of persons living in the United States (~ 3.5 million people) were served by community water systems (CWS) containing ≥ 1.1 mg/L naturally occurring fluoride. CWS supplying water with ≥ 1.5 mg/L naturally occurring fluoride served 0.59% of the U.S. population (~ 1.9 million people), and systems supplying water with ≥ 2 mg/L naturally occurring fluoride served 0.31% of the U.S. population (~1 million people) (<https://www.cdc.gov/fluoridation/data-tools/reporting-system.html>).

Controversy over community water fluoridation stems from concerns about the potential harmful effects of fluoride and the ethics of water fluoridation. Commonly cited health concerns related to

³ For many years, most fluoridated community water systems used fluoride concentrations ranging from 0.8 to 1.2 mg/L (US DHHS 2015).

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fluoride are bone fractures and skeletal fluorosis, lower intelligence quotient (IQ) and other neurological effects, cancer, and endocrine disruption. Effects on neurological function, endocrine function (e.g., thyroid, parathyroid, pineal), metabolic function (e.g., glucose metabolism), and carcinogenicity were assessed in the 2006 NRC report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* (NRC 2006). The NRC review considered adverse effects of water fluoride, focusing on a range of concentrations (2–4 mg/L) above the current 0.7-mg/L recommendation for community water fluoridation (NRC 2006). The NRC report concluded that the current MCLG should be lowered to protect against severe enamel fluorosis and to reduce the risk of bone fractures associated with skeletal fluorosis (NRC 2006). Other than severe fluorosis, the NRC did not find sufficient evidence of negative health effects at fluoride levels below 4.0 mg/L; however, the NRC concluded that the consistency of the results of IQ deficits in children exposed to fluoride at 2.5 to 4 mg/L in drinking water from a few epidemiological studies of Chinese populations appeared significant enough to warrant additional research on the effects of fluoride on intelligence. The NRC report noted several challenges to evaluating the literature, citing deficiencies in reporting quality, lack of consideration of all sources of fluoride exposure, incomplete consideration of potential confounding, selection of inappropriate control subject populations in epidemiological studies, absence of demonstrated clinical significance of reported endocrine effects, and incomplete understanding of the biological relationship between histological, biochemical, and molecular alterations with behavioral effects (NRC 2006).

In 2016, NTP conducted a systematic review of the evidence from experimental animal studies on the potential effects of fluoride exposure on learning and memory (NTP 2016). The NTP (2016) systematic review found a low-to-moderate level of evidence that learning and memory deficits occur in experimental animals exposed to fluoride. Based on the findings in NTP (2016), NTP decided to conduct additional animal studies before carrying out a full systematic review to incorporate human, animal, and potentially relevant mechanistic evidence in order to reach hazard identification conclusions for fluoride and learning and memory effects. As the NTP (2016) report on the experimental animal evidence focused on learning and memory and developed confidence ratings for bodies of evidence by life stage of exposure (i.e., exposure during development or adulthood), this report also evaluates two different age groups in humans (i.e., children and adults) with a focus on cognitive neurodevelopmental effects in children and cognitive effects in adults in order to address potential differences in the health impact based on timeframe of exposure (i.e., during development or during adulthood). This evaluation has been conducted separately from the 2016 experimental animal assessment, but like the 2016 assessment, it has assessed mainly learning and memory effects in experimental animal studies to determine whether the findings inform the assessment of cognitive neurodevelopmental effects in children and cognitive effects in adults. The September 6, 2019 draft of this monograph was reviewed by a committee convened by the National Academy of Sciences, Engineering, and Medicine (NASEM). The current document incorporates changes in response to that review.

OBJECTIVE AND SPECIFIC AIMS

Objective

The overall objective of this evaluation is to undertake a systematic review to develop NTP hazard identification conclusions on the association between exposure to fluoride and neurodevelopmental and cognitive effects based on integrating levels of evidence from human and non-human animal studies with consideration of the degree of support from mechanistic data.

Specific Aims

- Identify literature that assessed neurodevelopmental and cognitive health effects, especially outcomes related to learning, memory, and intelligence, following exposure to fluoride in human, animal, and relevant in vitro/mechanistic studies.
- Extract data on potential neurodevelopmental and cognitive health effects from relevant studies.
- Assess the internal validity (risk of bias) of individual studies using pre-defined criteria.
- Assess effects on thyroid function to help evaluate potential mechanisms of impaired neurological function.
- Summarize the extent and types of health effects evidence available.
- Describe limitations of the systematic review, limitations of the evidence base, identify areas of uncertainty, as well as data gaps and research needs for neurodevelopmental and cognitive health effects of fluoride.

Dependent on the extent and nature of the available evidence:

- Synthesize the evidence using a narrative approach or meta-analysis (if appropriate) considering limitations on data integration such as study design heterogeneity.
- Rate confidence in the body of evidence for human and animal studies separately according to one of four statements: High, Moderate, Low, or Very Low/No Evidence Available.
- Translate confidence ratings into level of evidence of health effects for human and animal studies separately according to one of four statements: High, Moderate, Low, or Inadequate.
- Combine the level of evidence ratings for human and animal data to reach one of five possible hazard identification conclusions: Known, Presumed, Suspected, Not classifiable, or Not identified to be a hazard to humans.

METHODS

Problem Formulation and Protocol Development

The research question and specific aims stated above were developed and refined through a series of problem formulation steps including:

- (1) receipt of nomination from the public in June 2015 to conduct analyses of fluoride and developmental neurobehavioral toxicity;
- (2) analysis of the extent of evidence available and the merit of pursuing systematic reviews, given factors such as the extent of new research published since previous evaluations and whether these new reports address or correct the deficiencies noted in the literature (NRC 2006, OEHHA 2011, SCHER 2011);
- (3) request for information in a Federal Register notice (dated October 7, 2015);
- (4) consideration of comments providing a list of studies to review through Federal Register notice and public comment period from October 7, 2015 to November 6, 2015;

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- (5) release of draft concept titled *Proposed NTP Evaluation on Fluoride Exposure and Potential for Developmental Neurobehavioral Effects* in November 2015;
- (6) presentation of draft concept at the NTP Board of Scientific Counselors (BSC) meeting on December 1–2, 2015;
- (7) consideration of comments on NTP’s draft concept from the NTP BSC meeting in December 2015; and
- (8) consideration of input on the draft protocol from review by technical advisors.

NTP published a systematic review of the animal evidence on the effects of fluoride on learning and memory (NTP 2016). NTP has conducted additional studies in animals to assess the effect of fluoride exposure on learning and memory. The results from this experimental animal work were published (McPherson *et al.* 2018) and are incorporated into the current review, which considers the epidemiological, animal, and mechanistic evidence in its conclusions. The protocol used to conduct this systematic review was posted in June 2017 with updates posted in May 2019 and September 2020 (<https://ntp.niehs.nih.gov/go/785076>).⁴ A brief summary of the methods is presented below.

NASEM Review

The September 6, 2019 draft of this monograph was peer reviewed by a committee convened by NASEM. The current draft reflects clarifications and changes in response to that review (NASEM 2020), including the addition of meta-analyses of the IQ studies in children.

PECO Statements

PECO (Population, Exposure, Comparators and Outcomes) statements were developed as an aid to identify search terms and inclusion/exclusion criteria as appropriate for addressing the overall research question (effects on neurodevelopmental or cognitive function and thyroid associated with fluoride exposure) for the systematic review (Higgins and Green 2011). The PECO statements are listed below for human, animal, and in vitro/mechanistic studies (see [Table 1](#), [Table 2](#), and [Table 3](#)).

Using the PECO statements, the evaluation searched for evidence of neurodevelopmental or cognitive function, and thyroid effects associated with fluoride exposure from human studies, controlled exposure animal studies, and mechanistic/in vitro studies. Mechanistic data can come from a wide variety of studies that are not intended to identify a disease phenotype. This source of experimental data includes in vitro and in vivo laboratory studies directed at cellular, biochemical, and molecular mechanisms that attempt to explain how a substance produces particular adverse health effects. The mechanistic data were first organized by general categories (e.g., biochemical effects in the brain and neurons, neurotransmitters, oxidative stress, etc.) to evaluate the information available. Categories focused on were those with more robust data at levels of fluoride more relevant to human exposure. The intent was not to develop a mechanism for fluoride induction of learning and memory effects, but to evaluate whether a plausible series of mechanistic events exists to support effects observed in the low-dose

⁴ NTP conducts systematic reviews following pre-specified protocols that describe the review procedures selected and applied from the general methods outlined in the OHAT Handbook for Conducting a Literature-Based Health Assessment (<http://ntp.niehs.nih.gov/go/38673>). The protocol describes project-specific procedures tailored to each systematic review.

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region (below approximate drinking water equivalent concentrations of 20 ppm) that may strengthen the hazard conclusion.

Table 1. Human PECO (Population, Exposure, Comparator and Outcome) Statement	
PECO Element	Evidence
Population	Humans without restriction as to age or sex, geographic location, or life stage at exposure or outcome assessment
Exposure	Exposure to fluoride based on administered dose or concentration, biomonitoring data (e.g., urine, blood, other specimens), environmental measures (e.g., air, water levels), or job title or residence. Relevant forms are those used as additives for water fluoridation: • Fluorosilicic acid (also called hydrofluorosilicate; CASRN 16961-83-4) • Sodium hexafluorosilicate (also called disodium hexafluorosilicate or sodium fluorosilicate; CASRN 16893-85-9) • Sodium fluoride (CASRN 7681-49-4) • Other forms of fluoride that readily dissociate into free fluoride ions (e.g., potassium fluoride, calcium fluoride, ammonium fluoride)
Comparators	Comparable populations not exposed to fluoride or exposed to lower levels of fluoride (e.g., exposure below detection levels)
Outcomes	Neurodevelopmental outcomes including learning, memory, intelligence, other forms of cognitive behavior, other neurological outcomes (e.g., anxiety, aggression, motor activity), and biochemical changes in the brain or nervous system tissue; or measures of thyroid function, biochemical changes, or thyroid tissue

Table 2. Animal PECO Statement	
PECO Element	Evidence
Population	Non-human mammalian animal species (whole organism)
Exposure	Exposure to fluoride based on administered dose or concentration, and biomonitoring data (e.g., urine, blood, other specimens). Relevant forms are those used as additives for water fluoridation: • Fluorosilicic acid (also called hydrofluorosilicate; CASRN 16961-83-4) • Sodium hexafluorosilicate (also called disodium hexafluorosilicate or sodium fluorosilicate; CASRN 16893-85-9) • Sodium fluoride (CASRN 7681-49-4) • Other forms of fluoride that readily dissociate into free fluoride ions (e.g., potassium fluoride, calcium fluoride, ammonium fluoride)
Comparators	Comparable animals that were untreated or exposed to vehicle-only treatment
Outcomes	Neurodevelopmental outcomes including learning, memory, intelligence, other forms of cognitive behavior, other neurological outcomes (e.g., anxiety, aggression, motor activity), and biochemical changes in the brain or nervous system tissue; or measures of thyroid function, biochemical changes, or thyroid tissue

Table 3. In Vitro/Mechanistic PECO Statement	
PECO Element	Evidence
Population	Human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays)
Exposure	Exposure to fluoride based on administered dose or concentration. Relevant forms are those used as additives for water fluoridation: • Fluorosilicic acid (also called hydrofluorosilicate; CASRN 16961-83-4) • Sodium hexafluorosilicate (also called disodium hexafluorosilicate or sodium fluorosilicate; CASRN 16893-85-9) • Sodium fluoride (CASRN 7681-49-4) • Other forms of fluoride that readily dissociate into free fluoride ions (e.g., potassium fluoride, calcium fluoride, ammonium fluoride)
Comparators	Comparable cells or tissues that were untreated or exposed to vehicle-only treatment
Outcomes	Endpoints related to neurological and thyroid function, including neuronal electrophysiology; mRNA, gene, or protein expression; cell proliferation or death in brain or thyroid tissue/cells; neuronal signaling; synaptogenesis, etc.

Literature Search

Main Literature Search

Search terms were developed to identify all relevant published evidence on developmental neurobehavioral toxicity or thyroid-related health effects potentially associated with exposure to fluoride by reviewing Medical Subject Headings for relevant and appropriate neurobehavioral and thyroid-related terms, and by extracting key neurological and thyroid-related health effects and

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developmental neurobehavioral terminology from reviews and a sample of relevant primary data studies. A combination of relevant subject headings and keywords were subsequently identified. A test set of relevant studies was used to ensure the search terms retrieve 100% of the test set. Six electronic databases were searched (see [Main Literature Database Search](#)) using a search strategy tailored for each database (specific search terms used for the PubMed search are presented in [Appendix 1](#); the search strategy for other databases are available in the protocol (<https://ntp.niehs.nih.gov/go/785076>)). A search of PubChem indicated that sodium fluoride was not found in either the Tox21 or ToxCast databases; therefore, these databases were not included in the search. No language restrictions or publication year limits were imposed. These six databases were searched in December 2016 and the search was regularly updated during the review process through April 1, 2019.

Evaluations must include cut-off dates for the literature search to enable synthesis and development of conclusions. Following the NASEM committee peer review in November 2019 (NASEM 2020), an additional search was conducted on May 1, 2020, where only primary human epidemiology studies were prioritized during screening. The review of the 2020 search results focused on the human studies because they formed the basis of the conclusions in the September 6, 2019 draft. A supplemental literature search of Chinese-language databases (described below) was also conducted.

Publications identified in these searches are categorized as “references identified through database searches” in [Figure 4](#). Studies identified from other sources or manual review that might impact conclusions were considered under “references identified through other sources” in [Figure 4](#). Literature searches for this systematic review were conducted independently from the literature search conducted for NTP (2016). The current literature search strategy was based on the search terms used for NTP (2016) and refined for the current evaluation, including the addition of search terms to identify human studies. Although the review process identified studies prior to 2015, the current assessment did not evaluate the studies published prior to 2015 and relied on the NTP (2016) assessment. The focus of the literature searches for this systematic review was to identify and evaluate relevant animal studies that were published since completion of the literature searches for the NTP (2016) assessment in addition to the human and mechanistic data that were not previously evaluated.

Supplemental Chinese Database Literature Search

Following NASEM committee peer review in November 2019 (NASEM 2020), additional searches were developed for non-English-language databases to systematically search for studies that were previously identified from other resources (e.g., Chinese-language studies from the Fluoride Action Network website). Non-English-language databases with the greatest potential to contain relevant non-English publications that were not previously identified through database searches were selected. Multiple non-English language databases were explored before finding two databases (CNKI and Wanfang) that covered studies previously identified from other sources. These two Chinese electronic databases were searched in May 2020 with no language restrictions or publication year limits. Search terms from the main literature search were refined to focus on human epidemiology studies. The CNKI and Wanfang databases have character limits in the search strings; therefore, key terms were prioritized using text analytics to identify the most prevalent terms from neurodevelopmental or cognitive human epidemiology studies previously identified as relevant. Search strings were designed to capture known relevant studies that were previously identified from searching other resources without identifying large numbers of non-relevant studies [the search strategy for both databases are available in the protocol (<https://ntp.niehs.nih.gov/go/785076>)]. Publications retrieved were compared to publications retrieved from the main literature search and duplicates were removed. The remaining relevant publications are categorized as “references identified through database searches” in [Figure 4](#). New animal and

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mechanistic references retrieved were scanned for evidence that might extend the information currently in the September 6, 2019 draft. Although additional studies were identified, data that would materially advance the animal and mechanistic findings were not identified; therefore, these studies were not extracted nor were they added to the draft. Newly-retrieved human references were reviewed to identify studies that might impact conclusions with priority given to identifying and translating null studies that may have been missed using previous approaches. Null studies that were identified were translated and included.

Databases Searched

Main Literature Database Search

- BIOSIS (Thomson Reuters)
- EMBASE
- PsycINFO (APA PsycNet)
- PubMed (NLM)
- Scopus (Elsevier)
- Web of Science (Thomson Reuters, Web of Science indexes the journal Fluoride)

Supplemental Chinese Database Literature Search

- CNKI
- Wanfang

Searching Other Resources

The reference lists of all included studies; relevant reviews, editorials and commentaries; and the Fluoride Action Network website (<http://fluoridealert.org/>) were manually searched for additional relevant publications. Following NASEM committee peer review in November 2019 (NASEM 2020), the Fluoride Action Network website was again searched for relevant references and contacted to identify null or no effect studies.

Unpublished Data

Unpublished data were eligible for inclusion provided the owner of the data was willing to have the data made public and peer reviewed (see protocol for more details <https://ntp.niehs.nih.gov/go/785076>). No unpublished data were identified during the literature search.

Study Selection

Evidence Selection Criteria

In order to be eligible for inclusion, studies had to satisfy eligibility criteria that reflect the PECO statement in [Table 1](#), [Table 2](#), and [Table 3](#). The following additional exclusion criteria were applied (see protocol for additional details; <https://ntp.niehs.nih.gov/go/785076>):

- (1) Case studies and case reports.
- (2) Articles without original data (e.g., reviews, editorials, or commentaries). Reference lists from these materials, however, were reviewed to identify potentially relevant studies not identified from the database searches. New studies identified were assessed for eligibility for inclusion.
- (3) Conference abstracts or reports.

Screening Process

References retrieved from the literature search were independently screened by two trained screeners at the title and abstract level to determine whether a reference met the evidence selection criteria. Screening procedures following the evidence selection criteria in the protocol were pilot-tested with experienced contract staff overseen by NTP. For citations with no abstract or non-English abstracts, articles were screened based on title relevance (title would need to indicate clear relevance); number of pages (articles ≤ 2 pages were assumed to be conference reports, editorials, or letters unlikely to contain original data); and/or PubMed Medical Subject Headings (MeSH). Using this approach, literature was manually screened for relevance and eligibility against the evidence selection criteria using a structured form in SWIFT-Active Screener. While the human screeners review studies, SWIFT-Active Screener aids in the process by employing a machine-learning software program used to priority-rank studies for screening (Howard *et al.* 2020). SWIFT-Active Screener also refines a statistical model that continually ranks the remaining studies according to their likelihood for inclusion. In addition, SWIFT-Active Screener employs active learning to continually incorporate user feedback during title and abstract screening to predict the total number of included studies, thus providing a statistical basis for a decision about when to stop screening (Miller *et al.* 2016). Title and abstract screening was stopped once the statistical algorithm in SWIFT-Active Screener estimated that 98% of the predicted number of relevant studies were identified.

Studies that were not excluded during the title and abstract screening were further screened for inclusion with a full-text review by two independent reviewers using [DistillerSR®](#) by Evidence Partners, a web-based, systematic-review software program with structured forms and procedures to ensure standardization of the process. Screening conflicts were resolved through discussion and consultation with technical advisor(s), if necessary. During full-text review, studies that were considered relevant were tagged to the appropriate evidence streams (i.e., human, animal, and/or in vitro). Studies tagged to human or animal evidence streams were also categorized by outcome as primary neurodevelopmental or cognitive outcomes (learning, memory, and intelligence); secondary neurobehavioral outcomes (anxiety, aggression, motor activity, or biochemical); or related to thyroid effects. In vitro data were tagged as being related to neurological effects or thyroid effects. Translation assistance was sought to assess the relevance of non-English studies. Following full-text review, the remaining studies were “included” and used for the evaluation.

Screening of the May 2020 Literature Search Update

Following the NASEM committee peer review in November 2019 (NASEM 2020), an additional search was conducted on May 1, 2020, where only primary human epidemiology studies were identified. The study screening and selection process was focused on the human studies with primary outcomes for the evaluation because they form the basis of the conclusions. Animal in vivo, human secondary outcome-only, and human and animal mechanistic references were identified as part of the screening process. These studies were then scanned for evidence that might extend the information in the September 6, 2019 draft. Studies from the May 2020 literature search update will be listed in an appendix; however, data from the studies were not extracted unless it was believed they would materially advance the findings.

Data Extraction

Data were collected (i.e., extracted) from included studies by one member of the evaluation team and checked by a second member of the team for completeness and accuracy. Any discrepancies in data extraction were resolved by discussion or consultation with a third member of the evaluation team.

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Data extraction was completed using the Health Assessment Workspace Collaborative (HAWC), an open source and freely available web-based interface application.⁵ Data extraction elements are listed separately for human, animal, and in vitro studies in the protocol (<https://ntp.niehs.nih.gov/go/785076>). Data for primary and secondary outcomes as well as thyroid hormone level data were extracted from human studies. Studies evaluating only goiters or thyroid size were not extracted. All primary outcomes and functional neurological secondary outcomes (e.g., motor activity) were extracted from animal studies identified since the NTP (2016) report. For animal mechanistic data, studies were tiered based on exposure dose (with preference given to fluoride drinking water equivalent exposures, which were calculated using the method described in the NTP (2016) report) of 20 ppm or less as deemed most relevant to exposures in humans), exposure duration or relevant time window (i.e., developmental), exposure route (with preference given to oral exposures over injection exposures), and commonality of mechanism (e.g., inflammation, oxidative stress, changes in neurotransmitters, and histopathological changes were considered pockets of mechanistic data). Data were not extracted from in vitro studies; however, these studies were evaluated for biological plausibility of the human and animal results. Thyroid data were also reviewed but not extracted. The data extraction results for included studies are publicly available and can be downloaded in Excel format through HAWC (<https://hawcproject.org/assessment/405/>). Methods for transforming and standardizing dose levels and results from behavioral tests in experimental animals are detailed in the protocol (<https://ntp.niehs.nih.gov/go/785076>).

In 2016, NTP conducted a systematic review of the evidence from experimental animal studies on the potential effects of fluoride exposure on learning and memory (NTP 2016). The literature searches for the current assessment identified and evaluated relevant animal studies published since the 2016 assessment and also included human and mechanistic data that were not previously evaluated. Although literature search activities for the current assessment identified experimental animal studies prior to 2015, the current assessment did not re-evaluate studies published prior to 2015, but relied on the NTP (2016) assessment.

Quality Assessment of Individual Studies

Risk of bias was assessed for individual studies using a tool developed by OHAT that outlines a parallel approach to evaluating risk of bias from human, animal, and mechanistic studies to facilitate consideration of risk of bias across evidence streams with common terms and categories. The risk-of-bias tool is comprised of a common set of 11 questions that are answered based on the specific details of individual studies to develop risk-of-bias ratings for each question. Study design determines the subset of questions used to assess risk of bias for an individual study (see [Table 4](#)).

Assessors were trained with an initial pilot phase undertaken to improve clarity of rating criteria and to improve consistency among assessors. Studies were independently evaluated by two trained assessors who answered all applicable risk-of-bias questions with one of four options in [Table 5](#) following pre-specified criteria detailed in the protocol (<https://ntp.niehs.nih.gov/go/785076>). The criteria describe aspects of study design, conduct, and reporting required to reach risk-of-bias ratings for each question

⁵ HAWC (Health Assessment Workspace Collaborative): A Modular Web-based Interface to Facilitate Development of Human Health Assessments of Chemicals (<https://hawcproject.org/portal/>).

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and specify factors that can distinguish among ratings (e.g., what separates “definitely low” from “probably low” risk of bias).

Key Risk-of-bias Questions

In the OHAT approach, some risk-of-bias questions or elements are considered potentially more important when assessing studies because there is more empirical evidence that these areas of bias have a greater impact on estimates of the effect size or because these issues are generally considered to have a greater effect on the credibility of study results in environmental health studies (Rooney *et al.* 2016). There were three Key Questions for observational human studies: confounding, exposure characterization, and outcome assessment. There were also three Key Questions for experimental animal studies: randomization, exposure characterization, and outcome assessment. In addition, for animal developmental studies, failure to consider the litter as the unit of analysis was also a key risk-of-bias concern. When there was not enough information to assess the potential bias for a risk-of-bias question and authors did not respond to an inquiry for further information, a conservative approach was followed, and the studies were rated probably high risk of bias for that question.

Table 4. OHAT Risk-of-bias Questions and Applicability by Study Design						
Risk-of-bias Questions	Experimental Animal*	Human Controlled Trials**	Cohort	Case-Control	Cross-Sectional***	Case Series
1. Was administered dose or exposure level adequately randomized?	X	X				
2. Was allocation to study groups adequately concealed?	X	X				
3. Did selection of study participants result in the appropriate comparison groups?			X	X	X	
4. Did study design or analysis account for important confounding and modifying variables?			X	X	X	X
5. Were experimental conditions identical across study groups?	X					
6. Were research personnel blinded to the study group during the study?	X	X				
7. Were outcome data complete without attrition or exclusion from analysis?	X	X	X	X	X	
8. Can we be confident in the exposure characterization?	X	X	X	X	X	X
9. Can we be confident in the outcome assessment (including blinding of outcome assessors)?	X	X	X	X	X	X
10. Were all measured outcomes reported?	X	X	X	X	X	X
11. Were there no other potential threats to internal validity?	X	X	X	X	X	X

*Experimental animal studies are controlled exposure studies. Non-human animal observational studies can be evaluated using the design features of observational human studies such as cross-sectional study design.

**Human Controlled Trials are studies in humans with controlled exposure (e.g., Randomized Controlled Trials, non-randomized experimental studies)

***Cross-sectional studies include population surveys with individual data (e.g., NHANES) and surveys with aggregate data (i.e., ecological studies).

Any discrepancies in ratings between assessors were resolved by a senior technical specialist and through discussion when necessary to reach the final recorded risk-of-bias rating for each question along with a statement of the basis for that rating. Members of the evaluation team were consulted for assistance if additional expertise was necessary to reach final risk-of-bias ratings based on specific aspects of study design or performance reported for individual studies. Study procedures that were not reported were assumed not to have been conducted, resulting in an assessment of “probably high” risk of bias. Authors were queried by email to obtain missing information and responses received were used to update risk-of-bias ratings.

Table 5. The Four Risk-of-bias Rating Options	
Answers to the risk-of-bias questions result in one of the following four risk-of-bias ratings	
	Definitely Low risk of bias: There is direct evidence of low risk-of-bias practices
	Probably Low risk of bias: There is indirect evidence of low risk-of-bias practices OR it is deemed that deviations from low risk-of-bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
 	Probably High risk of bias: There is indirect evidence of high risk-of-bias practices (indicated with “-”) OR there is insufficient information provided about relevant risk-of-bias practices (indicated with “NR” for not reported). Both symbols indicate probably high risk of bias.
	Definitely High risk of bias: There is direct evidence of high risk-of-bias practices

Organizing and Rating Confidence in Bodies of Evidence

Health Outcome Categories for Neurodevelopmental and Cognitive Effects

After data were extracted from all studies, the health effects results within the category of neurodevelopmental or cognitive effects were grouped across studies to develop bodies of evidence or collections of studies with data on the same or related outcomes. The grouping of health effect results was not planned a priori. The vast majority of the human studies evaluated intelligence quotient (IQ) in children as the single outcome; therefore, the discussion of cognitive neurodevelopmental effects in children focuses on IQ studies with supporting information from data on other endpoints. Cognitive function in adults was evaluated separately. Consistent with the NTP (2016) assessment, the primary focus within the animal study body of evidence was on animal studies with endpoints related to learning and memory.

Considerations for Pursuing a Narrative or Quantitative Evidence Synthesis

Heterogeneity within the available evidence was used to determine which type of evidence integration was appropriate—a quantitative synthesis (meta-analysis) or narrative approach for evidence integration. Choi *et al.* (2012) and Duan *et al.* (2018) conducted meta-analyses and found that high fluoride exposure was associated with lower IQ scores. Choi *et al.* (2012) was able to determine a risk ratio for living in an endemic fluorosis area but was unable to develop a dose-response relationship. Duan *et al.* (2018) suggested a significant non-linear dose-response relationship between fluoride dose and intelligence with the relationship stated to be most evident with exposures from drinking water

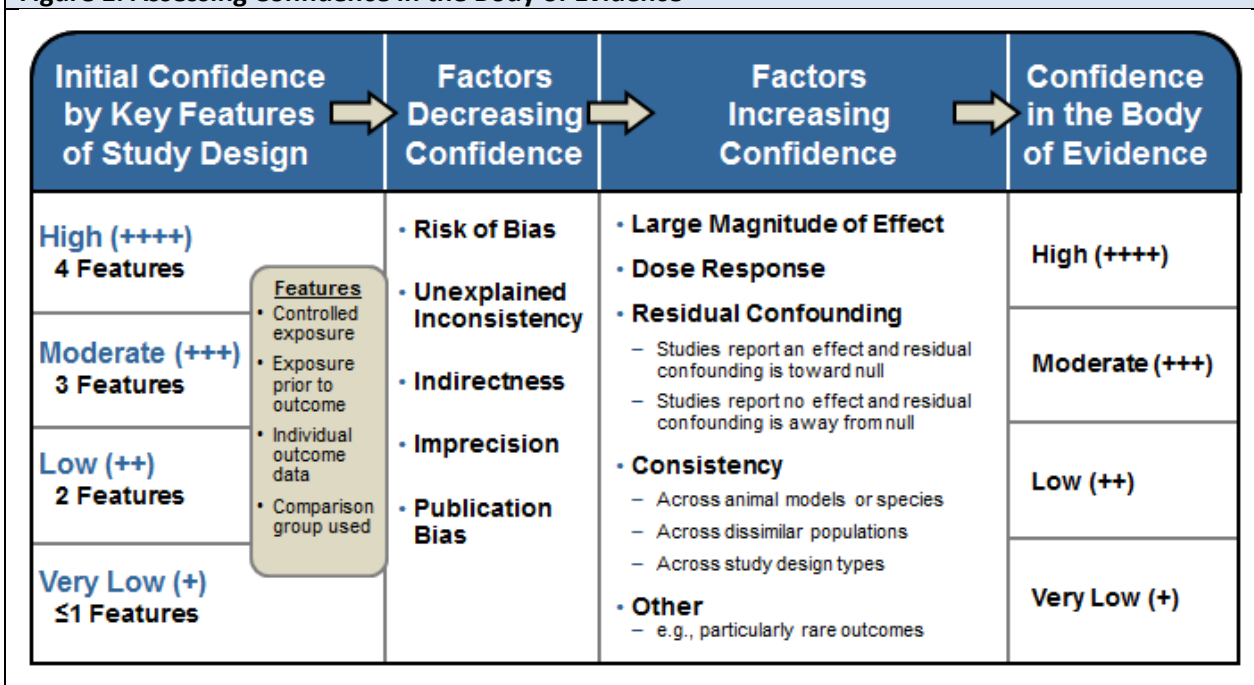
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containing above 4 mg/L (or 4 ppm). Duan *et al.* (2018) found similar results as Choi *et al.* (2012) for the standardized mean difference; however, the majority of the available studies in both analyses compare populations with high fluoride exposure to those with lower fluoride exposure (with the lower exposure levels frequently in the range of drinking water fluoridation in the United States). After evaluating the available data, NTP determined that a narrative review—not a meta-analysis or other quantitative assessment—was appropriate for evidence integration due to heterogeneity in dose among the available human evidence, and because a hazard conclusion could be reached without conducting a meta-analysis. However, in the November 2019 review of the September 6, 2019 draft monograph (NASEM 2020), NASEM recommended that a meta-analysis be conducted. In response, NTP performed a meta-analysis of IQ studies in children. The meta-analysis protocol can be found with the revised systematic review protocol posted in September 2020 (<https://ntp.niehs.nih.gov/go/785076>).

Confidence Rating: Assessment of Body of Evidence

The quality of evidence for neurodevelopmental and cognitive function outcomes was evaluated using the GRADE system for rating the confidence in the body of evidence (Guyatt *et al.* 2011, Rooney *et al.* 2014). More detailed guidance on reaching confidence ratings in the body of evidence as “high,” “moderate,” “low,” or “very low” is provided in the OHAT Handbook for Conducting a Literature-Based Health Assessment (<http://ntp.niehs.nih.gov/go/38673>, see STEP 5). In brief, available human and animal studies on a particular health outcome were initially grouped by key study design features, and each grouping of studies was given an initial confidence rating by those features. Starting at this initial rating (see column 1 of [Figure 1](#)), potential downgrading of the confidence rating was considered for factors that decrease confidence in the results (see column 2 of [Figure 1](#) [risk of bias, unexplained inconsistency, indirectness or lack of applicability, imprecision, and publication bias]); and potential upgrading of the confidence rating was considered for factors that increase confidence in the results (see column 3 of [Figure 1](#) [large magnitude of effect, dose response, consistency across study designs/populations/animal models or species, consideration of residual confounding, and other factors that increase our confidence in the association or effect]). Consideration of consistency across study designs, human populations, or animal species is not included in the GRADE guidance (Guyatt *et al.* 2011); however, it is considered in the modified version of GRADE used by OHAT (Rooney *et al.* 2014, NTP 2015).

Figure 1. Assessing Confidence in the Body of Evidence

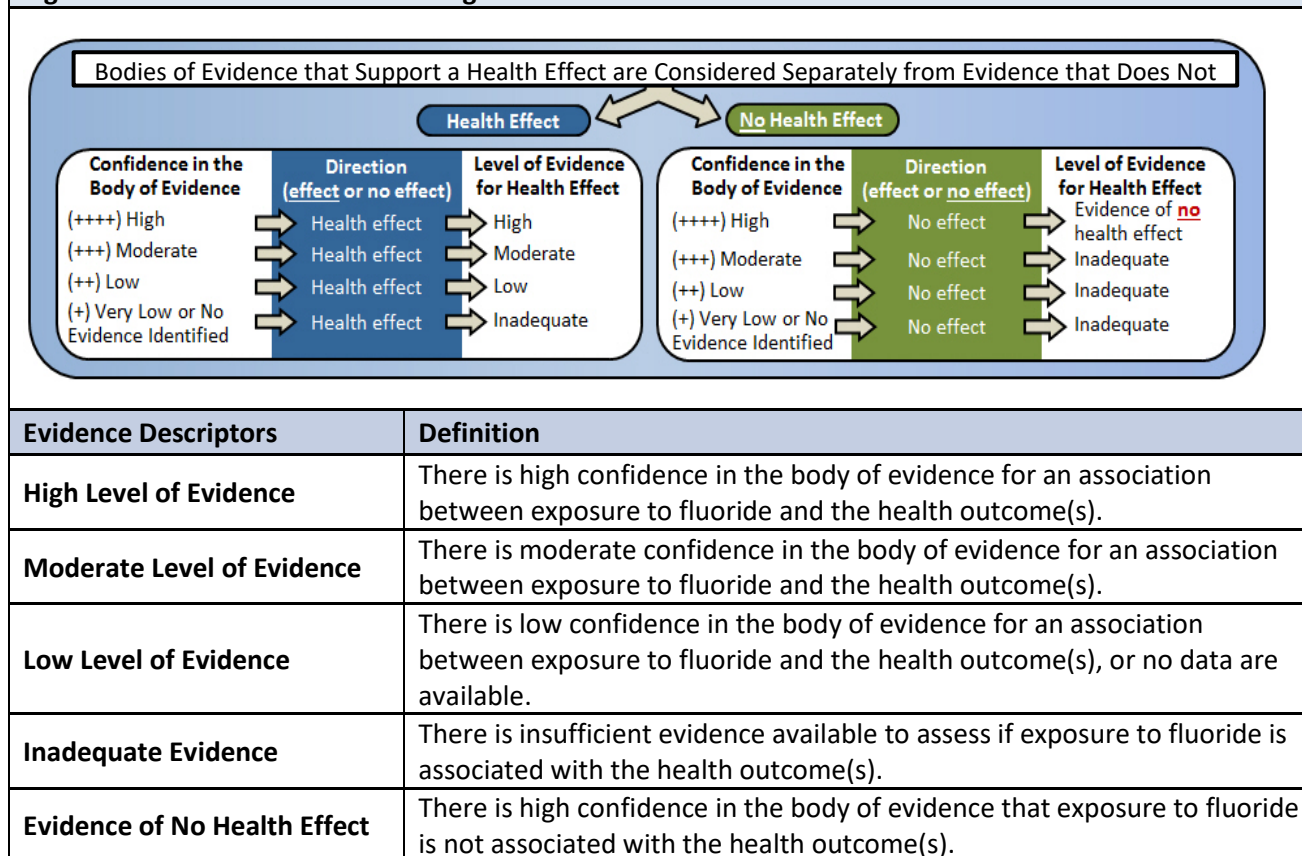


Confidence ratings were assessed by the evaluation team for accuracy and consistency, and discrepancies were resolved by consensus and consultation with technical advisors as needed. Confidence ratings for the primary outcomes are summarized in evidence profile tables for each outcome.

Preparation of Level of Evidence Conclusions

The confidence ratings were translated into level of evidence of health effects for each type of health outcome separately according to one of four statements: (1) High, (2) Moderate, (3) Low, or (4) Inadequate (see [Figure 2](#)). The descriptor “evidence of no health effect” is used to indicate confidence that the substance is not associated with a health effect. Because of the inherent difficulty in proving a negative, the conclusion “evidence of no health effect” is only reached when there is high confidence in the body of evidence.

Figure 2. Translate Confidence Ratings into Evidence of Health Effect Conclusions

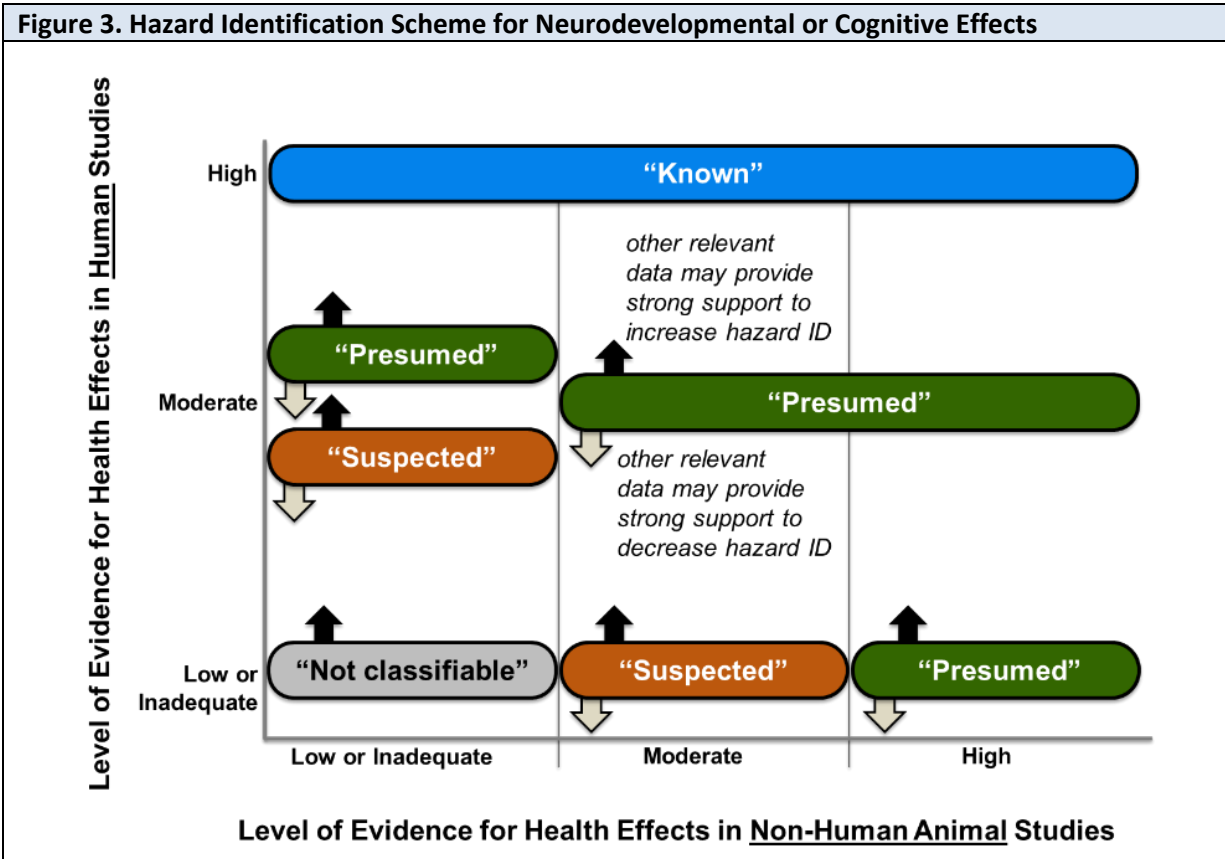


Integrate Evidence to Develop Hazard Identification Conclusions

Finally, the levels of evidence ratings for human and animal data were integrated with consideration of in vitro/mechanistic data to reach **one of five possible hazard identification categories: (1) Known, (2) Presumed, (3) Suspected, (4) Not classifiable, or (5) Not identified to be a neurodevelopmental hazard to humans (see Figure 3).**

Consideration of Human and Animal Data

Initial hazard identification conclusions were attempted by integrating the highest level-of-evidence conclusion for neurodevelopmental effects in children and cognitive effects in adults for the human and the animal evidence streams. The level-of-evidence conclusion for human data for neurodevelopmental or cognitive effects were considered with the level of evidence for non-human animal data to reach one of four initial hazard identification conclusions: Known, Presumed, Suspected, or Not classifiable. When either the human or animal evidence stream was characterized as “Inadequate Evidence,” then conclusions were based on the remaining evidence stream alone (which is equivalent to treating the missing evidence stream as “Low” in Figure 3). If a moderate level-of-evidence conclusion for human data was reached with “Inadequate or Low Evidence” for the animal evidence stream, a hazard identification conclusion of either “suspected to be a hazard to humans” or “presumed to be a hazard to humans” could be reached based on scientific judgement as to the robustness of the body of evidence that supports moderate confidence in the human data and consideration of the potential impact of additional studies (NTP 2019).



Consideration of Mechanistic Data

There is no requirement to consider mechanistic or mode-of-action data to reach a hazard identification conclusion regarding neurodevelopmental or cognitive health effects. However, when available, this and other relevant supporting types of evidence may be used to raise (or lower) the category of the hazard identification conclusion. Mechanistic data can come from a wide variety of studies that are not intended to identify a disease phenotype. This source of experimental data includes in vitro and in vivo laboratory studies directed at cellular, biochemical, genetic, and molecular mechanisms that attempt to explain how a chemical produces particular adverse effects.

For the evaluation of toxicity associated with fluoride exposure, NTP was interested in mechanistic or in vitro measures that comprise a coherent biological process that may support the plausibility of corresponding neurological outcomes reported from in vivo studies in animals or humans. The PECO statement in [Table 3](#) provides the specific endpoints considered including neuronal electrophysiology; mRNA, gene, or protein expression; cell proliferation or death in brain or thyroid tissue/cells; neuronal signaling; or synaptogenesis. In general, the mechanisms for fluoride-associated neurodevelopmental or cognitive effects are not well understood at this time, and mechanistic events identified in studies of animals receiving high fluoride exposures may not reflect biological processes occurring in humans at lower exposure levels. Mechanistic data from in vivo studies were used when feasible to examine the biological plausibility of the primary health outcomes considered in developing a hazard conclusion.

The factors outlined for increasing or decreasing confidence that the mechanistic data support biological plausibility are conceptually similar to those used to rate confidence in bodies of evidence for human or

animal in vivo studies are listed below and described in depth in the protocol (<https://ntp.niehs.nih.gov/go/785076>). Four factors were considered that contribute to increased confidence: potency, dose response, consistency in terms of cellular events observed at the same or lower doses than in vivo health effects, and consistency across cellular targets on the same functional pathway. Three factors were considered that contribute to decreased confidence: unexplained inconsistency across studies of the same endpoint, indirectness/applicability of the pathway for human health or concentrations for human exposure, and publication bias. Evaluations of the strength of evidence provided by mechanistic data were made on an outcome-specific basis based on discussion by the evaluation team and consultation with technical advisors as needed.

- If mechanistic data provided strong support for biological plausibility of the relationship between exposure and the health effect, the hazard identification conclusion may be upgraded (indicated by black “up” arrows in **Figure 3**) from that initially derived by considering the human and non-human animal evidence together.
- If mechanistic data provided strong opposition for biological plausibility of the relationship between exposure and the health effect, the hazard identification conclusion may be downgraded (indicated by gray “down” arrows in **Figure 3**) from that initially derived by considering the human and non-human animal evidence together.

Although it is envisioned that strong evidence for a relevant neurological effect from mechanistic data alone could indicate a potential that the substance is a neurodevelopmental hazard to humans, for this evaluation the mechanistic data were only considered to inform the biological plausibility of observed outcomes from in vivo exposure studies in humans or animals because of a general lack of understanding of the mechanistic basis for neurological outcomes.

RESULTS AND EVIDENCE SYNTHESIS

Literature Search Results

Literature Search Results Counts and Title and Abstract Screening

The electronic database searches retrieved 25,524 unique references in total (20,883 references during the initial search conducted in December 2016, 3,733 references during the literature search updates [including the final updated search conducted for the primary epidemiology studies on May 1, 2020], and 908 references from the supplemental Chinese database searches); 15 additional references were identified by technical advisors or from reviewing reference lists in published reviews and included studies. As a result of title and abstract screening, 1,038 references were moved to full-text review, 11,478 were excluded during manual title and abstract screening for not satisfying the PECO criteria, and an additional 13,023 were not screened and excluded based on the SWIFT algorithm.

Full-text Review

Among the 1,038 references that underwent full-text review, 499 references were excluded during the full-text review with reasons for exclusion documented at this stage; 332 references were excluded for not satisfying the PECO criteria; and 167 references from the May 2020 searches (main literature search update and supplemental Chinese database searches) were excluded for not including information that would materially advance the human, animal in vivo, or mechanistic findings (see the Literature Search Section for a description of the methodology). These screening results are outlined in a study selection diagram that reports numbers of studies excluded for each reason at the full text review stage (see [Figure 4](#)) [using reporting practices outlined in Moher *et al.* (2009)]. After full-text review, 539 studies were considered relevant with primary neurological outcomes, secondary neurological outcomes, and/or outcomes related to thyroid function (see [Appendix 2](#)). A few studies assessed data for more than one evidence stream (human, non-human mammal, and/or in vitro), and several human and animal studies assessed more than one type of outcome (e.g., primary and secondary outcomes). The number of included studies is summarized below. There are:

- 159 human studies (78 primary only; 13 secondary only; 5 primary and secondary; 6 primary and thyroid; 2 secondary and thyroid; and 55 thyroid only);
- 339 non-human mammal studies (7 primary only; 186 secondary only; 67 primary and secondary; 6 primary, secondary, and thyroid; 4 secondary and thyroid; and 69 thyroid only); and,
- 60 in vitro/mechanistic studies (48 neurological and 12 thyroid).

One publication contained human, experimental non-human mammal, and in vitro data. Three publications contained both human and experimental non-human mammal data. Fourteen publications contained data relevant to both experimental non-human mammal studies and in vitro studies.

Evaluation of SWIFT-Active Screener Results

During the initial title and abstract screening of 20,883 references using SWIFT-Active Screener, approximately 38%⁶ of the 20,883 studies were manually screened in duplicate to identify an estimated 98.6% of the predicted number of relevant studies using the statistical algorithm in SWIFT-Active Screener (13,023 references were not screened). SWIFT-Active Screener predicted that there were 739 relevant studies during the initial title and abstract screening, of which 729 studies were identified and moved to full-text review. The SWIFT-Active statistical algorithm predicted that 10 relevant studies at the title and abstract level (10 represents $1.4\% \times 739$ predicted relevant studies; or 739 predicted relevant studies minus 729 identified relevant studies during screening) were not identified by not screening the remaining 13,023 studies.

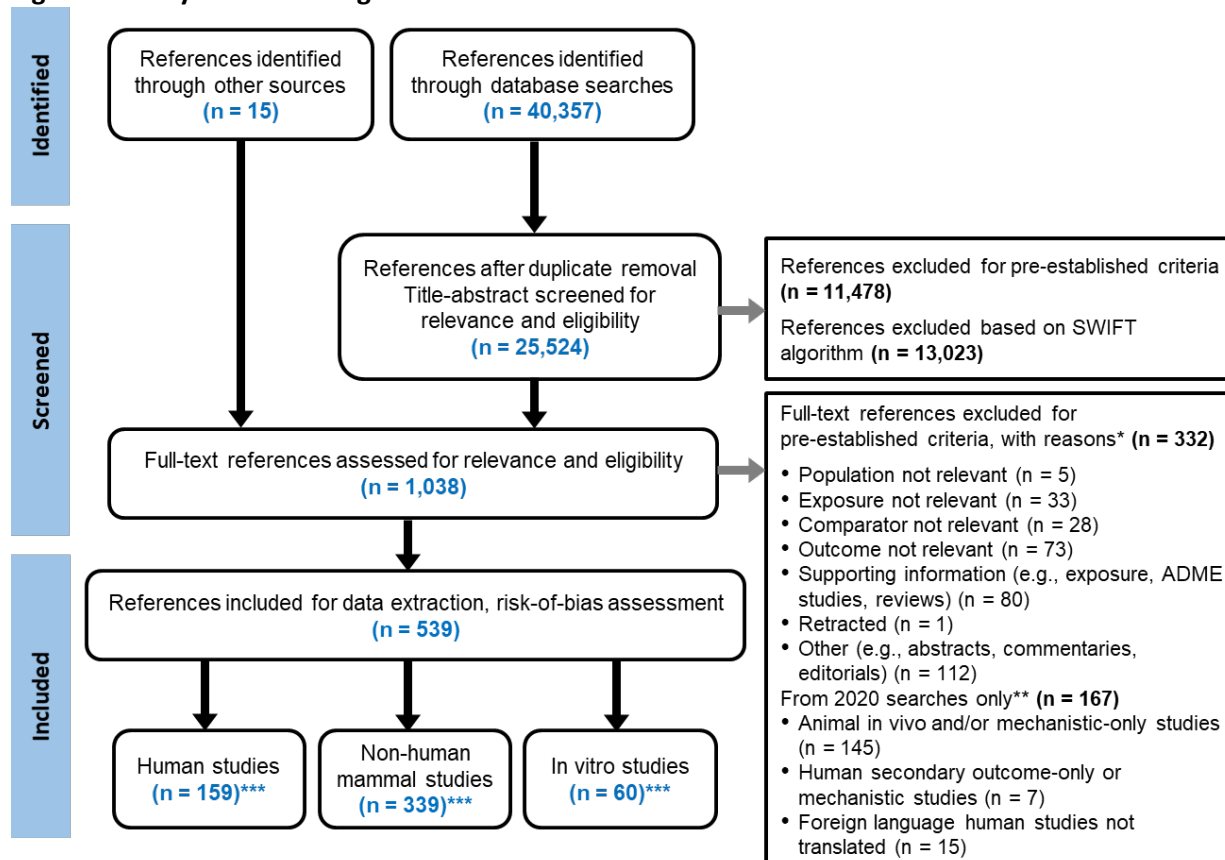
To further consider the impact of using SWIFT-Active Screener for this systematic review, NTP evaluated the SWIFT-Active screening results to gain a better understanding of the relevance of the last group of studies that were screened before 98% predicted recall was satisfied. The goal was to determine the likelihood of having missed important studies by not screening all of the literature. To do this, NTP evaluated subsets of studies screened in SWIFT-Active for trends and followed those studies through to full-text review for a final determination of relevance and potential impact (i.e., whether the studies had data on primary outcomes). Based on this evaluation, NTP estimates that the use of Swift-Active Screener may have resulted in missing 1–2 relevant human studies and 1–2 relevant animal studies with primary neurodevelopmental or cognitive outcomes.

Supplemental Chinese Database Searches and Human Epidemiology Studies

Following the NASEM committee peer review in November 2019 (NASEM 2020), supplemental searches were conducted in non-English language databases (CNKI and Wanfang). One focus of the screening of these supplemental search results was to identify null or no-effect studies that evaluated primary neurodevelopmental or cognitive outcomes (learning, memory, and intelligence) that may have been missed in previous approaches or may have been absent from the Fluoride Action Network website. Of the 908 references that were identified in the supplemental Chinese database searches, 16 relevant studies with primary neurological outcomes were identified (which were not identified through the main literature searches). Among these 16 studies, Kang *et al.* (2011) was the only null study with primary neurological outcomes that was identified through the supplemental Chinese database searches. NTP had the study translated to English, and the study was included. Note that Kang *et al.* (2011) is also identified by the Fluoride Action Network as a null study, but their website does not include an English translation of the study. The other 15 relevant studies contained results that would likely add to the body of evidence showing a negative association between fluoride exposure and primary neurological outcomes. Because this body of evidence is already so large, and because time was a factor in the revision of the monograph, these studies were not translated or included as this information would likely not materially advance the human findings.

⁶ Howard *et al.* (2020) evaluated the performance of the SWIFT-Active Screener methods for estimating total number of relevant studies using 26 diverse systematic review datasets that were previously screened manually by reviewers. The authors found that on average, 95% of the relevant articles were identified after screening 40% of the total reference list when using SWIFT-Active Screener. In the document sets with 5,000 or more references, 95% of the relevant articles were identified after screening 34% of the available references, on average, using SWIFT-Active Screener.

Figure 4. Study Selection Diagram



* Studies may have been excluded for more than one reason; the first reason identified by the screener was recorded.

** Animal in vivo, human secondary outcome-only, and human and animal mechanistic references from the 2020 database searches were scanned for evidence that might strengthen the information in the September 6, 2019 draft monograph. Although 145 additional animal in vivo and/or mechanistic studies and 7 additional human secondary outcome-only or mechanistic-only studies were identified, information that would materially advance the human, animal in vivo, and mechanistic findings was not identified; therefore, these studies were not included. Additionally, 15 human primary outcome studies from the 2020 Chinese database search were excluded based on English abstracts and google translations because information that would materially advance the human findings was not identified; 1 null publication from the 2020 Chinese database search (Kang *et al.* 2011) was identified, translated, and included.

*** One publication contained human, experimental non-human mammal, and in vitro data. Three publications contained both human and experimental non-human mammal data. Fourteen publications contained data relevant to both experimental non-human mammal studies and in vitro studies.

Neurodevelopmental and Cognitive Health Effects Results

All the neurodevelopmental and cognitive data were initially considered and evaluated, with more in-depth analysis where similar endpoints were evaluated across multiple studies (e.g., IQ). Hazard conclusions were developed separately for two different age groups (i.e., children and adults) to address potential differences in the health impact based on exposure during development compared to adulthood. Although the data cover a wide array of endpoints (see Figure 5), the hazard conclusion covers a single category for each age group. The largest bodies of evidence were for IQ (n = 71 studies), learning and memory (n = 8 studies), as well as other cognitive development effects (e.g., total

neurobehavioral scores and total mental capacity index in children and cognitive impairment in adults; n = 14 studies)⁷. Due to heterogeneity in the endpoints examined and the limited number of human or animal studies, congenital neurological malformations and neurological complications of fluorosis were not evaluated because the body of evidence was inadequate to evaluate these potential effects. These health outcomes are not further discussed in this assessment. To the extent possible, human and animal data were grouped into similar categories (e.g., IQ in humans was considered comparable to learning and memory in animals). NTP had previously assessed animal data related to effects on learning and memory associated with fluoride exposure (NTP 2016). Therefore, to update the conclusions of the NTP (2016) systematic review, only more recent animal studies were evaluated in this assessment. Although the previous NTP (2016) report was conducted through January 14, 2016, the current assessment included studies published from 2015 through April 2019 and considered studies from the NTP (2016) report. Thirty-five animal studies have been identified that met these criteria, including 23 studies with learning and memory endpoints and 12 studies with only motor and sensory endpoints. Consistent with the NTP (2016) assessment, only learning and memory studies have been considered in the development of hazard identification conclusions. The additional motor and sensory studies have been considered, along with information on motor and sensory effects reported in the learning and memory studies, to provide evidence of possible indirectness related to the learning and memory assessments.

Risk-of-bias Considerations

Risk-of-bias ratings for each individual study for all risk-of-bias questions are available in [Appendix 3](#). The risk of bias of individual studies in the body of evidence was considered in developing confidence ratings. The key risk-of-bias questions (i.e., confounding, exposure characterization, and outcome assessment for human studies and randomization, exposure characterization, and outcome assessment for experimental animal studies) are discussed in the consideration of the body of evidence. For this assessment, the key risk-of-bias questions, if not addressed appropriately, are considered to potentially have the greatest impact on the results. In addition, for developmental studies in animals, controlling for potential litter effects (i.e., adjusting for similarities in responses between littermates) was also a key risk-of-bias concern. The other risk-of-bias questions were also taken into consideration and were used to identify any other risk-of-bias concerns that may indicate serious issues with the studies. No study was excluded based on concerns for risk of bias; however, confidence conclusions were considered with and without higher risk-of-bias studies (i.e., studies rated probably high risk of bias for at least two key risk-of-bias questions or definitely high for any single question) to assess the impact of the higher risk-of-bias studies. The remaining studies (i.e., other than the higher risk-of-bias studies) were considered lower risk of bias. Based on NASEM recommendations (NASEM 2020), [Appendix 4](#) was created for the lower risk-of-bias studies to describe strengths and limitations of the studies identified during the assessment and to clarify why they are considered to pose lower risk of bias.

Human Neurodevelopmental and Cognitive Data

While there were several neurodevelopmental and cognitive endpoints assessed (see [Figure 5](#)), most of the available studies evaluated intelligence (e.g., IQ) in children. Other measures of neurodevelopment or cognitive function in children were also assessed, including general cognitive index (GCI), mental capacity, mental development index (MDI), or neonatal behavioral neurological assessment (NBNA). However, because the majority of studies evaluated intelligence, the discussion focuses primarily on IQ in children with separate discussions on other measures of cognitive function and neurobehavioral

⁷Some studies are included in more than endpoint category (e.g., IQ and other cognitive developmental effects); therefore, these counts are not mutually exclusive.

effects in children and cognitive effects in adults. The available body of literature that evaluates the association between fluoride exposure and neurodevelopmental and cognitive effects is relatively robust ($n = 92$) and confidence considerations in the body of evidence and hazard conclusions are focused on the studies with the least potential for bias ($n = 31$). Studies with higher potential for bias ($n = 61$) have also been evaluated and determined to have little impact on the confidence and hazard conclusions. A subgroup analysis within the meta-analysis (described in detail in [Appendix 5](#)) demonstrated that results were robust to the exclusion of higher risk-of-bias studies (see [Appendix 5, Figure A5-6](#)). All evaluated studies can be found in [Appendix 2](#).

This section is organized to present and explain NTP's two confidence ratings in the bodies of evidence from epidemiological studies that fluoride exposure is associated with cognitive neurodevelopmental effects in children and cognitive effects in adults. These confidence ratings were determined as described in [Figure 1](#).

Summary: There is moderate confidence in the body of evidence that fluoride exposure is associated with cognitive neurodevelopmental effects in children, and low confidence in the body of evidence that fluoride exposure is associated with cognitive effects in adults. The moderate confidence rating is supported by consistent evidence from the available studies of an association between high-fluoride exposure (mainly greater than the WHO Drinking Water Quality Guideline [>1.5 mg/L] (WHO 2011), but also high exposure via fluoridated salt and food) and lower IQ or cognitive function in children. There is also a recent study of lower IQ in children living in areas where drinking water fluoride concentrations are <1.5 mg/L. Specifically, a study conducted in Canada observed significantly lower IQ scores in boys and girls associated with higher estimated total maternal consumption of fluoride during pregnancy from drinking water and other water-based beverages including black and green tea. When looking at maternal urinary fluoride concentrations, the significant negative association with IQ scores was seen in boys but not girls (Green *et al.* 2019). Another study conducted in Mexico with similar maternal urinary fluoride concentrations during pregnancy as seen in Green *et al.* (2019) observed significantly lower IQ scores in boys and girls associated with higher perinatal exposure to fluoride (Bashash *et al.* 2017). Although the body of evidence in children supports lower IQ with increased fluoride exposure, there is a lack of evidence of an association between exposure to fluoride and cognitive effects in adults (Jacqmin *et al.* 1994, Li *et al.* 2016). The body of evidence available to examine the association between exposure to fluoride and cognitive effects in adults is limited to two lower risk-of-bias cross-sectional studies; due to the limited number of studies and a lack of an observed effect, this body of evidence is considered inadequate to evaluate whether fluoride exposure is associated with cognitive effects in adults (see [Table 7](#)).

Most of the available epidemiological studies that evaluated the association between fluoride exposure and cognitive neurodevelopmental effects assessed IQ and other measures of cognitive function in children (see [Figure 5](#)). Confidence conclusions are based on those studies with the lowest potential for bias ($n = 28$; 26 in children and 2 in adults) (see [Table 6](#)). Most of these studies measured fluoride levels in drinking water or urine. All but two of the studies were conducted in infants or children. The two studies in adults were conducted in older adult populations (≥ 60 years old; one in France and the other in a fluorosis-endemic area of China) to evaluate the effects of fluoride on cognitive impairment.

The studies in children were conducted in multiple populations. Of the 26 studies in children:

- 12 were conducted in 6 areas of China based on 8 study populations (1 study with both IQ and other neurodevelopmental outcomes, 9 studies with IQ only, and 2 studies with other neurodevelopmental outcomes);
- 6 were conducted in 4 areas of Mexico based on 5 study populations (1 study with both IQ and other neurodevelopmental outcomes, 2 studies with IQ only, and 3 studies with other neurodevelopmental outcomes);
- 4 were conducted in Canada using 2 separate cohorts (2 studies with IQ only and 2 studies with other neurodevelopmental outcomes);
- 3 were conducted in 3 areas of India (all IQ studies); and
- 1 was conducted in Iran (IQ study).

The IQ studies used many different tests to measure IQ. The IQ tests used often differed by population as not all IQ tests are appropriate for all populations (e.g., western vs. Asian populations). In some cases, different IQ tests were used to study similar populations. Overall, studies used IQ or cognitive tests appropriate for the population and were age appropriate. Other neurodevelopmental outcomes assessed in some studies included neurobehavioral effects (in infants), learning and memory impairment, and learning disabilities such as attention deficit hyperactivity disorder (ADHD). The different tests conducted and the populations on which the tests were conducted are indicated in [Table 6](#).

The lower risk-of-bias studies (i.e., studies not meeting criteria for higher risk of bias) showing associations with cognitive neurodevelopmental effects in children include 5 prospective cohort studies from 3 study populations (Bashash *et al.* 2017, Valdez Jimenez *et al.* 2017, Green *et al.* 2019, Bashash *et al.* 2018, Till *et al.* 2020) and 21 cross-sectional studies from 16 study populations (Li *et al.* 2004 [translated in Li *et al.* 2008a], Choi *et al.* 2015, Rocha-Amador *et al.* 2007, Rocha-Amador *et al.* 2009, Saxena *et al.* 2012, Seraj *et al.* 2012, Xiang *et al.* 2003a, Xiang *et al.* 2011, Zhang *et al.* 2015b, Ding *et al.* 2011, Barberio *et al.* 2017b, Yu *et al.* 2018, Cui *et al.* 2018, Cui *et al.* 2020, Wang *et al.* 2020b, Wang *et al.* 2020a, Wang *et al.* 2012, Soto-Barreras *et al.* 2019, Sudhir *et al.* 2009, Trivedi *et al.* 2012, Riddell *et al.* 2019) (see [Figure D1](#) through [Figure D12](#)). One limitation of the 21 cross-sectional studies was the lack of direct evidence that exposure to fluoride occurred prior to the development of the neurodevelopmental outcomes. However, several studies from different study populations (n = 5) indicated that a large portion of the exposed children had dental fluorosis (ranging from 43–100%) at the time of the assessment (Choi *et al.* 2015, Ding *et al.* 2011, Seraj *et al.* 2012, Yu *et al.* 2018, Sudhir *et al.* 2009). Because dental fluorosis occurs when fluoride is consumed during enamel formation usually during the first 6–8 years of life, the presence of dental fluorosis suggests that exposures to fluoride occurred prior to the outcome assessment. Ten studies from seven study populations (including Yu *et al.* (2018), Wang *et al.* (2012) listed above) excluded subjects that had not lived in the study area for a specified period of time, sometimes since birth (Rocha-Amador *et al.* 2007, Rocha-Amador *et al.* 2009, Saxena *et al.* 2012, Yu *et al.* 2018, Wang *et al.* 2020b, Wang *et al.* 2012, Xiang *et al.* 2011, Xiang *et al.* 2003a, Soto-Barreras *et al.* 2019, Sudhir *et al.* 2009). Another study evaluated fluoride exposure in mothers and included urine levels just prior to birth and assessed children a few days after birth (Li *et al.* 2004 [translated in Li *et al.* 2008a]). Because these areas were generally known to be fluoride-endemic areas for long periods of time, it can generally be assumed that in these 14 cross-sectional studies from 11 study populations, exposure occurred prior to the outcome. These exposure concerns were not an issue for the prospective studies because fluoride levels were measured prenatally. Therefore, the moderate confidence in the body of evidence in children is primarily based on the consistency of findings across different populations in the 5 lower risk-of-bias prospective cohort studies and the 14

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cross-sectional studies where exposure is considered to have occurred prior to the outcome with initial and final ratings of moderate confidence.

Figure 5. Number of Epidemiological Studies by Outcome and Age Categories*

Outcome Category	Age Category					
	Child	Adult	Child/Adult Combined	Infant	Fetus	
Intelligence (IQ)	68	3				
Learning/Memory	4	3		1		
Cognitive Development	3			1		
Cognitive Impairment		5				
Attention/Hyperactivity/Behavioral ..	7					
Motor/Sensory Function or Develop..	2	4		1		
Mood/Affect	1	1				
Visual-Spatial/Visual-Motor Function	2	2				
Brain Activity		1				
Brain Structure					2	
Neurological Biochemical	3	1	1		1	
Neurological Complications of Fluoro..		3				
Neurological Symptoms	1	3				
Birth Defects				3		
Thyroid Gland Function	14	5	2			
Thyroid Disease		2				

*Interactive figure and additional study details in

(https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_Epi_2020Update/Figure5)

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Children-IQ Studies					
China					
Choi <i>et al.</i> (2015)	Cross-sectional Mianning County/1 st grade children [51]	Drinking water GM: 2.20 mg/L Children's urine GM: 1.64 mg/L Severity of fluorosis (Dean Index)	Children (ages 6–8 years)	IQ: WISC-IV (square root block design and digit span)	Compared to normal/ questionable fluorosis, moderate/severe fluorosis significantly associated with lower total (adjusted β = -4.28; 95% CI: -8.22, -0.33) and backward digit span scores (adjusted β = -2.13; 95% CI: -4.24, -0.02); linear correlation between fluoride in urine (adjusted β = -1.67; 95% CI: -5.46, 2.12) and in drinking water (adjusted β = -1.39; 95% CI: -6.76, 3.98) with total digit span was observed but not significant; other outcomes not significantly associated with fluoride exposure Adjusted for child's age, child's gender, parity, illness before 3 years old, household income last year, and caretaker's age and education
Cui <i>et al.</i> (2018)	Cross-sectional Tianjin City (districts Jinghai and Dagang)/school children [323]	Children's urine Range (log- transformed): -1.2– 2.2	Children (ages 7–12 years)	IQ: Combined Raven's Test for Rural China	Significant correlation between IQ score and urinary fluoride (adjusted β = -2.47) Adjusted for child age, mother's education, family member smoking, stress, and anger
Cui <i>et al.</i> (2020)	Cross-sectional Tianjin City (all districts) /school children [498]	Children's urine <1.6–≥2.5 mg/L	Children (ages 7–12 years)	IQ: Combined Raven's Test	No significant difference in IQ score in the three urinary fluoride exposure groups based on a one-way ANOVA <1.6 mg/L = 112.16 ± 11.50 1.6-2.5 mg/L = 112.05 ± 12.01 ≥2.5 mg/L = 110 ± 14.92 No statistical adjustment for confounders

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Zhang <i>et al.</i> (2015b)	Cross-sectional Tianjin City (Jinnan District)/school children [180]	Drinking water Mean: 0.63 (control), 1.40 (endemic fluorosis) mg/L (SD not reported) Children's urine Mean (SD): 1.1 (0.67) (control), 2.4 (1.01) (endemic fluorosis) mg/L Children's serum Mean (SD): 0.06 (0.03) (control), 0.18 (0.11) (endemic fluorosis) mg/L	Children (ages 10–12 years)	IQ: Combined Raven's Test for Rural China	Significant correlation between IQ score and serum fluoride ($r = -0.47$) and urinary fluoride ($r = -0.45$); significant difference in IQ score for high-fluoride area (>1 ppm; 102.33 ± 13.46) compared with control area (109.42 ± 13.30) Adjusted for child's age and gender, if applicable
Yu <i>et al.</i> (2018)*	Cross-sectional Tianjin City (7 towns)/children [2,886]	Drinking water Mean (SD): 0.50 (0.27) (normal), 2.00 (0.75) (high) mg/L Children's urine Mean (SD): 0.41 (0.49) (normal), 1.37 (1.08) (high) mg/L	Children (ages 7–13 years)	IQ: Combined Raven's Test for Rural China	Significant difference in mean IQ scores in high water fluoride area (>1.0 mg/L; 106.4 ± 12.3 IQ) compared to the normal area (≤ 1.0 ppm; 107.4 ± 13.0 IQ); distribution of the IQ scores also significantly different ($p = 0.003$); every 0.5-mg/L increase in water fluoride was associated with a 4.29 lower IQ score (95% CI: $-8.09, -0.48$) between 3.40 and 3.90 mg/L Adjusted for child's age, child's gender, maternal education, paternal education, and low birth weight
Wang <i>et al.</i> (2020b)	Cross-sectional Tianjin City (villages not specified)/school children [571]	Drinking water Mean (SD): 1.39 (1.01) mg/L Children's urine Mean (SD): 1.28 (1.30) mg/L	Children (ages 7–13 years)	IQ: Combined Raven's Test for Rural China	Significant associations between IQ and water and urine fluoride concentrations in boys and girls combined based on both quartiles and continuous measures (water: -1.587 per 1-mg/L increase; urine: -1.214 per 1-mg/L increase); there was no significant modification effect of gender Adjusted for child's age, child's gender, BMI, maternal education, paternal education, household income, and low birth weight

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans^{a,b}

Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Ding <i>et al.</i> (2011)	Cross-sectional Inner Mongolia (Hulunbuir City)/ elementary school children [331]	Drinking water Mean (SD): 1.31 (1.05) mg/L Children's urine Range: 0.1–3.55 mg/L	Children (ages 7–14 years)	IQ: Combined Raven's Test for Rural China	Significant association between urinary fluoride and IQ score (each 1-mg/L increase was associated with a lower IQ score of 0.59 points (95% CI: –1.09, –0.08); dose response relationship between fluoride and dental fluorosis ($p < 0.0001$) Adjusted for child's age
Xiang <i>et al.</i> (2003a)	Cross-sectional Wamiao and Xinhui villages (Sihong County)/school children [512]	Drinking water Mean (SD): 0.36 (0.15) (control), 2.47 (0.79) (high fluoride) mg/L Children's urine Mean (SD): 1.11 (0.39) (control), 3.47 (1.95) (high fluoride) mg/L Village of residence (non-endemic v. endemic fluorosis)	Children (ages 8–13 years)	IQ: Combined Raven's Test for Rural China	Significant dose-related effect of fluoride on IQ score based on quintile levels with significantly lower IQ scores observed at water fluoride levels 1.53 mg/L or higher; Pearson correlation coefficient of –0.164 with urinary fluoride; IQ scores for children in non-endemic region (100.41 ± 13.21) significantly higher than endemic region (92.02 ± 13.00); calculated a lower-bound confidence limit benchmark concentration (BMCL) of 1.85 mg/L
Xiang <i>et al.</i> (2011)	Cross-sectional Wamiao and Xinhui villages (Sihong County)/school children (same population as Xiang <i>et al.</i> (2003a)) [512]	Children's serum Mean (SD): 0.041 (0.009) (control), 0.081 (0.019) (high fluoride) mg/L	Children (ages 8–13 years)	IQ: Combined Raven's Test for Rural China	Significant trend on association between quartiles of serum fluoride and children's IQ score < 80 (adjusted ORs for Q1 and Q2; Q1 and Q3; and Q1 and Q4, respectively: 1; 2.22 [95% CI: 1.42, 3.47]; and 2.48 [95% CI: 1.85, 3.32]); significant effects at ≥ 0.05 ppm fluoride Adjusted for child's age and gender
Wang <i>et al.</i> (2012)	Cross-sectional Wamiao and Xinhui villages (Sihong County)/school children (same population as Xiang <i>et al.</i> (2003a)) [526]	Drinking water Mean (SD): 0.36 (0.11) (control), 2.45 (0.80) (high fluoride) mg/L Children's total fluoride intake Mean (SD): 0.78 (0.13) (control), 3.05 (0.99) (high fluoride) mg/day Village of residence (non-endemic v. endemic fluorosis)	Children (ages 8–13 years)	IQ: Combined Raven's Test for Rural China	Significantly lower mean IQ in the high fluoride village (92.02 ± 13.00) compared to the control village (100.41 ± 13.21); when high exposure group was broken into 4 exposure groups, a dose- dependent decreasing IQ and increase in % with low IQ observed; significant correlation between total fluoride intake and IQ ($r = -0.332$); OR for IQ<80 per increase in total fluoride intake = 1.106; 95% CI 1.052–1.163). Adjusted for child's age and gender

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Mexico					
Rocha-Amador <i>et al.</i> (2007)	Cross-sectional Moctezuma and Salitral in San Luis Potosi State and 5 de Febrero of Durango State /elementary school children [132]	Drinking water Mean (SD): 0.8 (1.4), 5.3 (0.9), 9.4 (0.9) mg/L (3 rural areas) Children's urine Mean (SD): 1.8 (1.5), 6.0 (1.6), 5.5 (3.3) mg/L (3 rural areas)	Children (ages 6–10 years)	IQ: WISC-Revised Mexican Version	Significant associations between fluoride and IQ scores (full IQ adjusted β s of –10.2 with water and –16.9 with urine; CIs not reported); arsenic also present, but the effect was smaller (full IQ adjusted β s of –6.15 with water and –5.72 with urine; CIs not reported) Adjusted for blood lead, mother's education, SES, height-for-age z-scores, and transferrin saturation
Bashash <i>et al.</i> (2017)	Cohort (prospective) Mexico City/Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) participants [299] IQ analysis [211]	Maternal urine during pregnancy Mean (SD): 0.90 (0.35) mg/L Children's urine Mean (SD): 0.82 (0.38) mg/L	Children (ages 6–12 years)	IQ: WASI-Spanish Version	Significant effect between maternal urinary fluoride and offspring IQ score (adjusted β = –2.50; 95% CI: –4.12, –0.59); associations with children's urine not significant Adjusted for gestational age, weight at birth, child's gender, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked during the pregnancy vs. nonsmoker), marital status (married vs not married), age at delivery, education, IQ, and cohort

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Soto-Barreras <i>et al.</i> (2019)	Cross-sectional Chihuahua/school children [161]	Drinking water Range: 0.05–2.93 mg/L Children’s urine Range: 0.11–2.10 mg/L	Children (ages 9–10 years)	IQ: Raven’s Colored Progressive Matrices	No significant differences in fluoride exposure level (urine fluoride [p = 0.559], exposure dose [p = 0.389], or fluorosis index [p = 0.851]) between the different IQ grades No statistical adjustment for confounders
Canada					
Green <i>et al.</i> (2019)	Cohort (prospective) 10 cities/Maternal-Infant Research on Environmental Chemicals (MIREC) [512] Non-Fluoridated [238] Fluoridated [162] Boys [248] Girls [264]	Maternal urine during pregnancy Mean (SD): 0.51 (0.36) mg/L (0.40 [0.27] mg/L in non- fluoridated areas and 0.69 [0.42] mg/L in fluoridated areas) Maternal fluoride intake during pregnancy Mean (SD): 0.54 (0.44) mg/day (0.30 [0.26] and 0.93 [0.43] mg/day, respectively) Drinking water Mean (SD): 0.31 (0.23) mg/L (0.13 [0.06] and 0.59 [0.08] mg/L, respectively)	Children (ages 3–4 years)	IQ: full scale, performance, and verbal using Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)	Significantly lower full-scale IQ (adjusted β = –4.49; 95% CI: –8.38, –0.60) and performance IQ (adjusted β = –4.63; 95% CI: –9.01, –0.25) per 1-mg/L increase in maternal urine in boys, but not girls (adjusted β = 2.40; 95% CI: –2.53, 7.33 and adjusted β = 4.51; 95% CI: –1.02, 10.05, respectively); significantly lower full-scale IQ (adjusted β = –3.66; 95% CI: –7.16, –0.15) per 1-mg increase in maternal fluoride intake (no sex interaction); significantly lower full-scale IQ (adjusted β = –5.29; 95% CI: –10.39, –0.19) per 1-mg/L increase in water fluoride concentration (no sex interaction); no significant changes observed in verbal IQ Adjusted for city, HOME score, maternal education, race, child’s gender, and prenatal secondhand smoke exposure

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Till <i>et al.</i> (2020)	Cohort (prospective) 10 cities/ MIREC [398] Non-Fluoridated [247] Fluoridated [151] Breastfed as infants [200] Formula-fed as infants [198]	Maternal urine during pregnancy Mean (SD) <u>breastfed</u> : 0.42 (0.28) mg/L in non-fluoridated areas and 0.70 (0.39) mg/L in fluoridated areas <u>formula-fed</u> : 0.38 (0.27) mg/L in non-fluoridated areas and 0.64 (0.37) mg/L in fluoridated areas Infant fluoride intake Mean (SD) <u>breastfed</u> : 0.02 (0.02) mg/day in non-fluoridated areas and 0.12 (0.07) mg/day in fluoridated areas <u>formula fed</u> : 0.08 (0.04) mg/day in non-fluoridated areas and 0.34 (0.12) mg/day in fluoridated areas Drinking water Mean (SD) <u>breastfed</u> : 0.13 (0.06) mg/L in non-fluoridated areas and 0.58 (0.08) mg/L in fluoridated areas <u>formula fed</u> : 0.13 (0.05) mg/day in non-fluoridated areas and 0.59 (0.07) mg/L in fluoridated areas	Children (ages 3–4 years)	IQ: full-scale, performance, and verbal using Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)	Significantly lower performance IQ with water fluoride (–9.26 formula-fed, –6.19 breastfed) and fluoride intake from formula (–8.76); significantly lower full scale IQ with water fluoride in formula-fed (–4.40); lower full-scale IQ for water fluoride in breastfed (–1.34) and fluoride intake from formula (–2.69) were not significant; no significant changes in verbal IQ scores with fluoride exposure Adjusted for maternal education, maternal race, child’s age at IQ testing, child’s sex, HOME total score, and second-hand smoke status in the child’s house (separate analysis also adjusted for mother’s urinary fluoride)
India					
Sudhir <i>et al.</i> (2009)	Cross-sectional Nalgonda District (Andhra Pradesh)/school children [1,000]	Drinking water Level 1: <0.7 ppm Level 2: 0.7–1.2 ppm Level 3: 1.3–4.0 ppm Level 4: >4.0 ppm	Children (ages 13–15 years)	IQ: Raven's Standard Progressive Matrices	Significant increase in mean and distributions of IQ grades (i.e., increase in intellectually impaired children) with increasing drinking water fluoride levels No statistical adjustment for confounders

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Saxena <i>et al.</i> (2012)	Cross-sectional Madhya Pradesh/school children [170]	Drinking water ≥1.5 mg/L (high fluoride group) Children's urine Range: 1.7–8.4 mg/L	Children (age 12 years)	IQ: Raven's Standard Progressive Matrices	Significant correlation between water ($r = 0.534$; $p = 0.000$) and urinary fluoride ($r = 0.542$; $p = 0.000$) levels and IQ score; no significant differences in the levels of urinary lead or arsenic in children from the different groups Confounders included in the analysis were not reported
Trivedi <i>et al.</i> (2012)	Cross-sectional Kachchh, Gujarat/school children (6 th and 7 th grades) [84]	Drinking water Mean (SE): 0.84 (0.38) (low), 2.3 (0.87) (high) Children's urine Mean (SE): 0.42 (0.23) (low), 2.69 (0.92) (high)	Children (age 12– 13 years)	IQ: questionnaire prepared by Professor JH Shah (97% reliability rating)	Significantly lower IQ score in the high fluoride (92.53 ± 3.13) compared to the low fluoride (97.17 ± 2.54) areas in boys and girls combined (as well as separately) No statistical adjustment for confounders
Iran					
Seraj <i>et al.</i> (2012)	Cross-sectional Makoo/school children [293]	Drinking water Mean (SD): 0.8 (0.3) (normal), 3.1 (0.9) (medium), 5.2 (1.1) (high) mg/L	Children (ages 6–11 years)	IQ: Raven's Colored Progressive Matrices	Significant correlation between water fluoride and IQ score (adjusted $\beta = -3.865$; CIs not reported); significantly higher IQ score in normal area ($97.77 \pm$ 18.91) compared with medium (89.03 ± 12.99) and high (88.58 ± 16.01) areas Adjusted for child's age, child's gender, child's education level, mother's education level, father's education level, and fluorosis intensity
Children-Other Neurodevelopmental Studies					
China					
Choi <i>et al.</i> (2015)	Cross-sectional Mianning County/1 st grade children [51]	Drinking water GM: 2.20 mg/L Children's urine GM: 1.64 mg/L Severity of fluorosis (Dean Index)	Children (ages 6–8 years)	Learning and memory: Neuropsychological tests including WRAML Visual motor ability: WRAVMA Motor ability: Finger tapping task Manual dexterity: Grooved pegboard test	Outcomes unrelated to the IQ test not significantly associated with fluoride exposure Adjusted for child's age, child's gender, parity, illness before 3 years old, household income last year, and caretaker's age and education

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Li <i>et al.</i> (2004) [translated in Li <i>et al.</i> 2008a]	Cross-sectional Zhaozhou County, Heilongjiang Province/neonates [91]	Drinking water Range: 0.5–1.0 mg/L (control); 1.7–6.0 mg/L (high) Maternal urine during pregnancy Mean (SD): 1.74 (0.96) mg/L (control); 3.58 (1.47) mg/L (high)	Neonates (24–72 hours after delivery)	Neurodevelopmental: Neonatal behavioral neurological assessment (NBNA)	Significant differences in neurobehavioral assessment total scores between high- fluoride (36.48 ± 1.09) and control groups (38.28 ± 1.10); significant differences in total score of behavioral capability that includes measures of non- biological visual orientation reaction and biological visual and auditory orientation reaction between the two groups (11.34 ± 0.56 in controls compared to 10.05 ± 0.94 in high-fluoride group) No statistical adjustment for confounders
Wang <i>et al.</i> (2020a)	Cross-sectional Tongxu County/school children [325]	Children's urine Mean (SD): 1.54 (0.89) mg/L	Children (ages 7–13 years)	ADHD and behavior measures: Conners' Parent Rating Scale- Revised (Chinese version) (CPRS-48)	Significant association between psychosomatic problems and urinary fluoride level (per 1- mg/L increase $\beta=4.01$; 95% CI 2.74, 5.28; OR for T-score >70=1.97; 95% CI 1.19, 3.27) Adjusted for child's age, child's gender, child's BMI, urinary creatinine, mother migrated and father migrated
Mexico					
Rocha-Amador <i>et al.</i> (2009)	Cross-sectional Durango/elementary school children [80]	Children's urine GM (SD): 5.6 (1.7) mg/L	Children (ages 6–11 years)	Visuospatial organization and visual memory: Rey- Osterrieth Complex Figure Test, children's version	Significant correlation between urinary fluoride and visuospatial organization ($r = -0.29$) and visual memory scores ($r =$ -0.27); no significant correlation with arsenic Adjusted for age
Valdez Jimenez <i>et al.</i> (2017)	Cohort (Prospective) Durango City and Lagos de Moreno/infants [65]	Drinking water Range: 0.5–12.5 mg/L (all trimesters) Maternal urine Range: 0.16–8.2 mg/L (all trimesters)	Infants (ages 3–15 months)	Mental development index (MDI): Bayley Scales of Infant Development II (BSID-II)	Significant correlation between maternal urinary fluoride and MDI score during first trimester (adjusted $\beta = -19.05$; SE = 8.9) and second trimester (adjusted $\beta = -19.34$; SE = 7.46) Adjusted for gestational age, child's age, marginality index, and type of drinking water

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Bashash <i>et al.</i> (2017)	Cohort (prospective) Mexico City/Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) participants [299] GCI analysis [287]	Maternal urine during pregnancy Mean (SD): 0.90 (0.35) mg/L Children's urine Mean (SD): 0.82 (0.38) mg/L	Children (age 4 years)	General cognitive index (GCI): McCarthy Scales of Children's Abilities (MSCA)	Significant effect between maternal urinary fluoride and offspring GCI score (adjusted $\beta = -3.15$; 95% CI: $-5.42, -0.87$); associations with children's urine not significant Adjusted for gestational age, weight at birth, child's gender, parity (being the first child), age at outcome measurement, and maternal characteristics including smoking history (ever smoked during the pregnancy vs. nonsmoker), marital status (married vs not married), age at delivery, IQ, education, and cohort
Bashash <i>et al.</i> (2018)	Cohort (prospective) Mexico City/Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) participants [210]	Maternal urine during pregnancy Mean 0.85 (95% CI: 0.81, 0.90) mg/L	Children (ages 6–12 years)	ADHD: Conners' Rating Scales-Revised (CRS-R)	Significant associations between maternal urinary fluoride and CRS-R scores including Cognitive Problems + Inattention Index (adjusted $\beta = 2.54$; 95% CI: 0.44, 4.63), DSM-IV Inattention Index (adjusted $\beta = 2.84$; 95% CI: 0.84, 4.84), DSM-IV ADHD Total Index (adjusted $\beta = 2.38$; 95% CI: 0.42, 4.34), and ADHD Index (adjusted $\beta = 2.47$; 95% CI: 0.43, 4.50) Adjusted for gestational age, birth weight, child's gender, parity, age at outcome measurement, and maternal characteristics including smoking history (ever smoked vs. nonsmoker), marital status (married vs. not married), education, socioeconomic status, and cohort

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Canada					
Barberio <i>et al.</i> (2017b)	Cross-sectional General population/ Canadian Health Measures Survey (Cycles 2 and 3) [2,221]	Children's urine Mean Cycle 2: 32.06 (95% CI: 29.65, 34.46) µmol/L Mean Cycle 3: 26.17 (95% CI: 22.57, 29.76) µmol/L	Children (ages 3–12 years)	Learning disability, ADHD (Cycle 2 only): Parent or child self-report	Significant increase in adjusted OR for learning disability (adjusted OR = 1.02; 95% CI: 1.00, 1.03) only when Cycle 2 and 3 were combined using unadjusted urinary fluoride (associations no longer significant once adjusted for creatinine and specific gravity); no significant associations found between urinary fluoride and ADHD (only evaluated in Cycle 2) Adjusted for child's age, child's gender, household income adequacy, and highest attained education in the household
Riddell <i>et al.</i> (2019)	Cross-sectional General population/ Canadian Health Measures Survey (Cycles 2 and 3) [3,745]	Children's urine Mean (SD): 0.61 (0.39) mg/L; non-fluoridated water-0.46 (0.32) mg/L, fluoridated water-0.82 (0.54) Drinking water Mean (SD): 0.23 (0.24) mg/L; non-fluoridated water-0.04 (0.06) mg/L, fluoridated water-0.49 (0.22)	Children (ages 6–17 years)	Hyperactivity/inattention: Strengths and Difficulties Questionnaire (SDQ) ADHD: parent or self- reported physician diagnosis	Significantly increased risk of ADHD with fluoride in tap water (adjusted OR = 6.10 per 1-mg/L increase; 95% CI: 1.60, 22.8) or community water fluoridation status (1.21; 95% CI: 1.03, 1.42), but not with urinary fluoride; similar results observed with attention symptoms based on the SDQ scores Adjusted for child's age, child's gender, child's BMI, ethnicity, parental education, household income, blood lead, and smoking in the home

Table 6. Studies on Neurodevelopmental and Cognitive Function in Humans ^{a,b}					
Study	Study Design (Location/Subjects) [n]	Exposure Measures and Summary Statistics	Assessment Timing	Outcome and Methods	Neurological Outcome Summary
Adult Studies					
Jacqmin <i>et al.</i> (1994)	Cross-sectional France (Gironde and Dordogne)/elderly adults [3,490]	Drinking water Range: 0.03–2.03 mg	Adults (ages ≥ 65 years)	Cognitive function: Mini-Mental State (MMS) Examination	No significant increase in the prevalence of cognitive impairment with increasing fluoride quartiles No statistical adjustment for confounders
Li <i>et al.</i> (2016)	Cross-sectional China (Inner Mongolia)/adults [511]	Drinking water intake and urinary fluoride Mean (SD) levels reported for a subset of subjects with normal scores (2.23 [2.23] mg and 1.46 [1.04] mg/L, respectively) and subjects with cognitive impairment (3.62 [6.71] mg and 2.47 [2.88] mg/L, respectively)	Adults (ages ≥ 60 years)	Cognitive function: MMS Examination	Results suggested that degree of fluoride exposure was consistent with severity of skeletal fluorosis, and fluoride exposure may be a risk factor for cognitive impairment; however, neither water fluoride intake (adjusted ORs = 0.94 [95% CI: 0.85, 1.04] and 0.86 [95% CI: 0.69, 1.06] in the moderate and severe cognitive impairment groups, respectively) nor urinary fluoride levels (adjusted ORs = 1.12 [95% CI: 0.89, 1.42] and 1.25 [95% CI: 0.87, 1.81] in the moderate and severe cognitive impairment groups, respectively) were significantly correlated with cognitive impairment Adjusted for sex, age, education, marital status (married vs. not married), alcohol consumption (non-drinkers, light drinkers, moderate to heavy drinkers), smoking history (never smoker, ex-smoker, light smoker, heavy smoker), and serum homocysteine levels

*Three additional publications based on subsample (i.e., 50–60 children) of the larger Yu *et al.* (2018) cohort were identified (Zhao *et al.* 2020, Zhou *et al.* 2019, Zhao *et al.* 2019); however, these publications focused on mechanistic considerations and are not included in the study totals for IQ because the main study by Yu *et al.* (2018) is considered a better representation of the IQ results.

^aIncludes lower risk-of-bias studies.

^bDefinitions: **ADHD**: attention-deficit/hyperactivity disorder; **GCI**: General Cognitive Index; **GM**: geometric mean; **HOME**: Home Observation Measurement of the Environment; **IQ**: intelligence quotient; **MSCA**: McCarthy Scales of Children’s Abilities; **WASI**: Wechsler Abbreviated Scale of Intelligence (Spanish version); **WISC-IV**: Wechsler Intelligence Scale for Children-Revised; **WRAML**: Wide Range Assessment of Memory and Learning; **WRAVMA**: Wide Range Assessment of Visual Motor Ability.

Overall Risk-of-bias Discussion of the Body of Evidence

The confidence rating for the body of evidence in humans was based on studies with the lowest potential for bias (i.e., studies rated probably low or definitely low risk of bias for at least two of the three key risk-of-bias questions). Each of these 28 studies (including 26 studies in children and 2 in adults) had little or no risk-of-bias concerns, and confidence in the body of evidence was not

downgraded for risk of bias. However, the remaining studies in the human body of evidence were rated as probably high or definitely high risk of bias for at least two key risk-of-bias questions or had other major concerns. Risk-of-bias ratings for individual studies for all questions are available in [Figure A3-1](#) and [Figure A3-3](#). Among the studies with lower potential for bias (see [Figure A3-1](#) and [Figure A3-2](#)), the key risk-of-bias question with the most potential for bias was the potential for confounding. Potential confounding was a concern for 5 of the 26 lower risk-of-bias studies in children (see *Confounding* for further discussion). Among the studies with higher overall potential for bias, there were a number of risk-of-bias concerns, including potential confounding, poor exposure characterization, poor outcome assessment, and, in many cases, potential concern with participant selection (see [Figure A3-3](#) and [Figure A3-4](#)). Many of the studies (n = 32) included in the entire human body of evidence were initially published in a foreign language (mainly Chinese) and were either translated and published in volume 41 of the journal *Fluoride* (n = 19) or were translated by the Fluoride Action Network (n = 13) (http://fluoridealert.org/researchers/translations/complete_archive/). Most of these studies were considered to have high potential for bias due to lack of information across many key risk-of-bias questions. Therefore, in order to assess if the lack of information relevant to key risk-of-bias concerns was the result of a loss in translation, the original Chinese publications and the translated versions of the five studies that had the most potential for being included in the lower risk-of-bias group of studies were reviewed to determine if any of the risk-of-bias concerns could be addressed (An *et al.* 1992, Chen *et al.* 1991 [translated in Chen *et al.* 2008], Du *et al.* 1992 [translated in Du *et al.* 2008], Guo *et al.* 1991 [translated in Guo *et al.* 2008a], Li *et al.* 2009). For all five studies, the translations were determined to be accurate and there was no impact on the key risk-of-bias concerns.

Confounding

Potential confounding variables and/or effect modifiers that were considered key for all studies, populations, and outcomes included child's age, child's sex, and socioeconomic status (e.g., maternal education, household income, marital status, crowding). Additional potential confounding variables and/or effect modifiers considered important for this evaluation depending on the study population and outcome included race/ethnicity; maternal demographics (e.g., maternal age, body mass index [BMI]); parental behavioral and mental health disorders (e.g., ADHD, depression); smoking (e.g., maternal smoking status, secondhand tobacco smoke exposure); reproductive factors (e.g., parity); nutrition (e.g., BMI, growth, anemia); iodine deficiency/excess; minerals and other chemicals in water associated with neurotoxicity (e.g., arsenic, lead); maternal and paternal IQ; and quantity and quality of caregiving environment (e.g., Home Observation Measurement of the Environment [HOME] score). To be assigned a rating of probably low risk of bias for the key risk-of-bias question regarding confounding, studies were not required to address every potential confounder listed; however, studies were required to address the three key covariates for all studies, the potential for co-exposures if applicable (e.g., arsenic and lead, both of which could affect cognitive function), and any other potential confounders considered important for the specific study population and outcome. For example, studies of populations in China, India, and Mexico, where there is concern for exposures to high fluoride and high arsenic, were required to address arsenic, and smoking needed to be addressed in studies of adults when dementia was evaluated. In order to identify areas of China, India, and Mexico where arsenic is a concern, groundwater quality maps were evaluated (<https://www.gapmaps.org/Home/Public#>) (Podgorski and Berg 2020). If no arsenic measurements were available for the area, the arsenic groundwater quality predictions from the global arsenic 2020 map were used (Podgorski and Berg 2020). If an area had less than 50% probability of having arsenic levels greater than 10 µg/L (the WHO guideline concentration), the area was considered not to have an issue with arsenic that needed to be addressed by the study authors.

Among studies with lower risk-of-bias concerns, 21 of the 26 studies were considered to have lower potential for bias due to confounding. Relative to confounders considered key for all studies and populations (i.e., age, sex, and SES), one study did not address age, one study did not address sex, and two studies did not account for indicators of SES (e.g., parental education, household income). Nine of the 26 lower risk-of-bias studies accounted for maternal or family member smoking. Potential confounding related to co-exposure to arsenic was not accounted for in five lower risk-of-bias studies and was the main potential concern in these studies; however, three of these studies (Xiang *et al.* 2011, Wang *et al.* 2012, Xiang *et al.* 2003a) were still considered low risk of bias for confounding due to the fact that arsenic was observed in the low fluoride areas (which would bias the effect toward the null), but an effect was still observed. The other two studies did not address arsenic and were in areas that had potential for arsenic exposure to occur (Soto-Barreras *et al.* 2019, Valdez Jimenez *et al.* 2017). Seven studies did not consider co-exposures to lead; however, for all of these studies this co-exposure was considered unlikely to have an impact in these study populations as there was no evidence that lead was prevalent or occurring in relation to fluoride.

Although there is variability in the potential confounders considered and differences in populations evaluated, the consistency of the results among the lower risk-of-bias studies indicates that confounding is not a major concern in this body of evidence. Even though 5 of 26 lower risk-of-bias studies in children are considered to have higher potential for bias due to confounding that could not be ruled out for that specific population and outcome (see [Figure 6](#)), results were consistent across multiple populations; all but two of the lower risk-of-bias studies in children reported an association between higher fluoride exposure and lower IQ or another cognitive effect. Seven of the lower risk-of-bias studies confirmed the robustness of the results by conducting sensitivity analyses (Bashash *et al.* 2018, Bashash *et al.* 2017, Green *et al.* 2019, Yu *et al.* 2018, Wang *et al.* 2020a, Wang *et al.* 2020b, Till *et al.* 2020). None of the sensitivity analyses adjusting for additional confounders found meaningful shifts in the association between fluoride exposure and IQ or other measures of cognitive function. Bashash *et al.* (2017) found that adjusting for HOME score increased the association between maternal urinary fluoride and children's IQ. Bashash *et al.* (2018) examined several potential confounders in sensitivity analyses involving subsets of participants, including HOME scores, child contemporaneous fluoride exposure measured by child urinary fluoride adjusted for specific gravity, and maternal lead and mercury exposures. The authors reported that no sensitivity analyses indicated appreciable changes in the fluoride-related association with behaviors related to ADHD, nor did they find evidence of effect modification between sex and maternal urinary fluoride. Green *et al.* (2019) found that adjusting for lead, mercury, manganese, perfluorooctanoic acid, and arsenic concentrations did not substantially alter the associations with IQ. Sensitivity analyses by Yu *et al.* (2018) that adjusted for covariates (including age, sex, and socioeconomic status) did not find differences in the results compared to the primary analyses. Both Wang *et al.* (2020a) and Wang *et al.* (2020b) found the results of the sensitivity analysis to be the same as the results from the preliminary analysis. Till *et al.* (2020) found that adjusting for maternal urinary fluoride levels had little effect on the results.

As previously mentioned, most of the higher risk-of-bias studies in the human body of evidence did not address the potential confounders of greatest concern. Many of these studies conducted only simple statistical analyses without accounting for any potential confounders (50 of 61 higher risk-of-bias studies), and many studies did not report whether the study subjects were from areas of similar socioeconomic status or environmental conditions (n = 20 higher risk-of-bias studies). Potential confounding related to important co-exposures (e.g., arsenic and lead) was often not addressed in higher risk-of-bias studies. In studies where there was high exposure to fluoride via drinking water with high naturally-occurring fluoride or from the use of coal-containing fluoride, most researchers did not

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account for potential exposures to arsenic, which is commonly found in coal and drinking water in fluoride-endemic areas of China and Mexico. In general, researchers did not account for potential exposures to lead; however, studies reporting lead levels in fluoride-endemic areas, including areas in China, often reported low levels of lead (Xiang *et al.* 2011, Choi *et al.* 2012, Seraj *et al.* 2012, Choi *et al.* 2015, Yu *et al.* 2018, Saxena *et al.* 2012, Xiang *et al.* 2003b). Therefore, lead is not assumed to be a common exposure in fluoride-endemic areas. Most of the studies did not account for smoking or socioeconomic status, nor did they provide information to lessen the risk-of-bias concern (e.g., list of study characteristics indicating no significant differences between comparison groups). However, as noted for the lower risk-of-bias studies, given the consistency of the evidence, confounding among higher risk-of-bias studies is likely less of a concern for the body of evidence as a whole than for any individual study.

Figure 6. Potential Confounders Considered in Lower Risk-of-bias Studies Conducted in Children

Study (Location) ¹	Potential Confounding Factors Considered ²															Notes	Reported Effect of Fluoride ⁴	
	Subject Characteristics				Other Exposures				Socioeconomic Factors		Parental Characteristics				Other ³			
	Age	Sex	Race/Ethnicity	Health Factors ⁵	Arsenic	Smoking	Iodine	Lead	Other ⁶	SES	Caregiving Environment (e.g., HOME score)	Demographics ⁷	Reproductive Factors ⁸	Health Factors ⁹	IQ			
Overall RoB Rating for Confounding: Probably Low																		
Barberio 2017b (Canada)	✓	✓	–	–	✓	–	–	✓	–	✓	–	–	–	–	–	–	Other exposures: Hg, Ca Demographics: maternal age	Yes
Bashash 2017 (Mexico)	✓	✓	–	–	✓	✓	–	✓	✓	✓	✓	✓	✓	–	✓	✓	Reproductive: parity, birth order, birth weight, gestational age at delivery Other: cohort	Yes
Bashash 2018 (Mexico)	✓	✓	–	–	✓	✓	–	✓	✓	✓	✓	✓	✓	–	–	✓	Other exposures: Hg, Ca Demographics: maternal age Reproductive: parity, birth order, birth weight, gestational age at delivery Other: cohort	Yes
Choi 2015 (China)	✓	✓	–	✓	✓	–	–	✓	–	✓	–	✓	✓	✓	–	✓	Health: subject Fe deficiency, illnesses before age 3, medical history of subject and caretakers Demographics: parental age Reproductive: parity Other: residential history	Yes
Cui 2018 (China)	✓	✓	✓	✓	✓	✓	✓	–	–	✓	–	✓	✓	✓	–	✓	Health: subject BMI, stress/anger/anxiety/depression, psychological trauma, having a cold, in relatives; thyroid diseases, cancer, mental retardation Demographics: maternal age Reproductive: abnormal birth Other: alcohol consumption, proximity to factory, physical activity, various dietary factors, environmental noise	Yes
Green 2019 (Canada)	✓	✓	✓	–	✓	✓	–	✓	✓	✓	✓	✓	✓	–	–	✓	Other exposures: Hg, Mn, PFOA Demographics: parental age, pre-pregnancy BMI Reproductive: parity, weeks of gestation, birth weight, maternal chronic condition during pregnancy Other: alcohol consumption, birth country, voiding interval in urine sampling, breastfeeding duration	Yes
Li et al., 2004 (translated in Li 2008a) (China)	✓	✓	–	–	✓	–	–	–	–	✓	–	✓	✓	–	–	–	Demographics: living habits, cultural background Reproductive: gestational age, birth weight, birth method Other: nutritional conditions	Yes
Riddell 2019 (Canada)	✓	✓	✓	✓	✓	✓	–	✓	–	✓	–	–	–	–	–	–	Health: subject BMI	Yes
Rocha-Amador 2007 (Mexico)	✓	✓	–	✓	✓	–	–	✓	–	✓	–	–	–	–	–	–	Health: subject height and weight by age, transferrin saturation	Yes
Saxena 2012 (India)	✓	✓	–	✓	✓	–	✓	✓	–	✓	–	–	–	–	–	✓	Health: subject height for age ratio, weight for height ratio, medical history Other: residential history	Yes
Seraj 2012 (Iran)	✓	✓	–	–	✓	–	✓	✓	–	✓	–	–	–	–	–	✓	Other: fluorosis intensity	Yes
Sudhir 2009 (India)	✓	✓	–	–	✓	–	–	✓	–	✓	–	–	–	–	–	✓	Other: staple food consumed, liquids routinely consumed, aids used for oral hygiene maintenance (fluoridated or nonfluoridated)	Yes
Till 2020 (Canada)	✓	✓	✓	–	✓	✓	–	–	–	✓	✓	–	–	–	–	✓	Other: city	Yes
Trivedi 2012b (India)	✓	✓	–	–	✓	–	✓	–	–	✓	–	–	–	–	–	–		Yes
Wang 2020a (China)	✓	✓	–	✓	✓	–	–	✓	✓	✓	–	✓	–	–	–	–	Other exposures: cadmium and mercury Health: subject BMI Demographics: mother and father migration, living habits Other: diet, industrial pollution within 1 km of living environment	Yes
Wang 2020b (China)	✓	✓	–	✓	✓	✓	✓	✓	–	✓	–	–	✓	–	–	✓	Health: subject BMI, exclusions based on diseases affecting intelligence, history of trauma or neurological disorders, positive screening test history Reproductive: low birth weight Other: alcohol consumption	Yes
Wang 2012 (China)	✓	✓	–	✓	–	–	✓	✓	–	✓	–	–	–	✓	–	✓	Health: medical conditions Other: transportation, natural environment, and lifestyle	Yes
Xiang 2003 (China)	✓	✓	–	–	–	–	✓	✓	–	✓	–	–	–	–	–	–		Yes
Xiang 2011 (China)	✓	✓	–	–	–	–	✓	✓	–	✓	–	–	–	–	–	–		Yes
Yu 2018 (China)	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	–	–	✓	–	–	✓	Health: subject BMI Reproductive: disease history during pregnancy, delivery conditions Other: dental fluorosis prevalence, consanguineous marriage	Yes
Zhang 2015b (China)	✓	✓	–	✓	✓	–	✓	✓	✓	✓	–	–	–	–	–	✓	Health: subject physical and mental health status Other: thyroid hormone levels, residential history, having knowledge of fluorosis, COMT genotype	Yes

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Study (Location) ¹	Potential Confounding Factors Considered ²													Notes	Reported Effect of Fluoride ⁴			
	Subject Characteristics			Other Exposures				Socioeconomic Factors		Parental Characteristics			Other ³					
	Age	Sex	Race/Ethnicity	Health Factors ³	Arsenic	Smoking	Iodine	Lead	Other ³	SES	Caregiving Environment (e.g., HOME score)	Demographics ³	Reproductive Factors ³			Health Factors ³	IQ	
Overall RoB Rating for Confounding: Probably High																		
Cui 2020 (China)	-	√	-	√	√	√	√	-	-	√	-	√	√	√	-	√	Health: stress/anger/anxiety, having a cold, in relatives: mental retardation Demographics: maternal age Reproductive: abnormal birth, smoking and drinking during pregnancy Other: thyroid hormone levels	No
Ding 2011 (China)	√	-	-	-	√	-	√	√	-	-	-	-	-	-	-	-	-	Yes
Rocha-Amador 2009 (Mexico)	√	√	-	√	√	-	-	√	-	-	-	-	-	-	-	-	Health: subject height and weight by age	Yes
Soto-Barreras 2019 (Mexico)	√	√	-	-	-	-	-	-	-	√	-	-	-	-	-	-	-	No
Valdez Jimenez 2017 (Mexico)	√	√	-	-	-	-	-	-	-	√	-	√	√	√	-	√	Demographics: maternal age Health: pre-pregnancy history of drugs, vaccines, diseases Reproductive: prenatal history, parity, type of birth, week of birth, weight and length at birth, gestational age, Apgar and health conditions of the baby during the first month of life Other: infant feeding type (breastfeeding, formula)	Yes

Notes:

¹Includes all lower risk-of-bias studies in children. Studies are organized as those with an overall risk-of-bias rating for confounding as probably low (green) followed by those with an overall risk-of-bias rating for confounding as probably high (yellow).

²Potential confounding factors and/or effect modifiers represented here are those considered important for this evaluation. See study details provided in HAWC for information on additional confounders.

Factors outlined in blue (subject age, subject sex, arsenic, SES) are considered key confounders.

A √ indicates that a factor was considered (and may or may not have been adjusted for in final model). For 'Other Exposures', a √ might also be used when a co-exposure was not expected to be an issue because there is no evidence to indicate that the co-exposure was prevalent or occurring in relation to fluoride. See risk-of-bias explanations in HAWC for details. A hyphen (-) indicates that the factor was not considered.

³See the "Notes" column for additional details.

⁴Extent of reported effects varies by study. "Yes" indicates that study authors reported one or more significant effects on IQ or other cognitive functions associated with fluoride exposure.

Exposure assessment

Exposure was assessed using a variety of methods in the human body of evidence. Studies provided varying levels of details on the methods used and employed different exposure characterization methods to group study subjects into exposed and reference groups. Exposure metrics included spot urine (from children or mothers during at least one trimester), serum, individual drinking water, intake from infant formula, estimated total exposure dose, municipal drinking water (with residence information), area of residence (endemic versus a non-endemic fluorosis area with or without individual validation of exposure), burning coal (with or without fluoride), and occupation type. Analytical methods to measure fluoride in biological or water samples also varied, some of which included atomic absorption, ion selective electrode methods, colorimetric methods, or the hexamethyldisiloxane microdiffusion method. Individual-level measures of exposure were generally considered more accurate than group-level measures; however, using group-level measures (e.g., endemic versus non-endemic area) in an analysis was less of a concern if the study provided water or urine fluoride levels from some individuals to verify that there were differences in the fluoride exposure between groups. Studies that provided results by area but also reported individual urinary or serum fluoride concentrations or other biochemical measures, including dental fluorosis in the children or urinary levels in mothers during pregnancy, were considered to have probably low risk of bias.

In general, there were few or no risk-of-bias concerns regarding exposure assessment in the lower risk-of-bias studies. Many of the lower risk-of-bias studies used individual urine or water measures with appropriate analyses. Urinary fluoride levels include all ingested fluoride and are considered a valid measure to estimate fluoride exposure (Villa *et al.* 2010, Watanabe *et al.* 1995); however, some concerns exist. Urinary fluoride is thought to reflect recent exposure but can be influenced by the timing of exposure (e.g., when water was last consumed, when teeth were last brushed). When compared to 24-hour urine samples, spot urine samples are more prone to these influences and can also be affected by differences in dilution; however, many studies attempted to account for dilution either using urinary creatinine or specific gravity. Good correlations between 24-hour samples and urinary fluoride concentrations from spot samples adjusted for urinary dilution have been described (Zohouri *et al.* 2006). Despite potential issues with spot urine samples, if authors made appropriate efforts to reduce the concern for bias, studies that used this metric were generally considered to have probably low risk of bias for exposure.

Although there are concerns related to using maternal urine samples, many studies provide evidence to suggest that urinary fluoride is a reasonable measure of exposure. Using three methods to account for urine dilution, Till *et al.* (2018) reported that adjusted risk estimates did not differ from unadjusted estimates. Analyzing the same study population as Till *et al.* (2018), Green *et al.* (2019) found that adjusting for time of urine collection or time of collection since last void during pregnancy did not substantially affect associations with IQ results in either boys or girls. In addition, adjusting the maternal urinary fluoride for creatinine did not substantially alter the association observed (Green *et al.* 2019). To provide a more accurate and sensitive measurement of maternal urinary fluoride than a single measurement provides, Green *et al.* (2019) only included participants with valid fluoride measurements at each trimester in their analysis. Several other studies also measured urinary fluoride multiple times throughout pregnancy (Bashash *et al.* 2018, Bashash *et al.* 2017, Green *et al.* 2019, Valdez Jimenez *et al.* 2017). Other studies demonstrated correlations between the urinary fluoride and fluoride in the drinking water, fluorosis, or estimated dose based on water (Green *et al.* 2019, Saxena *et al.* 2012, Zhang *et al.* 2015b, Ding *et al.* 2011, Choi *et al.* 2015, Yu *et al.* 2018). Till *et al.* (2018) demonstrated that there was a linear association between urinary fluoride concentrations in pregnant women and drinking water fluoride concentrations regardless of method to correct for urine dilution or whether or not

adjustments were made for dilution. Bashash *et al.* (2017) excluded exposure outliers but found that doing so did not change the results in a meaningful way. Taken together, these studies suggest that urinary fluoride is a reasonable measure of exposure despite some of the potential issues.

A frequent critical limitation among the higher risk-of-bias studies was lack of information regarding exposure or poor exposure characterization. Many of the higher risk-of-bias studies only compared subjects living in two regions with differing levels of fluoride exposure, and while most of them did provide some differentiation in levels of fluoride between the areas, limited or no individual exposure information was reported. Among studies that provided drinking water levels of fluoride in two areas being compared, sufficient information to determine if the individual study subjects were exposed to these levels was often not reported. Some studies also lacked information on fluoride analysis methods and timing of the exposure measurements. In some cases ($n = 3$), study areas that were considered endemic for dental and/or skeletal fluorosis were compared to non-endemic areas, or high-fluoride areas were compared to low-fluoride areas, with no other information provided on fluoride levels in the areas (Sun *et al.* 1991, Li *et al.* 2003 [translated in Li *et al.* 2008c], Ren *et al.* 1989 [translated in Ren *et al.* 2008]). While living in an area endemic for fluorosis could be an indicator of exposure, these studies did not specify if the study subjects themselves had fluorosis. Another study used only dental fluorosis as a measure of fluoride exposure in subjects that were all from an endemic area with similar drinking water fluoride levels (Li *et al.* 2010).

Outcome assessment

Studies included in this evaluation used a wide variety of methods to measure IQ and other cognitive effects. Measures of IQ were generally standardized tests of IQ; however, for these standardized methods to be considered low potential for bias they needed to be conducted in the appropriate population or modified for the study population. Because results of these tests can be subjective, it was important that the outcome assessors were blind to the fluoride exposure when evaluating the results of the tests. If the study reported that the assessor was blind to the exposure, this was assumed to mean that the outcome assessor did not have any knowledge of the exposure, including whether the study subjects were from high-fluoride communities.

The lower risk-of-bias studies have few concerns regarding outcome assessment. Four studies (Barberio *et al.* 2017b, Riddell *et al.* 2019, Sudhir *et al.* 2009, Wang *et al.* 2020a) had concerns for potential bias in the outcome assessment and that was due to either the use of self-reported of outcomes or the lack of accounting for blinding at the time of the outcome assessment in cases where there was potential concern. The remainder of the studies used appropriate measures of IQ or other cognitive effects for the study population. Seventeen of the studies reported blinding of the outcome assessors or correspondence with the study authors indicated that it was not likely an issue. For the remainder of the studies, it was assumed that the outcome assessors were most likely blind because exposure was assessed via urine or drinking water obtained at the same time as the outcome assessment.

Among the studies with higher risk of bias, the main limitation in the outcome assessment was the lack of reporting on whether the outcome was assessed without knowledge of exposure. Although there is little concern that the children's knowledge of their own exposure would bias the way they took the IQ tests, there is potential for bias if the tests were administered by an interviewer, or if the scoring of results could be subjective (e.g., drawing tests), and the interviewer or scorer had knowledge of the children's exposure. Most of the studies did not provide sufficient information on the person scoring or administering the tests or other information on the assessment methods to alleviate concerns for potential interviewer or reviewer bias. In some cases, the outcomes were not considered sensitive

measures (e.g., Seguin Form Board Test to test for IQ), or the test was not considered appropriate for the study population (e.g., a test validated in a western population was used on a rural Chinese population).

IQ in Children

The results from 17 studies (3 prospective cohort and 14 cross-sectional studies from 13 different study populations) with lower potential for bias that evaluated IQ in children (Bashash *et al.* 2017, Choi *et al.* 2015, Ding *et al.* 2011, Rocha-Amador *et al.* 2007, Saxena *et al.* 2012, Seraj *et al.* 2012, Xiang *et al.* 2003a, Xiang *et al.* 2011, Zhang *et al.* 2015b, Yu *et al.* 2018, Green *et al.* 2019, Cui *et al.* 2018, Wang *et al.* 2020b, Wang *et al.* 2012, Sudhir *et al.* 2009, Till *et al.* 2020, Trivedi *et al.* 2012) provide consistent evidence that exposure to fluoride is associated with lower IQ scores (see [Figure D1](#) through [Figure D7](#)); however, the analyses performed and the specific results varied by study. Consistent results between increased fluoride levels and lower IQ scores were seen across studies using different exposure measures [e.g., single serum samples (Xiang *et al.* 2011, Zhang *et al.* 2015b), single spot urine samples in children (Xiang *et al.* 2003a, Rocha-Amador *et al.* 2007, Ding *et al.* 2011, Saxena *et al.* 2012, Zhang *et al.* 2015b, Cui *et al.* 2018, Yu *et al.* 2018, Wang *et al.* 2020b), and prenatal maternal urinary measures (Bashash *et al.* 2017, Green *et al.* 2019)] (see [Figure D6](#) and [Figure D7](#)). The consistency also occurs across different study designs and study populations. There were two studies with lower potential for bias (Cui *et al.* 2020, Soto-Barreras *et al.* 2019) that did not provide evidence of an association between fluoride exposure and IQ, but evaluating the association between fluoride and IQ levels was not the primary focus in either of these studies.

The three prospective cohort studies all found an association between increasing fluoride exposure and lower IQ in children. Two of the studies (Green *et al.* 2019, Till *et al.* 2020) were based on the same study population but evaluated fluoride exposure differently. Bashash *et al.* (2017) observed a significant inverse association between children's IQ and maternal urinary fluoride during pregnancy (measured during all three trimesters and included if at least one measurement was available; an increase of 0.5 mg/L of maternal urinary fluoride was associated with a 2.5-point lower IQ score [95% CI: -4.12, -0.59]) in boys and girls combined (see [Figure D7](#)); however, the association between IQ level and children's urinary fluoride levels, while inverse, was not significant (single spot urine sample; an increase of 0.5 mg/L of child urinary fluoride was associated with a 0.89-point lower IQ score [95% CI: -2.63, 0.85]) (Bashash *et al.* 2017). Green *et al.* (2019) also observed a significantly lower IQ for boys associated with maternal urinary fluoride averaged across trimesters (a significant 4.49-point lower IQ score [95% CI: -8.38, -0.60] in IQ per 1-mg/L increase in maternal urinary fluoride); results were not significant in girls (2.40-point increase [95% CI: -2.53, 7.33] in IQ) or in boys and girls combined (1.95-point lower IQ score per 1-mg/L increase; 95% CI: -5.19, 1.28). Other measures of prenatal exposure (maternal fluoride intake or water fluoride concentrations) were associated with lower IQ scores in boys and girls combined although the authors did not report boys and girls separately, as they found no significant effect measure modification between child sex and fluoride exposure in these analyses (Green *et al.* 2019). Specifically, when evaluating the association between estimated maternal fluoride intake based on maternal water and beverage consumption during pregnancy and IQ in children, a 1-mg increase in daily maternal consumption of fluoride during pregnancy was associated with a significantly lower IQ score of 3.66 points in boys and girls combined (95% CI: -7.16, -0.15). Similarly, water fluoride concentrations for pregnant women from fluoridated areas (mean water fluoride levels of 0.59 ± 0.08 mg/L) versus pregnant women from non-fluoridated areas (mean water fluoride levels of 0.13 ± 0.06 mg/L) were associated with a significant 5.29-point lower IQ score per 1-mg/L increase in fluoride in both boys and girls combined (95% CI: -10.39, -0.19) (Green *et al.* 2019). Using the same study population as Green *et al.* (2019), but using fluoride intake from formula or water concentrations in

formula-fed versus breastfed infants, Till *et al.* (2020) observed a significantly lower performance IQ scores regardless of the comparison used. They did not observe any effect on verbal IQ, and full-scale IQ was only significantly lower in formula-fed infants using water fluoride concentrations as the exposure measure. All other comparisons showed negative associations but were not significant.

Cross-sectional studies also demonstrated a consistent association between fluoride and lower IQ scores. Rocha-Amador *et al.* (2007) observed significant negative correlations between IQ and both water and children's single spot urinary fluoride levels in a population in Mexico (adjusted $\beta = -10.2$ per log fluoride increase [CIs not reported] and -16.9 per log fluoride increase [CIs not reported], respectively) (see [Figure D7](#)). The authors also observed a significant inverse association between IQ and children's drinking water and single spot urinary arsenic levels (adjusted $\beta = -6.15$ [CIs not reported] and -5.72 [CIs not reported], respectively). Because fluoride and arsenic were highly correlated in the study area, the authors were not able to adjust for exposure to arsenic when evaluating the effects of fluoride exposure (Rocha-Amador *et al.* 2007). Ding *et al.* (2011) reported a negative dose-response relationship between children's single spot urinary fluoride levels and IQ (see [Figure D4](#)); after adjusting for age, using multiple linear regression, they found a 0.59-point lower IQ score (95% CI: $-1.09, -0.08$) per 1-mg/L increase in urinary fluoride (p -value < 0.0001) (see [Figure D7](#)). Cui *et al.* (2018) observed a significant association between log-transformed children's single spot urine fluoride and lower IQ scores (2.47-point lower IQ scores [95% CI: $-4.93, -0.01$] per unit increase in urinary fluoride), and the association was the strongest in subjects with the TT polymorphism in the dopamine receptor D2 gene which, according to the authors, probably results in a reduced D2 receptor density (12.31-point lower IQ score [95% CI: $-18.69, -5.94$] per unit increase in urinary fluoride) (Cui *et al.* 2018).

Although Green *et al.* (2019) observed a significant negative association between maternal fluoride levels and IQ scores in boys but not girls in a Canadian population, sex differences were not observed in a cross-sectional study conducted using children spot urine fluoride concentrations in China (Wang *et al.* 2020b). Wang *et al.* (2020b) evaluated boys and girls combined and separately and observed significant decreasing trends in the sexes both combined and alone by urinary fluoride quartiles. When evaluated as a continuous variable, spot urinary fluoride levels (per 1-mg/L increase) were significantly associated with lower IQ scores in both girls (-1.379 [95%CI: $-2.628, -0.129$]) and boys (-1.037 [95% CI: $-2.040, -0.035$]), as well as, combined (-1.214 [95%CI: $-1.987, -0.442$]). Green *et al.* (2019) did not find any sex difference when using water fluoride concentrations, but Wang *et al.* (2020b) found that based on water fluoride quartiles there was a significant trend in girls and in boys and girls combined but not in boys alone. While there was a decreasing trend in boys, the results did not achieve statistical significance ($p = 0.077$). However, when water fluoride levels were evaluated as a continuous variable (per 1 mg/L increase), there were significant associations between lower IQ scores in both girls (-1.649 [95%CI: $-3.201, -0.097$]) and boys (-1.422 [95%CI: $-2.792, -0.053$]), as well as, combined (-1.587 [95%CI: $-2.607, -0.568$]).

Other cross-sectional studies also observed consistent results across populations, but there were some slight variations based on exposure measurement, level of exposure, or based on the outcome measured. Choi *et al.* (2015) conducted a pilot study with 51 children in an area of China with a wide range of fluoride concentrations in the drinking water. Aside from observing no association between the square root block design test score and fluoride exposure from drinking water, the authors observed consistent negative associations between IQ measures and fluoride in children's single spot urine or drinking water and significant associations between specific tasks from an omnibus IQ test (i.e., significantly lower WISC-IV backward and total digit span scores) and fluoride exposure based on moderate or severe dental fluorosis in children (see [Figure D7](#)). While observing no association between

IQ and low children's single spot urinary fluoride levels (0.01–1.60 mg/L), Yu *et al.* (2018) observed significant negative associations (p values not reported) between IQ and median children's urinary fluoride levels (1.60–2.50 mg/L)—with an IQ score 2.67 points lower (95% CI: –4.67, –0.68) for every 0.5-mg/L increment of urinary fluoride—and high children's urinary fluoride levels at 2.50–5.54 mg/L with an IQ score of 0.84 points lower (95% CI: –2.18, 0.50) for every 0.5-mg/L increment of urinary fluoride (see [Figure D7](#)). The authors also reported a significant negative association between drinking water fluoride levels at 3.40–3.90 mg/L (4.29-point lower IQ score [95% CI: –8.09, –0.48] for every 0.5-mg/L increment of water fluoride); a 0.04-point lower IQ score (95% CI: –0.33, 0.24) was observed for 0.5-mg/L increments of water fluoride at levels of 0.20–3.40 mg/L. When comparing water fluoride concentrations of >1 mg/L to ≤1 mg/L, there was an increased risk (adjusted OR = 1.25; 95% CI: 0.69, 2.26) for marginal intelligence (i.e., IQ score = 70–79) and a decreased risk (adjusted OR = 0.47; 95% CI: 0.32, 0.71) of excellent intelligence (i.e., IQ score ≥ 130) (see [Figure D4](#)). Similar results were observed using children's urinary fluoride levels (adjusted OR for marginal intelligence = 1.44; 95% CI: 0.72, 2.91; adjusted OR for excellent intelligence = 0.49; 95% CI: 0.26, 0.93) (Yu *et al.* 2018).

Two lower risk-of-bias studies (Cui *et al.* 2020, Soto-Barreras *et al.* 2019) did not observe a significant association between fluoride and IQ in children; however, both studies only performed simple comparisons between IQ and fluoride exposure. Cui *et al.* (2020) studied children in the same region as Cui *et al.* (2018)—and possibly included some of the same subjects but over a longer timeframe—and did not observe a significant change in IQ score with increasing urinary fluoride levels. Although there was a 2-point drop in IQ between the lowest fluoride exposure group (i.e., spot urine fluoride < 1.6 mg/L) and the highest fluoride exposure group (i.e., ≥ 2.5 mg/L), the difference in IQ (112.16 ± 11.50 versus 110.00 ± 14.92) was not significant (p = 0.58). However, this study did not account for age in the analysis, even though they reported a significant difference in IQ score based on age (p < 0.001). Soto-Barreras *et al.* (2019) also did not find an association between various fluoride exposure metrics (water, spot urine, exposure dose, and fluorosis index) and IQ grade. However, this study only compared fluoride exposure levels within the 5 IQ grades and did not adjust for any potential confounders.

The results from 47 studies with higher potential for bias that evaluated IQ in children provide consistent supporting evidence of decrements in IQ associated with exposures to fluoride. Forty-one of the 47 studies reported an association between high fluoride exposure and lower IQ scores in children.

Meta-analysis

In response to the recommendations of the NASEM review of the September 6, 2019 draft monograph (NASEM 2020), a two-part meta-analysis was conducted. The first part was an update to two previous meta-analyses (Choi *et al.* 2012, Duan *et al.* 2018) of group-level exposures from studies that reported a comparison of the mean IQ score between two or more exposure groups. The second part was a new meta-analysis and included studies with more precise individual-level exposures (e.g., urine, water, fluoride intake). The meta-analysis protocol can be found with the revised systematic review protocol posted in September 2020 (<https://ntp.niehs.nih.gov/go/785076>).

Group-level exposures

For the group-level exposure meta-analysis, a comparison on the mean outcome measure (IQ score) was conducted across two exposure groups (“exposed” and “reference”). If there were more than two exposure groups, the highest exposure group was designated the exposed group and the lowest exposure group was designated the reference group. For studies that had more than one exposed group (n = 17), a sensitivity analysis was performed to evaluate the impact of using any exposed group compared to the reference group. Using mean IQ levels with measures of uncertainty (95% confidence

interval [CI], standard error [SE], and sample size [N]) for exposed versus reference groups, the standardized mean difference (SMD) and corresponding 95% CI were calculated for each study. Given the heterogeneity of the studies, random effects models were used to obtain the pooled effect estimate, calculated as a weighted SMD with a corresponding 95% CI. These methods are consistent with both the Choi *et al.* (2012) and Duan *et al.* (2018) meta-analyses. More detailed methods are provided in [Appendix 5](#) and in the meta-analysis protocol, which can be found with the revised systematic review protocol posted in September 2020 (<https://ntp.niehs.nih.gov/go/785076>).

Characteristics of the 46 studies that compared mean IQ scores between groups of children with different levels of fluoride exposure are shown in [Table A-1](#). One study was conducted in New Zealand, 1 study was conducted in Mexico, 4 studies were conducted in Iran, 9 studies were conducted in India, and the remaining 31 studies were performed in China ([Table A-1](#)). Five study populations were exposed to fluoride from coal burning (Guo *et al.* 1991 [translated in Guo *et al.* 2008a], Li *et al.* 1994 [translated in Li *et al.* 2008b], Li *et al.* 1995, Li *et al.* 2009, Bai *et al.* 2014); otherwise, it is assumed that study populations were exposed to fluoride through drinking water. Measures of fluoride exposure included water fluoride ($n = 28$), dental fluorosis ($n = 7$), and other non-drinking water sources of exposure to fluoride (e.g., fluoride exposure from coal burning [$n = 11$]). Thirteen studies presented results for males and 12 studies reported results for females; 9 studies examined children < 10 years old and 11 studies examined children ≥ 10 years old. The CRT-RC was used to measure children's IQ in 23 studies. Other measures of IQ included Wechsler intelligence tests (Ren *et al.* 1989 [translated in Ren *et al.* 2008], Wang *et al.* 1996 [translated in Wang *et al.* 2008b], An *et al.* 1992, Broadbent *et al.* 2015), the Binet IQ test (Guo *et al.* 1991 [translated in Guo *et al.* 2008a], Xu *et al.* 1994), the Raven's test (Yao 1997, Yao *et al.* 1996, Seraj *et al.* 2006, Seraj *et al.* 2012, Eswar *et al.* 2011, Poureslami *et al.* 2011, Shivaprakash *et al.* 2011, Khan *et al.* 2015, Sebastian and Sunitha 2015, Mondal *et al.* 2016), the Raymond B Cattell test (Karimzade *et al.* 2014), the Japan IQ test (Sun *et al.* 1991, Zhang *et al.* 1998), the Index of Mental Capacity (Li *et al.* 1994 [translated in Li *et al.* 2008b]), the Sequin Form Board test (Nagarajappa *et al.* 2013), and other tests using a doctor-prepared questionnaire (Trivedi *et al.* 2012, Trivedi *et al.* 2007). This meta-analysis includes 27 studies that were also included in Choi *et al.* (2012) and 25 studies that were also included in Duan *et al.* (2018). Also included in this meta-analysis were an additional 3 studies published since the Duan *et al.* (2018) publication and 11 studies that were not captured in either of the previous meta-analyses. Overall, the updated group-level results were highly consistent with these previous meta-analyses (Choi *et al.* 2012, Duan *et al.* 2018) ([Table A5-1](#)).

The random-effects pooled SMD estimated from the 46 studies included in the meta-analysis was -0.50 (95% CI: $-0.61, -0.39$) ([Table A5-1](#), [Figure A5-1](#)). There was evidence of heterogeneity ($I^2 = 89\%$, $p < 0.001$, [Table A5-1](#)) and publication bias (funnel plot and Egger's $p < 0.001$, Begg's $p = 0.08$; [Figure A5-2](#), [Figure A5-3](#)). Eliminating publication bias through trim-and-fill analysis supports the results with an adjusted pooled effect estimate of -0.42 (95% CI: $-0.54, 0.30$) ([Figure A5-4](#)). Among the 46 studies, all but two showed SMD estimates that indicated an inverse association, ranging from -5.34 (95% CI: $-6.34, -4.34$) to -0.04 (95% CI: $-0.45, 0.36$). The studies with a positive association (Broadbent *et al.* 2015) reported an SMD estimate of 0.01 (95% CI: $-0.19, 0.22$) to 0.13 (95% CI: $-0.16, 0.42$). Three studies (Aravind *et al.* 2016, Kundu *et al.* 2015, Razdan *et al.* 2017) were excluded from the main analysis due to uncertainties about the way the intelligence assessment for children was performed, but sensitivity analyses that included these studies did not reveal any substantial changes in the pooled SMD estimate (-0.57 [95% CI: $-0.69, -0.45$]) (see [Figure A-35](#)).

Several subgroup analyses, discussed in [Appendix 5](#) and outlined in the meta-analysis protocol (found with the revised systematic review protocol posted in September 2020

[<https://ntp.niehs.nih.gov/go/785076>], included risk of bias, gender, age group, country, outcome assessment type, and exposure assessment type. Among the lower risk-of-bias studies ($n = 9$), the random-effects pooled SMD was -0.31 (95% CI: $-0.52, -0.10$) with an I^2 of 87% and heterogeneity test p -value < 0.001 (Table A5-1 and Figure A5-6). There was no evidence of publication bias (funnel plot and Egger's $p = 0.72$, Figure A5-7 and Figure A5-8). Among the higher risk-of-bias studies ($n = 37$), the random-effects pooled SMD was -0.56 (95% CI: $-0.68, -0.43$) with an I^2 of 88% and heterogeneity test p -value < 0.001 (Table A5-1 and Figure A5-6). There was evidence of publication bias among the higher risk-of-bias studies (funnel plot and Egger's $p < 0.001$, Figure A5-7 and Figure A5-8); eliminating publication bias through trim-and-fill analysis supports the results with an adjusted pooled SMD estimate of -0.35 (95% CI: $-0.50, -0.21$) (Figure A5-7 and Figure A5-9).

Subgroup analyses by gender, age group, country, outcome assessment type, and exposure assessment type further support the consistent and robust pattern of results (Table A5-1). Except for the subgroup analysis of the four studies from Iran, heterogeneity remained at an I^2 of $\geq 70\%$ when the analyses were restricted by subgroup. Sensitivity analyses that removed an outlier (Khan *et al.* 2015) or compared all exposed groups versus the reference (i.e., exposed groups were combined if a study reported more than one exposed group) also did not appreciably change the results (Figure A-45, Table A5-1, and Figure A-25).

Individual-level exposures

The individual-level exposure meta-analysis included 6 studies with individual-level exposures that reported effect estimates as beta coefficients and included a 95% CI or SE. Characteristics of the studies with individual-level exposures are shown on Table B-1. All studies included in this meta-analysis were considered lower risk of bias. Adjusted effect estimates were used, and if results from multiple models were reported within a single study, the most adjusted results were selected. (For more details, see the meta-analysis protocol, which can be found with the revised systematic review protocol posted in September 2020 [<https://ntp.niehs.nih.gov/go/785076>].) To ensure consistent units across studies, units of fluoride exposure were transformed to 1 mg/L. For Bashash *et al.* (2017), Yu *et al.* (2018), and Till *et al.* (2020), units of exposure were transformed from 0.5 mg/L to 1 mg/L. For Cui *et al.* (2018), units of exposure were transformed from 1 log mg/L to 1 mg/L. Cui *et al.* (2018) reported an association between IQ and log transformed exposure. A sensitivity analysis was performed to evaluate the impact of using Cui *et al.* (2018), since the relationship between IQ and exposure evaluated in this study was not linear (as was the case among the other studies included). Yu *et al.* (2018) reported estimates from piecewise linear regression models and provided three ranges for urinary fluoride exposure (low 0.01–1.60 mg/L, medium 1.60–2.50 mg/L, high 2.50–5.54 mg/L) and two ranges for water fluoride (low 0.20–3.40 mg/L and high 3.40–3.90 mg/L). Since these piecewise effect estimates are likely correlated, the study-specific pooled effect estimates were used for urine and water fluoride exposures for the overall effect meta-analysis. A sensitivity analysis was performed to evaluate the impact of using pooled estimates rather than piecewise estimates from Yu *et al.* (2018).

For studies with overlapping populations (i.e., multiple studies that used the same cohort), results were selected considering the following factors: most appropriate exposure metric, exposure range, exposure period, number of subjects, and statistical adjustment for potential confounders. In the overall effect analysis, for studies reporting multiple measures of fluoride exposure, the results associated with measured or estimated individual-level exposures, biomarker levels (such as urinary fluoride), or fluoride intake levels were prioritized over water fluoride concentrations (revised protocol posted in September 2020 [<https://ntp.niehs.nih.gov/go/785076>]); however, subgroup analyses by exposure metric (urinary fluoride, fluoride intake, and water fluoride) were also performed. Yu *et al.* (2018) and

Wang *et al.* (2020b) used the same study cohort of children recruited in 2015 from the rural areas of Tianjin City, China. Since Wang *et al.* (2020b) ($n = 571$) used a subset of the original study sample from Yu *et al.* (2018) ($n = 2,668$), only results from Yu *et al.* (2018) were included in the meta-analysis. A sensitivity analysis was performed to evaluate the impact of using the effect estimate from Wang *et al.* (2020b) rather than the pooled effect estimate from Yu *et al.* (2018). Green *et al.* (2019) and Till *et al.* (2020) used the same Maternal-Infant Research on Environmental Chemicals (MIREC) cohort that reported drinking tap water in 10 Canadian cities with the studies overlapping for 398 mother-child pairs. Both studies reported effect estimates for maternal urinary fluoride (MUF) and water fluoride concentrations. In the Green *et al.* (2019) study, 512 mother-child pairs had MUF data (and all covariates) compared to 398 pairs in Till *et al.* (2020). Water fluoride levels were available for 420 pairs in Green *et al.* (2019) compared to 398 pairs in Till *et al.* (2020). Both studies reported effect estimates adjusted for maternal education, maternal race, child's sex, HOME total score, and secondhand smoke status in the child's home. In addition, Till *et al.* (2020) adjusted for child's age at IQ testing (the age range for all children was 3–4 years old). Because of the larger sample size and covariate adjustments were similar, results from Green *et al.* (2019) were included in the main analysis. However, because of the more adjusted estimates from Till *et al.* (2020) compared to Green *et al.* (2019), a sensitivity analysis was performed using the water fluoride result for formula-fed children and the MUF result from Till *et al.* (2020). For fluoride from intake, the estimates from both studies were used since they represent total fluoride intake (Green *et al.* 2019) and infant fluoride intake from formula (Till *et al.* 2020).

The overall pooled effect estimate based on 6 lower risk-of-bias studies with individual-level measures of exposure shows that a 1-mg/L increase in urinary fluoride was associated with a statistically significant lower IQ score of 1.40 (95% CI: $-2.33, -0.47$) points. Studies with individual-level urinary fluoride measures had evidence of moderate heterogeneity ($I^2 = 46\%$, $p = 0.101$; [Table A5-2](#), [Figure A5-16](#)). Eliminating publication bias through trim-and-fill analysis supports the conclusion that a 1-mg/L increase in individual-level exposure to urinary fluoride was associated with lower IQ, with an adjusted pooled effect estimate of -0.82 (95% CI: $-1.81, 0.17$) ([Figure A5-19](#)). Fluoride intake and water fluoride were also significantly associated with an IQ score of 3.31 points lower (95% CI: $-6.12, -0.50$) and 4.77 points lower (95% CI: $-9.10, -0.45$), respectively ([Table A5-2](#)); however, the results for both metrics were based on two studies each and should be interpreted with caution.

No substantial changes in the pooled effect estimates were seen in sensitivity analyses to evaluate the following scenarios: using the piecewise estimates from Yu *et al.* (2018) (-1.37 , 95% CI: $-2.38, -0.37$) ([B-1](#)); using effect estimates from Wang *et al.* (2020b) rather than Yu *et al.* (2018) (-1.24 , 95% CI: $-1.94, -0.54$) ([Figure B-6](#)); and using the water fluoride result for formula-fed children and MUF result from Till *et al.* (2020) rather than effect estimates from Green *et al.* (2019) (-1.50 , 95% CI: $-2.44, -0.57$) ([Figure B-11](#)).

Other Neurodevelopmental or Cognitive Effects in Children

Among the studies with lower potential for bias, the results from three prospective cohort studies (Bashash *et al.* 2017, Valdez Jimenez *et al.* 2017, Bashash *et al.* 2018) and six cross-sectional studies (Li *et al.* 2004 [translated in Li *et al.* 2008a], Rocha-Amador *et al.* 2009, Choi *et al.* 2015, Barberio *et al.* 2017b, Wang *et al.* 2020a, Riddell *et al.* 2019) based on seven study populations provide mostly consistent results for associations of fluoride exposure with cognitive impairment in children other than decrements in IQ, such as hand-eye coordination, neurobehavioral assessment, behavioral capacity, and learning disabilities (see [Figure D8](#) through [Figure D10](#)). Because IQ cannot be assessed in infants, other neurodevelopmental tests were conducted. Two studies (Li *et al.* 2004 [translated in Li *et al.* 2008a],

Valdez Jimenez *et al.* 2017), based in China and Mexico, evaluated neonates (within 3 days of birth) or infants (3–15 months) (see [Figure D8](#) and [Figure D10](#)).

In neonates, the high fluoride group (based on a single maternal urine fluoride level just prior to birth [3.58 ± 1.47 mg/L] compared to controls [1.74 ± 0.96 mg/L]) had significant lower ($p < 0.05$) total neurobehavioral assessment scores (38.28 ± 1.10 in controls compared to 36.48 ± 1.09 in high fluoride group) and total behavioral capacity scores (11.34 ± 0.56 in controls compared to 10.05 ± 0.94 in high fluoride group) as measured by a standard neonatal behavioral neurological assessment (NBNA) method (Li *et al.* 2004 [translated in Li *et al.* 2008a]). In infants, the Mental Development Index (MDI)—which measures functions including hand-eye coordination, manipulation, understanding of object relations, imitation and early language development—was significantly negatively correlated with maternal urinary fluoride in both the first and second trimesters (adjusted β s = -19.05 with standard error of 8.9 for first trimester and -19.34 with standard error of 7.46 for second trimester) (Valdez Jimenez *et al.* 2017). This study did not find an association between maternal fluoride during any trimester and Psychomotor Developmental Index (PDI), which measures gross motor development (adjusted β s = 6.28 and 5.33 for first and second trimesters, respectively; no variance provided) (Valdez Jimenez *et al.* 2017). The General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities (MSCA) in 4-year-old children was significantly negatively associated with maternal creatinine-adjusted urinary fluoride levels during pregnancy (collected during each trimester) even after adjusting for maternal bone lead (adjusted β = -3.15 [95% CI: -5.42 , -0.87] in a model adjusting for main covariates (e.g., gestational age, weight at birth, sex, maternal smoking, and indicators of socioeconomic status); adjusted β = -5.63 [95% CI: -8.53 , -2.72] in a model limited to a subset of cases who had data on maternal bone lead and adjusted for main covariates and maternal bone lead) (Bashash *et al.* 2017) (see [Figure D10](#)). Choi *et al.* (2015), however, evaluated cognitive function endpoints in addition to IQ and found no significant associations between concurrent water or urinary fluoride levels and Wide Range Assessment of Visual Motor Ability (WRAVMA) scores, finger tapping, and the grooved pegboard test although there were some significant associations based on degree of fluorosis (see [Figure D10](#)). Another study using construction and memory scores in children 6–11 years old observed statistically significant lower scores with increasing concurrent child single spot urinary fluoride even after adjusting for age ($p < 0.05$; -0.29 and -0.27 for copy and immediate recall, respectively [CIs not reported]); however, scores were not significantly associated with urinary arsenic levels (-0.05 and 0.02 for copy and immediate recall, respectively [CIs not reported]) (Rocha-Amador *et al.* 2009) (see [Figure D9](#)).

Barberio *et al.* (2017b) evaluated learning disabilities in children 3–12 years of age, including ADHD, attention deficit disorder (ADD), and dyslexia, as part of the Canadian Health Measures Survey and found a small but significantly increased risk in self-reported (children 12 years of age) or parent- or guardian-reported (children 3–11 years of age) learning disabilities associated with higher spot urinary fluoride levels in children (adjusted OR = 1.02; 95% CI: 1.00, 1.03) (see [Figure D11](#)); however, significant associations were not observed in analyses using creatinine- or specific gravity-adjusted urinary fluoride (Barberio *et al.* 2017b). Barberio *et al.* (2017b) also reported no associations between single spot urinary fluoride and ADHD in children ages 3 to 12 years. Riddell *et al.* (2019) used the same Canadian Health Measured Survey, but evaluated children 6–17 years old. Riddell *et al.* (2019) found a significantly increased risk for ADHD diagnosis with both tap water fluoride (adjusted OR per 1-mg/L increase = 6.10; 95% CI: 1.60, 22.8) and community water fluoridation status (adjusted OR = 1.21; 95% CI: 1.03, 1.42). A similar increase in hyperactivity-inattention symptoms score based on the Strengths and Difficulties Questionnaire was observed with both tap water fluoride (adjusted β per 1-mg/L increase = 0.31; 95% CI: 0.04, 0.58) and community fluoridation status (adjusted β = 0.11; 95% CI: 0.02, 0.20). As was observed with Barberio *et al.* (2017b), Riddell *et al.* (2019) did not observe an association with either

ADHD diagnosis (adjusted OR per 1-mg/L increase = 0.96; 95% CI: 0.63, 1.46) or hyperactivity-inattention symptoms (adjusted β = 0.31; 95% CI: -0.04, 0.66) and specific-gravity-adjusted spot urinary fluoride concentrations. Bashash *et al.* (2018) evaluated behaviors associated with ADHD in children ages 6–12 years using the Conners' Rating Scales-Revised (CRS-R) and observed significant associations between maternal urinary fluoride (measured during each trimester) and ADHD-like symptoms, particularly those related to inattention (an increase in 0.5 mg/L of maternal urinary fluoride was associated with a 2.84-point increase [95% CI: 0.84, 4.84] in the DSM-IV Inattention Index and a 2.54-point increase [95% CI: 0.44, 4.63] in the Cognitive Problems and Inattention Index). These two scales contributed to the global ADHD Index and the DSM-IV ADHD Total Index, which were also associated with higher levels of prenatal fluoride exposure (an increase of 0.5 mg/L in maternal urinary fluoride was associated with a 2.38-point increase [95% CI: 0.42, 4.34] in the DSM-IV ADHD Total Index and a 2.47-point increase [95% CI: 0.43, 4.50] in the ADHD Index) (see [Figure D10](#)). Significant associations were not observed between maternal urinary fluoride concentrations during pregnancy and child performance on measures of hyperactivity nor were there any significant results in children using the Connors' Continuous Performance Test (CPT-II, 2nd Edition), a computerized test of sustained attention and inhibitory control (Bashash *et al.* 2018). Wang *et al.* (2020a) also used a Connors' Parent Rating Scale (Chinese version), but only found a significant association between spot urinary fluoride concentrations (model adjusted for creatinine) and psychosomatic problems (adjusted OR for T-score > 70 = 1.97; 95% CI: 1.19, 3.27 and adjusted β = 4.01; 95% CI: 2.74, 5.28). No associations were found between spot urinary fluoride and ADHD index or other behavioral measures.

Higher risk-of-bias studies (n = 5) also provide some evidence of associations of fluoride exposure with neurodevelopmental or cognitive effects in children other than effects on IQ, but the results are inconsistent with heterogeneous outcomes (Li *et al.* 1994 [translated in Li *et al.* 2008b], Shannon *et al.* 1986, Malin and Till 2015, Morgan *et al.* 1998, Mustafa *et al.* 2018).

Cognitive Effects in Adults

Results from two lower risk-of-bias studies in adults did not find consistent evidence for an association between cognitive impairment (based on the Mini-Mental State Examination) and exposure to fluoride (Jacqmin *et al.* 1994, Li *et al.* 2016). Jacqmin *et al.* (1994) did not find an association between drinking water fluoride and cognitive impairment in populations in France (n = 3,490) and found prevalence rates of cognitive impairment to be the same regardless of fluoride exposure (see [Figure D12](#)). In an analysis of 38 cognitively-impaired cases and 38 controls matched for several confounders including age, gender, education, alcohol consumption, and smoking, Li *et al.* (2016) did find significantly higher urinary fluoride levels and skeletal fluorosis scores in the cognitively-impaired group compared with the control group; however, the authors found no significant correlation between cognitive impairment and total daily water fluoride intake (adjusted ORs = 0.94 [95% CI: 0.85, 1.04] and 0.86 [95% CI: 0.69, 1.06] in the moderate and severe cognitive impairment groups, respectively) or urinary fluoride levels (adjusted ORs = 1.12 [95% CI: 0.89, 1.42] and 1.25 [95% CI: 0.87, 1.81] in the moderate and severe cognitive impairment groups, respectively) in subjects from fluorosis-endemic areas of China (n = 511).

Higher risk-of-bias studies (n = 7) provide some evidence of cognitive impairment in adults associated with exposure to fluoride. In aluminum factory workers (exposed to gaseous and particulate fluoride emissions during the production of aluminum metal), significant decreases in IQ (Duan *et al.* 1995), diminished performance on several neurobehavioral core battery tests (NCTBs) (Guo *et al.* 2001 [translated in Guo *et al.* 2008b]), and impaired psychomotor performance and memory were observed (Yazdi *et al.* 2011). One study conducted on adult subjects with fluorosis (dental and skeletal) from a fluorosis-endemic area compared with healthy subjects from a non-endemic area observed significant

differences for some cognitive function tests (i.e., tests of speech fluency, recognition, and working memory) but not others and generally did not observe a significant change in IQ except in the operation scores (Shao 2003). One prospective cohort study evaluated exposure to fluoride in children at age of 5 years based on whether or not the children resided in areas with community water fluoridation or used fluoride toothpaste or fluoride tablets, and found no clear differences in IQ scores of the subjects at age 38 years (Broadbent *et al.* 2015). One additional study suggested that populations living in areas with higher drinking water fluoride had lower levels of dementia (Still and Kelley 1980); however, the study was not focused on effects of fluoride, but rather if fluoride was able to reduce the risk associated with aluminum by competing with aluminum and reducing the aluminum bioavailability. Therefore, the study was considered inadequate to evaluate the effects of fluoride on dementia (Still and Kelley 1980). A more recent study in Scotland evaluated dementia rates associated with aluminum and fluoride drinking water concentrations and observed an increase in dementia only in the highest quartile of fluoride (56.3 µg/L) compared to the lowest quartile (<44.4 µg/L), but found a significant increase with all quartiles of aluminum compared with the reference group (Russ *et al.* 2019). In addition to studies that reported on cognitive impairment and exposure to fluoride, two studies were identified that reported effects on motor and sensory function (Rotton *et al.* 1982) and a higher prevalence of self-reported headaches, insomnia, and lethargy (Sharma *et al.* 2009).

Mechanistic Data in Humans

Eight lower risk-of-bias studies were available that evaluated mechanistic data in humans associated with fluoride exposure that was considered potentially relevant to neurological effects, including effects on thyroid hormones in children (Singh *et al.* 2014, Zhang *et al.* 2015b, Kumar *et al.* 2018), adults (Kheradpisheh *et al.* 2018b, Kheradpisheh *et al.* 2018a, Malin *et al.* 2018), or children and adults combined (Barberio *et al.* 2017a). In addition, some studies evaluated self-reported thyroid conditions in children and adults combined (Barberio *et al.* 2017a) and thyroid diseases in adults (Kheradpisheh *et al.* 2018b, Peckham *et al.* 2015) (see [Figure A3-5](#) and [Figure A3-6](#)). Although the lower risk-of-bias studies provide some evidence of mechanistic effects (primarily changes in thyroid stimulating hormone [TSH] levels in children), the studies were too heterogeneous or limited in number to make any determination on mechanism (see [Figure 7](#)).

Among the seven lower risk-of-bias studies that reported on changes in thyroid hormones, three studies were conducted in children (Zhang *et al.* 2015b, Singh *et al.* 2014, Kumar *et al.* 2018) and reported increases in TSH levels. Zhang *et al.* (2015b) reported significant increases in TSH in children from a fluorosis-endemic area (median fluoride drinking water concentration = 1.40 mg/L; interquartile range = 1.23–1.57 mg/L) compared with a non-fluorosis-endemic area (median fluoride drinking water concentration = 0.63 mg/L; interquartile range = 0.58–0.68 mg/L), while 3,5,3'-triiodothyronine (T₃) or thyroxine (T₄) were not significantly different between the two groups. Similarly, Singh *et al.* (2014) observed significantly higher TSH levels in children without dental fluorosis who lived in a fluorosis-endemic area (fluoride drinking water concentrations of 1.6–5.5 mg/L) compared with children without dental fluorosis who lived in a non-fluorosis-endemic area (fluoride drinking water concentrations of 0.98–1.00 mg/L). Higher TSH levels in children with dental fluorosis from the fluorosis-endemic area compared with children without dental fluorosis from the non-fluorosis-endemic area were observed but did not reach statistical significance. Significant differences in T₄ or T₃ were not observed between groups (Singh *et al.* 2014). Kumar *et al.* (2018) also observed a significant increase in TSH levels in children from a fluorosis endemic area (1.5–5.8 mg/L fluoride) compared with a control area (0.94–1.08 mg/L fluoride). There were also decreases in T₃ and T₄, but results were not statistically significant.

Barberio *et al.* (2017a) evaluated fluoride effects on TSH levels in children and adults combined and found no relationship between fluoride exposure (measures in urine and tap water) and TSH levels. In the one study that evaluated thyroid hormone levels in adults but not children, Kheradpisheh *et al.* (2018b) found a significant increase in TSH associated with higher fluoride concentrations in drinking water in both adults with and without thyroid diseases such as hypothyroidism, hyperthyroidism, thyroid nodules, or thyroid cancer. Significant increases in T₃ were associated with higher fluoride in drinking water in adults without thyroid diseases, but increases in T₃ were not significant in adults with thyroid diseases. A significant association between T₄ and higher fluoride in drinking water was not observed in adults with or without thyroid diseases (Kheradpisheh *et al.* 2018b).

Other than changes in hormone levels, there is limited evidence of fluoride-related mechanistic effects in the three lower risk-of-bias studies that evaluated thyroid-related effects. Barberio *et al.* (2017a) found no relationship between fluoride exposure and self-reported thyroid conditions in children and adults (children were older than 12). Kheradpisheh *et al.* (2018b) also found no association between fluoride exposure and hypothyroidism in an adult population in Iran. One study found a significantly higher prevalence of hypothyroidism in areas with higher fluoride concentrations in drinking water (>0.7 mg/L) compared with areas with lower fluoride drinking water concentrations (≤0.7 mg/L) (Peckham *et al.* 2015).

Several higher risk-of-bias studies were available that evaluated potential mechanistic data in humans associated with fluoride exposure, including effects on thyroid hormones mostly in children (n = 11 studies); catecholamines in adults (Michael *et al.* 1996) or in subjects of unknown ages (Chinoy and Narayana 1992); acetylcholinesterase (AChE) or serotonin levels in children (Singh *et al.* 2013, Lu *et al.* 2019); brain histopathology or biochemistry in aborted fetuses (Du *et al.* 1992 [translated in Du *et al.* 2008], Yu *et al.* 1996 [translated in Yu *et al.* 2008]); and mitochondrial fission/fusion molecules in children (Zhao *et al.* 2019). Similar to the lower risk-of-bias studies, the higher risk-of-bias studies provide some evidence of mechanistic effects (primarily changes in TSH levels in children); however, the data are insufficient to identify a clear mechanism by which fluoride causes neurodevelopmental or cognitive effects in humans.

Among higher risk-of-bias studies (see [Figure A3-7](#) and [Figure A3-8](#)), varying results were reported in 11 studies that evaluated fluoride exposure and effects on thyroid hormones, and a few of these studies (Lin *et al.* 1991, Yang *et al.* 1994 [translated in Yang *et al.* 2008], Wang *et al.* 2001) were complicated by high or low iodine in the high fluoride area. When considering fluoride effects on each of the hormones individually, similar to results from lower risk-of-bias studies, the most consistent evidence of fluoride-associated effects on a thyroid hormone was reported as changes in TSH levels in children, although there was some variation in the direction of effect. Six of the nine higher risk-of-bias studies that evaluated changes in TSH levels in children reported increases in TSH levels with higher fluoride (Lin *et al.* 1991, Susheela *et al.* 2005, Wang *et al.* 2001, Yang *et al.* 1994 [translated in Yang *et al.* 2008], Yao *et al.* 1996, Yasmin *et al.* 2013). Two of the nine higher risk-of-bias studies reported decreases in TSH levels in children with higher fluoride (Khandare *et al.* 2017, Khandare *et al.* 2018). One of the nine studies found no significant alterations in TSH levels in children from fluorosis-endemic areas (Hosur *et al.* 2012) (see [Figure 8](#)).

When considering fluoride-associated effects on TSH, T₃, and T₄ levels together, studies that evaluated changes in all three thyroid hormones reported varying combinations of increases, decreases, or no changes in levels across the three hormones, although among the eight lower and higher risk-of-bias studies that evaluated the effects of fluoride exposure on TSH, T₃, and T₄ levels and reported increases

in TSH levels in children, seven of the eight studies found no alterations in T₃ levels (one study found an increase in T₃), and six of the eight studies found no alterations in T₄ levels (two studies found an increase in T₄). Studies also displayed variation by age in fluoride-associated effects on TSH, T₃, and T₄. Due to the dynamic relationship between the thyroid gland, the pituitary gland, and the production and clearance of TSH, T₃, and T₄, the variations in results are not unexpected and do not eliminate the possibility of a mechanistic link between thyroid effects and neurodevelopmental or cognitive effects; however, the data do not support a clear indication that thyroid effects are a mechanism by which fluoride causes these effects in humans.

In addition to evaluating thyroid hormone levels, a few higher risk-of-bias studies evaluated other mechanistic data associated with fluoride exposure; however, the data are insufficient to identify a clear mechanism by which fluoride might cause neurodevelopmental or cognitive effects in humans. Serum epinephrine and norepinephrine were significantly increased in a fluoride-endemic region (not reported whether subjects were children or adults) compared to a non-endemic region (Chinoy and Narayana 1992). Serum adrenaline and noradrenaline were significantly increased in adults in a fluoride-endemic area (fluoride in the drinking water ranged from 1.0–6.53 ppm) compared to a control area (fluoride in the drinking water ranged from 0.56–0.72 ppm) (Michael *et al.* 1996). Serum AChE was significantly reduced in children from a high fluoride region compared to a lower fluoride region (Singh *et al.* 2013). Serum serotonin was significantly increased in children from Turkey who were drinking water containing 2.5 mg/L of fluoride compared to children drinking bottled water or water containing <0.5 mg/L of fluoride (Lu *et al.* 2019). Aborted fetuses from high fluoride areas in China were found to have histological changes in the brain and significant changes in neurotransmitter levels compared to a control area (Du *et al.* 1992 [translated in Du *et al.* 2008], Yu *et al.* 1996 [translated in Yu *et al.* 2008]).

There are also two more recent lower risk-of-bias studies that evaluated polymorphisms in dopamine-related genes; however, a determination on mechanism cannot be made at this time due to the limited number of studies. For children (10–12 years old) with a Val158Met polymorphism in the *COMT* gene (i.e., catechol-O-methyltransferase), which results in slower degradation and greater availability of dopamine within the brain, a stronger association between increasing urinary fluoride levels and decreasing IQ was reported (Zhang *et al.* 2015b). For children (7–12 years old) with a dopamine receptor-2 (DRD2) Taq 1A polymorphism (which is involved in reduced D2 receptor density and availability) and the TT (variant) genotype, a significant inverse relationship between log urine fluoride and IQ was observed; however, this significant relationship was not observed in children with the CC (wild-type) or CT (hybrid) genotypes (Cui *et al.* 2018).

Figure 7. Number of Lower Risk-of-bias Studies that Evaluated Thyroid Hormones in Children and Adults by Endpoint and Direction of Effect*

Endpoint	Direction of Effect		Grand Total
	↑	NS	
serum T3	1	3	4
serum T4		4	4
serum TSH	5	2	7
self-reported thyroid condition		1	1
thyroid disease		1	1
hypothyroidism prevalence	1		1

*Interactive figure and additional study details in [Tableau®](https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7) (https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7). This figure displays study counts for lower risk-of-bias studies in both children and adults, as these counts are most relevant to the summary of fluoride-related mechanistic effects in lower risk-of-bias studies. Counts for higher risk-of-bias studies and studies by age (i.e., children, adults, or children/adults combined) can also be accessed in the interactive figure in [Tableau®](https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7). Study counts are tabulated by significance (unless if study footnotes in Tableau indicate that statistical significance was not tested)—statistically significant increase (↑), statistically significant decrease (↓), or not significant (NS). For example, the “↑” column displays numbers of unique studies with significantly increased results.

Figure 8. Number of Higher Risk-of-bias Studies that Evaluated Thyroid Hormones in Children by Endpoint and Direction of Effect*

Endpoint	Direction of Effect			Grand Total
	↑	↓	NS	
serum T3	1	1	6	8
serum T4	3		5	8
serum TSH	6	2	1	9

*Interactive figure and additional study details in [Tableau®](https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7) (https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7). This figure displays study counts for higher risk-of-bias studies in children, as these counts are most relevant to the summary of fluoride-related effects on thyroid hormones in higher risk-of-bias studies. Counts for lower risk-of-bias studies, studies in adults, or all studies combined, can also be accessed in the interactive figure in [Tableau®](https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_EpiThyroid_UPDATE/Figures6and7). Study counts are tabulated by significance (unless if study footnotes in Tableau indicate that statistical significance was not tested)—statistically significant increase (↑), statistically significant decrease (↓), or not significant (NS). For example, the “↑” column displays numbers of unique studies with significantly increased results.

Animal Learning and Memory Data

[Note: An earlier version of the monograph underwent NASEM committee peer review in November 2019 (NASEM 2020). In this earlier review the committee criticized this section primarily over concerns that the NTP’s risk-of-bias evaluations failed to adequately capture a number of important threats to internal validity that are specific to neurobehavioral outcomes in animal tests. The committee found

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several examples of studies cited in the monograph where national or international guidelines for performance or statistical analyses were not followed or descriptions of methods were insufficient to evaluate their adequacy. Additionally, the committee took issue with a conclusion of the prior peer reviewed systematic review of the experimental animal literature (NTP 2016) concerning the degree to which motor activity deficits might compromise neurobehavioral assessments, affecting the directness of applicability of deficits in animal learning and memory to support the plausibility of IQ deficits in exposed children.

The NTP generally does not take issue with the NASEM peer review comments and acknowledges that further efforts to disentangle the potential for motor activity deficits to influence tests of learning and memory in the fluoride literature are warranted. The NTP agrees with the comments of the NASEM committee concerning the overall poor quality of the experimental animal database, with many studies suffering from major reporting deficiencies. NTP also found these to be general issues with the experimental animal database and were identified as deficiencies that led to the inadequate conclusion. However, the following experimental animal study section remains largely unchanged from the initial version of the monograph reviewed by NASEM in November 2019. The reasons for this are: (1) because a more critical risk-of-bias assessment would result in fewer relevant animal studies judged to be of high quality; (2) because the highest quality experimental animal study reviewed for this monograph (McPherson *et al.* 2018) did not find effects of fluoride on learning, memory or motor activity in the critical ≤ 20 ppm in drinking water concentration range; and (3) because of the availability of a large number of human epidemiology studies directly addressing neurobehavioral and cognitive effects of fluoride in children, a decision was made to focus efforts to address comments on the critical human epidemiology evaluation in this revised and updated monograph. NTP acknowledges the helpful comments of the NASEM committee on the following section and refers readers to the NASEM review (NASEM 2020) when considering the information provided. For the purpose of this updated review the NTP considers that the experimental animal data remain *inadequate* to inform conclusions on whether fluoride exposure is associated with cognitive effects (including cognitive neurodevelopmental effects) in humans. NTP is aware of a number of additional relevant experimental animal studies published since the literature cutoff date for the monograph. These additional studies have not been formally reviewed and may shed further light on these issues].

In 2016, NTP conducted a systematic review of the available experimental animal studies to develop level-of-evidence conclusions on the association between fluoride exposure and neurobehavioral effects, specifically effects related to learning and memory impairment (NTP 2016). As previously discussed, the evaluation of the animal body of evidence in this assessment is an extension of the NTP (2016) systematic review and is consistent with the methodology and format used in that report.

NTP (2016) identified two main issues with the animal body of evidence related to effects of fluoride exposure on learning and memory: indirectness and concerns for risk of bias. The concern related to indirectness was based on the fact that many learning and memory tests rely on a motor response (e.g., latency to achieve the desired effect). Changes in motor function or activity levels associated with fluoride exposures could complicate the interpretation of the results on learning and memory test performance depending on the outcome measured. The directness of the measure as an indicator of learning and memory (i.e., the ability to rule out impaired motor or sensory function) was considered when addressing confidence in the data. Concerns in these studies related to risk of bias included the following factors: lack of randomization, lack of blinding or other methods to reduce potential bias at outcome, lack of exposure information, lack of control for litter effects, lack of expected response in the

control animals, and lack of reporting of other key study information such as sample size or sex of the animals.

Since the NTP (2016) report was published, additional experimental animal studies were identified that evaluated learning and memory impairment associated with fluoride exposure, including 12 developmental exposure studies (Banala and Karnati 2015, Mesram *et al.* 2016, Zhu *et al.* 2017, Sun *et al.* 2018, Wang *et al.* 2018, Ge *et al.* 2018b, McPherson *et al.* 2018, Zhao *et al.* 2019, Ge *et al.* 2018a, Chen *et al.* 2018, Bartos *et al.* 2018, Banala *et al.* 2018); 5 Morris water maze study in adults (Zheng *et al.* 2016, Niu *et al.* 2018, Dong *et al.* 2017, Sharma *et al.* 2018, Yang *et al.* 2018); and 7 other maze studies in adults (Pulungan *et al.* 2016, Shalini and Sharma 2015, Sharma *et al.* 2018, Sudhakar *et al.* 2017, Nageshwar *et al.* 2018, Yuan *et al.* 2019, Raju *et al.* 2019). In addition, 12 studies were identified that evaluated motor activity/coordination or sensory effects without evaluating learning and memory impairment (Adedara *et al.* 2017a, Nageshwar *et al.* 2017, Nkpaa and Onyeso 2018, Sudhakar *et al.* 2018b, Ahmad *et al.* 2017, Kinawy and Al-Eidan 2018, Manusha *et al.* 2019, Sudhakar *et al.* 2018a, Agustina *et al.* 2018, Lu *et al.* 2019, Jia *et al.* 2019, Li *et al.* 2019).

Although Adedara *et al.* (2017a) and Nkpaa and Onyeso (2018) evaluated exploration, the authors concluded that the track plots in the open field novel environment test were consistent with impaired locomotor activity in the fluoride-treated animals. The additional studies reviewed did not address the concern of indirectness and most included risk-of-bias concerns; however, a few of these more recent studies are notable in that they provide results on learning and memory effects that could possibly be distinguished from effects on motor activity. Bartos *et al.* (2018) used a step-down inhibitory avoidance test to evaluate short-term and long-term memory in rat offspring. Although the authors did not discuss activity in the animals, this test would be expected to result in increased latency in animals if there was decreased activity with fluoride exposure. The fluoride-treated female offspring, however, had decreased latency indicating diminished memory of the foot shock. Chen *et al.* (2018) also evaluated female rat offspring (treatment continued until the offspring were 6 months old) and observed an effect of fluoride on latency to reach the platform and the number of platform crossings in the Morris Water Maze; however, swimming speed was measured, and no changes were observed. The tracks during the spatial probe test were also very different in the two higher exposed groups (i.e., 50 and 100 mg/L NaF), suggesting that the animals did not know the location of the platform. It is not clear if litter effects were addressed in the study.

After further evaluation of the data available in NTP (2016) and in this update, it is concluded that the animal data are inadequate to evaluate the effects of fluoride on learning and memory primarily due to the inability to separate the learning and memory effects from the effects on motor activity or motor coordination. The majority of the studies that evaluated effects of fluoride on learning and memory did not also evaluate a motor activity component to determine if the learning and memory effects could be attributed to motor activity or coordination deficits. Of the studies that did evaluate both learning and memory and motor activity/coordination, studies mainly found an association between fluoride exposure and both types of neurological outcomes or found no effect of fluoride exposure on either type of neurological outcome irrespective of the dose range or duration of dosing. In addition, studies that found effects on motor activity/coordination or learning and memory often did not provide sufficient indicators of general health of the animals to reliably attribute impaired performance on a task to a specific acquisition of learning and memory or motor activity/coordination. The few studies that provided this information used different test methods or results were inconsistent. Thus, it is difficult to conclude that evidence from experimental animal studies is meaningful when considering the specific question of fluoride's potential influence on human IQ or cognitive function, particularly at

human -relevant exposure levels. Based on this consideration, the experimental animal body of evidence does not contribute to confidence in conclusions derived from human epidemiological studies with respect to effects on human IQ. Although the evidence supports an association between fluoride exposure and neurodevelopmental effects, the data are not sufficient to support the primary effect evaluated in children (i.e., IQ) nor is it sufficient to support a conclusion on cognitive effects in adults especially in the absence of additional adult human data.

Mechanistic Data in Animals

There are a wide variety of studies in animals that evaluate mechanistic effects potentially related to neurological changes following oral fluoride exposure (see [Figure 9](#)). Categories of mechanistic endpoints with the largest amount of available data include changes in biochemical components of the brain or neurons, neurotransmitters, oxidative stress, histopathology, and thyroid function. Limiting the data to studies with at least one exposure at or below 20 ppm fluoride drinking water equivalents (gavage and dietary exposures were back calculated into equivalent drinking water concentrations for comparison) still provided a sufficient number of studies for evaluation of these mechanistic endpoints. Neurotransmitter and biochemical changes in the brain and neurons were considered to be the mechanistic areas with the greatest potential to demonstrate effects of fluoride on the brain of animals in the lower dose range and provide evidence of changes in the brain that may relate to lower IQ in children (see [Figure 10](#)). Histological data can be useful in determining whether effects are occurring in the brain at lower fluoride concentrations; however, author descriptions of these effects may be limited thereby making it difficult to directly link histological changes in the brain to learning and memory effects. Oxidative stress is considered a general mechanistic endpoint that cannot be specifically linked to neurodevelopmental or cognitive effects in humans; however, like histopathology, it may help in identifying changes in the brain occurring at lower concentrations of fluoride. Although any effects in the brain or neurological tissue at lower concentrations of fluoride may support reduced IQ in humans, it may be difficult to distinguish the potential effects of fluoride on learning and memory functions from other neurological or general health outcomes.

Figure 9. Number of Animal Mechanistic Studies for Fluoride by Mechanistic Category and Exposure Level*

Mechanism	Dose Level	
	All	≤20 ppm
Biochemical (brain/neurons)	66	25
Neurotransmitters	53	23
Oxidative stress	78	25
Histopathology	67	30
Apoptosis/cell death	19	7
Inflammation	7	5
Thyroid	50	17
Other	3	2

*Interactive figure and additional study details in [Tableau®](#)

(https://public.tableau.com/profile/ntp.visuals#!/vizhome/Animal_Mechanisms_All_June2019/Figure8). The number of

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studies that evaluated mechanistic effects associated with at least one exposure at or below 20 ppm fluoride is tabulated in the “≤20 ppm” column. The total number of studies per mechanistic category are summarized in the “All” column.

The following sections summarize the mechanistic data by category of mechanistic endpoint. Although there is some evidence of consistency in mechanistic effects, overall these data are insufficient to increase confidence or support a change to hazard conclusions.

Neurotransmitters

Twenty of 23 neurotransmitter studies assessed changes in brain cholinesterase activity associated with fluoride exposure at or below 20 ppm fluoride. Acetylcholine is a major neurotransmitter involved in learning, memory, and intelligence (Chen 2012, Gais and Schonauer 2017). AChE is responsible for the breakdown of acetylcholine in the synapses of nerve cells. Changes in cholinesterase, acetylcholine, or AChE could be related to effects on memory. Evidence of an effect varied among the lower risk-of-bias studies that assessed changes in cholinesterase or acetylcholine (n = 11 drinking water studies) (Gao *et al.* 2009, Baba *et al.* 2014, Adedara *et al.* 2017a, Khan *et al.* 2017, Gao *et al.* 2008a, Akinrinade *et al.* 2015a, Sun *et al.* 2000 [translated in Sun *et al.* 2008], Chouhan *et al.* 2010, Mesram *et al.* 2016, Liu *et al.* 2010, Nkpaa and Onyeso 2018), with the majority of studies reporting evidence of an effect that is considered inconsistent with the phenotypic outcome. Decreases in cholinesterase will cause increases in acetylcholine, which can have a positive effect on learning and memory; however, long-term decreases in cholinesterase can lead to secondary neuronal damage occurring in the cholinergic region of the brain (Chen 2012).

Five of the 11 studies with lower risk of bias (Gao *et al.* 2009, Baba *et al.* 2014, Adedara *et al.* 2017a, Khan *et al.* 2017, Nkpaa and Onyeso 2018) found statistically significant decreases in cholinesterase or AChE in brain homogenates (with some brains dissected into specific regions prior to homogenizing) with fluoride concentrations in drinking water at or below 20 ppm, and 4 of the 5 studies found statistically significant decreases in cholinesterase or AChE below 10 ppm. The 5 studies were conducted in rats (Wistar or Sprague-Dawley) with exposure ranging from 28 days to 6 months. An additional 2 out of 11 studies (Gao *et al.* 2008a, Akinrinade *et al.* 2015a) reported decreases in brain homogenate AChE at concentrations at or below 20 ppm fluoride in drinking water, but statistical significance was not reached. These studies were also conducted in rats with exposure for 30 days or 3 months. Gao *et al.* (2008a) reported a dose-dependent decrease in brain homogenate AChE in the low (5 ppm fluoride) and high (50 ppm fluoride) treatment groups compared with the control group, but the decrease was only statistically significant in the high dose group. Similarly, Akinrinade *et al.* (2015a) observed a dose-dependent decrease in percent intensity of AChE immunohistochemistry in the prefrontal cortex associated with 2.1 and 10 ppm sodium fluoride in the drinking water, but neither result was statistically significant. Gao *et al.* (2009) found lower brain homogenate AChE levels in the 5-ppm animals compared with the 50-ppm animals; therefore, the results were not always dose dependent.

Relative to the above-mentioned studies, 2 of the 11 lower risk-of-bias studies observed opposite effects on brain cholinesterase levels. Sun *et al.* (2000) [translated in Sun *et al.* 2008] observed a significant increase in brain cholinesterase in Kunming mice associated with fluoride drinking water concentrations from 10 to 100 mg/L, but did not observe a dose response. Chouhan *et al.* (2010) did observe a dose-related increase in AChE levels in brain homogenate of Wistar rats with sodium fluoride concentrations of 1 to 100 ppm for 12 weeks and noted statistically significant results at 1, 50, and 100 ppm but not at 10 ppm.

Mesram *et al.* (2016) did not assess changes in AChE but observed a significant decrease in acetylcholine levels in cerebral cortex homogenate through 30 days of age in rats treated in utero with 20 ppm

sodium fluoride, which may suggest an increase in AChE levels. Likewise, Liu *et al.* (2010) did not assess changes in AChE, but measured nicotinic acetylcholine receptors (nAChRs) in brain homogenate of rats following drinking water fluoride exposure, which the authors stated could modulate physiological and pharmacological functions that are involved in learning and memory-related behaviors. Significant decreases in the protein expressions of nAChR subunits at 2.26 ppm fluoride were observed; however, the corresponding receptor subunit mRNAs did not exhibit any changes (Liu *et al.* 2010).

The studies that assessed other neurotransmitters of the brain and neurons were too heterogeneous or limited in number to make any determination on mechanism, even before limiting the review of the data to lower risk-of-bias studies. There were only five studies that evaluated dopamine and/or metabolites (Tsunoda *et al.* 2005, Chouhan *et al.* 2010, Reddy *et al.* 2014, Banala *et al.* 2018, Sudhakar and Reddy 2018). Four of the studies observed decreases in dopamine levels in the brain with exposures less than 20 ppm fluoride (Reddy *et al.* 2014, Chouhan *et al.* 2010, Banala *et al.* 2018, Sudhakar and Reddy 2018); however, the fifth study (Tsunoda *et al.* 2005) observed increased dopamine and metabolites at fluoride exposures below 20 ppm (with statistical significance achieved only for the metabolite homovanillic acid in one brain region). No differences from the control group were observed at levels above 20 ppm fluoride. Other neurotransmitters were evaluated at or below 20 ppm fluoride exposure, but generally only in a couple of studies.

Biochemistry (brain/neurons)

Similar to above, the endpoints measured in brain biochemistry studies were too heterogeneous or limited in number to make any determination on potential relevance of mechanism, even before limiting the review of the data to lower risk-of-bias studies (see [Figure 10](#)). Endpoints related to biochemical changes in the brain or neurons included carbohydrate or lipid changes, RNA or DNA changes, changes in gene expression, or changes in protein expression. For the most part, only a single study was available for any given endpoint. The largest body of evidence on biochemistry was on protein level in various brain regions. Eleven lower risk-of-bias studies were identified that evaluated protein levels; however, few studies evaluated the same proteins or areas of the brain. In the few cases where the same protein was evaluated, results were not always consistent. These data are insufficient to increase confidence or support a change to hazard conclusions.

Histopathology

Histopathology of the brain was evaluated in 31 studies with concentrations at or below 20 ppm fluoride, of which 15 studies had a lower potential for bias (Adedara *et al.* 2017b, Akinrinade *et al.* 2015a, Bhatnagar *et al.* 2002, Bhatnagar *et al.* 2011, Chouhan *et al.* 2010, Guner *et al.* 2016, Jiang *et al.* 2014, Lou *et al.* 2013, McPherson *et al.* 2018, Mesram *et al.* 2016, Niu *et al.* 2018, Pulungan *et al.* 2016, Nageshwar *et al.* 2018, Zhao *et al.* 2019, Jia *et al.* 2019). In all but one lower risk-of-bias study [Pulungan *et al.* (2016); gavage], animals were exposed to fluoride via drinking water. All lower risk-of-bias studies were conducted in rodents, and all but three studies were conducted in rats (Wistar [seven studies]; Sprague-Dawley [four studies]; Long-Evans hooded [one study]). Overall, the lower risk-of-bias studies that evaluated histopathology in the brain had low potential for bias for key questions regarding randomization and exposure characterization; however, eight studies were rated as probably high risk of bias for the key risk-of-bias question regarding outcome assessment based on lack of reporting of blinding of outcome assessors and/or inadequate description of outcome measures or lesions. Moreover, low image quality in some of the studies hampered the ability to verify the quality of the data. Further technical review of the 15 lower risk-of-bias studies was conducted by a board-certified pathologist. Based on confidence in the results for each study, the technical reviewer further categorized the lower risk-of-bias studies as studies with higher or lower confidence in the outcome

assessment, which is reflected in the following summary of the brain histopathology results. Main limitations of the histopathology data identified by the pathologist included lack of information on methods of euthanasia and fixation. Perfusion fixation is generally considered the best practice for lesions of the central nervous system in addition to complete fixation of the brain prior to its removal from the skull (Garman *et al.* 2016). Four of the lower risk-of-bias studies reported that they used this method (Bhatnagar *et al.* 2002, Bhatnagar *et al.* 2011, McPherson *et al.* 2018, Pulungan *et al.* 2016). Two of the lower risk-of-bias studies handled the brains before fixation was complete, which can produce artifacts that can resemble dead neurons (Zhao *et al.* 2019, Nageshwar *et al.* 2018). Fixation and brain removal details were inadequately described in the remaining lower risk-of-bias studies.

Although there was heterogeneity in the endpoints reported (e.g., cell size, shape, and counts; nuclei fragmentation; increased vacuolar spaces) and some variation in the consistency of the evidence based on the area of the brain evaluated, the majority of the lower risk-of-bias studies (11 of 14 drinking water studies) found some histological change in the brain of rats or mice treated with fluoride at concentrations at or below 20 ppm, of which 8 studies reported histological changes in the brain at or below 10 ppm. Histological changes in the hippocampus (one of the areas of the brain most evaluated for histological changes) associated with fluoride exposures at or below 20 ppm were reported in three of four lower risk-of-bias studies with higher confidence in the outcome assessment (Bhatnagar *et al.* 2002, Bhatnagar *et al.* 2011, Guner *et al.* 2016) and in three of four lower risk-of-bias studies with lower confidence in the outcome assessment (Jiang *et al.* 2014, Niu *et al.* 2018, Nageshwar *et al.* 2018). McPherson *et al.* (2018) was the only drinking water study (with higher confidence in the histopathology outcome assessment) that did not observe any histological changes in hippocampus at 10 or 20 ppm fluoride in male Long-Evans hooded rats exposed in utero through adulthood (>PND80). Although there are too few studies to definitively explain the inconsistency in results, McPherson *et al.* (2018) also did not observe any associations between fluoride exposure and impairments to learning and memory, which is inconsistent with the majority of developmental exposure studies that observed learning and impairments associated with fluoride exposure for other strains of rats. Similarly, histological changes in the cortex were reported in three of the four lower risk-of-bias drinking water studies with higher confidence in the outcome assessment (Chouhan *et al.* 2010, Bhatnagar *et al.* 2011, Akinrinade *et al.* 2015a) and in three of four lower risk-of-bias studies with lower confidence in the outcome assessment (Lou *et al.* 2013, Mesram *et al.* 2016, Nageshwar *et al.* 2018).

Histological changes were also consistently reported in other areas of the brain in studies with higher confidence in the outcome assessment, including the amygdala, caudate putamen, cerebellum, and hypothalamus, although each of these areas of the brain were only evaluated in one lower risk-of-bias study (Bhatnagar *et al.* 2011, Guner *et al.* 2016). Pulungan *et al.* (2016), one of two lower risk-of-bias studies with higher confidence in the outcome assessment that did not report histological changes in the brain, observed a decreasing trend in the number of pyramidal cells in the prefrontal cortex with increasing dose, but this was not changed at concentrations below 20 ppm (study administered sodium fluoride via gavage; the 5-mg/kg-day dose was considered to be equivalent to 15.3 ppm fluoride in drinking water) nor were any of the results statistically significant.

Oxidative stress

Oxidative stress in the brain was evaluated in 25 studies that examined concentrations at or below 20 ppm fluoride, of which 15 studies had lower potential for bias (Adedara *et al.* 2017a, Adedara *et al.* 2017b, Akinrinade *et al.* 2015b, Chouhan *et al.* 2010, Gao *et al.* 2008b, Guner *et al.* 2016, Mesram *et al.* 2016, Nkpaa and Onyeso 2018, Shan *et al.* 2004, Zhang *et al.* 2015a, Chouhan and Flora 2008, Gao *et al.* 2009, Khan *et al.* 2017, Bartos *et al.* 2018, Nageshwar *et al.* 2018). All of the lower risk-of-bias studies

were conducted in rats (mainly Wistar or Sprague-Dawley) and administered fluoride via drinking water with exposure durations ranging from 28 days to 7 months. Although there was heterogeneity in the endpoints reported (i.e., varying measures of protein oxidation, antioxidant activity, lipid peroxidation, and reactive oxygen species [ROS]) and some variation in the consistency of the evidence based on the endpoint, the majority of the studies (13 of 15 studies) (Adedara *et al.* 2017a, Adedara *et al.* 2017b, Akinrinade *et al.* 2015b, Gao *et al.* 2008b, Gao *et al.* 2009, Guner *et al.* 2016, Mesram *et al.* 2016, Nkpaa and Onyeso 2018, Shan *et al.* 2004, Zhang *et al.* 2015a, Khan *et al.* 2017, Nageshwar *et al.* 2018, Bartos *et al.* 2018) found evidence of oxidative stress in the brains of rats treated with fluoride at concentrations at or below 20 ppm, of which 10 studies reported oxidative stress in the brain below 10 ppm fluoride. The most consistent evidence of oxidative stress in the brain was reported through changes in antioxidant activity. Eleven of the 12 lower risk-of-bias studies that evaluated antioxidant activity reported an effect at concentrations at or below 20 ppm (Adedara *et al.* 2017a, Adedara *et al.* 2017b, Akinrinade *et al.* 2015b, Gao *et al.* 2008b, Gao *et al.* 2009, Guner *et al.* 2016, Mesram *et al.* 2016, Nkpaa and Onyeso 2018, Khan *et al.* 2017, Bartos *et al.* 2018, Nageshwar *et al.* 2018). Decreases in antioxidant activity using measures of superoxide dismutase (SOD) activity were reported in seven of eight lower risk-of-bias studies (Adedara *et al.* 2017a, Adedara *et al.* 2017b, Akinrinade *et al.* 2015b, Mesram *et al.* 2016, Nkpaa and Onyeso 2018, Khan *et al.* 2017, Nageshwar *et al.* 2018) and, among these seven studies, all that also measured changes in catalase (CAT) activity (n = 6 studies) also reported decreased activity (Adedara *et al.* 2017a, Adedara *et al.* 2017b, Mesram *et al.* 2016, Nkpaa and Onyeso 2018, Khan *et al.* 2017, Nageshwar *et al.* 2018). A decrease in total antioxidant capacity (T-AOC) as a measure of antioxidant activity was also consistently reported in two lower risk-of-bias studies (Gao *et al.* 2008b, Gao *et al.* 2009), and a decrease in glutathione peroxidase (GPx) activity was reported in two of three lower risk-of-bias studies (Adedara *et al.* 2017b, Nkpaa and Onyeso 2018).

Relative to the above-mentioned studies, 2 of the 15 lower risk-of-bias studies (Chouhan and Flora 2008, Chouhan *et al.* 2010) did not observe statistically significant effects on oxidative stress in the brain with concentrations at or below 20 ppm fluoride; however, the measure of oxidative stress evaluated in Chouhan and Flora (2008) and Chouhan *et al.* (2010) (glutathione [GSH] to oxidized glutathione [GSSG] ratio as an indication of antioxidant activity and ROS levels) were not evaluated in any other lower risk-of-bias study. Chouhan and Flora (2008) observed a dose-dependent increase in ROS levels associated with 10, 50, and 100 mg/L sodium fluoride in the drinking water; however, results were not statistically significant at any dose. In Chouhan *et al.* (2010), the levels of ROS were significantly higher at 50 ppm sodium fluoride in drinking water, but statistical significance was not met at doses below 20 ppm fluoride (1 and 10 ppm sodium fluoride) or at 100 ppm sodium fluoride; yet, hydrogen peroxide levels as a measure of ROS were found to be significantly increased at 15 ppm sodium fluoride in drinking water in studies conducted by another group of authors (Adedara *et al.* 2017a, Adedara *et al.* 2017b).

Apoptosis/cell death

Seven lower risk-of-bias studies were identified that evaluated apoptosis with concentrations at or below 20 ppm fluoride. Results from these studies were inconsistent and were insufficient for evaluating fluoride-induced apoptosis. These data are insufficient to increase confidence or support a change to hazard conclusions.

Inflammation

Five lower risk-of-bias studies were identified that evaluated potential effects of fluoride on inflammation with concentrations at or below 20 ppm. The inflammation markers were too heterogeneous or limited in number to make any determination on potential relevance of mechanism,

even before limiting the review of the data to lower risk-of-bias studies. These data are insufficient to increase confidence or support a change to hazard conclusions.

Thyroid

Seventeen studies were identified that evaluated potential effects of fluoride on the thyroid with concentrations at or below 20 ppm (see [Figure 9](#)). These animal thyroid data are not further described because this endpoint has been directly evaluated in a number of human studies that have failed to identify consistent evidence to suggest that thyroid effects are a requisite mechanism by which fluoride causes neurodevelopmental or cognitive effects in humans.

Figure 10. Number of Lower Risk-of-bias Animal Studies that Evaluated Biochemical, Neurotransmission, and Oxidative Stress Effects at or Below 20 ppm by Mechanism Subcategory and Direction of Effect*

Mechanism	Mechanism Subcategory	Direction of Effect			Grand Total
		↑	↓	NS	
Biochemistry (brain/neurons)	Carbohydrate/lipid-related		1	1	2
	Gene expression		1		1
	Protein levels associated with brain function	8	7	7	11
	Other biochemical	2			2
Neurotransmitters	Cholinesterase	2	7	3	11
	Dopamine and metabolites		1		1
	Other neurotransmitters	2	2	1	2
Oxidative stress	Antioxidant activity	1	10	4	12
	Lipid peroxidation byproduct	7		4	11
	Protein oxidation	2		1	2
	ROS	2		2	4

*Interactive figure and additional study details in [Tableau®](#)

(https://public.tableau.com/profile/ntp.visuals#!/vizhome/Fluoride_Animal_SelectMechanisms_UPDATE/Figure9). This figure displays study counts for lower risk-of-bias studies, as these counts are most relevant to the text in this section. Counts for higher risk-of bias studies or all studies combined can be accessed in the interactive figure in [Tableau®](#). Study counts are tabulated by significance—statistically significant increase (↑), statistically significant decrease (↓), or not significant (NS). For example, the “↑” column displays numbers of unique studies with at least one endpoint in the mechanistic subcategory with significantly increasing results at fluoride exposure levels of ≤20 ppm. These columns are not mutually exclusive (i.e., a study may report on multiple endpoints with varying results within a single mechanistic subcategory and therefore may be reflected in the counts for the “↑”, “↓”, and NS columns, but would only be counted once in the Grand Total column). Endpoints, species, strain, sex, and exposure duration are available for each study in the interactive figure in [Tableau®](#).

In Vitro/Mechanistic Data on Neurodevelopmental or Cognitive Effects

Although in vitro data were collected as part of the systematic review process, NTP determined that the information on neurological effects obtained from these studies is too general, and results cannot necessarily be attributed to effects on learning and memory or other cognitive functions at this time. The in vitro data may help support specific mechanisms identified from in vivo mechanistic data; however, as described above, no specific mechanism has been determined for fluoride effects on learning and memory or other neurodevelopmental or cognitive outcomes.

Evidence Synthesis for Neurodevelopmental or Cognitive Effects

There is consistent evidence that exposure to fluoride is associated with cognitive neurodevelopmental effects in children. There is moderate confidence in the human data in children from 5 well-conducted

prospective studies, supported by 14 cross-sectional studies where exposure was identified as likely occurring prior to outcome. The human body of evidence in adults is considered inadequate to evaluate whether fluoride exposure is associated with cognitive effects due to low confidence in the human data in adults, a limited number of studies, and a lack of evidence of an effect (i.e., there is not sufficient evidence of an effect, but the confidence in the data is not high enough to conclude that there is no effect). The animal data are inadequate to evaluate for learning and memory effects primarily due to the uncertainty in distinguishing effects on cognitive outcomes from secondary effects on the nervous system or general health including motor activity issues; however, these data do provide evidence of other neurodevelopmental effects. There is also evidence from mechanistic studies of adverse neurological effects of fluoride in humans and animals of unknown relationship to cognition.

The initial moderate confidence is based on 19 studies where exposure occurred prior to outcome and that evaluated individual-based outcomes and used a comparison group. Factors considered for upgrading or downgrading the confidence are as follows:

- **Risk of bias:** Only studies that were considered to have lower risk of bias were included in the moderate confidence rating; therefore, there is no downgrade for risk-of-bias concerns.
- **Unexplained inconsistencies:** The data are relatively consistent and there was no downgrade for this factor. In terms of IQ data, 17 studies observed significant effects associated with fluoride, and 2 studies found no significant association but neither of these studies adjusted for confounders. Consistency among neurodevelopmental effects other than IQ was also considered; however, the conclusions are based on the IQ data so these other neurodevelopmental effects would not impact a potential adjustment in confidence. Studies measuring neurodevelopmental effects other than IQ did not show consistent effects. It is not known whether fluoride exposure would be expected to be associated with neurodevelopmental outcomes in addition to IQ or other cognitive measures.
- **Indirectness:** IQ in humans is a direct measure of effect and therefore no adjustment in confidence is warranted.
- **Imprecision:** The meta-analysis indicates that there was no reason to downgrade due to imprecision.
- **Publication bias:** While the meta-analysis that estimated the pooled SMD among 46 included studies (both higher and lower risk-of-bias) indicated that there was potential for publication bias, a subgroup analysis indicated that there was no publication bias among the lower risk-of-bias studies (see [Figure A5-8](#)). Among the higher risk-of-bias studies, the trim-and-fill analysis estimated that, in the absence of publication bias, the negative direction of effect and statistical significance remained ([Figure A5-9](#)). For the meta-analysis that calculated a pooled effect estimate among the studies with individual-level measures, the funnel plot indicated publication bias; however, the trim-and-fill analysis estimated that once adjusted for publication bias, the negative direction of effect remained ([Appendix 5, Figure A5-16](#) and [Figure A5-18](#)). Therefore, no downgrade was applied for publication bias.
- **Large magnitude of effect:** While some individual studies indicate a large magnitude of effect, the overall pooled effect estimate from the meta-analysis of studies with individual-level

measures does not demonstrate a large magnitude of effect ([Appendix 5](#)). Therefore, the overall data would not support an upgrade due to a large magnitude of effect.

- **Dose-response:** Linear dose-response models provide the best fit to the data in studies examining individual-level measures of fluoride exposure and IQ. A meta-analysis of studies that compared mean IQ scores between groups of children with different levels of fluoride exposure showed a significantly lower mean SMD at higher concentrations of fluoride (>1.5 mg/L) from water (SMD: -0.14; 95% CI: -0.19, -0.08; n = 31 studies) and urine (SMD: -0.18; 95% CI: -0.31, -0.05; n = 22 studies) ([Appendix 5](#)); however, the dose-response relationship at fluoride concentrations below 1.5 mg/L fluoride in urine or drinking water is less certain. The overall dose-response could be used to upgrade the confidence in the body of evidence.
- **Residual confounding:** Xiang *et al.* (2003a), Xiang *et al.* (2011), and Wang *et al.* (2012) studied the same population where arsenic occurred in the area with low fluoride, but did not occur in the area with high fluoride. This would have biased the results toward the null, but there was a significantly lower IQ scores in the area with high fluoride. The remaining studies do not provide enough information to consider residual confounding as an impactful factor for the body of evidence. Therefore, the overall data would not support an upgrade due to residual confounding.
- **Consistency:** There is consistent evidence across study populations and study designs that fluoride is associated with lower IQ scores at higher concentrations of fluoride. There is uncertainty and less of a consistent pattern at concentrations below 1.5 mg/L. There is also a lack of consistency observed with and among other types of neurodevelopmental effects. The consistency in the overall results of the data set could increase the confidence.

Summary judgement on potential upgrades or downgrades in the confidence: Although the OHAT approach for evidence integration allows for the initial confidence in the body of evidence to be increased based on consistency or dose response, the NTP judgement is that the magnitude of effect and the overall strength and quality of the human literature base provides a moderate confidence in the body of evidence that fluoride causes cognitive neurodevelopmental effects in children.

The moderate confidence in the body of evidence in children translates to a moderate level of evidence that fluoride is associated with lower IQ and other cognitive neurodevelopmental effects in children.

The limited and weaker evidence of cognitive effects in adults is considered to provide an inadequate level of evidence that fluoride is associated with cognitive effects in adults. The animal body of evidence is also considered to provide an inadequate level of evidence for cognitive effects in adults.

Integration of these level-of-evidence conclusions supports an initial hazard conclusion of *presumed to be a cognitive neurodevelopmental hazard to humans* because of the extent and consistency of effect in the available data in children. Because most of the available studies evaluated intelligence in children, the primary focus in human data was on IQ and other cognitive neurodevelopmental effects, which is the primary basis for the hazard conclusion. A separate conclusion on other neurodevelopmental effects was not reached based on limited information in humans.

The moderate level of evidence in the human data in children supports a hazard conclusion of *presumed* instead of *suspected* due to the relatively large and consistent body of evidence, especially in relation to measures of IQ (17 of 19 lower risk-of-bias studies that assessed IQ reported an association between

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higher fluoride and lower IQ scores) across multiple populations. A conclusion of *presumed* is supported by a statistically significant effect observed in the meta-analysis. Furthermore, the *presumed* hazard conclusion is supported by the low expectation that new studies would decrease the hazard conclusion.

Effects in children

- **Human body of evidence:** Moderate Confidence = Moderate Level of Evidence
- **Animal body of evidence:** Overall poor quality of studies and few studies that specifically assess effects on learning and memory after exposure during developmental periods separately from other neurological effects including motor activity = Inadequate Level of Evidence
- **Initial hazard conclusion (Moderate Human x Inadequate Animal)** = Presumed to be a Cognitive Neurodevelopmental Hazard to Humans
- **Final hazard conclusion (after consideration of biological plausibility)** = Presumed to be a Cognitive Neurodevelopmental Hazard to Humans

Effects in adults

- **Human body of evidence:** Low Confidence with no discernible effect = Inadequate Level of Evidence
- **Animal body of evidence:** Overall poor quality of studies and few studies that specifically assess effects on learning and memory after exposure in adulthood separately from other neurological effects including motor activity = Inadequate Level of Evidence
- **Initial hazard conclusion (Inadequate Human x Inadequate Animal)** = Not classifiable
- **Final hazard conclusion (after consideration of biological plausibility)** = Not classifiable

Table 7. Neurodevelopmental and Cognitive Function Evidence Profile for Fluoride										
INITIAL CONFIDENCE for each body of evidence (# of studies)	Factors decreasing confidence “---” if no concern; “↓” if serious concern to downgrade confidence					Factors increasing confidence “---” if not present; “↑” if sufficient to upgrade confidence				FINAL CONFIDENCE RATING
	Risk of Bias	Unexplained Inconsistency	Indirectness	Imprecision	Publication Bias	Large Magnitude	Dose Response	Residual Confounding	Consistency Species/Model	
Human IQ or cognitive function tests in children*										
Initial Moderate (5 prospective cohort studies ^a ; 14 cross-sectional studies ^b)	---	---	---	---	---	---	---	---	---	Moderate
Initial Low (7 cross-sectional studies) ^c	---	---	---	---	---	---	---	---	---	Low
Human IQ or cognitive function tests in adults**										
Initial Low (2 cross-sectional studies) ^d	---	---	---	---	---	---	---	---	---	Low
Animal learning and memory or cognitive function										
Inadequate to assess effects in human										
References:										
Human: Barberio <i>et al.</i> (2017b) ^c ; Bashash <i>et al.</i> (2017) ^a ; Bashash <i>et al.</i> (2018) ^a ; Choi <i>et al.</i> (2015) ^b ; Cui <i>et al.</i> (2018) ^c ; Cui <i>et al.</i> (2020) ^c ; Das and Mondal (2016); Ding <i>et al.</i> (2011) ^b ; Green <i>et al.</i> (2019) ^a ; Jacqmin <i>et al.</i> (1994) ^d ; Li <i>et al.</i> (2004) [translated in Li <i>et al.</i> 2008a] ^b ; Li <i>et al.</i> (2016) ^d ; Riddell <i>et al.</i> (2019) ^c ; Rocha-Amador <i>et al.</i> (2007) ^b ; Rocha-Amador <i>et al.</i> (2009) ^b ; Saxena <i>et al.</i> (2012) ^b ; Seraj <i>et al.</i> (2012) ^b ; Soto-Barreras <i>et al.</i> (2019) ^b ; Sudhir <i>et al.</i> (2009) ^b ; Till <i>et al.</i> (2020) ^a ; Trivedi <i>et al.</i> (2012) ^c ; Valdez Jimenez <i>et al.</i> (2017) ^a ; Wang <i>et al.</i> (2012) ^b ; Wang <i>et al.</i> (2020b) ^b ; Wang <i>et al.</i> (2020a) ^c ; Xiang <i>et al.</i> (2003a) ^b ; Xiang <i>et al.</i> (2011) ^b ; Yu <i>et al.</i> (2018) ^b ; Zhang <i>et al.</i> (2015b) ^c										
*This includes learning disabilities, neonatal behavioral neurological assessment, mental development index, memory score for copy, and immediate recall.										
**This includes Mini-Mental State Examination scores, psychomotor performance, and memory.										

DISCUSSION

The overall objective of this evaluation was to undertake a systematic review of published literature to reach conclusions concerning the potential for exposure to fluoride to affect neurodevelopment and cognition. This review only addresses whether exposure to fluoride could present a potential hazard (i.e., has the potential to cause harm at any exposure level, including exposures that are higher than typically encountered from consuming fluoridated drinking water in the United States). Benefits of fluoride with respect to oral health are not addressed in this monograph.

Given this context, when focusing on human epidemiology studies with exposures in ranges typically found in the water distribution systems in the United States (0.7 mg/L for optimally fluoridated community water systems)⁸ that can be evaluated for dose response, effects on cognitive neurodevelopment are inconsistent and therefore unclear. However, given the totality of the data, including studies with exposures to fluoride levels higher than the WHO safe water guideline of 1.5 mg/L in water (WHO 2011), the NTP concludes that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans*. This conclusion is based on a moderate level of evidence that shows a consistent and robust pattern of findings in human studies across several different populations demonstrating that higher fluoride exposure (e.g., >1.5 mg/L in drinking water) is associated with lower IQ and other cognitive effects in children. Limited and weaker evidence is considered to provide an inadequate level of evidence that fluoride is associated with cognitive effects in adults. The primary focus of the human data was on IQ and cognitive neurodevelopmental effects; therefore, the conclusion was based on these data. After further evaluation of the experimental animal data available in NTP (2016) and in this systematic review, NTP concludes that in terms of evaluating the effects of fluoride on learning and memory to support the cognitive effects observed in humans, the animal data are inadequate. The animal data do provide evidence for effects of fluoride on neurodevelopment; however, other neurodevelopmental outcomes were not further evaluated because of the limited information in humans. Biological plausibility of effects from mechanistic studies was considered but did not significantly influence the conclusions. Although multiple categories of mechanistic data were evaluated and provide some evidence of adverse effects in the brain, a coherent series of mechanistic events to account for fluoride-associated cognitive neurodevelopmental deficits is not sufficiently understood for these findings to contribute to the overall confidence assessment.

The human body of evidence provides a consistent and robust pattern of findings that higher fluoride exposure is associated with lower IQ scores in children. The moderate level of evidence is based on 5 lower risk-of-bias prospective cohort studies and 14 lower risk-of-bias cross-sectional studies that are considered to have sufficient evidence of fluoride exposure occurring prior to the outcome. The evaluation of the animal body of evidence in this assessment is an extension of the NTP (2016) systematic review on the association between fluoride exposure and neurobehavioral effects related to learning and memory in animals, which identified a concern related to indirectness. This concern was that many of the learning and memory tests rely on a motor response (e.g., latency to achieve the desired effect). The review of animal data published since the 2016 review focused on addressing this

⁸As of April 2020, 1.08% of persons living in the United States (~ 3.5 million people) were served by CWS containing ≥ 1.1 mg/L naturally occurring fluoride. CWS supplying water with ≥ 1.5 mg/L naturally occurring fluoride served 0.59% of the U.S. population (~ 1.9 million people), and systems supplying water with ≥ 2 mg/L naturally occurring fluoride served 0.31% of the U.S. population (~1 million people) (<https://www.cdc.gov/fluoridation/data-tools/reporting-system.html>).

indirectness concern. Further examination of the literature has not provided clarification of this issue. Due to the inability to separate these effects from effects on general health and other effects on the nervous system, the animal body of evidence is now considered inadequate to contribute to the evaluation of cognitive effects in humans. Although the animal data are not considered sufficient to specifically support the IQ changes observed in children, the data do support possible neurodevelopmental effects.

The NTP conclusion that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans* is supported by the extent, consistency, and robustness of the effect in the available data in children. Seventeen of the 19 lower risk-of-bias studies reported an association between higher fluoride exposure and lower IQ scores in children across multiple populations. Meta-analyses conducted at the recommendation of NASEM based on their review of the September 6, 2019 draft monograph provide further support for the hazard conclusion of *presumed* (NASEM 2020). The random-effects pooled SMD estimate from the 46 studies included in the group-level meta-analysis was consistent with two previous meta-analyses reporting statistically significant associations between higher fluoride exposure and lower IQ in children. A risk-of-bias subgroup analysis demonstrated that the significant negative association remained when the meta-analysis was restricted to 9 lower risk-of-bias studies. Further subgroup analyses by gender, age group, country, outcome assessment type, and exposure assessment type support a consistent and robust pattern of results. A second meta-analysis of the individual-level data from six lower risk-of-bias studies also provided evidence of a statistically significant negative association between fluoride exposure and lower IQ in children (overall pooled effect estimate per 1-mg/L increase in urinary fluoride was associated with a 1.40-point lower IQ score [95% CI: -2.33, -0.47]). Given the evidence, there is a low expectation that new studies would change the hazard conclusion.

There are few studies in humans and numerous studies in animals that evaluate mechanistic effects related to fluoride exposure. There are sufficient mechanistic data to determine that fluoride exposure at lower concentrations has effects on the nervous system; however, for the cognitive neurodevelopmental outcome evaluated, there are insufficient data to support a specific mechanism or mode of action. Due to the large number of mechanistic studies conducted in animals, evaluation of the mechanistic data in animals focused on studies that had exposures more relevant to humans (i.e., ≤ 20 ppm in the drinking water). Changes in AChE, which could potentially be related to cognitive effects such as IQ, were evaluated in one study of children and several studies of animals (measured in both the blood and in areas of the brain); however, the majority of these studies, including the study of children, reported results inconsistent with the phenotypic outcome. Animal studies that evaluated changes in other neurotransmitters and other biochemical measures provide some evidence of effects in the brain, but the data are limited due to the heterogeneity of the outcomes measured. Most consistently, studies evaluating histopathology and oxidative stress demonstrated that effects can occur in the brains of animals at or below 20 ppm, which, without supporting a specific mechanism or mode of action relevant to learning and memory impairments, provides evidence of an association between exposure to lower concentrations of fluoride and neurological effects in animals. Therefore, the evidence of neurological effects at exposure levels more relevant to humans that is demonstrated in the mechanistic data supports the NTP conclusion that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans*; however, it does not provide enough evidence to increase confidence in the human body of evidence or support a higher hazard identification conclusion.

Generalizability to the U.S. Population

For many years, fluoride concentrations were adjusted to levels between 0.8 and 1.2 mg/L in fluoridated community water systems in the United States. The U.S. Public Health Service recommended an adjustment downward to a fluoride concentration of 0.7 mg/L because of evidence of an increase in dental fluorosis in children (US DHHS 2015). In April 2020, the CDC Water Fluoridation Reporting System estimated that the majority (i.e., 97.5%) of fluoride concentrations in water for U.S. children and adolescents (≤ 19 years old) are below 1.2 mg/L (<https://www.cdc.gov/fluoridation/data-tools/reporting-system.html>).

NTP's conclusion that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans* is based on consistent evidence from 26 lower risk-of-bias studies that evaluated fluoride exposure and effects on children's IQ and other cognitive effects. Although there are many studies that evaluated associations between fluoride in the drinking water and IQ in children, no studies evaluating IQ were conducted in the United States. Generalizing the results from the IQ studies in this evaluation to the U.S. population can be difficult, in part because many studies were conducted in areas with fluoride drinking water concentrations that are much higher than drinking water fluoride concentrations in the United States. Among the human body of evidence evaluated for this assessment (including lower and higher risk-of-bias studies), there are 33 studies that evaluated associations between fluoride in drinking water and IQ in children and compared a reference or low exposure group to higher fluoride-exposed groups. Of these 33 studies, only 10 studies included fluoride exposure groups with fluoride concentrations < 1.5 mg/L (i.e., fluoride exposure groups that would potentially be relevant to levels observed in the United States) (Xu *et al.* 1994, Xiang *et al.* 2003a, Qin *et al.* 1990 [translated in Qin *et al.* 2008], Kang *et al.* 2011, Broadbent *et al.* 2015, Sebastian and Sunitha 2015, Sudhir *et al.* 2009, Zhang *et al.* 2015b, Zhang *et al.* 1998, Wang *et al.* 2020b). Of these 10 studies, 4 were considered to have lower risk of bias (Zhang *et al.* 2015b, Xiang *et al.* 2003a, Wang *et al.* 2020b, Sudhir *et al.* 2009).

In addition to the four studies mentioned above, several other studies that evaluated fluoride exposure on a continuous basis could be used to assess generalizability to the United States. This includes studies that examined fluoride exposure levels below 1.5 mg/L for which a dose response could be assessed. **Table 8** provides a summary of children's IQ studies that evaluated lower fluoride exposures (< 1.5 mg/L) in drinking water and/or urine (assuming, for comparison purposes, an approximate 1-to-1 equivalence between drinking water fluoride and urinary fluoride concentrations) and provided information to evaluate dose response in the lower fluoride exposure range (e.g., three or more fluoride exposure groups or dose-response curve provided). Based on review of these studies (discussed further below), there is uncertainty if IQ changes in children occur at lower fluoride levels.

Among studies with lower risk of bias for which a dose response could be assessed, four of nine studies that examined fluoride exposure levels below 1.5 mg/L (**Table 8**) (Green *et al.* 2019, Zhang *et al.* 2015b, Xiang *et al.* 2003a, Wang *et al.* 2020b) applied regression models to individual exposure outcome measures and observed a linear association between urinary fluoride levels and lower IQ in children even at the lower fluoride concentrations. However, two of these studies (Xiang *et al.* 2003a, Zhang *et al.* 2015b) did not find an association between IQ and drinking water levels below 1.5 mg/L. Xiang *et al.* (2003a) observed a significantly lower IQ in endemic versus nonendemic villages, but when they grouped children from the endemic villages by exposure level, they did not observe a significantly lower IQ score for children exposed to lower mean exposure levels of fluoride (0.75 mg/L). Although a significant difference in IQ might not be expected due to the fact that there were only nine children in this group, the difference was less than one point in IQ. Zhang *et al.* (2015b) used a simple correlation

and did not observe a significant relationship between fluoride levels in the drinking water (with concentrations up to 1.57 mg/L) and IQ. Sudhir *et al.* (2009) observed a significant increase in IQ grade (which is associated with lower IQ) at concentrations of 0.7–1.2 mg/L. The other four of nine studies do not provide a clear dose response at the lower fluoride levels. Bashash *et al.* (2017) concluded that there was no clear association between IQ scores and maternal urinary fluoride below 0.8 mg/L. Yu *et al.* (2018) observed a correlation between lower IQ in children and fluoride exposure only with concentrations in drinking water above 3.4 mg/L or with urinary fluoride concentrations of 1.6 mg/L or higher. The study authors did note a decreased probability of having an IQ above 130 (i.e., 40% fewer people with high IQ for every 0.5-mg/L increase in fluoride) with water fluoride levels between 0.20 and 1.40 mg/L, but this was not observed with higher levels of fluoride. Although Cui *et al.* (2018) noted that IQ decreased in a “roughly linear manner” with increasing urinary fluoride, this is only apparent in the results for the TT genotype; based on the dose response, the authors concluded that the “safety threshold” was 1.73 mg/L. Ding *et al.* (2011) looked at mean differences for 10 different exposure groups and found notable decreases from the mean above approximately 1 mg/L.

Although there is less confidence in the findings from higher risk-of-bias studies, six studies identified with potential dose-response information demonstrated a similar uncertainty at the lower fluoride concentrations. Surprisingly, three of the studies (Aravind *et al.* 2016, Qin *et al.* 1990 [translated in Qin *et al.* 2008], Xu *et al.* 1994) found that the lowest IQ scores were in areas with the lowest and the highest fluoride concentrations. In these studies, the lowest fluoride concentrations ranged from 0.1–0.2 mg/L fluoride in Qin *et al.* (1990) [translated in Qin *et al.* 2008] to <1.2 mg/L in Aravind *et al.* (2016). Li *et al.* (1995) and Sebastian and Sunitha (2015) only observed lower IQ scores at concentrations above 2 mg/L. Das and Mondal (2016) found a steady decline in IQ with increasing urinary fluoride levels or exposure dose.

To further examine the dose response for lower IQ in the lower exposure region (e.g., <1.5 mg/L fluoride in drinking water or urine), a meta-analysis ([Appendix 5](#)) using a linear mixed model to analyze mean-effect estimates was performed. Twelve observations from 9 studies were included that reported one or more IQ measurements associated with drinking water fluoride exposures of < 1.5 mg/L and a reference group. This analysis did not show a statistically significant association with the mean SMD in children’s IQ scores between exposed and reference groups (SMD = 0.32; 95% CI: –0.57, 1.20). A dose-response meta-analysis including seven observations from four studies with at least one exposure group < 1.5 mg/L urinary fluoride showed a non-statistically significant decrease in mean SMD (SMD = –0.13; 95% CI: –0.29, 0.03). Based on these results, effects of fluoride exposure on children’s IQ at levels < 1.5 mg/L remain unclear and more studies at lower exposure levels are needed. A dose-response meta-analysis of studies with individual-level data could not be conducted due to the small number of studies (n = 10), the various types of exposure metrics, and the different types of reported effect estimates. More studies with lower levels of fluoride exposure from drinking water are still needed to fully understand potential effects at exposures in ranges typically found in the United States (i.e., <1.5 mg/L). Of note, the negative association between IQ and fluoride exposure via drinking water was statistically significant when extending the dose-response meta-analysis to include IQ measures from groups exposed to <2 mg/L in drinking water (SMD = –0.27; 95% CI: –0.36, –0.17). A statistically significant decrease in mean SMD in children’s IQ scores was not seen in urinary fluoride measures of < 2 mg/L (SMD = –0.09; 95% CI: –0.22, 0.03) ([Table A5-3](#)).

When generalizing findings from the cited studies to exposures in the United States from fluoride in drinking water, it is important to consider that drinking water only comprises a portion of total exposures to fluoride. Although it can be assumed that children in all the studies cited in this document

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are also exposed to fluoride from sources other than drinking water, these other exposures are likely to vary considerably depending on individual circumstances. Fluoride concentrations in drinking water alone do not reflect the magnitude of fluoride exposures to children who consume excessive amounts of fluoridated toothpaste or to formula-fed babies who consume powdered formula that is reconstituted with fluoridated water. A few studies also support the possibility of heightened sensitivities to the detrimental cognitive effects of fluoride exposures in individuals with certain polymorphisms in dopamine receptor D2, or catechol-O-methyltransferase (Cui *et al.* 2018, Zhang *et al.* 2015b), impacting dopamine catabolism and receptor sensitivity. Differential exposures to fluoride and genetic susceptibilities of children to fluoride appear to warrant further research.

Table 8. Human Studies with Lower Fluoride Exposure and Effects on IQ		
Study	Exposure measures [mean $\pm$ SD (range)]	Notes
Lower risk-of-bias studies		
Bashash <i>et al.</i> (2017)	Maternal urine during pregnancy (mg/L) 0.90 $\pm$ 0.35 (0.23–2.36)	Authors concluded that the model suggested a nonlinear relationship with no clear association between IQ scores and maternal urine below 0.8 mg/L.
	Children’s urine (mg/L) 0.82 $\pm$ 0.38 (0.18–2.8)	
Green <i>et al.</i> (2019)	Maternal urine during pregnancy (mg/L) 0.51 $\pm$ 0.36 (0.06–2.44) 0.40 $\pm$ 0.27 non-fluoridated areas 0.69 $\pm$ 0.42 fluoridated areas	Statistical methods indicated that including quadratic or natural-log effects of maternal urine or intake did not significantly improve the model. In addition, the authors tested separate models with two linear splines to see if the effect of maternal urinary fluoride or maternal fluoride intake significantly differed between lower and higher levels based on knots set at 0.5, 0.8, and 1.0 mg/L for urine and 0.4, 0.8, and 1 mg for intake. There were no differences.
	Maternal intake during pregnancy (mg/day) 0.54 $\pm$ 0.44 (0.01–2.65) 0.30 $\pm$ 0.26 non-fluoridated areas 0.93 $\pm$ 0.43 fluoridated areas	
	Drinking water (mg/L)* 0.31 $\pm$ 0.23 (0.04–0.87 ¹) 0.13 $\pm$ 0.06 non-fluoridated areas 0.59 $\pm$ 0.08 fluoridated areas	
Cui <i>et al.</i> (2018)	Drinking water (mg/L)* 0.20–1.00 non-endemic 1.52–2.49 endemic	Study authors noted that the IQ decreased in a “roughly linear manner as the log-urine fluoride increased.” TT genotypes of the dopamine receptor D2 gene had the strongest negative correlation between log-urine fluoride and IQ scores. The study authors determined a safety threshold of urine fluoride levels in subgroup TT as 1.73 mg/L. Drinking water fluoride levels were used to select children from different areas but were not used in the analysis.
	Children’s urine Levels not provided; log-transformed with range of approximately –1.2–2.2	
Ding <i>et al.</i> (2011)	Drinking water (mg/L) * 1.31 $\pm$ 1.05 (0.24–2.84)	Although there was a significant correlation between urinary fluoride and IQ score, the main drop in IQ occurred at urinary fluoride levels of approximately 0.7–1.2 mg/L. At levels below 0.7 mg/L, data suggest a plateau with no apparent change in IQ compared with the mean. Drinking water fluoride levels were not used in the analysis.
	Children’s urine (mg/L) 0.10–3.55	

Table 8. Human Studies with Lower Fluoride Exposure and Effects on IQ		
Study	Exposure measures [mean $\pm$ SD (range)]	Notes
Sudhir <i>et al.</i> (2009)	Drinking water (mg/L)* <0.7 (level 1 villages) 0.7–1.2 (level 2 villages) 1.3–4.0 (level 3 villages) >4.0 (level 4 villages)	The number of intellectually impaired children gradually increased with increasing fluoride concentration in drinking water with an increase in IQ grade (which indicates a decrease in IQ) observed in the 0.7–1.2-mg/L villages. Children were placed in exposure groups based on Water Works Department records. Although children brought in water for verification of strata, it was not collected from all children but only from the first child using a different source of water. Therefore, these are considered group-level data. Note that all groups had a large proportion in the “intellectually impaired” category.
Wang <i>et al.</i> (2020b)	Drinking water (mg/L)* 1.39 $\pm$ 1.01 (0.20–3.90)	There was a significantly lower IQ in quartile 3 (1.00–1.90 mg/L) and quartile 4 (>1.90 mg/L), but not quartile 2 (0.70–1.00 mg/L) of drinking water. Urinary fluoride was only associated with a significantly lower IQ in quartile 4 (>2.28 mg/L).
	Children’s urine (mg/L) 1.28 $\pm$ 1.30 (0.01–5.54)	
Xiang <i>et al.</i> (2003a)	Drinking water (mg/L)* 0.36 $\pm$ 0.15 (0.18–0.76) non-endemic village 2.47 $\pm$ 0.79 (0.57–4.50) endemic village Endemic subgroups: group A: 0.75 $\pm$ 0.14 group B: 1.53 $\pm$ 0.27 group C: 2.46 $\pm$ 0.30 group D: 3.28 $\pm$ 0.25 group E: 4.16 $\pm$ 0.22	IQ in group A in the endemic village was not significantly lower than the non-endemic village, but IQ in all other groups was significantly lower. Although there were only 9 children in group A, the IQ difference was <1 point. Based on simple regression, there was a steady decline in IQ with increasing urinary fluoride.
	Children’s urine (mg/L) 1.11 $\pm$ 0.39 (0.37–2.50) non-endemic village 3.47 $\pm$ 1.95 (0.90–12.50) endemic village	
Yu <i>et al.</i> (2018)	Drinking water (mg/L)* 0.50 $\pm$ 0.27 normal 2.00 $\pm$ 0.75 high	Study authors reported that participants' intelligence presented inverse non-linear dose-response relationships with fluoride content, with obvious decreases at relatively high level of fluoride exposure (drinking water fluoride levels at 3.4–3.90 mg/L and urinary fluoride levels at 1.60–2.50 mg/L). Study authors also note a decreased odds for having IQ $\geq$ 130 with drinking water fluoride at 0.20–1.40 mg/L (40% decrease with each 0.5-mg/L increase in fluoride), but not at higher concentrations.
	Children’s urine (mg/L) 0.41 $\pm$ 0.49 normal 1.37 $\pm$ 1.08 high	

Table 8. Human Studies with Lower Fluoride Exposure and Effects on IQ		
Study	Exposure measures [mean ± SD (range)]	Notes
Zhang <i>et al.</i> (2015b)	Drinking water (mg/L)* 0.63 (0.58–0.68) control 1.40 (1.23–1.57) endemic fluorosis	There was a steady decline in IQ with increasing serum or urinary fluoride levels. A simple correlation did not find drinking water fluoride significantly correlated with IQ.
	Children’s urine (mg/L) 1.1 ± 0.67 control 2.4 ± 1.01 endemic fluorosis	
	Children’s serum (mg/L) 0.06 ± 0.03 control 0.18 ± 0.11 endemic fluorosis	
Higher risk-of-bias studies		
Aravind <i>et al.</i> (2016)	Drinking water (mg/L)* <1.2 low fluoride area 1.2–2 medium fluoride area >2 high fluoride area	Mean IQ scores (transformed into percentiles) were highest in the medium fluoride area for both boys and girls.
Das and Mondal (2016)	Groundwater (mg/L)* 2.11 ± 1.64 (0.25–9.40)	Based on simple regression, there was a steady decline in IQ with increasing urinary fluoride and increasing exposure dose.
	Children’s urine (mg/L) 0.45–17.00	Groundwater fluoride levels were not used in the analysis but were used in calculating the children’s exposure dose.
	Children’s exposure dose (mg/kg-day) 0.017–0.203	
Li <i>et al.</i> (1995)	Children’s urine (mg/L) 1.02 non-fluorosis area 1.81 slight fluorosis area 2.01 medium fluorosis area 2.69 severe fluorosis area	A significantly lower IQ score was observed in the medium and severe fluorosis areas compared to the non-fluorosis area. Children’s urine was used as an individual measure of exposure to verify that the areas had different fluoride exposure levels; however, analysis was conducted based on residential area.
Qin <i>et al.</i> (1990) [translated in Qin <i>et al.</i> 2008]	Drinking water (mg/L)* 0.1–0.2 low fluoride area 0.5–1.0 normal fluoride area 2.1–4.0 high fluoride area	Average IQ scores (transformed into percentages) were significantly lower in both the low and high fluoride areas compared with the normal fluoride area.
Sebastian and Sunitha (2015)	Drinking water (mg/L)* 0.40 (low fluoride village) 1.2 (normal fluoride village) 2.0 (high fluoride village)	A significantly lower mean IQ score of children living in the high fluoride area compared with the low and normal fluoride areas was reported. Binary regression models using the low fluoride village as a reference observed an increased odds ratio (1.74) for increased IQ scores in the normal fluoride village and a decreased odds ratio (0.59) in the high fluoride village.
Xu <i>et al.</i> (1994)	Drinking water (mg/L)* 0.8 (control area) 0.38 (low fluoride area) 1.8 (high fluoride area)	Both low and high fluoride areas had IQ levels approximately 3 points below the IQ levels in the control area. There was no difference in IQ between the low and high fluoride areas.

*Data are group-level exposure data; exposure data without the asterisks are individual-level exposure data.

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¹Range data were obtained from Till *et al.* (2018).

The conclusion that fluoride is *presumed to be a cognitive neurodevelopmental hazard in children* is based on the consistency of the data; however, most lower risk-of-bias studies observed effects with drinking water concentrations above 1.5 mg/L. As noted above, describing the effects at 1.5 mg/L or below, which is more relevant to the exposures observed in the U.S. population, including from community water fluoridation, is more difficult. In the reviewed studies, when limiting studies to those that evaluated IQ at fluoride levels across a continuum that included the low dose range, results are less consistent.

Limitations of the Evidence Base

Few limitations exist in the lower risk-of-bias epidemiological studies used for the basis of the hazard conclusion. The main limitations in lower risk-of-bias epidemiological studies include:

- Few studies were available that assessed the association between fluoride exposure and the following:
 - Neurodevelopmental or cognitive effects in subjects from communities served by optimally fluoridated versus non-fluoridated water systems.
 - Neurobehavioral (i.e., cognitive) effects (particularly IQ) in adults.
 - Attention-related disorders including ADHD.
- Studies rarely separated the results by gender or provided information to indicate that gender was not a modifying factor, which limits the ability to evaluate how the association between fluoride exposure and cognitive neurodevelopmental effects in children might differ by gender.

Limitations in the epidemiological studies with higher risk of bias include:

- Many of the original publications were in a foreign language and provided limited details on methodology.
- Some studies lacked information regarding exposure and/or had serious limitations in the exposure assessment. Exposure assessment concerns include limited individual exposure information, a lack of information on fluoride sampling methods and timing of the exposure measurements, a lack of quantitation of levels of fluoride in drinking water, and a lack of individual-level information on fluorosis in areas reported to be endemic for fluorosis.
- The comparison groups in studies conducted in areas endemic for fluorosis may have still been exposed to high levels of fluoride or levels similar to those used in water fluoridation in the United States. This factor may have limited the ability to detect true effects.
- Most studies did not provide sufficient direct information (e.g., participation rates) to evaluate selection bias.
- Failure to address potential confounders was a main issue. Many studies conducted simple statistical analyses without accounting for any potential confounders. In cases where adjustments in analyses were made, often these studies did not account for potential confounders considered critical for that study population and outcome.

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- Studies conducted in areas with high, naturally-occurring fluoride levels in drinking water often did not account for potential exposures to arsenic or iodine deficiencies in study subjects.
- Many studies did not account for potential exposures to lead as a residual confounder.
- Many studies lacked information on whether the outcome assessors were blind to the exposure group, including studies that examined children in their schools and subjects from high-fluoride communities.

Limitations in the animal studies include:

- The main limitation in the animal studies was the inability to separate possible learning and memory effects from effects on motor activity/coordination or sensory effects.
- Few learning and memory studies in animals evaluated motor activity or sensory effects. Studies that did evaluate motor activity or sensory effects often lacked discussion on general health of the animals when the endpoints measured could be affected by deficits in motor activity or sensory, such as latency to achieve a desired result.

A key data gap in the human and animal bodies of evidence includes the need for mechanistic insight into fluoride-related neurodevelopmental or cognitive changes.

Limitations of the Systematic Review

There are no major limitations of the systematic review. The human body of evidence included a large database of observational studies. Most of the observational studies were cross-sectional; however, nine of these were considered to be functionally prospective in nature. In addition, the systematic review covered a wide range of study designs, populations, and measures of fluoride exposure. The systematic review was designed to cover reports on all potential mechanistic data including effects on the thyroid. After review of the studies evaluating thyroid effects, studies that only evaluated goiters and other effects on thyroid size were not considered in this review. This is not considered a limitation because changes in thyroid size are not functional changes to the thyroid that could specifically indicate a mechanism for thyroid involvement in neurodevelopment. In addition, review of the mechanistic data was limited to in vivo studies with at least one concentration below 20 ppm. This is not considered a limitation for the systematic review since the mechanistic body of evidence was used to evaluate biological plausibility for the effects observed in humans; therefore, data were limited to concentrations that would be more reflective of human exposures. The decision to not more closely evaluate the in vitro data is not considered a limitation because there were sufficient in vivo data, and no key events were identified where in vitro data would provide additional insight.

CONCLUSION

Because the majority of available studies evaluated cognitive neurodevelopmental effects in children, the focus of the hazard conclusions is on cognitive neurodevelopmental effects, primarily IQ. When focusing on findings from studies with exposures in ranges typically found in drinking water in the

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United States (0.7 mg/L for optimally fluoridated community water systems)⁹ that can be evaluated for dose response, effects on cognitive neurodevelopment are inconsistent and, therefore, unclear. However, when considering all the evidence, including studies with exposures to fluoride levels higher than 1.5 mg/L in water, NTP concludes that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans*. This conclusion is based on a moderate level of evidence that shows a consistent and robust pattern of findings in human studies across several different populations demonstrating that higher fluoride exposure (e.g., >1.5 mg/L in drinking water) is associated with lower IQ and other cognitive effects in children. Limited and weaker evidence is considered to provide an inadequate level of evidence that fluoride is associated with cognitive effects in adults. The evidence from animal studies is inadequate to inform conclusions on cognitive effects, and the mechanisms underlying fluoride-associated cognitive neurodevelopmental effects are not well characterized.

⁹As of April 2020, 1.08% of persons living in the United States (~ 3.5 million people) were served by CWS supplying ≥ 1.1 mg/L naturally occurring fluoride. CWS supplying water at ≥ 1.5 mg/L naturally occurring fluoride served 0.59% of the U.S. population (~ 1.9 million people), and systems supplying water at ≥ 2 mg/L naturally occurring fluoride served 0.31% of the U.S. population (~1 million people) (<https://www.cdc.gov/fluoridation/data-tools/reporting-system.html>).

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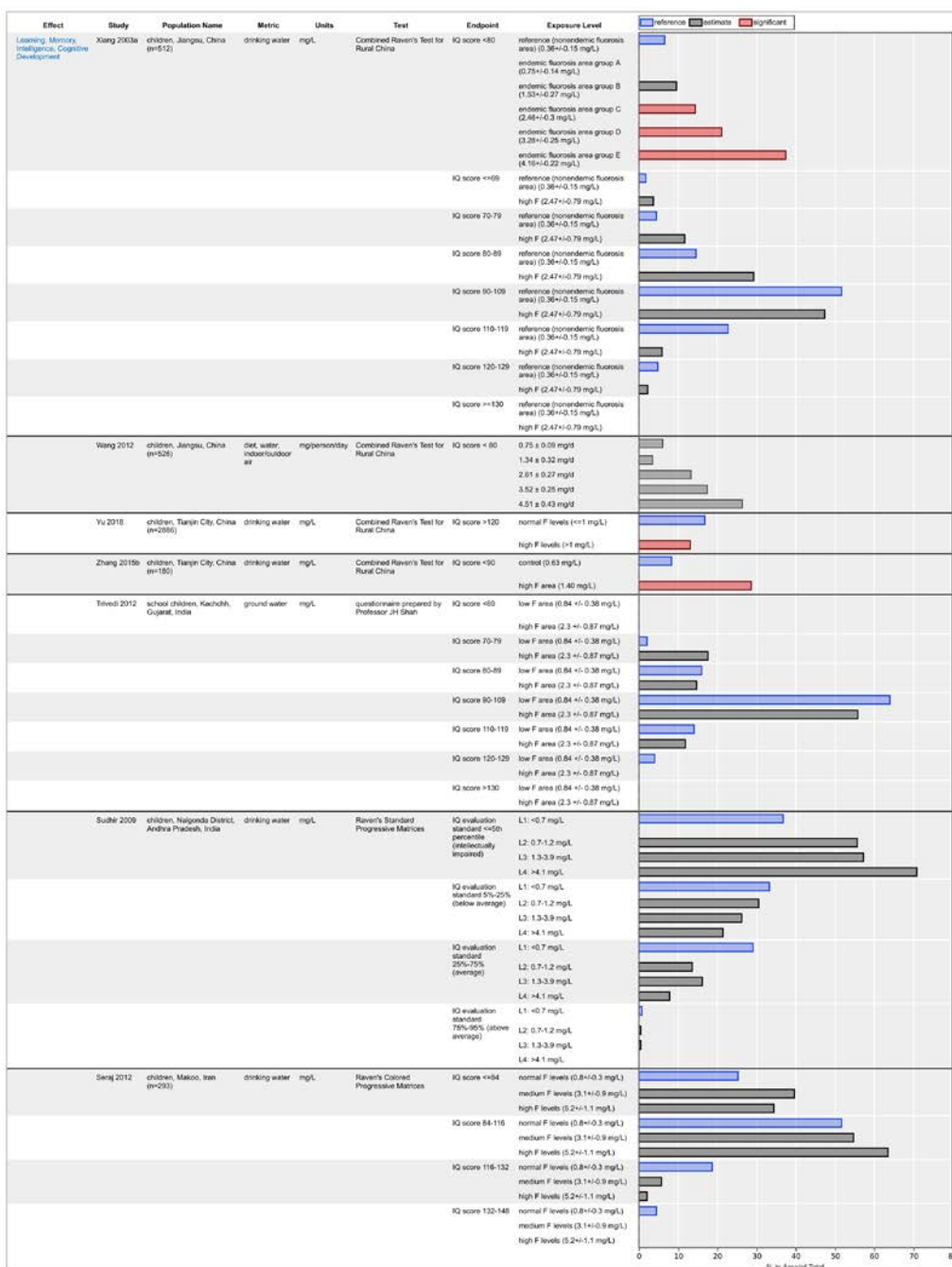
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DATA FIGURES

Neurodevelopmental or Cognitive Effects and Outcomes

Figure D1. IQ Distribution in Children by Fluoride Exposure (lower risk-of-bias studies; presented as % in area or % of total group)



Interactive figure and additional study details in HAWC [here](#). "F" represents fluoride. Differences in intelligence between the reference group and treatment groups were statistically significant although significance was not reported separately for each score level.

Figure D2. Mean IQ in Children by Fluoride Exposure (lower risk-of-bias studies)

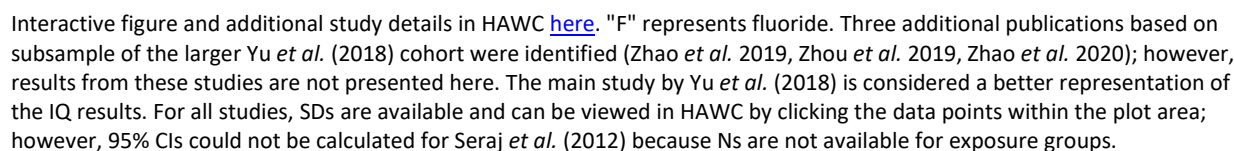
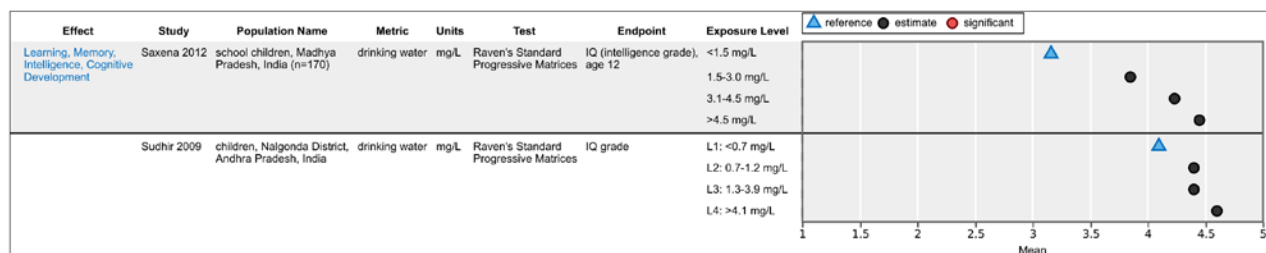
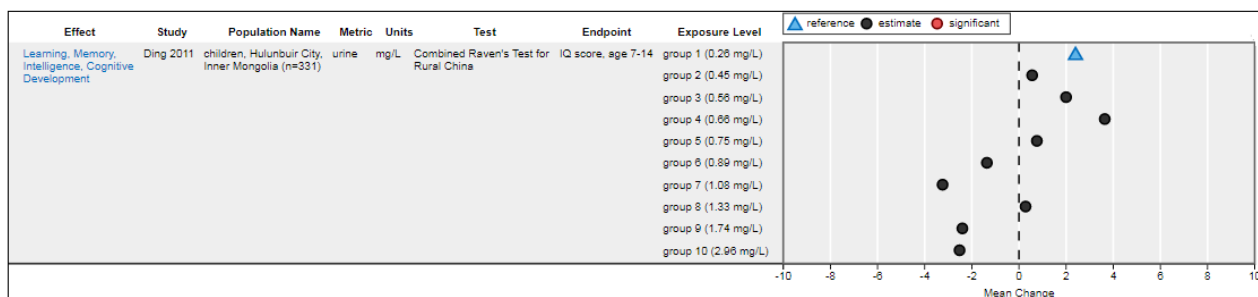


Figure D3. Intelligence Grade in Children by Fluoride Exposure (lower risk-of-bias studies; presented as mean)



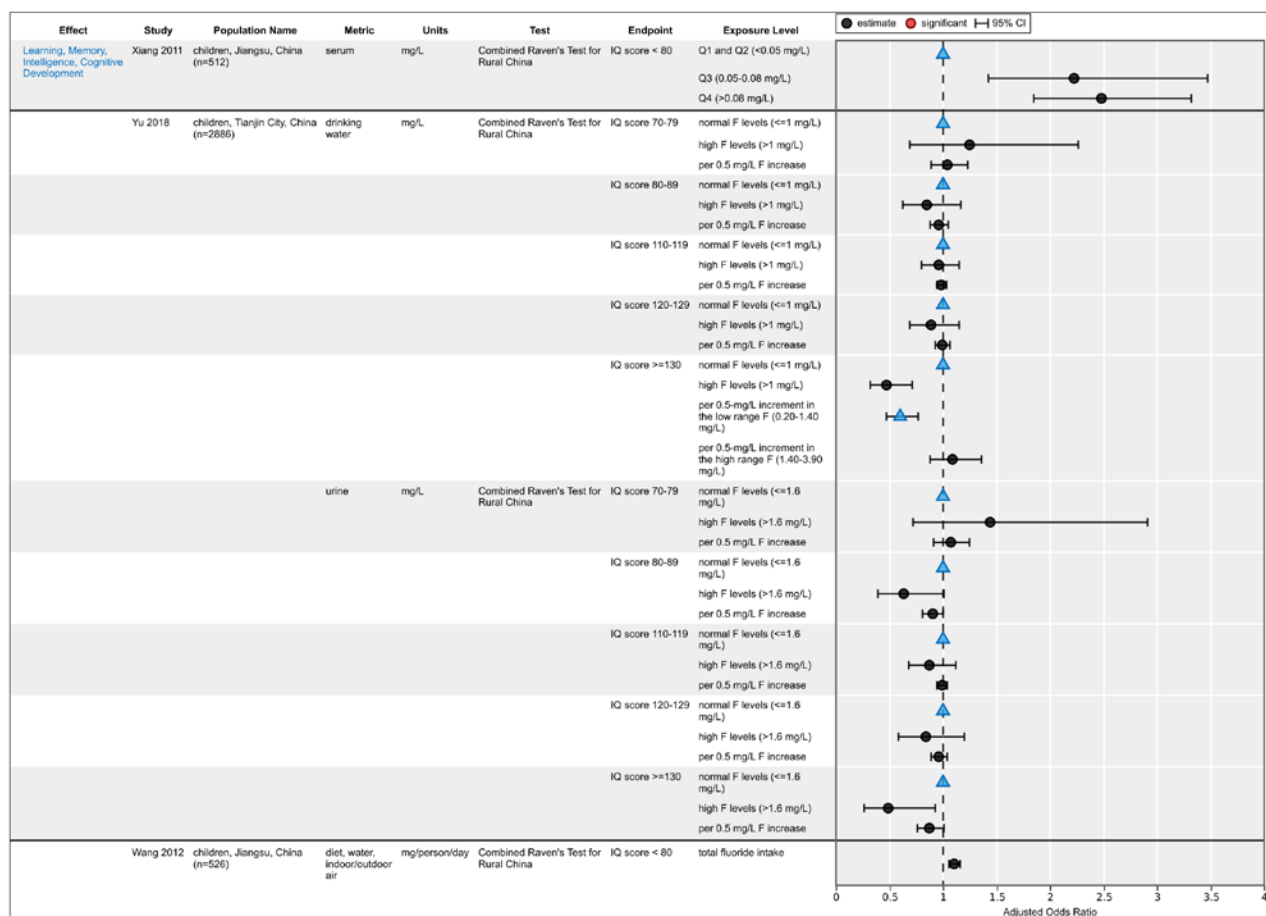
Interactive figure and additional study details in HAWC [here](#). For Saxena *et al.* (2012), children's intelligence was measured using the Raven's Standard Progressive Matrices. Children's scores were converted to percentile and specific grades were allotted based on the percentiles. Grades ranged from intellectually superior (Grade I) to intellectually impaired (Grade V). Results for Soto-Barreras 2019 are not presented here. Outcomes in the study were presented as levels of fluoride exposure associated with each intelligence grade. Results reported were not significant.

Figure D4. Mean Change in IQ in Children by Fluoride Exposure (lower risk-of-bias studies)



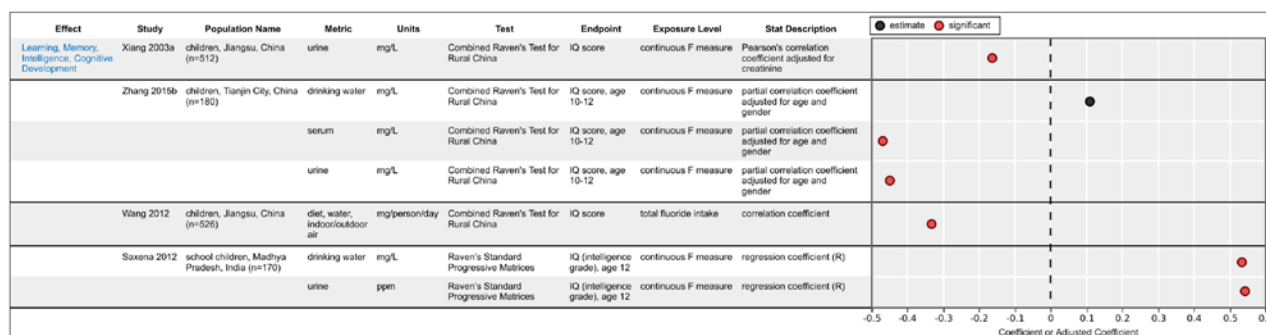
Interactive figure and additional study details in HAWC [here](#). For Ding *et al.* (2011), SDs are available and can be viewed in HAWC by clicking the data points within the plot area; however, 95% CIs could not be calculated because Ns for each exposure group are not available.

Figure D5. IQ Score in Children by Fluoride Exposure (lower risk-of-bias studies; presented as adjusted OR)



Interactive figure and additional study details in HAWC [here](#). For Xiang *et al.* (2011), there was a significant linear trend across different levels of serum fluoride for IQ score < 80 ($p < 0.001$). For Yu *et al.* (2018), significance levels by IQ score were not reported.

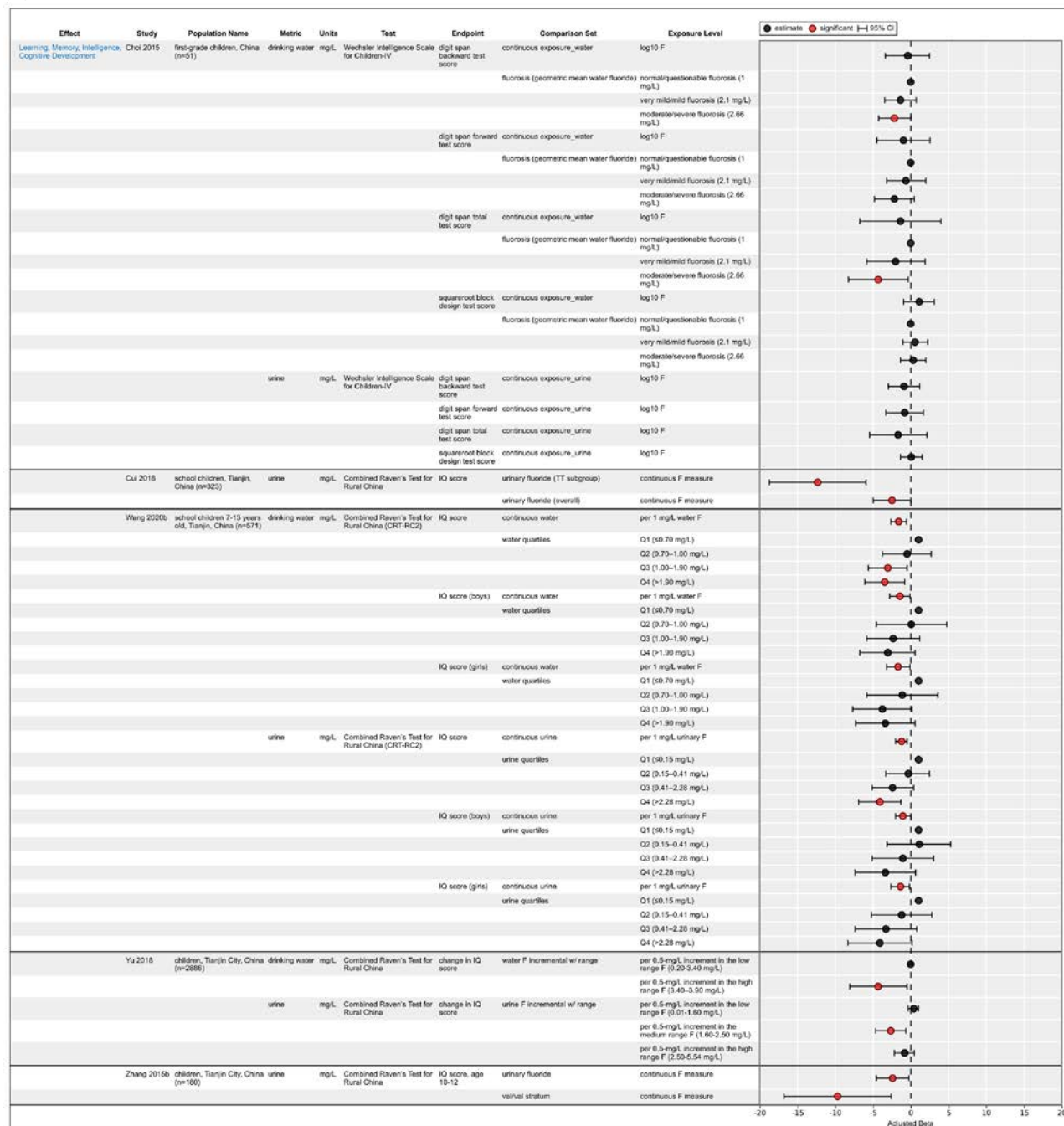
Figure D6. Correlations between IQ Score and Fluoride Exposure in Children (lower risk-of-bias studies; presented as coefficient)



Interactive figure and additional study details in HAWC [here](#). "F" represents fluoride. For Saxena *et al.* (2012), a significant relationship between water fluoride level and intelligence grade was observed. Increasing intelligence grades reflected increasing levels of impairment (reduced intelligence) in children. Zhao *et al.* (2020) and Zhou *et al.* (2019) also had correlations, but these were based on a subsample of the Yu *et al.* (2018) study (which presented betas and provided a better representation of the IQ data).

Figure D7. Correlations between IQ Score and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted beta)—(a) China; (b) all other areas

(a)



(b)

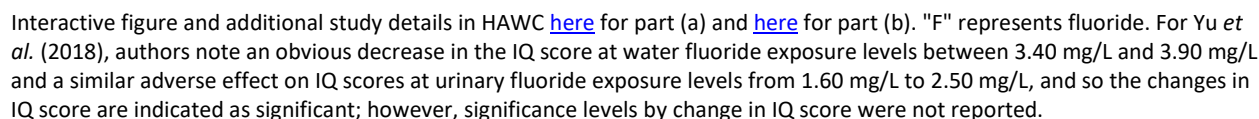
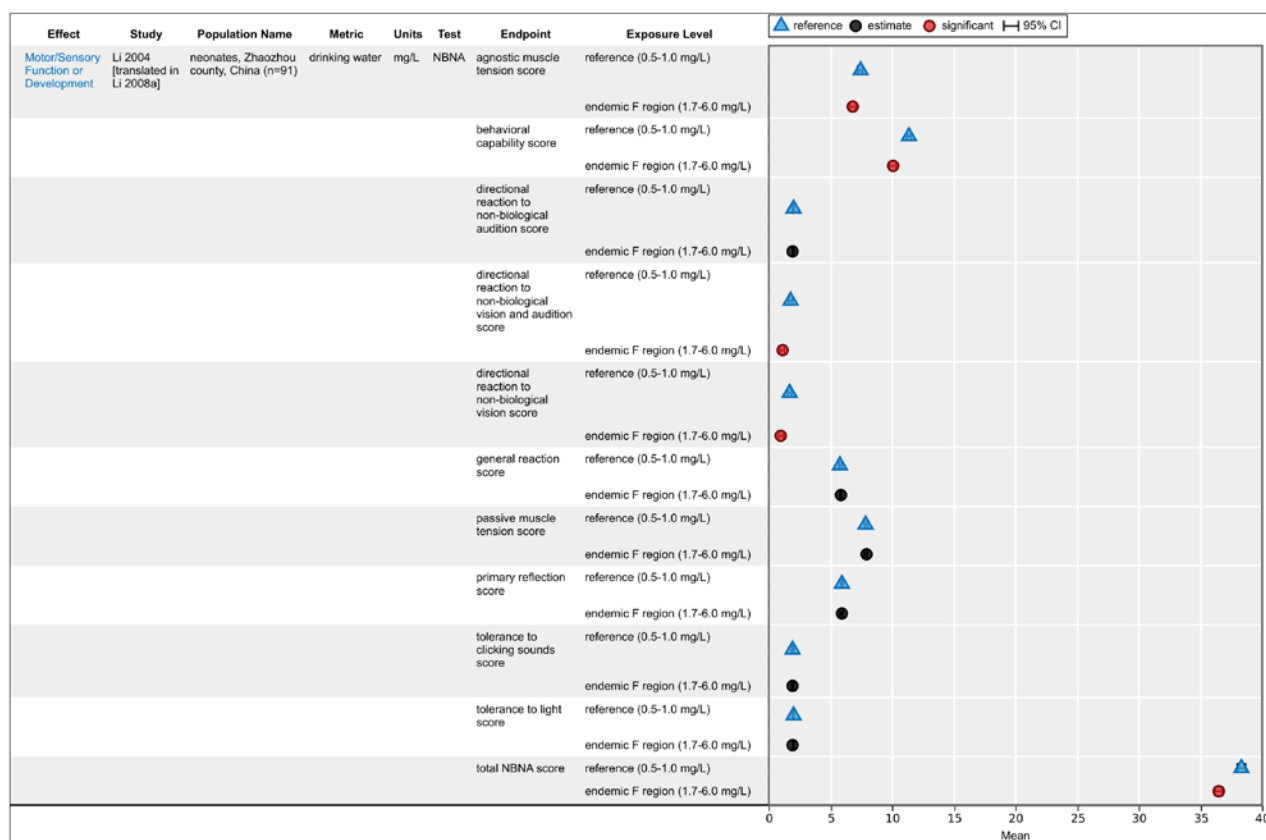
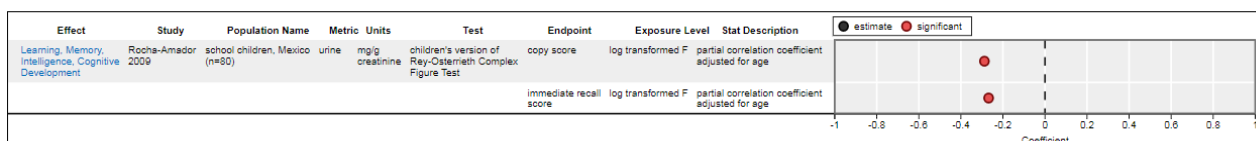


Figure D8. Mean Motor/Sensory Scores in Children by Fluoride Exposure (lower risk-of-bias studies)



Interactive figure and additional study details in HAWC [here](#). "F" represents fluoride. 95% CIs are small and are within figure symbols and may be difficult to see. Values for SDs and 95% CIs can be viewed in HAWC by clicking the data points within the plot area.

Figure D9. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk-of-bias studies; presented as coefficient)



Interactive figure and additional study details in HAWC [here](#). "F" represents fluoride.

Figure D10. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted beta)

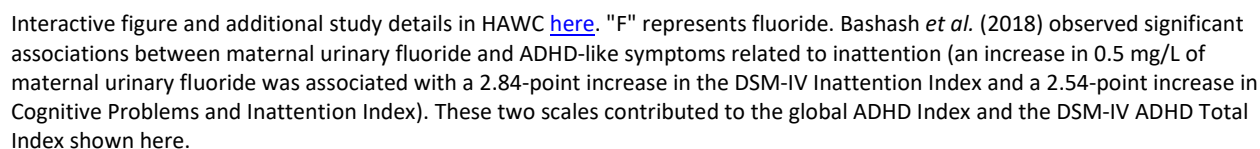
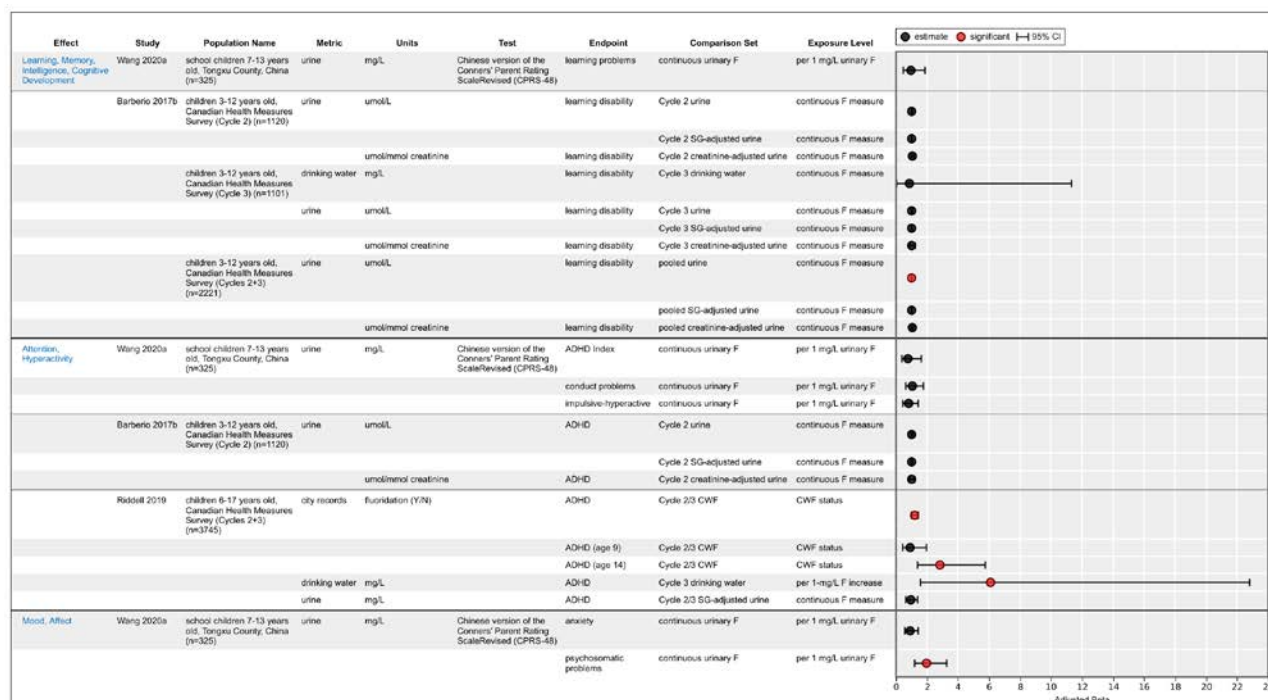
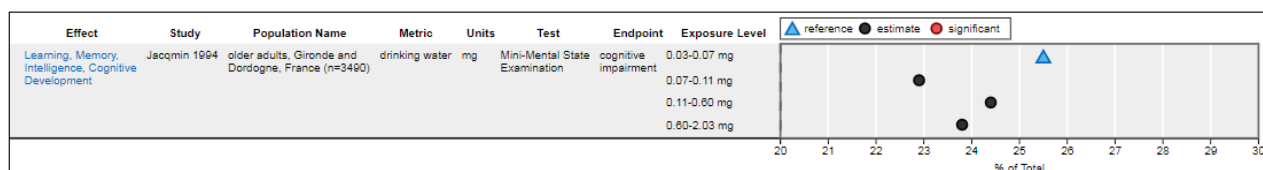


Figure D11. Correlations between Other Neurological Effects and Fluoride Exposure in Children (lower risk-of-bias studies; presented as adjusted OR)



Interactive figure and additional study details in HAWC [here](#). "F" represents fluoride. Drinking water results for Barberio *et al.* (2017b) have a large confidence interval and are not completely visible in the figure. 95% CIs are 0.068–11.33 and can be viewed in HAWC by clicking the OR within the plot area.

Figure D12. Cognitive Impairment in Adults by Fluoride Exposure (lower risk-of-bias studies; presented as % of total group)



Interactive figure and additional study details in HAWC [here](#). Results from Li *et al.* (2016) suggested that fluoride exposure may be a risk factor for cognitive impairment in elderly subjects; however, results from the study were not conducive to presentation in this visualization.

ABOUT THIS REVIEW

Sources of Support

National Institute of Environmental Health Sciences/Division of the National Toxicology Program

Contributors

Evaluation Team

The evaluation team is composed of federal staff and contractor staff support.

Name	Affiliation
Kyla Taylor, PhD	NIEHS/DNTP, Project Lead
John Bucher, PhD	NIEHS/DNTP
Andrew Rooney, PhD	NIEHS/DNTP
Vickie Walker	NIEHS/DNTP
Cynthia J. Willson, PhD, DVM, DACVP	ILS
Louise Assem, PhD	ICF ^f
Carlye A. Austin, PhD	ICF ^d
Robyn Blain, PhD	ICF ^{abcdefg}
Natalie Blanton, MPH	ICF ^a
Kristin Bornstein, PhD	ICF ^f
Camden Byrd	ICF ^a
Michelle Cawley	ICF ^c
Jonathan Cohen, PhD	ICF ^g
Ryan Cronk, PhD	ICF ^d
Sorina E. Eftim, PhD	ICF ^{fg}
Anna Engstrom, PhD	ICF ^{abcdf}
Jeremy S. Frye, MLS	ICF ^a
Kaitlin Geary	ICF ^c
Susan Goldhaber, MPH	ICF ^e
Ali Goldstone, MPH	ICF ^{fg}
Pamela Hartman, MEM	ICF ^{abceg}
Cara Henning, PhD	ICF ^a
Melinda Hoang, MPH	ICF ^d
Tao Hong	ICF ^{ef}
Jennifer Hsieh, MSPH	ICF ^f
Penelope Kellar	ICF ^a
Courtney Lemeris	ICF ^a
Cynthia J. Lin, PhD MSPH	ICF ^g
Alex Lindahl, MPH	ICF ^f
Kristen Magnuson, MESM	ICF ^{abcde}
Rachel McGill	ICF ^c
Shannon McGinnis, PhD	ICF ^d

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Name	Affiliation
William Mendez, PhD	ICF ^b
Whitney Mitchell	ICF ^a
Revathi Muralidharan	ICF ^{de}
Johanna Rochester, PhD	ICF ^{def}
Amanda Ross, MEd	ICF ^d
Pam Ross, MSPH	ICF ^{df}
Jennifer Seed, PhD	ICF ^{de}
Karen E. Setty, MESM, PhD	ICF ^d
Codi Sharp	ICF ^{de}
Robert Shin, MHS	ICF ^e
Kelly Shipkowski, PhD	ICF ^{df}
Christopher A. Sibrizzi, MPH	ICF ^{abcdefg}
Raquel A. Silva, PhD	ICF ^d
Samantha J. Snow, PhD, DABT	ICF ^{ef}
Parnian Soleymani, MS	ICF ^d
Anna Stamatogiannakis	ICF ^a
Nicole Vetter, MLS	ICF ^a
River Williams, BS	ICF ^c

Note: the roles of individual contractors differed: ^a indicates monograph development; ^b indicates review of data, results, and analyses; ^c indicates database and HAWC support; ^d indicates literature screening, ^e indicates data extraction, ^f indicates risk-of-bias assessment, ^g indicates meta-analysis

Peer Reviewers

The peer reviewers were outside experts selected for their experience with fluoride, developmental neurobehavioral toxicity, and systematic review procedures. Peer reviewers were screened for conflict of interest prior to their service and did not report any conflicts of interest. Service as a peer reviewer does not necessarily indicate that the reviewer endorses the final document.

Protocol Reviewers

Name	Affiliation
Joseph Braun, PhD ^a	Brown University
Marie Sutton, PhD ^a	Health Research Board
Thomas Zoeller, PhD ^a	University of Massachusetts, Amherst
Thomas Webster, PhD ^a	Boston University
Gail Wasserman, PhD ^a	Columbia University
Suril Mehta, MPH ^b	NIEHS
Tianjing Li, PhD ^b	University of Colorado Denver

^a Reviewer of the systematic review protocol; ^b Reviewer of meta-analysis protocol
no conflicts of interest declared

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Technical Review of Draft Monograph

Name	Affiliation
Freya Kamal, PhD	NIEHS (retired)

no conflicts of interest declared

Protocol History and Revisions

Date	Activity or revision
December 14, 2016	Draft evaluation protocol reviewed: sent to technical advisors for peer review
April 10, 2017	Draft human risk-of-bias protocol reviewed; sent to technical advisors for peer review
May 2, 2017	Draft animal risk-of-bias protocol reviewed; sent to technical advisors for peer review
June 2017	Evaluation protocol finalized: Review protocol finalized for use and posting
May 2019	Revised protocol: Revised review protocol posted
September 2020	Revised protocol: Revised review protocol posted

APPENDICES

Appendix 1. Literature Search Strategy

The strategy for this search is broad for the consideration of neurodevelopmental or cognitive endpoints and comprehensive for fluoride as an exposure or treatment in order to ensure inclusion of relevant papers. The search terms for PubMed are provided below. The specific search strategies for other databases are available in the protocol (<https://ntp.niehs.nih.gov/go/785076>).

Database	Search Terms
PUBMED	((Fluorides[mh:noexp] OR fluorides, topical[mh] OR sodium fluoride[mh] OR Fluorosis, Dental[mh] OR fluorosis[tiab] OR fluorid*[tiab] OR flurid*[tiab] OR fluorin*[tiab] OR florin*[tiab]) NOT (18F[tiab] OR f-18[tiab] OR 19F[tiab] OR f-19[tiab] OR f-labeled[tiab] OR "fluorine-18"[tiab] OR "fluorine-19"[tiab] OR pet-scan[tiab] OR radioligand*[tiab])) AND ((Aryl Hydrocarbon Hydroxylases[mh] OR Aryl Hydrocarbon Receptor Nuclear Translocator[mh] OR Behavior and Behavior Mechanisms[mh] OR Gene Expression Regulation[mh] OR Glucuronosyltransferase[mh] OR Intelligence tests[mh] OR Malate Dehydrogenase[mh] OR Mediator Complex Subunit 1[mh] OR Mental disorders[mh] OR Mental processes[mh] OR Monocarboxylic Acid Transporters[mh] OR Myelin Basic Protein[mh] OR nervous system[mh] OR nervous system diseases[mh] OR nervous system physiological phenomena[mh] OR Neurogranin[mh] OR Oligodendroglia[mh] OR Peroxisome Proliferator-Activated Receptors[mh] OR Psychological Phenomena and Processes[mh] OR Receptors, thyroid hormone[mh] OR Receptors, thyrotropin[mh] OR Retinoid X Receptors[mh] OR thyroid diseases[mh] OR thyroid hormones[mh] OR Thyrotropin-releasing hormone[mh] OR Thyroxine-Binding Proteins[mh] OR Pregnane X Receptor[supplementary concept] OR thyroid-hormone-receptor interacting protein[supplementary concept] OR Constitutive androstane receptor[supplementary concept] OR Academic performance[tiab] OR auditory[tiab] OR cortical[tiab] OR delayed development[tiab] OR developmental impairment[tiab] OR developmental-delay*[tiab] OR developmental-disorder*[tiab] OR euthyroid[tiab] OR gait[tiab] OR glia*[tiab] OR gliogenesis[tiab] OR hyperactiv*[tiab] OR impulse-control[tiab] OR iodide peroxidase[tiab] OR IQ[tiab] OR ischemi*[tiab] OR locomotor[tiab] OR mental deficiency[tiab] OR mental development[tiab] OR mental illness[tiab] OR mental-deficit[tiab] OR mobility[tiab] OR mood[tiab] OR morris-maze[tiab] OR morris-water[tiab] OR motor abilit*[tiab] OR Motor activities[tiab] OR motor performance[tiab] OR nerve[tiab] OR neural[tiab] OR neurobehav*[tiab] OR Neurocognitive impairment[tiab] OR neurodegenerat*[tiab] OR Neurodevelopment*[tiab] OR neurodisease*[tiab] OR neurologic*[tiab] OR neuromuscular[tiab] OR neuron*[tiab] OR neuropath*[tiab] OR obsessive compulsive[tiab] OR OCD[tiab] OR olfaction[tiab] OR olfactory[tiab] OR open-field-test[tiab] OR passive avoidance[tiab] OR plasticity[tiab] OR senil*[tiab] OR sociab*[tiab] OR speech*[tiab] OR spelling[tiab] OR stereotypic-movement*[tiab] OR synap*[tiab] OR tauopath*[tiab] OR Thyroglobulin[tiab] OR Thyroid disease*[tiab] OR thyroid gland[tiab] OR thyroid hormone*[tiab] OR thyronine*[tiab] OR visual motor[tiab] OR Visuospatial processing[tiab] OR water maze[tiab]) OR ((active-avoidance[tiab] OR ADHD[tiab] OR alzheimer*[tiab] OR amygdala[tiab] OR antisocial[tiab] OR anxiety[tiab] OR anxious[tiab] OR asperger*[tiab] OR attention deficit[tiab] OR autism[tiab] OR autistic[tiab] OR behavioral[tiab] OR behaviors[tiab] OR behavioural[tiab] OR behaviours[tiab] OR bipolar[tiab] OR cerebellum[tiab] OR cognition[tiab] OR cognitive[tiab] OR communication-disorder*[tiab] OR comprehension[tiab] OR cranial[tiab] OR dementia[tiab] OR dendrit*[tiab] OR dentate-gyrus[tiab] OR depression[tiab] OR dextrothyroxine[tiab] OR diiodothyronine*[tiab] OR diiodotyrosine[tiab] OR down syndrome[tiab] OR dyslexia[tiab] OR entorhinal cortex[tiab] OR epilep*[tiab] OR gangli*[tiab] OR goiter[tiab] OR graves-disease[tiab] OR hearing[tiab] OR hippocamp*[tiab] OR human development[tiab] OR hyperthyroid*[tiab] OR hypothalam*[tiab] OR hypothyroid*[tiab] OR impulsiv*[tiab] OR Intellectual

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Database	Search Terms
	disability[tiab] OR intelligence[tiab] OR language[tiab] OR learning[tiab] OR lewy bod*[tiab] OR long-term potentiation[tiab] OR long-term synaptic depression[tiab] OR memory[tiab] OR mental disorder*[tiab] OR mental recall[tiab] OR moniodotyrosine[tiab] OR Motor activity[tiab] OR motor skill*[tiab] OR multiple sclerosis[tiab] OR myxedema[tiab] OR Nervous system[tiab] OR nervous-system[tiab] OR neurit*[tiab] OR optic[tiab] OR palsy[tiab] OR panic[tiab] OR parahippocamp*[tiab] OR paranoia[tiab] OR paranoid[tiab] OR parkinson*[tiab] OR perception[tiab] OR perforant*[tiab] OR personality[tiab] OR phobia[tiab] OR problem solving[tiab] OR proprioception[tiab] OR psychomotor[tiab] OR reflex[tiab] OR risk taking[tiab] OR schizophrenia[tiab] OR seizure*[tiab] OR sensation*[tiab] OR sleep[tiab] OR smell[tiab] OR spatial behavior[tiab] OR stroke[tiab] OR substantia-nigra[tiab] OR taste[tiab] OR thyroiditis[tiab] OR thyrotoxicosis[tiab] OR Thyrotropin[tiab] OR thyroxine[tiab] OR triiodothyronine[tiab] OR vision[tiab]) NOT medline[sb]))

Appendix 2. List of Included Studies

Studies in Humans

As described in [Figure 4](#), 159 human studies were included; however, full data extraction was only conducted on studies with neurological outcomes or thyroid hormone data. Data extraction was completed using HAWC. Data were extracted from a subset of included studies in humans (n = 116) and are available in HAWC based on outcome. The following lists of references are organized as studies that are available in HAWC followed by studies that are not available in HAWC. Specifically, data for primary neurodevelopmental or cognitive outcomes (learning, memory, and intelligence) and secondary neurobehavioral outcomes (anxiety, aggression, motor activity, or biochemical changes), as well as thyroid hormone level data, were extracted from included human studies and are available in HAWC. Data for included studies identified through the 2020 literature search update were only extracted for primary neurodevelopmental or cognitive outcomes; a subset of these studies (n = 5) also included secondary neurobehavioral outcomes and/or thyroid hormone level data that were not extracted because those data would not materially advance the human or mechanistic findings. Included human studies that only evaluated other thyroid-related effects such as goiters or thyroid size (n = 43) were not extracted and are not available in HAWC. The list below presents the 159 human studies that were included in the review. An overview of the screening results is outlined in the study selection diagram ([Figure 4](#)) that reports numbers of included studies as well as numbers of studies excluded for each reason at the full text review stage.

Studies Available in HAWC

- An J, Mei S, Liu A, Fu Y, Wang C. 1992. [Effect of high level of fluoride on children's intelligence]. *Chin J Control Endem Dis* 7(2): 93-94.
- Aravind A, Dhanya RS, Narayan A, Sam G, Adarsh VJ, Kiran M. 2016. Effect of fluoridated water on intelligence in 10-12-year-old school children. *J Int Soc Prev Community Dent* 6(Suppl 3): S237-S242.
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- Ding Y, Sun H, Han H, Wang W, Ji X, Liu X, Sun D. 2011. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. *J Hazard Mater* 186: 1942-1946.
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Studies in Non-human Animals

As described in [Figure 4](#), 339 non-human mammal studies were included; however, full data extraction was only conducted on studies with primary neurological outcomes and/or secondary functional neurological outcomes (e.g., motor activity). Data extraction was completed using HAWC. Data were extracted from a subset of included studies in animals (n = 123) and are available in HAWC based on outcome. The following lists of references are organized as studies that are available in HAWC followed by studies that are not available in HAWC. Specifically, all primary outcomes and functional neurological secondary outcomes (e.g., motor activity) were extracted from animal studies and are available in HAWC, including studies from the NTP (2016) assessment. Studies are also available in HAWC that evaluated mechanistic effects related to oral fluoride exposure at or below 20 ppm fluoride drinking water equivalents for categories of mechanistic endpoints with the largest amount of available data (i.e., biochemistry of the brain or neurons, neurotransmission, oxidative stress, and histopathology [n = 70]); however, these mechanistic data were generally not extracted. Several animal studies assessed primary neurological outcomes and/or functional neurological secondary outcomes and mechanistic effects in the four mechanistic categories listed above (n = 56). In total, 140 animal studies are available in HAWC (70 with primary neurological outcomes and/or secondary functional neurological outcomes without relevant mechanistic data; 15 with relevant mechanistic data only; and 55 with primary/or secondary functional neurological outcomes with relevant mechanistic data). Studies that evaluated other mechanistic endpoints, as well as studies that only assessed mechanistic effects at fluoride levels above 20 ppm fluoride drinking water equivalents, are not available in HAWC (n = 199). The list below presents the 339 non-human animal studies that were included in the review. An overview of the screening results is outlined in the study selection diagram ([Figure 4](#)) that reports numbers of included studies as well as numbers of studies excluded for each reason at the full text review stage.

Studies Available in HAWC

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In Vitro Experimental Studies

As described in [Figure 4](#), 60 in vitro experimental studies were included; however, data extraction was not conducted on in vitro studies. Therefore, in vitro experimental studies are not available in HAWC with the exception of in vitro studies that also reported in vivo non-human animal data that meet the relevant criteria for being made available in HAWC. The following lists of references are organized as studies that are available in HAWC (n = 6) followed by studies that are not available in HAWC (n = 54).

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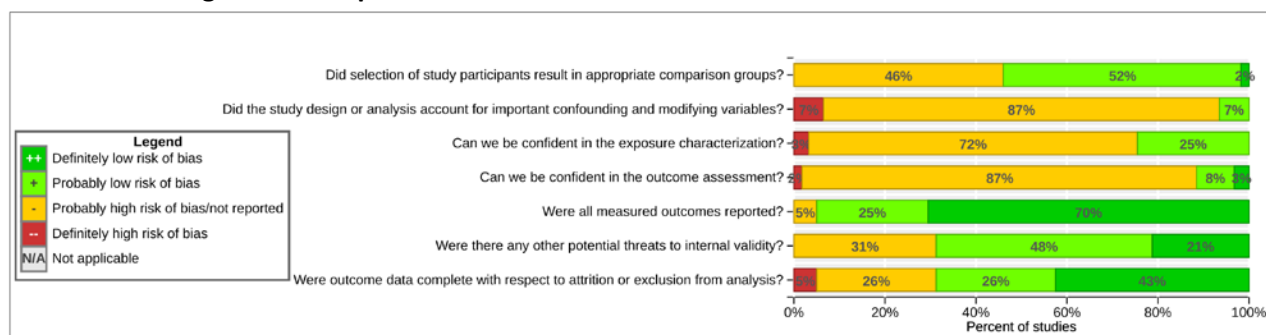
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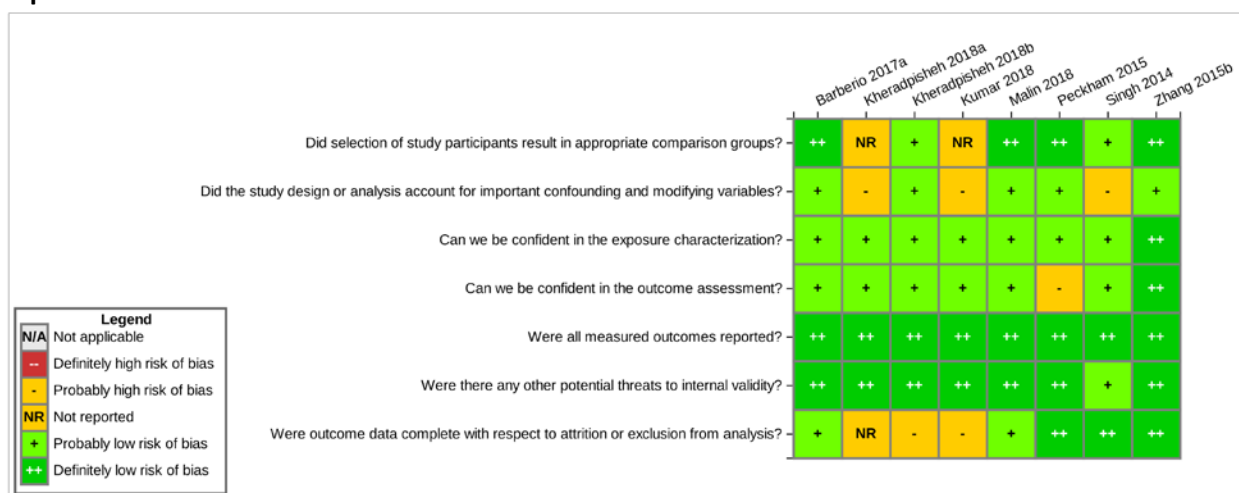
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- Zhao XL, Gao WH, Zhao ZL. 1994. [Effects of sodium fluoride on the activity of Ca²⁺Mg(2+)-ATPase in synaptic membrane in rat brain]. *Chin J Prev Med* 28: 264-266.

Figure A3-4. Risk-of-bias Bar Chart for Higher Risk-of-bias Human Neurodevelopmental or Cognitive Studies Following Fluoride Exposure



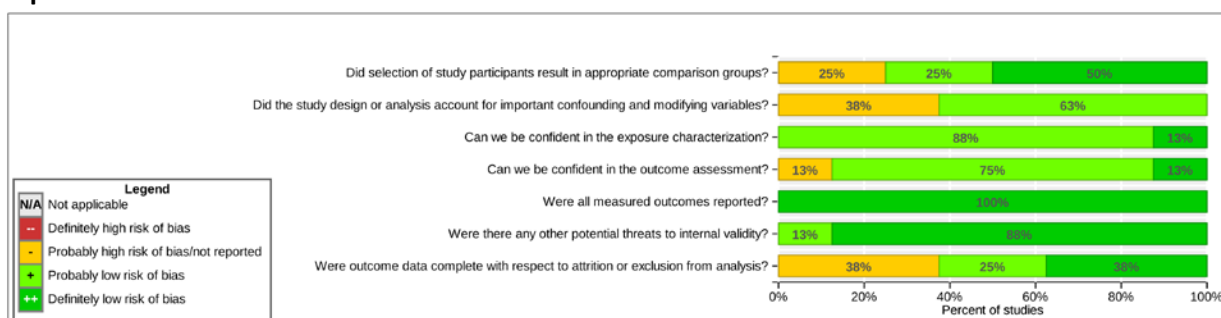
Interactive figure and additional study details in HAWC [here](#).

Figure A3-5. Risk-of-bias Heatmap for Lower Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure



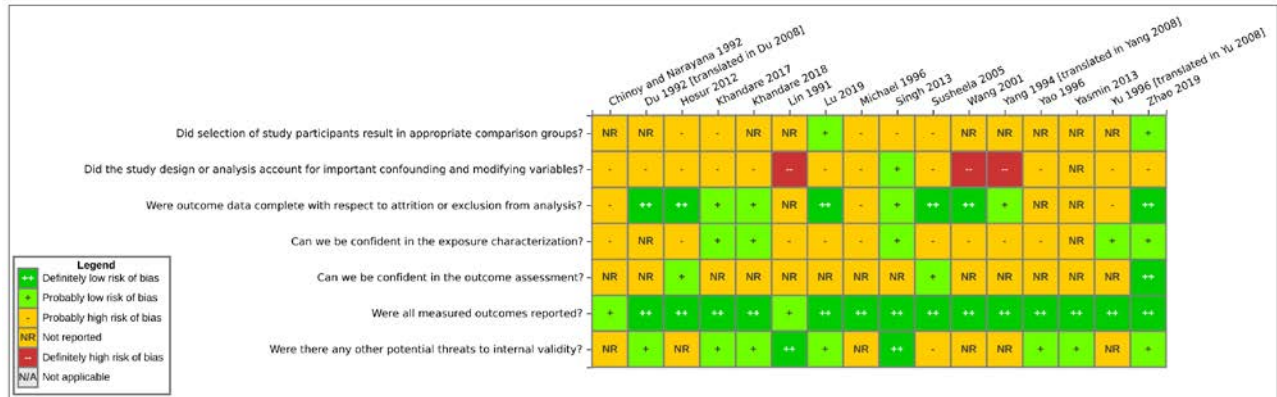
Interactive figure and additional study details in HAWC [here](#).

Figure A3-6. Risk-of-bias Bar Chart for Lower Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure



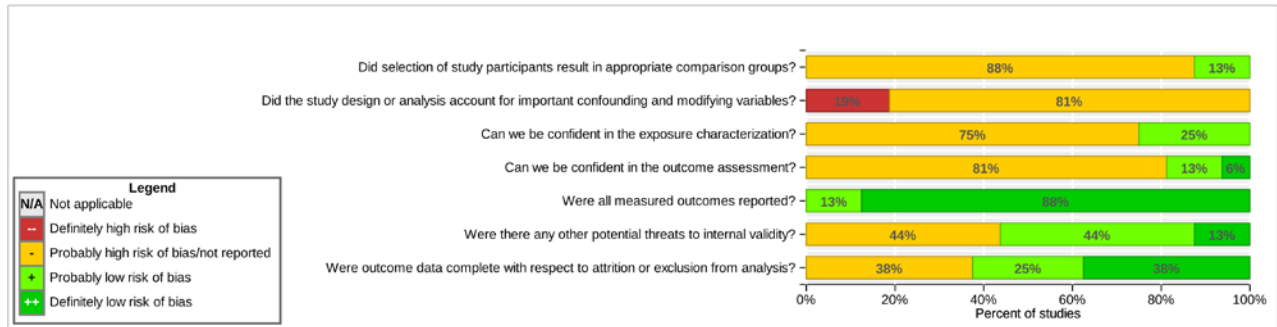
Interactive figure and additional study details in HAWC [here](#).

Figure A3-7. Risk-of-bias Heatmap for Higher Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

Figure A3-8. Risk-of-bias Bar Chart for Higher Risk-of-bias Human Mechanistic Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

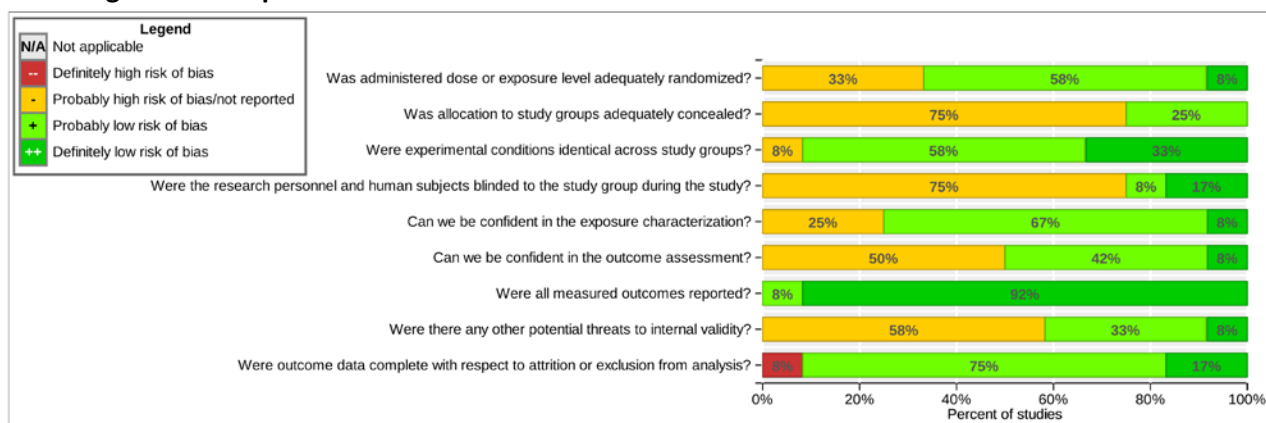
Studies in Non-human Animals

Figure A3-9. Risk-of-bias Heatmap for New Developmental Animal Learning and Memory Studies Following Fluoride Exposure



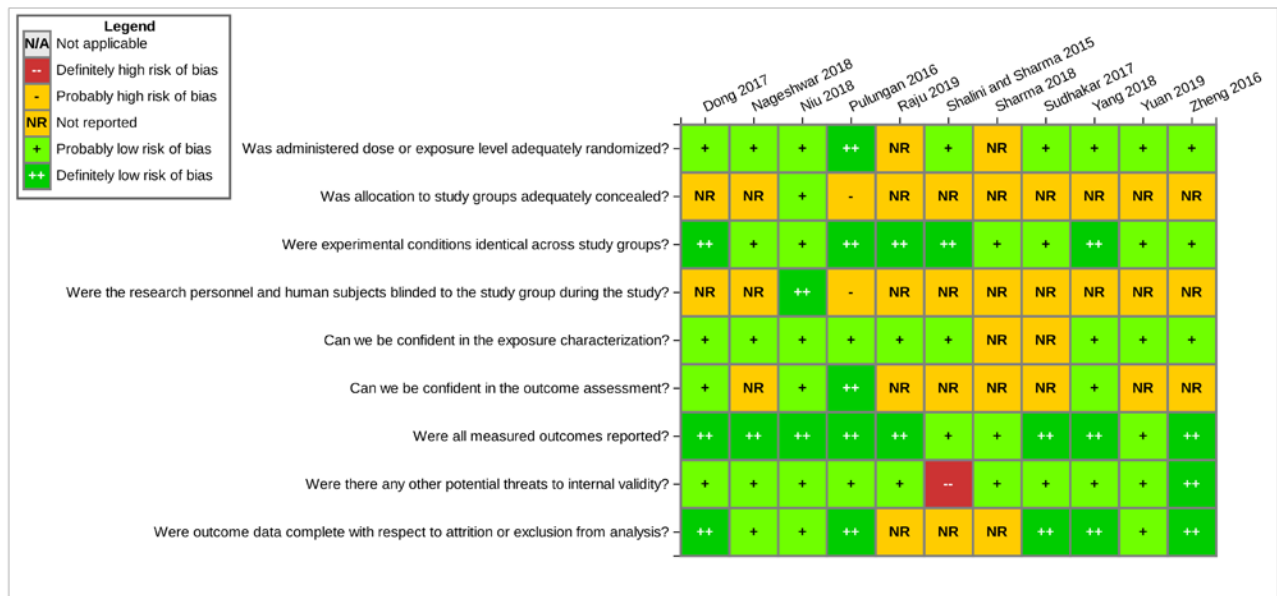
Interactive figure and additional study details in HAWC [here](#).

Figure A3-10. Risk-of-bias Bar Chart for New Developmental Animal Learning and Memory Studies Following Fluoride Exposure



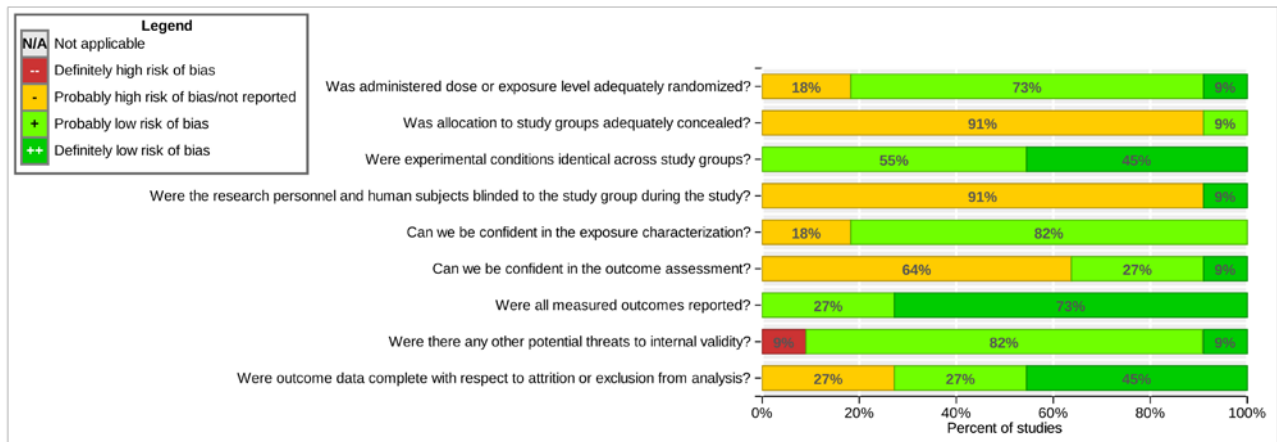
Interactive figure and additional study details in HAWC [here](#).

Figure A3-11. Risk-of-bias Heatmap for New Adult Animal Learning and Memory Studies Following Fluoride Exposure



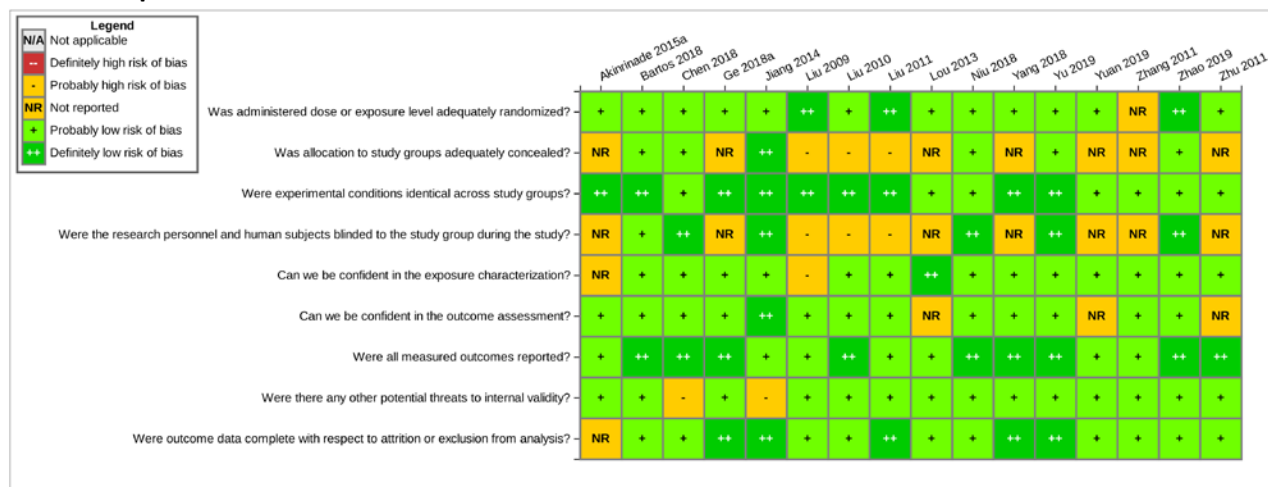
Interactive figure and additional study details in HAWC [here](#).

Figure A3-12. Risk-of-bias Bar Chart for New Adult Animal Learning and Memory Studies Following Fluoride Exposure



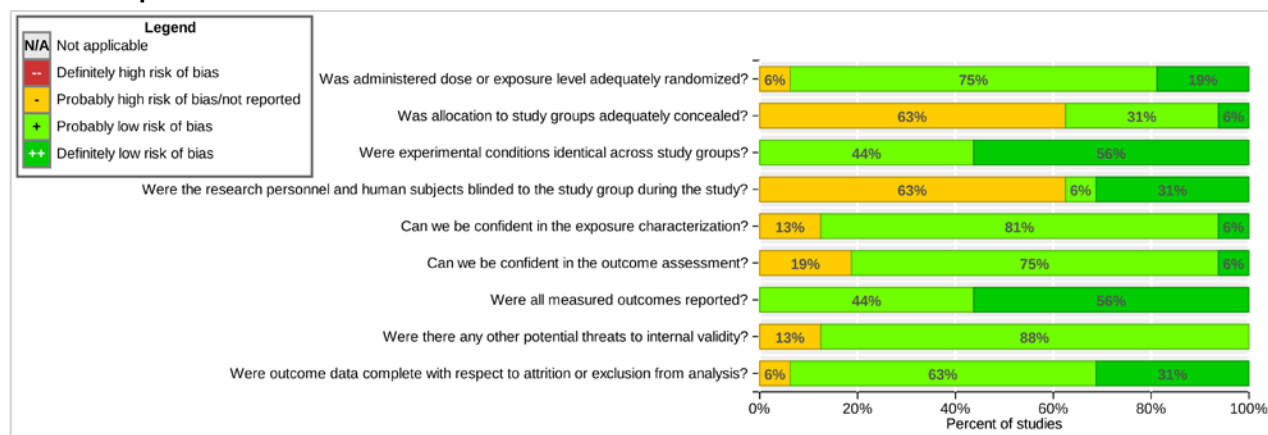
Interactive figure and additional study details in HAWC [here](#).

Figure A3-13. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure



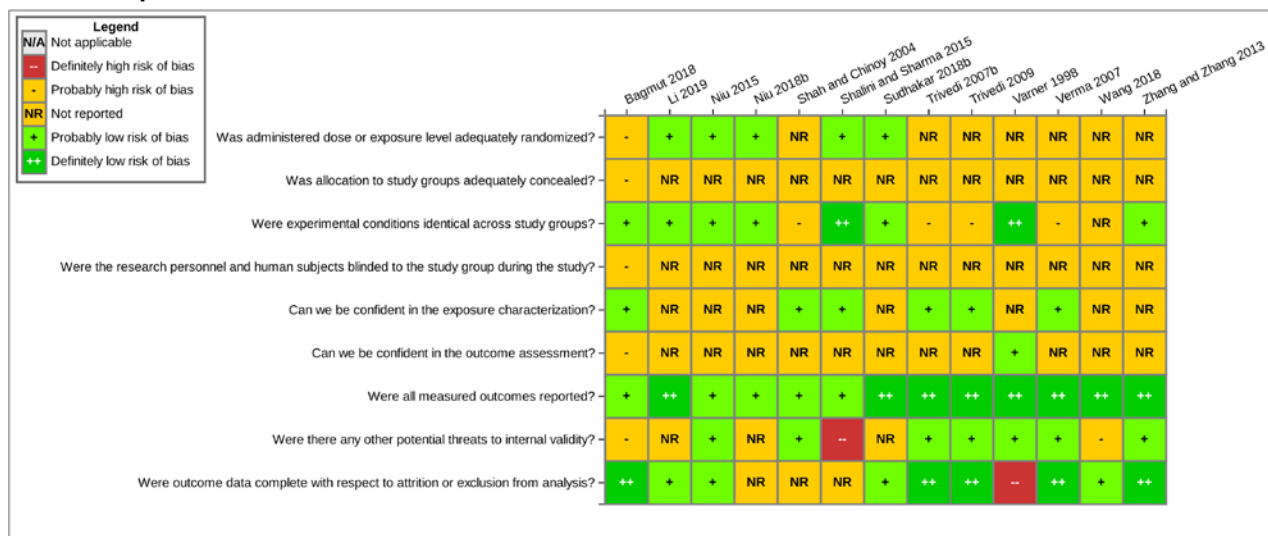
Interactive figure and additional study details in HAWC [here](#).

Figure A3-14. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure



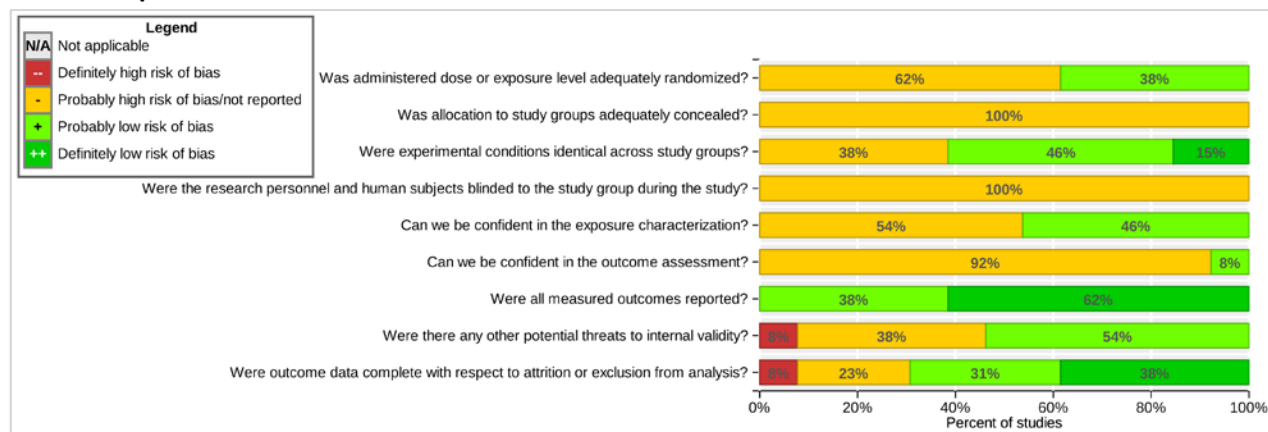
Interactive figure and additional study details in HAWC [here](#).

Figure A3-15. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure



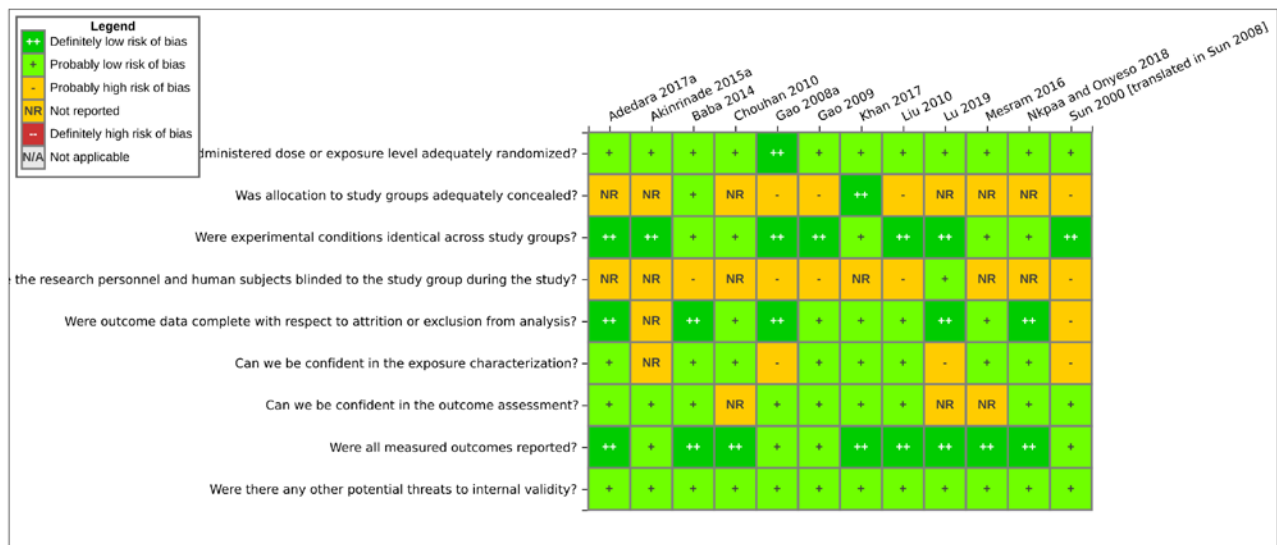
Interactive figure and additional study details in HAWC [here](#).

Figure A3-16. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Biochemical Studies Following Fluoride Exposure



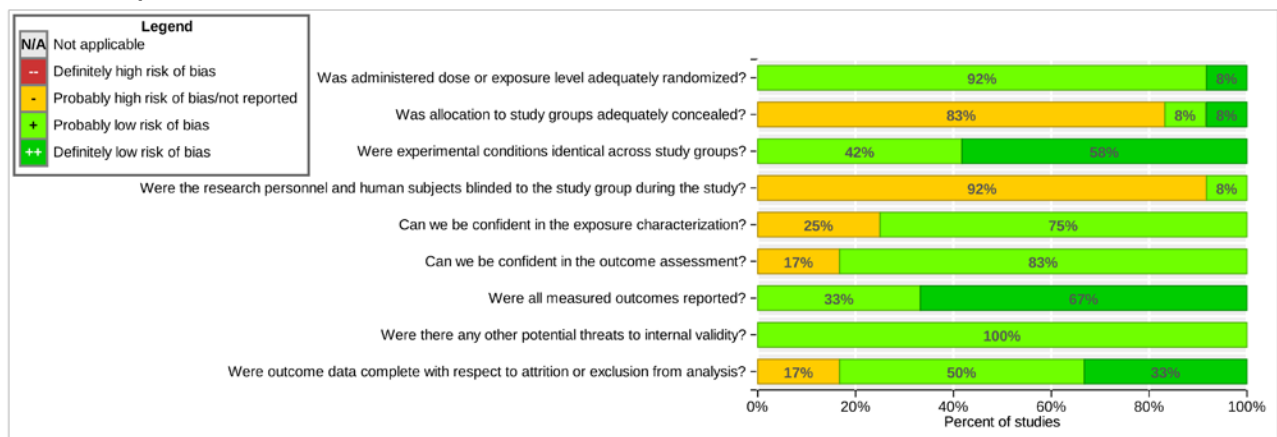
Interactive figure and additional study details in HAWC [here](#).

Figure A3-17. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

Figure A3-18. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure



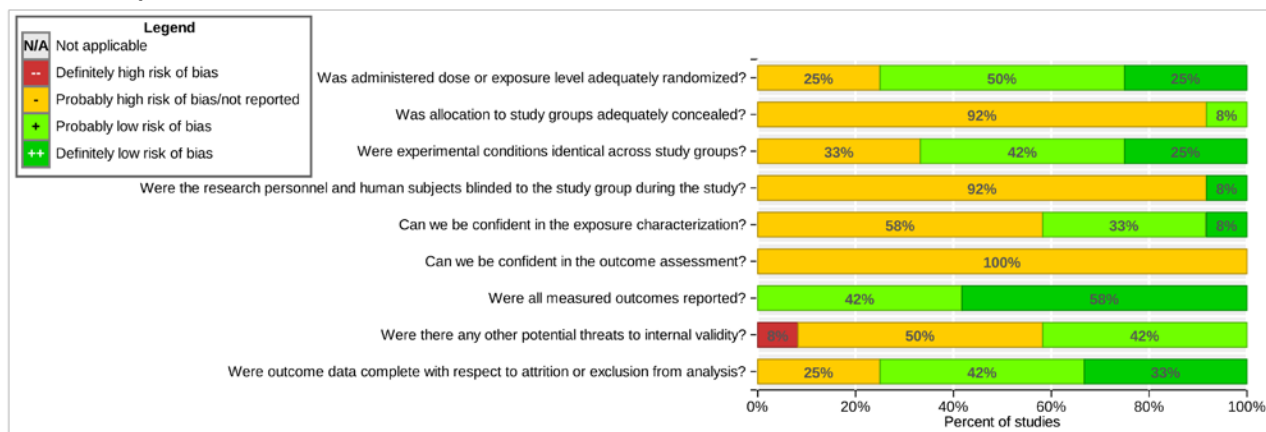
Interactive figure and additional study details in HAWC [here](#).

Figure A3-19. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure



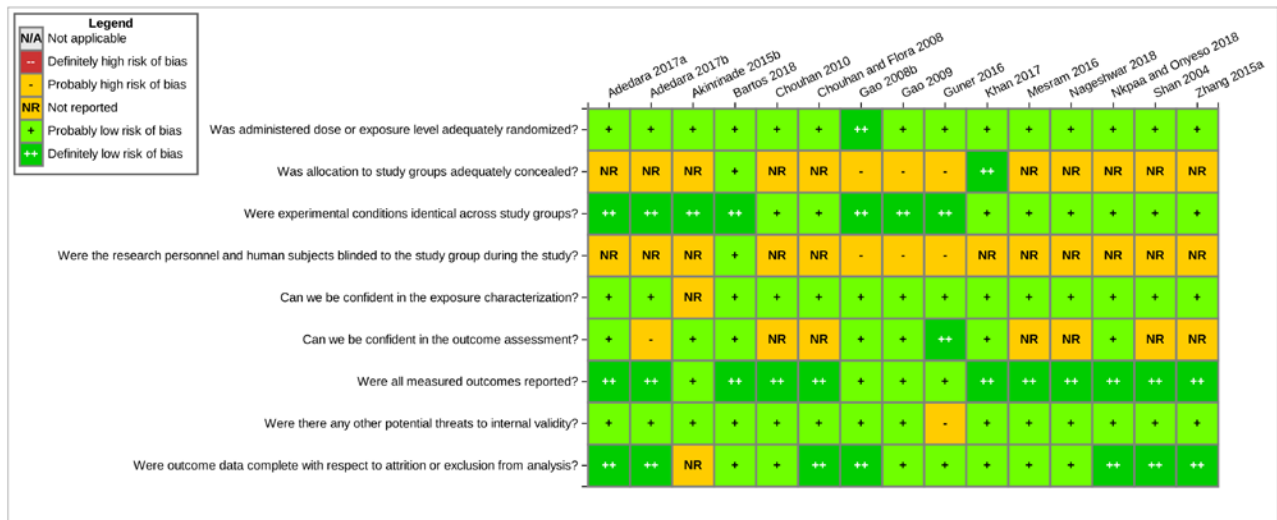
Interactive figure and additional study details in HAWC [here](#).

Figure A3-20. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Neurotransmission Studies Following Fluoride Exposure



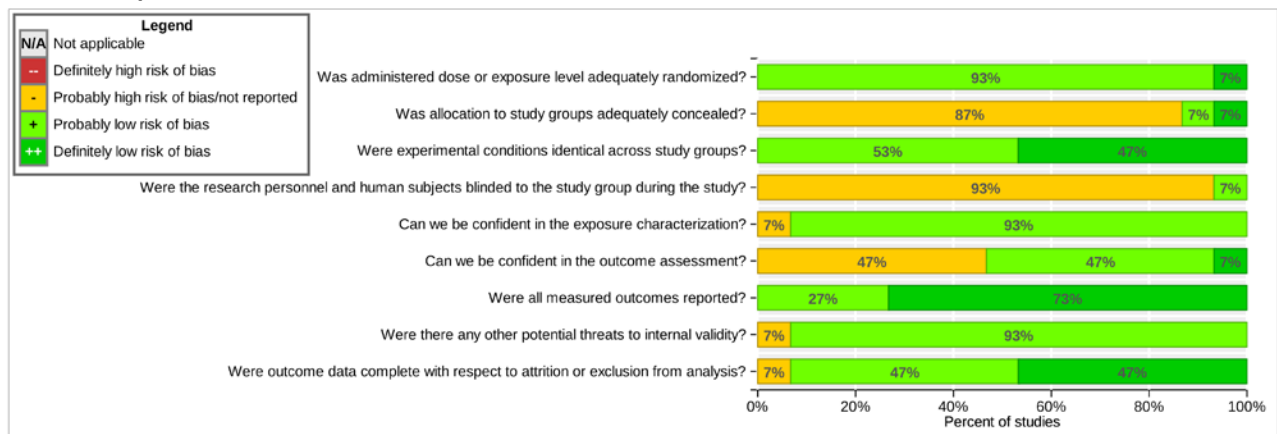
Interactive figure and additional study details in HAWC [here](#).

Figure A3-21. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

Figure A3-22. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure



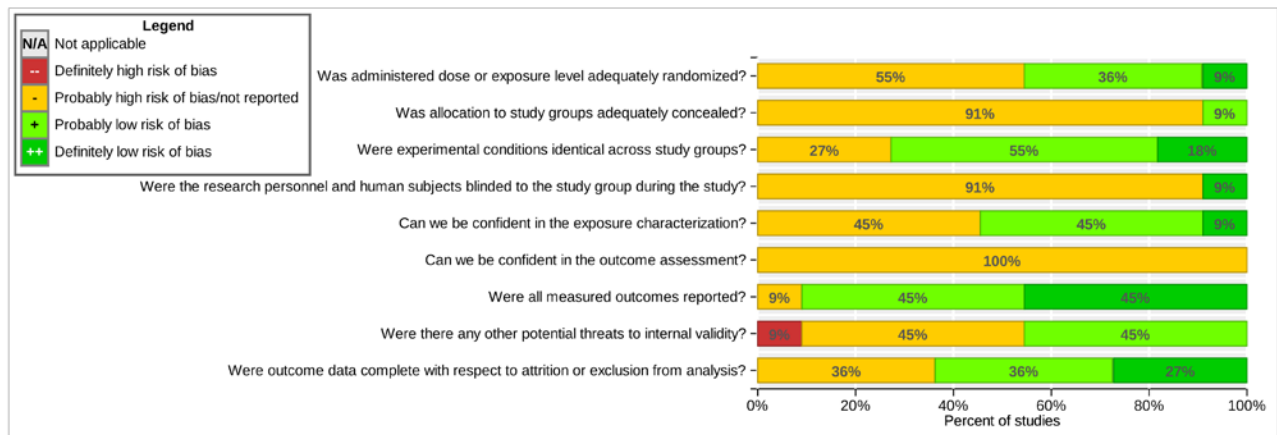
Interactive figure and additional study details in HAWC [here](#).

Figure A3-23. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure



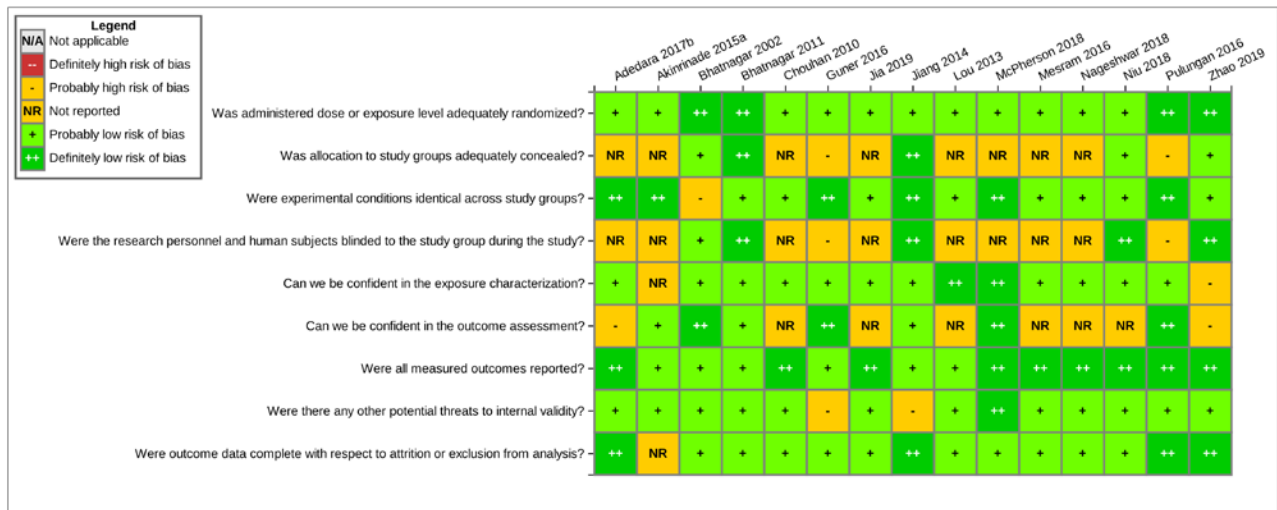
Interactive figure and additional study details in HAWC [here](#).

Figure A3-24. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Oxidative Stress Studies Following Fluoride Exposure



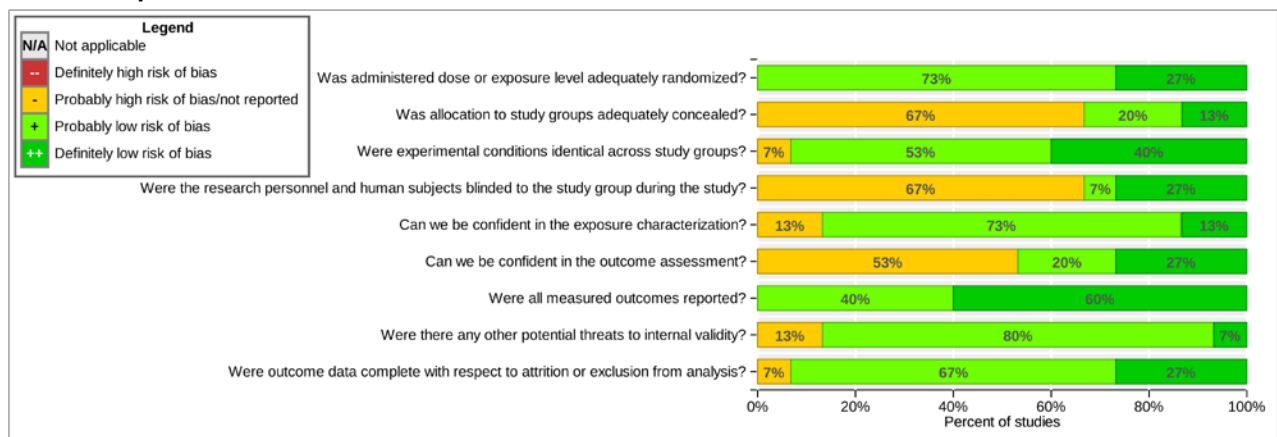
Interactive figure and additional study details in HAWC [here](#).

Figure A3-25. Risk-of-bias Heatmap for Lower Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure



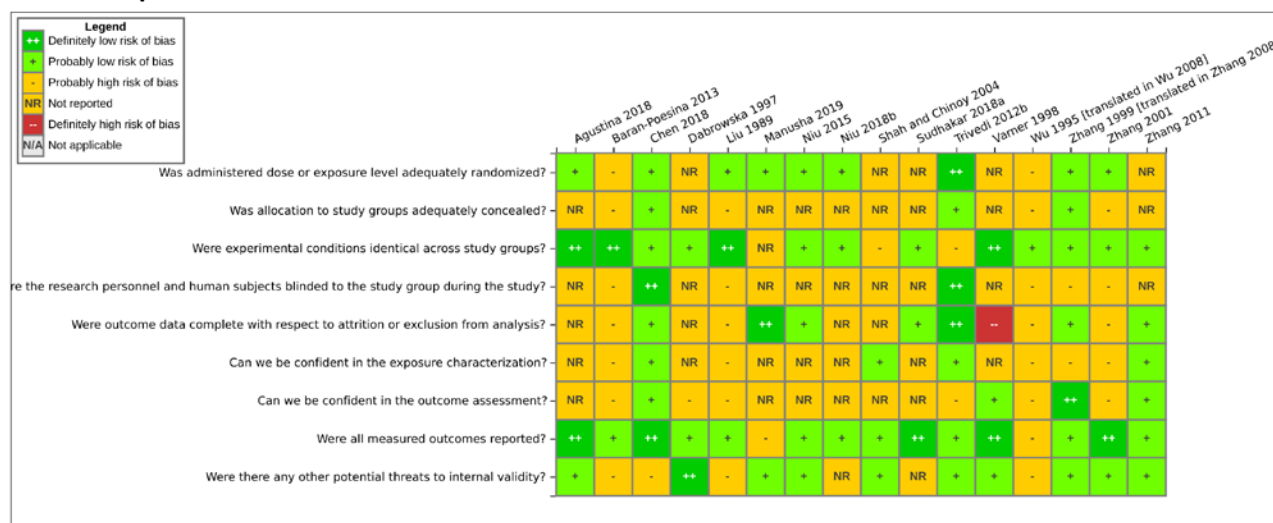
Interactive figure and additional study details in HAWC [here](#).

Figure A3-26. Risk-of-bias Bar Chart for Lower Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure



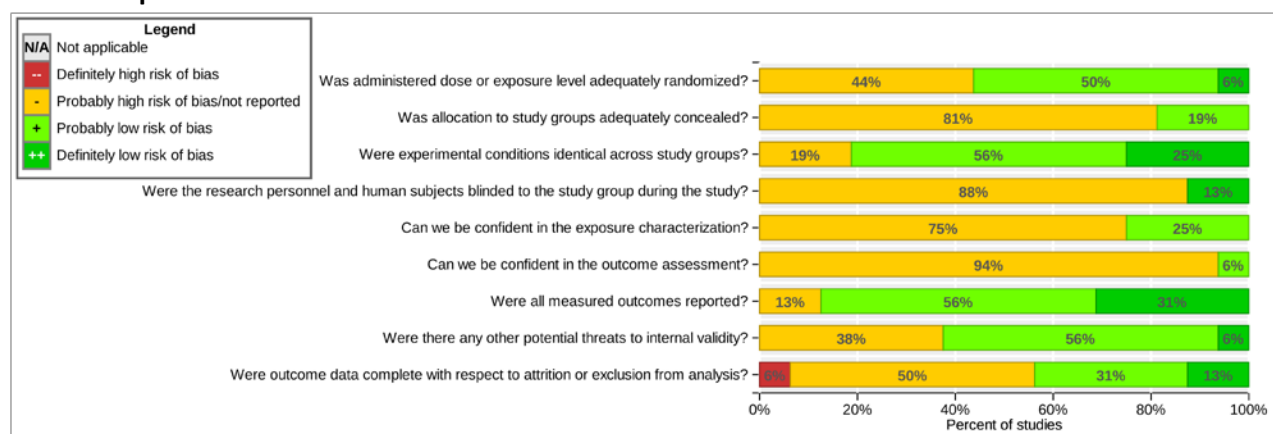
Interactive figure and additional study details in HAWC [here](#).

Figure A3-27. Risk-of-bias Heatmap for Higher Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

Figure A3-28. Risk-of-bias Bar Chart for Higher Risk-of-bias Animal Histopathology Studies Following Fluoride Exposure



Interactive figure and additional study details in HAWC [here](#).

Appendix 4. Details for Lower Risk-of-bias Studies

Barberio *et al.* (2017b)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Canadian Health Measures Survey (cycles 2 and 3) participants (children aged 3–12 years)
- **Study area:** general population of Canada
- **Sample size:** 2,221 children (1,120 from Cycle 2, 1,101 from Cycle 3)
- **Data relevant to the review:** Associations between learning disability or ADHD (Cycle 2 only) assessed by parent or child self-report and urinary fluoride.
- **Reported association with fluoride exposure:** Yes: Significant increase in adjusted OR for learning disability with unadjusted urinary fluoride (1.02; 95% CI: 1.00, 1.03) when Cycle 2 and 3 were combined. No significant associations with urinary fluoride when adjusted for creatinine and/or specific gravity. No significant association between urinary fluoride and ADHD.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** The comparison groups were selected from Cycles 2 and 3 of the Canadian Health Measures Survey. This is a nationally representative sample of residents living in 10 provinces, with clear exclusion criteria provided. Exclusion only represented about 4% of the target population (all Canadian residents 3–79 years old living in 10 provinces). A table of characteristics of the study population is provided.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the subjects were recruited from the same population using the same methods during the same time frame and exposure groups were similar.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The study adjusted for sex, age (3–12 years old), household education, and household income adequacy. Variables to discern fluoride source, including drinking water and dental products, were also considered. Cycle 2 data also included adjustments for: 1) children for whom tap water (vs. bottled or other) was the primary source of drinking water at home or away from home and 2) children who had lived in his or her current home for 3 or more years. Confounders such as parental behavioral and mental health disorders, smoking, and nutrition were not discussed. Co-exposure to lead and arsenic are less likely an issue in this population and the lack of information is not considered to appreciably bias the results.
 - **Potentially important study-specific confounders:** All key confounders were considered in this study.
 - **Direction/magnitude of effect:** Not applicable.

- **Basis for rating:** Probably low risk of bias based on direct evidence that key confounders were addressed and indirect evidence that the methods used to collect the information were valid and reliable and that co-exposures were not an issue.
- **Attrition:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Covariate data were missing for less than 5% of all analyses, apart from household income; household income was reported for only 71–77% of participants and was imputed for the remainder.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Estimates of urinary fluoride ($\mu\text{mol/L}$) from spot urine were available for a subsample of respondents. Analysis was performed under standardized operating procedures at the Human Toxicology Laboratory of the Institut National de Santé Publique du Québec (accredited under ISO 17025). Fluoride content of urine samples was analyzed using an Orion pH meter with a fluoride ion-selective electrode with limits of detection of 20 $\mu\text{g/L}$ (Cycle 2) and 10 $\mu\text{g/L}$ (Cycle 3). Urinary dilution was addressed by using creatinine-adjusted levels as well as specific gravity-adjusted levels. In Cycle 3 only, estimates of the fluoride concentration of tap water samples collected from randomly selected households were available. The subsample of households selected for tap water sample collection corresponded to the person-level urine fluoride subsample. Analysis of the fluoride concentration of tap water was performed using a basic anion exchange chromatography procedure, with a limit of detection of 0.006 mg/L . QC methods were not addressed.
 - **Direction/magnitude of effect:** There is not any specific direction or magnitude of bias expected. Urinary fluoride levels are reflective of a recent exposure. Having a single concurrent measurement may not be reflective of the exposure associated with the outcome, but if subjects lived in the same area throughout life the exposure may be an adequate representation. Although there is possible exposure misclassification it would be non-differential.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - **Rating:** Probably high risk of bias (-)
 - **Summary:** The primary outcome variable, diagnosis of a learning disability by a health professional, was based on a single item from a household survey asked to all respondents: "Do you have a learning disability?". Answer options were: "yes", "no", "don't know", or the participant refused to answer. For Cycle 2, those who indicated having a learning disability were also asked what kind, with the answer options of: "ADD", "ADHD", "dyslexia", or "other". This question was omitted in Cycle 3 and the reason for omission is not described. Parents or guardians answered all questions for children aged 3–11 years, while children 12 years and older answered questions

themselves. The self-reporting of a learning disability did not appear to have been confirmed by medical records or a health professional. (- for methods based on self-report of diagnosis by a health care professional also in Cycle 3 no specific disabilities were described). Blinding was not a concern as spot urine samples were sent to a separate lab and self-reports would not have knowledge of their urine or tap water exposure level (+ for blinding). Overall rating = -.

- o **Basis for rating:** Probably high risk of bias based on indirect evidence that the outcome was measured using an insensitive method in the study population.
- **Selective Reporting:**
 - o **Rating:** Definitely low risk of bias (++)
 - o **Summary:** All outcomes outlined in the abstract, introduction, and methods sections were reported in sufficient detail.
 - o **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - o **Rating:** Definitely low risk of bias (++)
 - o **Summary:**
 - *Statistical analyses:* Statistical analyses were appropriate for the study.
 - *Other potential concerns:* None identified.
 - o **Basis for rating:** Definitely low risk if bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding and exposure. Study strengths include individual exposure measurements and the addressing of potential key confounders but was limited by the cross-sectional study design and insensitive outcome measures.

Bashash et al. (2017)

Study Details:

- **Study design:** Prospective cohort
- **Population:** Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) participants (pregnant mothers and their children aged 4 or 6–12 years).
- **Study area:** Mexico City, Mexico
- **Sample size:** 299 mother–child pairs, of whom 287 and 211 had data for the general cognitive index (GCI) and IQ analyses, respectively.
- **Data relevant to the review:** Adjusted and unadjusted associations between GCI or IQ scores and maternal or child’s urinary fluoride concentrations.
- **Reported association with fluoride exposure:** Yes: Significant effect between maternal urinary fluoride and IQ score (adjusted $\beta = -2.50$; 95% CI: $-4.12, -0.59$) and GCI score (adjusted $\beta = -3.15$; 95% CI: $-5.42, -0.87$). No significant effects associated with children’s urine.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: Study participants were selected from two different cohorts from three hospitals in Mexico City that serve low-to-moderate income populations. One cohort was from an observational study of prenatal lead exposure and neurodevelopment outcomes and the other was from a randomized trial of the effect of calcium on maternal blood lead levels. The authors state that participants had no history of psychiatric disorders, high-risk pregnancies, gestational diabetes, illegal drug use, or continuous prescription drugs, but they do not include any information on smoking habits. Study populations appear to be similar, but there may be some differences because subjects were selected from two different cohorts that were recruited from slightly different time periods.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the exposure groups were similar despite the subjects coming from different original study populations where different methods were used for recruitment.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: Data were collected via questionnaire on maternal age, education, marital status at first prenatal visit, birth order, birth weight, gestational age at delivery, maternal smoking, maternal IQ, and HOME scores. All models were adjusted for gestational age at birth, child's sex, birth weight, birth order, child's age at testing, maternal marital status, smoking history, age at delivery, maternal IQ, education, and cohort, with additional testing for children's urinary fluoride, mercury, lead, and calcium. Sensitivity analyses additionally adjusted for HOME score. Confounders not considered included BMI, iodine deficiency, arsenic, and maternal mental health and nutrition. Arsenic is assumed not to be a potential co-exposure in this population as the study authors did not discuss it as an issue but did discuss other co-exposures. Arsenic may have been included in the water quality control program in Mexico City.
 - Potentially important study-specific confounders: All key confounders were addressed.
 - Direction/magnitude of effect: Not applicable.
 - Basis for rating: Probably low risk of bias based on direct evidence that key confounders including other potential co-exposures were addressed and indirect evidence that the methods used to collect the information were valid and reliable and that arsenic is not likely to be an issue in this study population.
- **Attrition:**
 - Rating: Probably low risk of bias (+)
 - Summary: Although there was a large amount of attrition, the study authors clearly describe all reasons for attrition and also provide characteristics to compare those participants included to those excluded. There were some slight differences between those included and those excluded, but there is nothing to indicate that the attrition would potentially bias the results.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Urinary fluoride concentrations were determined in spot urine samples (2nd morning void) collected from mothers (during at least one trimester) and children ages 6–12 years. Fluoride content was measured using ion-selective electrode-based assays. QC methods were described including between laboratory correlations. All samples were measured in duplicate. Extreme outliers were excluded. Urinary dilution was addressed by using creatinine-adjusted levels.
 - *Direction/magnitude of effect:* Not applicable.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Outcome was assessed using the McCarthy Scales of Children's Abilities (MSCA) in 4-year-old children (translated into Spanish) and the Wechsler Abbreviated Scale of Intelligence (WASI) in 6–12-year-olds. The WASI is a well-established test and the validity of both tests is well documented by the authors. Inter-examiner reliability was evaluated and reported with a correlation of 0.99 (++ for methods). The study report stated that psychologists were blind to the children's fluoride exposure (++ for blinding). Overall rating for methods and blinding = ++.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - *Statistical analyses:* Statistical analyses used were appropriate for the study.
 - *Other potential concerns:* None identified.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements, outcome blindly assessed, and the prospective cohort study design.

Bashash *et al.* (2018)

Study Details:

- **Study design:** Prospective cohort
- **Population:** ELEMENT participants (pregnant mothers and their children aged 6–12 years)
- **Study area:** Mexico City, Mexico
- **Sample size:** 210 mother–child pairs
- **Data relevant to the review:** Associations between ADHD and other attention/impulsivity scores and maternal urinary fluoride concentrations.
- **Reported association with fluoride exposure:** Yes: Significant associations between maternal urinary fluoride and Conners' Rating Scales-Revised (CRS-R) scores, including Cognitive Problems + Inattention Index (adjusted $\beta = 2.54$; 95% CI: 0.44, 4.63), DSM-IV Inattention Index (adjusted $\beta = 2.84$; 95% CI: 0.84, 4.84), DSM-IV ADHD Total Index (adjusted $\beta = 2.38$; 95% CI: 0.42, 4.34), and ADHD Index (adjusted $\beta = 2.47$; 95% CI: 0.43, 4.50).

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Participants were a subset of mother-child dyads enrolled in various longitudinal birth cohort studies of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) project. Subjects were included from two of the four cohorts for which maternal urinary samples were available. Participants in cohort 2A were recruited between 1997 and 1999, and participants in cohort 3 were recruited from 2001 to 2003. Inclusion and exclusion criteria were applied consistently across the two cohorts. A table of subject characteristics was provided in the study and any differences were considered in the analysis. Study populations appear to be similar, but there may be some differences because subjects were selected from two different cohorts: one from an observational study on prenatal lead exposure and the other from a randomized trial on the effects of calcium on blood lead levels. In addition, they were recruited from slightly different time periods.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposed groups were similar, and any differences were taken into account in the analysis.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Questionnaires were used to collect information on maternal age, maternal education, history of smoking, and marital status during the first pregnancy visit. Child information at birth included birth weight, sex, birth order, and gestational age as calculated by the nurse. Mothers also responded to an SES questionnaire during the visit when the psychometric tests were administered. The Home Observation for Measurement of the Environment (HOME) score was evaluated in a subset of participants. Covariates were selected a priori. Models adjusted for maternal age at

delivery, years of education, marital status, smoking history, gestational age at birth, age at outcome assessment, child's sex, birth order, SES, cohort, and calcium intervention.

- o Potentially important study-specific confounders: None identified, although this study did not specifically address arsenic or other co-exposures. Bashash *et al.* (2017) addressed potential co-exposure to lead and mercury but did not address arsenic. Arsenic was potentially addressed as part of the water quality program in Mexico City.
 - Direction/magnitude of effect: Not applicable.
- o Basis for rating: Probably low risk of bias based on direct evidence that key confounders were addressed and indirect evidence that the methods used to collect the information were valid and reliable and that arsenic and other potential co-exposures are not likely to be an issue in this study population.
- **Attrition:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Although there was a large amount of attrition from the original cohorts, it was unlikely related to outcome or exposure and there were very little missing data from those included in the study. Of the 231 mothers with a minimum of one maternal urine fluoride measurement and matching outcome identified for the project, only 17 were excluded based on incomplete demographic and outcome information.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: Mothers provided at least one spot urine sample during pregnancy. As described in Bashash *et al.* (2017), urinary concentrations were determined on second morning void. Fluoride content was measured using ion-selective electrode-based assay. Bashash *et al.* (2017) describes QC methods. All samples were measured in duplicate and extreme outliers were excluded. Urinary dilution was addressed by using creatinine-adjusted levels.
 - Direction/magnitude of effect: N/A
 - o Basis for rating: Definitely low risk of bias based on direct evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: Behaviors associated with ADHD were assessed using the Spanish version of the Conners' Rating Scales-Revised, which has been validated for the evaluation of ADHD. Mothers completed the CRS-R at the same follow-up visit that the child completed the CPT-II tests. All tests were applied under the supervision of an experienced psychologist (++) for methods); however, a limitation of the study noted by the authors was only using parent reports and not teacher reports as they can vary from one another. Blinding was not reported, but it is unlikely that the mothers were aware of their urinary fluoride levels. Although mothers may have had knowledge that they were receiving fluoride through fluoridated salt or naturally occurring fluoride in their water, they would not have knowledge that this was relevant to the study purpose as

the ADHD tests were conducted for the original cohort (as was acknowledged by the study authors in the discussion). (++) for blinding). Overall rating = ++.

- **Basis for rating:** Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes outlined in the abstract, introduction, and methods were reported in sufficient detail.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - *Statistical analyses:* Statistical analyses used were appropriate for the study.
 - *Other potential concerns:* None identified.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements, outcome blindly assessed, and the prospective cohort study design.

Choi et al. (2015)

Study Details:

- **Study design:** Cross-sectional
- **Population:** First grade children (ages 6–8 years)
- **Study area:** Mianning County in southern Sichuan, China
- **Sample size:** 51 first grade children
- **Data relevant to the review:** Associations between learning, memory, IQ (digit span for auditory span and working memory and block design for visual organization and reasoning components of WISC-IV only), visual motor ability, motor ability, and manual dexterity with continuous urine or drinking water fluoride levels. Study also had information based on dental fluorosis score.
- **Reported association with fluoride exposure:** Yes: Compared to the normal/questionable dental fluorosis, the moderate/severe dental fluorosis group was associated with significantly lower total (adjusted $\beta = -4.28$; 95% CI: $-8.22, -0.33$) and backward digit span scores (adjusted $\beta = -2.13$; 95% CI: $-4.24, -0.02$). Linear correlation between fluoride in urine (adjusted $\beta = -1.67$; 95% CI: $-5.46, 2.12$) and in drinking water (adjusted $\beta = -1.39$; 95% CI: $-6.76, 3.98$) with total digit span was observed but not significant. Other outcomes not significantly associated with fluoride exposure.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Subjects were selected during the same time frame using the same methods. Fifty-one first-grade children residing in Mianning County in southern Sichuan, China were included in this pilot study. It is not specified if the 51 children represented all the first-grade children from this area or if some refused to participate. Children who did not speak Chinese, were not students at the Primary School of Sunshui Village in Mianning County, or those with chronic or acute disease that might affect neurobehavioral function tests were excluded. Demographic characteristics are presented in Table 1 of the study, which indicates that subjects were similar. Potential confounders are adjusted for in the statistical analyses.
 - Basis for Rating: Definitely low risk of bias based on direct evidence that the exposure groups were similar and were recruited within the same time frame using the same methods with no evidence of differences in participation/response rates.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: The parents or guardians completed a questionnaire on demographic and personal characteristics of the children (sex, age at testing, parity, illnesses before age 3, and past medical history) and caretakers (age, parity, education and occupational histories, residential history, and household income). A 20- μ L capillary blood sample was collected at the school by a Mianning County Center for Disease Control (CDC) health practitioner and tested for possible iron deficiency which could be used as a covariate of neurodevelopmental performance. Confounders that were not assessed include: maternal BMI, parental mental health, maternal smoking status, maternal reproductive factors, parental IQ, and HOME score. However, the study authors noted that confounding bias appeared to be limited due to the minimal diversity in the social characteristics of the subjects. The study authors indicated that CDC records documented that levels of other contaminants including arsenic and lead were very low in the area. Iodine differences were not specifically addressed, but there is no indication from the information provided that this might be a concern.
 - Potentially important study-specific confounders: All key confounders were considered in this study.
 - Direction/magnitude of effect: Not applicable.
 - Basis for rating: Probably low risk of bias because there is direct evidence that the key confounders are taken into account and indirect evidence that co-exposure to arsenic is likely not an issue in this area and that methods used for collecting the information were valid and reliable.
- **Attrition:**
 - Rating: Probably low risk of bias (+)
 - Summary: The majority of results were reported for the 51 children stated to be included in the pilot study. In Table 5 of the study, the N for each dental fluorosis

category only totals 43, but the text indicates 8 children did not have a Dean Index because teeth had not erupted.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The study used three different measurements of fluoride exposure: well water fluoride concentrations from the residence during pregnancy and onwards, fluoride concentrations from children's first morning urine samples, and degree of children's dental fluorosis. Fluoride concentrations in community well water were measured and recorded by Mianning County CDC; specific methods were not reported, but they likely used standard methods as they were conducted by the CDC and were likely the same as those used to measure the fluoride in urine. Migration of subjects was noted to be limited. Well water fluoride concentrations of the mother's residence during pregnancy and onward were used to characterize a child's lifetime exposure. To provide a measure of the accumulated body burden, each child was given a 330-mL (11.2-oz) bottle of Robust© distilled water (free from fluoride and other contaminants) to drink the night before the clinical examinations, after emptying the bladder and before bedtime. The first urine sample the following morning was collected at home, and the fluoride concentration was determined on a 5-mL sample using an ion-specific electrode at the Mianning CDC. There is no indication that urinary fluoride levels accounted for dilution nor was it clear that the method of administering water to the children and collection methods sufficiently controlled for differences in dilution. One of the investigators, a dentist, performed a blinded dental examination on each child's permanent teeth to rate the degree of dental fluorosis using the Dean Index. The Dean Index is a commonly used index in epidemiological studies and remains the gold standard in the dentistry armamentarium. The Index has the following classifications: normal, questionable, very mild, mild, moderate, and severe. Quality control (QC) procedures are not reported but were likely appropriate.
 - **Direction/magnitude of effect:** Current levels were used to assess lifetime exposure. This is likely to be a non-differential exposure misclassification and direction of bias is unknown. Because subject migration appears to be limited, it is likely that the current fluoride levels are adequate reflections of past exposure. Dental fluorosis would be an indicator that exposure occurred in the past and there was a fair correlation between degree of dental fluorosis and current urine and water fluoride levels, with both increasing with increasing levels of dental fluorosis.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measure exposure.
- **Outcome:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The study authors adopted culture-independent tests considered feasible for children aged 6 to 8 years. The Wide Range Assessment of Memory and Learning

(WRAML) was used for the assessment of memory and learning. Three subtests were also used. The Finger Windows subtest assesses sequential visual memory. The Design Memory subtest assesses the ability to reproduce designs from memory following a brief exposure. The Visual Learning subtest assesses the ability to learn the locations of pictured objects over repeated exposures. The Wechsler Intelligence Scale for Children-Revised (WISC-IV) included digit span for auditory span and working memory and block design for visual organization and reasoning. The grooved pegboard test assesses manual dexterity. The tests used have been validated on a western population. Although there is no information provided to indicate that they were validated on the study population, the study authors indicated that the tests were culture-independent (+ for methods). Blinding of the outcome assessors or steps to minimize potential bias was not reported. However, it is unlikely that the assessors had knowledge of the individual exposure as children all came from the same area, and water and urine levels were tested at the CDC. (+ for blinding). Overall = +.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that all outcomes were assessed blindly using instruments that were valid and reliable in the study population.
 - **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes outlined in the abstract, introduction, and methods are reported in sufficient details.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
 - **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - *Statistical analyses:* Statistical analyses were appropriate. Data were log-transformed when necessary.
 - *Other potential concerns:* It should be noted that this study was a pilot study and, therefore, had a relatively small sample size (i.e., 51 children).
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
 - **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in the confounding, exposure, and outcome risk-of-bias domains. Study strengths include individual fluoride measurements with blinding at outcome assessment likely. All key confounders and many other confounders were taken into account in the study design or analysis.
-

Cui et al. (2018)

Study Details:

- **Study design:** Cross-sectional

- **Population:** School children aged 7–12 years from four schools in two districts in China with different fluoride levels
- **Study area:** Jinghai and Dagang in Tianjin City, China
- **Sample size:** 323 school children
- **Data relevant to the review:** IQ scores by urine fluoride levels.
- **Reported association with fluoride exposure:** Yes: Significant correlation between IQ score and urinary fluoride (adjusted $\beta = -2.47$).

Risk of Bias:

- **Author contacts:**
 - Authors were contacted in June 2019 to obtain additional information for risk-of-bias evaluation.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Four schools were selected from the same district in China. The schools were selected based on levels of fluoride in the local drinking water and the degree of school cooperation. No details were provided on the number of schools in given areas or the difficulty in getting school cooperation. It was noted that the residents in the four areas had similar living habits, economic situations, and educational standards. Although authors do not provide the specific data to support this, fluoride levels and IQ scores were provided by different subject characteristics. The areas were classified as historically endemic fluorosis and non-fluorosis. Cluster sampling was used to select the grades in each school according to previously set child ages, and classroom was randomly selected with all students within a selected classroom included. Reasons for exclusion do not appear to be related to exposure or outcome.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposure groups were similar and recruited within the same time frame using the same methods, with no evidence of differences in participation/response rates.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The measurements of all covariates were obtained by structured questionnaires that were completed by children with the help of their parents. Confounders that were assessed include: child's gender, child's ethnicity, child's age, child's BMI, birth (normal vs abnormal), mother's age at delivery, mother's education, income per family member, mother's smoking/alcohol during pregnancy, family member smoking, environmental noise, iodine region (non-endemic vs iodine-excess-endemic area), factory within 30 m of residence, iodine salt, diet supplements, seafood/pickled food/tea consumption, surface water consumption, physical activity, stress, anger, anxiety/depression, trauma, having a cold 5 times a year, thyroid disease in relatives, mental retardation in relatives, and cancer in relatives. Covariates not considered include parity, maternal and paternal IQ, and quantity and quality of caregiving environment (e.g., HOME score). The authors report that there are no other environmentally toxic substances that may affect intelligence, such as high arsenic or iodine deficiency according to the Tianjin Centers for Disease Prevention and Control.

- o Potentially important study-specific confounders: All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
- o Basis for rating: Probably low risk of bias because there is indirect evidence that the key confounders are considered, methods for collecting the information are valid and reliable, and co-exposure to arsenic is likely not an issue in this area.
- **Attrition:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Of the 400 children enrolled, 35 were excluded because they did not have informed consent signed by a guardian or they moved out of the area. Forty-two children were excluded because they did not have a DRD2 genotyping measurement. It is unclear if these children were from the same schools or if they were evenly distributed throughout the study area. It was also unclear if the excluded subjects were similar to those included in the study. In the study, some analyses had fewer than the 323 subjects, but this seems reasonable given the subgroups that were being evaluated.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Although children were selected based on area fluoride levels, fluoride in the urine was used in the analysis. Urine was collected from each child the morning of enrollment and analyzed within a week. Fluoride levels were measured using an ion-selective electrode according to the China standard. A brief description of the method was provided, but no QC methods were reported. The study authors did not account for urinary dilution in the spot samples.
 - *Direction/magnitude of effect:* Not accounting for dilution could cause there to be some exposure misclassification. The direction and magnitude would depend on where the differences occurred.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using acceptable methods that provide individual levels of exposure.
- **Outcome:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: IQ was measured by professionals using the Combined Raven's Test-The Rural in China method, which is the appropriate test for the study population (++ for methods). Blinding or other methods to reduce bias were not reported. Although it is unlikely that the outcome assessor would have knowledge of the child's urine fluoride levels, there is potential that they would know if the child was from an endemic or non-endemic area if the IQ tests were conducted at the child's school, and there was no information provided on how the IQ tests were administered. Correspondence with the study author noted the cross-sectional nature of the study with outcome and exposure assessed at the same time making the outcome assessors blind to the exposure. However, there is still potential for knowledge of the area (+ for blinding).

- **Basis for rating:** Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes in the abstract, introduction, and methods are reported in sufficient details.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - **Statistical analyses:** Statistical analyses were appropriate. Data were log-transformed when necessary.
 - **Other potential concerns:** None identified.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements but is limited by the cross-sectional study design and lack of accounting for urine dilution. All key confounders were accounted for in the study design or analysis.

Cui *et al.* (2020)

Study Details:

- **Study design:** Cross-sectional
- **Population:** School children aged 7–12 years
- **Study area:** Tianjin City, China (one randomly selected school from each district based on iodine levels in the water), presumably was an expansion of the Cui *et al.* (2018)
- **Sample size:** 498 school children
- **Data relevant to the review:** IQ scores by urine fluoride levels.
- **Reported association with fluoride exposure:** No: No significant difference in IQ score based on a one-way ANOVA in the three different urinary fluoride categories.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for the 2020 publication. Authors were contacted in June 2019 for additional information on the Cui *et al.* (2018) publication. Information obtained from that correspondence may have been used for additional information in the 2020 publication.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)

- Summary: Subjects were recruited from 2014 to 2018. One school was selected from each district where water concentrations of water iodine were <10, 10–100, 100–150, 150–300 and >300 µg/L. In each school, classes were randomly sampled for the appropriate age group of 7–12 years old. A table of subject characteristics was provided by IQ. A total of 620 children were recruited, and 122 children who did not have complete information or enough blood sample were excluded. Reasons for exclusion do not appear to be related to exposure or outcome. The characteristics of the 498 included children are presented.
- Basis for rating: Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited within the same time frame using the same methods, with no evidence of differences in participation/response rates.
- **Confounding:**
 - Rating: Probably high risk of bias (-)
 - Summary: It was noted by the study authors that there were no other environmental poisons except water fluoride. Other studies also conducted in this area of China noted specifically that arsenic was not a concern. Iodine was addressed as that was one of the main points of the study. Twenty-one factors (provided in Table 1 of the study) were selected as confounders, and a homemade questionnaire of unspecified validity was used for obtaining the information. It was noted that child age, stress, and anger were significantly associated with IQ although it is unclear if these varied by fluoride level. However, Cui *et al.* (2018) indicates that stress and anger were not significantly associated with fluoride, and it is assumed that results would be similar for this study even though more children were included in the current study.
 - Potentially important study-specific confounders: Age (children 7–12 years old)
 - Direction/magnitude of effect: Age is a potential confounder for IQ, even in the narrow age range evaluated in this study. The direction of effects may depend on the number of children in each age group within the different urinary fluoride categories; however, these data were not provided. In general, there were fewer subjects ≤ 9 years of age (i.e., 111) compared to > 9 years of age (i.e., 387) with a significantly higher IQ in the ≤9-year-old age group. Therefore, if exposure were higher in the older subjects, this could bias away from the null.
 - Basis for rating: Probably high risk of bias because there is indirect evidence that age was not addressed as a confounder and it may be related to both IQ and exposure.
- **Attrition:**
 - Rating: Probably low risk of bias (+)
 - Summary: Of the 620 (20%) children recruited, 122 were excluded due to incomplete information or inadequate blood sample. No information was provided to indicate if there were similarities or differences in the children included versus the children excluded, but exclusion is unlikely to be related to either outcome or exposure.
 - Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - Rating: Probably low risk of bias (+)

- o Summary: Children's morning urine was collected with a clean polyethylene tube and fluoride was measured using a fluoride ion-selective electrode following Chinese standard WS/T 89-2015. A brief description was provided, but no QC methods were reported. The study authors do not account for urinary dilution in the spot samples.
 - *Direction/magnitude of effect:* Not accounting for dilution could cause there to be some exposure misclassification. The direction and magnitude would depend on where the differences occurred.
- o Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using acceptable methods that provide individual levels of exposure.
- **Outcome:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: IQ was measured using the Combined Raven's Test, which is an appropriate test for the study population (++ for methods). Blinding was not mentioned; however, the outcome assessors would not likely have knowledge of the child's urinary fluoride. Subjects appear to have been recruited based on iodine levels and it is, therefore, unlikely that there would be any knowledge of potential fluoride exposure. Correspondence with the study authors for the Cui *et al.* (2018) study also indicated that the outcome assessors would have been blind.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: All outcomes in the abstract, introduction, and methods are reported in sufficient details.
 - o Basis for rating: Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - o Rating: Probably low risk of bias (+)
 - o Summary:
 - *Statistical analyses:* The IQ scores are stated to be normally distributed, but there is no evidence that this was in fact tested. A t-test or one-way ANOVA was used to make comparisons between IQ and fluoride. The primary focus of the study was to evaluate associations between thyroid hormones or dopamine levels on IQ (not between fluoride and IQ). It should also be noted that regardless of the analysis conducted, there is no adjustment for school and no accounting for the clustering of children from the same school.
 - *Other potential concerns:* None identified.
 - o Basis for rating: Probably low risk if bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in exposure and outcome. Study strengths include individual exposure measurements, but the

study is limited by the cross-sectional study design, lack of accounting for urine dilution, and by not addressing age as a potential confounder.

Ding et al. (2011)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Elementary school children aged 7–14 years old
- **Study area:** Hulunbuir City, Inner Mongolia, China
- **Sample size:** 331 school children
- **Data relevant to the review:** IQ mean difference based on 10 categories of urine fluoride.
- **Reported association with fluoride exposure:** Yes: Significant association between urinary fluoride and IQ score (each increase in urinary fluoride of 1 mg/L was associated with an IQ score 0.59 points lower; 95% CI: –1.09, –0.08).

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The study randomly selected 340 7–14-year-olds from four nearby elementary schools in Hulunbuir. Authors stated that the four elementary schools appeared to be very similar in teaching quality. The study authors noted that they followed the principles of matching social and natural factors like economic situation, educational standards, and geological environments as much as possible; however, how this was done is unclear and no table of study subject characteristics by group was provided.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited within the same time frame using the same methods, with no evidence of differences in participation/response rates.
- **Confounding:**
 - **Rating:** Probably high risk of bias (-)
 - **Summary:** It was noted that none of the four sites had other potential neurotoxins including arsenic in their drinking water. While they did not provide the specifics, they did provide a reference. In addition, iodine deficiency was noted as not being issue in any of the four areas. Age was the only confounder adjusted in the model. While dental fluorosis severity by % female was reported, not enough data were provided to determine if it was a confounder that should have been considered in the regression. The study authors note that future studies will include covariates such as parents' educational attainment, mother's age at delivery, and household income.
 - **Potentially important study-specific confounders:** Gender
 - **Direction/magnitude of effect:** There is not enough information to determine if there is an effect from gender. There were some differences in dental fluorosis

level by gender, but it is unclear how this might impact the results or if the distribution of gender differed by age.

- **Basis for rating:** Probably high risk of bias based on indirect evidence that there were differences in gender that were not considered in the study design or analyses.
- **Attrition:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Data were relatively complete (i.e., <5% loss). Of the 340 subjects selected for inclusion, 5 were excluded because they lived in the area for less than a year with an additional 4 not consenting to participate.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that exclusion of subjects from analysis was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Spot urine samples were collected and measured using China CDC standards. All samples were analyzed twice using a fluoride ion-selective electrode. Recovery rates were specified as 95–105% with an LOD of 0.05 mg/L. Water samples were collected from small-scale central water supply systems and tube wells with handy pumps and were processed using standard methods similar to the urine samples. Quality assurance validation was reported. A blind professional examiner evaluated the children for dental fluorosis using the Dean's Index. All urine and water samples were above the LOD. Urine levels were the primary exposure measure used in the analysis. The study authors did not account for urinary dilution in the spot samples. The mean urine fluoride concentration was correlated with the dental fluorosis levels.
 - *Direction/magnitude of effect:* Spot urine samples that did not account for dilution could have exposure misclassification. The misclassification is likely non-differential and potential direction of bias is unknown.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measure exposure.
- **Outcome:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** IQ was determined using the Combined Raven's Test-The Rural in China (CRT-RC3) (++) for methods). Although blinding was not reported, it is unlikely that the IQ assessors had knowledge of the children's urine levels or even of the water levels from the four sites as these were sent to a separate lab for testing (+ for blinding). Overall rating for methods and blinding = +.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes outlined in the abstract, introduction, and methods are reported in sufficient details.

- o **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - o **Rating:** Probably low risk of bias (+)
 - o **Summary:**
 - **Statistical analyses:** Statistical analyses were reasonable (ANOVA and multiple linear regression), but consideration of homogeneity of variance was not reported. The NASEM (2020) review pointed out a potential concern for the lack of accounting for clustering at the school-level since children were selected from four elementary schools. However, as pointed out in the **Selection** domain, the authors stated that they followed the principles of matching social and natural factors like economic situation, educational standards, and geological environments as much as possible and that the four elementary schools appeared to be very similar in teaching quality.
 - **Other potential concerns:** None identified.
 - o **Basis for rating:** Probably low risk of bias based on indirect evidence that the statistical analyses were appropriate and that there were no other potential threats to risk of bias.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in exposure and outcome. Study strengths include individual exposure measurements, but the study is limited by the cross-sectional study design, lack of accounting for urine dilution, and by not addressing gender as a potential confounder.

Green et al. (2019)

Study Details:

- **Study design:** Prospective cohort
- **Population:** Maternal-Infant Research on Environmental Chemicals (MIREC) participants (pregnant mothers and their children aged 3–4 years)
- **Study area:** 10 cities, Canada
- **Sample size:** 512 mother–child pairs (238 from non-fluoridated areas, 162 from fluoridated areas; 264 females, 248 males)
- **Data relevant to the review:** Adjusted linear regression models evaluating associations between IQ in both genders together and separate with maternal urinary fluoride across all three trimesters or estimated maternal fluoride intake.
- **Reported association with fluoride exposure:** Yes: Significantly lower full-scale IQ with 1-mg/L increases in maternal urinary fluoride in boys (adjusted $\beta = -4.49$), but not girls (adjusted $\beta = 2.40$) and not in sexes combine (adjusted $\beta = -1.95$); significantly lower full-scale IQ with 1-mg increases in maternal intake in sexes combined (adjusted $\beta = -3.66$ [no sex interaction]); significantly lower full-scale IQ with 1-mg/L increases in drinking water fluoride in sexes combined (adjusted $\beta = -5.29$ [no sex interaction]).

Risk of Bias:

- **Author contacts:**

- Authors were contacted in June 2019 for additional information for the risk of bias evaluation.
- **Population selection:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Pregnant women were recruited from the same population, during the same timeframe, and using the same methods as the MIREC program. Methods were reported in detail.
 - Basis for rating: Definitely low risk of bias based on direct evidence that the exposed groups were similar and were recruited with the same methods during the same time frame.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: The study considered several possible covariates including maternal age, pre-pregnancy BMI, marriage status, birth country, race, maternal education, employment, income, HOME score, smoking during pregnancy, secondhand smoke in the home, alcohol consumption during pregnancy, parity, child's gender, child's age at testing, gestational age, birth weight, time of void, and time since last void. The study also conducted secondary analyses to test for lead, mercury, arsenic, and PFOA. There is no indication of any other potential co-exposures in this study population. Iodine deficiency or excess could not be assessed but is not expected to differentially occur. The study was not able to assess parental IQ or mental health disorders. Methods used to obtain the information included questionnaires and laboratory tests.
 - Potentially important study-specific confounders: All key confounders were addressed.
 - *Direction/magnitude of effect:* Not applicable.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and reliable and direct evidence that key confounders including potential co-exposures were addressed.
- **Attrition:**
 - Rating: Probably low risk of bias (+)
 - Summary: Of the 610 recruited children, 601 (98.5%) completed testing. Of the 601 mother-child pairs, 512 (85.2%) had all three maternal urine samples and complete covariate data, and 400 (66.6%) had data available to estimate fluoride intake.
 - Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - Rating: Probably low risk of bias (+)
 - Summary: Spot urine samples from all three trimesters of pregnancy were evaluated using appropriate methods, and results were adjusted for creatinine and specific gravity. Fluoride intake was estimated based on fluoride water levels and information on consumption of tap water and other water-based beverages (e.g., tea, coffee) was obtained via questionnaire.
 - *Direction/magnitude of effect:* There is not any specific direction or magnitude of bias expected. Urinary fluoride levels are reflective of a recent exposure.

Having measurements from all three trimesters of pregnancy provides a better representation of actual exposure than a single measurement although the potential for missed high exposure is possible. However, the possibility of the occurrence of missed high exposure would be similar in all females and would be non-differential. For the fluoride intake, exposure was based on the fluoride levels in the water at the residence. If women worked outside the home and the majority of intake occurred from areas outside the home (and were different from levels in the home), there is potential to bias toward the null.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The Wechsler Preschool and Primary Scale of Intelligence was normalized for ages 2.5–<4.0 and child sex using the U.S population-based norms. Blinding was not reported, but it is unlikely that the outcome assessors had knowledge of the maternal fluoride level or were aware if the city had fluoridated water.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes were reported.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - **Statistical analyses:** Linear regression was performed. Regression diagnostics were used to test assumptions for linearity, normality, and homogeneity. There were two potential influential observations (based on Cook's distance), and sensitivity analyses re-estimated the models without these two variables. Further sensitivity analyses were also conducted. Although city was accounted for as a covariate in the regression models, the city effect should have been a random effect rather than a fixed effect to account for potential clustering of results within each city. Although the analysis used individual-level exposure rather than city-level exposure, if the exposure levels within a city are highly correlated (which might be expected given that some cities were fully on fluoridated water and others were not), the fixed-effect model could still produce biased estimates. However, correspondence with the study authors indicated that a supplemental analysis using a random effects multi-level model showed similar results to the main model.
 - **Other potential concerns:** None identified.

- **Basis for rating:** Definitely low risk if bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements, prospective cohort design, and addressing potential key confounders.

Li et al. (2004) [translated in Li et al. 2008a]

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** Full term, normal neonates 24–72 hours old from healthy mothers
- ***Study area:*** Zhaozhou County, Heilongjiang Province, China
- ***Sample size:*** 91 neonates (46 males and 45 females)
- ***Data relevant to the review:*** Comparison of neurobehavioral capacity between children in the high-fluoride area compared to the control area.
- ***Reported association with fluoride exposure:*** Yes: Significant differences in neurobehavioral assessment total scores between high-fluoride (36.48 ± 1.09) and control groups (38.28 ± 1.10); significant differences in total neurobehavioral capacity scores as measured by non-biological visual orientation reaction and biological visual and auditory orientation reaction between the two groups (11.34 ± 0.56 in controls compared to 10.05 ± 0.94 in high-fluoride group).

Risk of Bias:

- ***Author contacts:***
 - Authors were not contacted for additional information because it was not necessary.
- ***Population selection:***
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** There is indirect evidence that the exposure groups were similar. They were recruited during the same time frame using the same methods. From 2002 to 2003, 273 neonates were born in a hospital in Zhaozhou County, China. Ninety-one of 273 full-term neonates (46 males, 45 females) were randomly selected. Mothers ranged in age from 20 to 31 years, met multiple health criteria, and had not changed residence during pregnancy. Authors report that the two study groups are located in the same area with similar climate, living habits, economic and nutritional conditions, and cultural backgrounds, but do not provide these data in the manuscript. There is no statistically significant difference in the mode of delivery, birth weight, infant length, or sex. Subjects were separated into exposure groups after random selection.
 - **Basis for Rating:** Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited within the same time frame using the same methods with no evidence of differences in participation/response rates.
- ***Confounding:***
 - **Rating:** Probably low risk of bias (+)

- Summary: No confounders were specifically controlled in the analysis. The study authors note similarities in characteristics in the two populations (i.e., living habits, economic and nutritional conditions, and cultural backgrounds), but do not provide these data nor do they indicate what specific characteristics were considered. There were no significant differences in infant gender, birth method, gestational age, or infant weight and length. All tests were conducted when children were 1–3 days old. No potential co-exposures were discussed. Although arsenic is considered a potential issue in China, water quality maps indicate that there is a 25–50% probability that the drinking water in that area exceeds the WHO guideline for arsenic of 10 µg/L.
 - Potentially important study-specific confounders: Key confounders, including child's age, child's gender, and measures of socioeconomic status (SES), were similar between exposure groups; however, arsenic was not taken into account. Arsenic often occurs in the drinking water along with fluoride in some Chinese populations; however, based on water quality maps, arsenic does not appear to be an issue in Zhaozhou County of the Heilongjiang Province. Iodine deficiencies are not mentioned.
 - Direction/magnitude of effect: The presence of arsenic would potentially bias away from the null if it were present with fluoride. Deficiencies in iodine would potentially bias away from the null if it were present in areas of higher fluoride, but toward the null if it were present in areas of lower fluoride.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the key confounders are taken into account, co-exposure to arsenic is likely not an issue in this area, and methods used for collecting the information are valid and reliable.
- **Attrition:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Although authors did not discuss why they only randomly selected 91 of the 273 neonates available, results were available for all 91 subjects.
 - Basis for rating: Definitely low risk of bias based on results being available for all subjects.
- **Exposure:**
 - Rating: Probably low risk of bias (+)
 - Summary: Subjects were split into control and high-fluoride groups based on fluoride levels in their places of residence. Although the levels were provided (1.7–6.0 mg/L for the high-fluoride group compared to 0.5–1.0 mg/L for the control group), it was not reported how or when these levels were measured. Urine was collected when women were hospitalized, but before labor began. Urine samples were sent to a specific lab for measurement using fluoride ion-selective electrode. It was noted that this procedure strictly followed the internal controls of the laboratory indicating quality control. Level of detection (LOD) was not provided. Urinary fluoride levels were significantly higher in the high-fluoride mothers (3.58 ± 1.47 mg/L) compared to the control-group mothers (1.74 ± 0.96 mg/L). There was indirect evidence that exposure was consistently assessed using well-established methods that directly measure exposure. Although results were mainly based on exposure area, they were supported by urine data making exposure misclassification less of a concern.

- *Direction/magnitude of effect:* There is high variability in both water fluoride and urine fluoride in the subjects from the high-exposure area. Although there is no overlap in the water fluoride levels in the exposure areas, there is some overlap in the urine concentrations in the mothers from the two areas. This may reflect the single measurement and pose no specific bias, or it could indicate that some mothers in the high-fluoride area have lower fluoride exposure, which could bias the results toward the null.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measure exposure.
- **Outcome:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* A standard neonatal behavioral neurological assessment method was carried out by professionals in the pediatric department working in neonatal section trained specifically for these programs and passing the training exams. (+ for methods). The examinations were carried out 1 to 3 days after delivery. Because urine samples were collected on the day of delivery and sent to a separate laboratory, it is likely that the outcome assessors were blind. Although the subjects were separated by fluoride exposure area, it is not likely that the professionals were aware of the exposure as the tests were conducted in the hospital (+ for blinding).
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the outcome was assessed blindly using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* The study authors reported numerous endpoints in sufficient detail; however, because they did not provide a list of endpoints tested there is no direct evidence that all were reported.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that all the study's measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:*
 - *Statistical analyses:* Statistical analyses were reasonable (t-test), but consideration of homogeneity of variance was not reported. This was a translated study.
 - *Other potential concerns:* It should be noted that, although the study states that subjects were randomly selected, it is unclear why only 91 subjects were included and if they were randomly selected to obtain equal groups in the high-fluoride and control groups.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that statistical analyses were appropriate and that there were no other potential threats to risk of bias.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in the confounding, exposure, and outcome risk-of-bias domains. Study strengths include individual fluoride measurements to support the differences in the two areas. Tests were noted

to be conducted at the hospital providing indirect evidence that blinding was not a concern during the outcome evaluation. Although there was some potential for bias due to the lack of accounting for arsenic or iodine deficiencies, co-exposure to arsenic is likely not a major concern according to groundwater quality maps.

Riddell et al. (2019)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Canadian Health Measures Survey (cycles 2 and 3) participants (children aged 6–17 years)
- **Study area:** general population, Canada
- **Sample size:** 3,745 children
- **Data relevant to the review:** Adjusted odds ratios for ADHD and attention symptoms per 1 unit increase in urinary fluoride, by water fluoride in the tap water, or community fluoridation status.
- **Reported association with fluoride exposure:** Yes: Significantly increased odds of ADHD diagnosis (adjusted OR = 6.10; 95% CI: 1.60, 22.8) or hyperactivity/inattentive symptoms (adjusted beta = 0.31; 95% CI: 0.04, 0.58) per 1-mg/L increase in tap water fluoride. Also, a significant association between ADHD diagnosis (adjusted OR = 1.21; 95% CI: 1.03, 1.42) or hyperactivity/inattentive symptoms (adjusted beta = 0.11; 95% CI: 0.02, 0.58) and community water fluoridation status. No significant associations with urinary fluoride levels.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Subjects were part of Cycles 2 and 3 of the Canadian Health Measures Survey. This is a nationally representative sample of residents living in 10 provinces. Specific inclusion criteria were provided. This study was restricted to children 6–17 years of age with different fluoride measurements that consisted of three participant samples. One of the samples was only available in Cycle 3.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the exposed groups were similar and were recruited with the same methods during the same time frame.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Covariates included in all models included child's age at test, child's sex, ethnicity, BMI, parents' education, total household income, exposure to cigarette smoke inside the home, and log-transformed concurrent blood lead levels. Confounders such as parental behavioral and mental health disorders, quantity and quality of caregiving environment, and co-exposure to arsenic were not discussed. Rationale for selection of covariates was based on relationship to ADHD diagnosis and to fluoride metabolism based on literature review and consultation with an ADHD expert. There is no

information of the source if data for covariates, but this is likely the questionnaires from the Canadian Health Measures Survey, which are considered standardized and validated.

- o Potentially important study-specific confounders: All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
- o Basis for rating: Probably low risk of bias because there is indirect evidence that the key confounders are taken into account, co-exposure to arsenic is likely not an issue in this area, and methods used for collecting the information were valid and reliable.
- **Attrition:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: There is no information indicating that there were any data excluded due to missing covariates. All exclusions of children were described and reasonable (i.e., drinking bottled water when considered city fluoridation as a measure of fluoride exposure). Outliers were stated to be excluded, but methods for determining this were provided and it was noted that the outliers were 0.27% of the values.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: **Urinary Fluoride:** Spot urine samples were collected under normal non-fasting conditions and analyzed using an Orion pH meter with a fluoride ion-selective electrode after being diluted with an ionic adjustment buffer. Analysis was performed at the Human Toxicology Laboratory of the Institut National de Sante Publique du Quebec. The precision and accuracy of the fluoride analyses, including quality control and quality assurance, were described by Health Canada (2015). The limits of detection were 20 µg/L for Cycle 2 and 10 µg/L for Cycle 3 with no values below detection. Fluoride levels were adjusted for specific gravity.
Water Fluoride in Tap water: Tap water was collected at the subjects' homes in Cycle 3 only. Samples were analyzed for fluoride concentrations using anion exchange chromatography procedure with a LOD of 0.006 mg/L. Values below the LOD were imputed with LOD/square root 2. Of the 980 samples, 150 (16%) were below detection.
Chlorinate Water Fluoride status: This was determined by viewing reports on each city's website or contacting the water treatment plant (provided in supplemental material). Children were excluded if they drank bottled water, had a well, had a home filtration system, lived in the current residence for 2 years or less, or lived in an area with mixed city fluoridation.
 - *Direction/magnitude of effect:* There is not any specific direction or magnitude of bias expected. Urinary fluoride levels are reflective of a recent exposure, but the study authors adjusted to account for dilution. The possibility of exposure misclassification would be similar in all subjects and would be non-differential. There is less potential for exposure misclassification in regard to tap water or chlorinated water fluoride status as children who drank bottled water were

excluded and children who had a home filtration system were excluded from the chlorinated water status.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - **Rating:** Probably high risk of bias (-)
 - **Summary:**

Strengths and Difficulties Questionnaire (SDQ): The questionnaire was administered to youths under 18 years. Children aged 6–11 years had SDQ ratings provided by parents and guardians, but youths aged 12–17 years completed the questionnaire themselves. Tests consist of 25 items with a 3-point scale. Items were divided into five subscales: emotional problems, conduct problems, hyperactivity-inattention, peer problems, and prosocial behavior. The current study only used the hyperactivity-inattention subscale. Validation of this method was not reported (- for methods).

ADHD: Ninety percent of youths with ADHD are diagnosed after age 6 years. For children aged 6–11 years, ADHD diagnosis was provided by parents, but youths age 12–17 years completed the questionnaire themselves. Cycle 2 asked "Do you have a learning disability?" and if yes asked to specify the type (4 options available and described). In Cycle 3, parents were asked directly whether they had ADHD, and children 12 years and older were asked if they had a physician diagnosis of ADHD and, if so, what subtype. (- for methods because different methods were used and only the children 12 years and older in cycle 3 were asked specifically about doctor diagnosis). Both were measured in both cycles. Blinding is not likely an issue as subjects would not have knowledge of the urine or tap water fluoride levels. However, they would likely have knowledge of the city.
 - **Basis for rating:** Probably high risk of bias based on indirect evidence that the outcome was assessed using insensitive methods that varied based subject age.
- **Selective Reporting:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** All outcomes outlined in the abstract, introduction, and methods sections were reported in sufficient details.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:**
 - **Statistical analyses:** Logistic regression was used for ADHD results. Box-Tidewell tests were used to check the linearity of the relationship with the continuous predictors. Linear regression was used for the SDQ scores using Huber-White standard errors. All regressions were tested for interactions between age and fluoride and sex and fluoride. Sensitivity analyses were conducted to test the different cycles.
 - **Other potential concerns:** None identified.

- ***Basis for rating:*** Definitely low risk if bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Probably low risk-of-bias ratings in confounding and exposure. Study strengths include individual exposure measurements and the addressing of potential key confounders but was limited by the cross-sectional study design and insensitive outcome measures.

Rocha-Amador *et al.* (2007)

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** Children aged 6–10 years
- ***Study area:*** Moctezuma (low fluoride, low arsenic) and Salitral (high fluoride, high arsenic) of San Luis Potosí State and 5 de Febrero (high fluoride, high arsenic) of Durango State, Mexico
- ***Sample size:*** 132 children
- ***Data relevant to the review:*** Associations between full-scale IQ, performance IQ, verbal IQ and child's urine or water fluoride levels.
- ***Reported association with fluoride exposure:*** Yes: Significant associations between fluoride and IQ scores (full-scale IQ adjusted β s of –10.2 with water and –16.9 with urine; CIs not reported); arsenic also present, but the effect was smaller (full-scale IQ adjusted β s of –6.15 with water and –5.72 with urine; CIs not reported).

Risk of Bias:

- ***Author contacts:***
 - Authors were not contacted for additional information because it was not necessary.
- ***Population selection:***
 - ***Rating:*** Probably low risk of bias (+)
 - ***Summary:*** All children in 1st through 3rd grades in three rural areas in Mexico (n = 480) were screened for study eligibility including age, time at residence, and address. Authors report that the three selected communities were similar in population and general demographic characteristics. Children who had lived in the area since birth and were 6–10 years old were eligible to participate (n = 308). Of the 308 children, 155 were randomly selected and the response rate was 85%, but participation was not reported by area. It was noted, however, that no significant differences in age, gender, or time of residence were observed between participants and non-participants. Timeframe for selection was not mentioned but appears to be similar. Sociodemographic characteristics of subjects was provided in Table 1 of the study. There was a significant difference in SES and transferrin saturation, but these were taken into account in the analysis.
 - ***Basis for rating:*** Probably low risk of bias based on indirect evidence that the populations were similar and differences were noted and addressed in the analysis.
- ***Confounding:***

- o Rating: Probably low risk of bias (+)
- o Summary: The study design or analysis accounted for child's age, sex, SES, transferrin saturation, weight, height, blood lead levels, and mother's education. Arsenic levels were highly correlated with fluoride levels and it was stated that each was tested alone, and arsenic was found to have less of an effect. The authors noted in the methods that they tested for an interaction between arsenic and fluoride. Smoking was not addressed and methods for measuring many of the confounders were not reported.
- o Potentially important study-specific confounders: Arsenic
 - *Direction/magnitude of effect:* Presence of arsenic, which also demonstrated an association, would bias away from the null.
- o Basis for rating: Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and reliable and direct evidence that key confounders were addressed.
- **Attrition:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Of 155 children randomly selected for study participation, 85% responded to enroll. According to the authors, there were no significant differences in age, gender, or time of residence between responders and non-responders. However, no data are provided to support this, and no breakdown of responders/non-responders by region is provided. Data were provided for the 132 children agreeing to participate.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: Urine samples were collected on the same day as psychological evaluations and were analyzed for fluoride according to NIOSH Method 8308 (Fluoride in Urine). For QC, a reference standard was also used (NIST SRM 2671a). Urine samples were also analyzed for arsenic by using the Atomic Absorption Spectrophotometer with hydride system (Perkin-Elmer, model AAnalyst 100, Wellesley, United States) and used a reference standard for QC. Levels were adjusted for urinary creatinine levels to account for dilution in the spot samples. Tap water samples were collected from each child's home on the day of biological monitoring. Fluoride was measured with a sensitive, specific ion electrode. Detailed methods are provided including internal quality controls. It was noted that in the high fluoride group it was common to drink bottled water low in fluoride and to only use the tap water for cooking; therefore, urine was considered the most appropriate measure of exposure. Only children who had lived at the same residence since birth were included.
 - *Direction/magnitude of effect:* Not applicable.
 - o Basis for rating: Definitely low risk of bias based on direct evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - o Rating: Probably low risk of bias (+)

- Summary: Neuropsychological profiles were assessed through the WISC-RM (revised for Mexico). This is a well-established test appropriately adjusted for the study population. However, no additional validation is provided (+ for methods). The study report stated that the test assessors were masked to both arsenic and fluoride water levels (++ for blinding). Overall rating for methods and blinding = +.
- Basis for rating: Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - Rating: Probably high risk of bias (-)
 - Summary: It was reported that an interaction between fluoride and arsenic was measured, but it was only noted in the discussion that the study design precluded testing statistical interaction between fluoride and arsenic. This provides indirect evidence of selective reporting.
 - Basis for rating: Probably high risk of bias based on indirect evidence that there was selective reporting.
- **Other potential threats:**
 - Rating: Definitely low risk of bias (++)
 - Summary:
 - Statistical analyses:
 - Statistical analyses: Statistical analyses used were appropriate for the study.
 - Other potential concerns: None identified.
 - Basis for rating: Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements and outcomes blindly assessed, but it is limited by the cross-sectional study design and not being able to completely rule out the influence of arsenic in the results.

Rocha-Amador et al. (2009)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 6–11 years
- **Study area:** Durango, Mexico
- **Sample size:** 80 children
- **Data relevant to the review:** Associations between visuospatial organization and visual memory (using the Rey-Osterrieth Complex Figure Test, children's version) and urinary fluoride levels in the children.
- **Reported association with fluoride exposure:** Yes: Significant correlation between urinary fluoride and visuospatial organization ($r = -0.29$) and visual memory ($r = -0.27$) scores. No significant correlations with arsenic.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: Subjects were from the same population and were recruited during the same time frame using the same methods. Although this study compared three sites with antecedents of environmental pollution to mixtures of either F–As, Pb–As, or DDT–PCBs, authors evaluated each contaminant separately. The only area of interest is the area with F and As contamination. The area in Durango state (5 de Febrero) where drinking water is polluted naturally with F and As at levels exceeding 6 and 19 times, respectively, the World Health Organization (WHO) limits (WHO 2008). Children attending public schools were screened through personal interviews for study eligibility. Inclusion criteria were children between 6 and 11 years old, living in the study area since birth, and whose parents signed the agreement to participate. Children with a neurological disease diagnosed by a physician and reported by the mother were excluded from the study. The final sample for the F–As was 80. Participation rates were not reported. Selected demographic characteristics are presented in Table 1 of the study.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the populations were similar and recruited during the same time frame using the same methods.
- **Confounding:**
 - Rating: Probably high risk of bias (-)
 - Summary: Confounding factors in children tested in the analysis included blood lead (PbB), age, gender, and height-for-age z-scores; only age had significant associations and was included in the final analysis. Arsenic was also assessed and analyzed separately from fluoride. Arsenic in urine was analyzed by atomic absorption spectrophotometer coupled to a hydride system (Perkin-Elmer model AAnalyst 100). Although the model did not adjust for arsenic, arsenic in the F–As group was not associated with either endpoint. PbB was analyzed with a Perkin-Elmer 3110 atomic absorption spectrophotometer using a graphite furnace. Authors note that the mean blood lead level in the F–As study area was 5.2 µg/dL and 8% of the children had values above the reference value of 10 µg/dL. PbB was stated not to affect results and was not included in the final analysis. Other confounding data were obtained during the study interview. Father's education was provided and, in the F–As group, was stated to range from 0–16 years, but this was not considered. Maternal education, smoking, and SES were also not considered. The authors provide an SES score of 5.9 ± 1.4 for the 5 de Febrero region (the fluoride region). It is not clear if this would vary by fluoride or arsenic levels.
 - Potentially important study-specific confounders: SES.
 - Direction/magnitude of effect: There are insufficient data to determine the magnitude or direction of effect. If there is an association between fluoride exposure and SES, the direction of effect would depend on the association.

- *Basis for rating:* Probably high risk of bias based on indirect evidence that the SES was not accounted for in the study design or analysis and may have varied by fluoride levels.
- ***Attrition:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* Data are complete. All 80 participants stated to be the final sample for the site of interest (F–As) were included in all analyses.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that there was no attrition.
- ***Exposure:***
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* Fluoride in urine (FU) was analyzed according to method 8308 (“fluoride in urine”) from the National Institute of Occupational Safety and Health (NIOSH 1984) with a sensitive specific ion electrode. As a quality control check, reference standard “fluoride in freeze dried urine” (NIST SRM 2671a) was analyzed. The accuracy was 97.0 +/- 6.0%. Levels of FU and AsU were adjusted for urinary creatinine, which was analyzed by a colorimetric method (Bayer Diagnostic Kit, Sera-Pak1 Plus). However, details on the collection methods were not reported.
 - *Direction/magnitude of effect:* Spot urine samples in a small sample size (i.e., 80 children) may have some exposure misclassification. Adjusting for dilution reduces the potential for misclassification based on differences in dilution. Exposure misclassification would be non-differential.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- ***Outcome:***
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* IQ is assessed through the Rey-Osterrieth Complex Figure Test (ROCF). This is a less well-established method, although the authors provide citations suggesting it has been validated and standardized for the Mexican population (+ for methods). According to the study report, the neuropsychologist who administered the test was blinded to all exposure types and levels. (++) for blinding). Overall rating for methods and blinding = +.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- ***Selective Reporting:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods were reported in sufficient details.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- ***Other potential threats:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:*
 - *Statistical analyses:* Statistical analyses used were appropriate for the study.
 - *Other potential concerns:* None identified.

- **Basis for rating:** Definitely low risk if bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Probably low risk-of-bias ratings in exposure and outcome. Study strengths include individual exposure measurements and outcomes blindly assessed, but it is limited by the cross-sectional study design, lack of addressing SES in the study population, co-exposure with arsenic, and use of spot samples in a small population.

Saxena et al. (2012)

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** Children aged 12 years
- ***Study area:*** Madhya Pradesh, India
- ***Sample size:*** 170 children
- ***Data relevant to the review:*** Mean IQ grade (not standard scores) by water fluoride quartiles or continuous or by continuous urinary fluoride.
- ***Reported association with fluoride exposure:*** Yes: Significant correlation between water ($r = 0.534$; $p = 0.000$) and urinary ($r = 0.542$; $p = 0.000$) fluoride levels and IQ score.

Risk of Bias:

- ***Author contacts:***
 - Authors were contacted in August of 2017 to obtain additional information for risk-of-bias evaluation.
- ***Population selection:***
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** There was indirect evidence that subjects were similar and were recruited using the same methods during the same time frame. The study participants were selected from a stratified cluster of geographic areas based on fluoride concentration in groundwater. According to the authors, the selected villages were similar in population and demographic characteristics. Data are provided to show the breakdown in SES, parental education, height/age, and weight/height and no significant differences were noted. Participation was stated to be voluntary, but participation rates were not provided. It is unclear if the 170 subjects were selected with 100% participation or if the 170 subjects were all that were asked to participate, but it appears that all subjects participated. Timing of the recruitment was not provided but is assumed to occur during the same time frame.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that subjects were similar and recruited using the same methods during the same time frame.
- ***Confounding:***
 - **Rating:** Probably low risk of bias (+)

- Summary: There was indirect evidence that key confounders including potential co-exposures were addressed using reasonable methods. A questionnaire, completed with the assistance of parents, was used to collect information on child characteristics (age, sex, height, weight), residential history, medical history (including illness affecting nervous system and head trauma), educational level of the head of the family (in years), and SES of the family. The SES was recorded according to the Pareek and Trivedi classification. The nutritional status of the children was calculated using the Waterlow's classification, which defines two groups for malnutrition using height for age ratio (chronic condition) and weight for height ratio (acute condition). Within both groups, it categorizes the malnutrition as normal, mildly impaired, moderately impaired, or severely impaired. Urinary lead and arsenic were analyzed using the atomic absorption spectrophotometer (Perkin-Elmer, Wellesley, United States). Urinary iodine was measured using the Dunn method. Authors do not report which covariates were included in the multivariate regression models; however, there was no difference in reported demographic characteristics. All subjects were the same age, and there was no difference in iodine, lead, or arsenic between the groups. Mean urinary arsenic levels did increase with increasing fluoride even though there was no significant difference by group.
- Potentially important study-specific confounders: All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
- Basis for rating: Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and reliable and that key confounders including potential co-exposures were addressed.
- **Attrition:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Results were provided for all 170 children stated to be included in the study.
 - Basis for rating: Definitely low risk of bias based on direct evidence of no attrition.
- **Exposure:**
 - Rating: Probably low risk of bias (+)
 - Summary: A sample of 200 mL of drinking water was collected at each child's home. The fluoride levels were analyzed by a fluoride ion-selective electrode, Orion 9609BN (Thermo Fisher Scientific Inc., West Palm Beach, United States). Each subject was also asked to collect a sample of their first morning urine. The fluoride content in the urine was determined using a fluoride ion-selective electrode, Orion 9609BN (Thermo Fisher Scientific Inc., West Palm Beach, United States). QA/QC and LOD were not reported and urinary dilution was not assessed. Although only current levels were measured, children who had changed water source since birth were excluded.
 - *Direction/magnitude of effect:* Spot urine samples that did not account for dilution could have exposure misclassification. The misclassification is likely non-differential and not likely to bias in any specific direction. Children who had changed water since birth were excluded, but it was not specifically noted that the fluoride in the water source was stable over the years.

- *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- ***Outcome:***
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* Intelligence is assessed using the Raven's Standard Progressive Matrices and categorized into five grade levels. Although it was not noted that the test was validated to the study population, the test is visual and would be applicable to most populations (+ for methods). There is no mention of blinding by test administrators or evaluators and the exposure groups come from different geographic areas. It was also not reported who measured the levels of fluoride from the home or urine samples. Correspondence with the study authors indicated that the outcome assessors were blind to the children's fluoride status (++ for blinding). Overall rating for methods and blinding = +.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- ***Selective Reporting:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- ***Other potential threats:***
 - *Rating:* Probably low risk of bias (+)
 - *Summary:*
 - *Statistical analyses:* Statistical analyses were reasonable (ANOVA), but consideration of homogeneity of variance was not reported.
 - *Other potential concerns:* None identified.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the statistical analyses were appropriate, and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements and the addressing of potential key confounders, but it was limited by the cross-sectional study design and lack of addressing dilution in the urine samples.

Seraj et al. (2012)

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** Children aged 6–11 years
- ***Study area:*** five villages, Makoo, Iran
- ***Sample size:*** 293 children

- **Data relevant to the review:** IQ (mean and distribution) assessed by Raven's Colored Progressive Matrices and presented by fluoride area, beta was also provided for water fluoride.
- **Reported association with fluoride exposure:** Yes: Significant correlation between water fluoride and IQ score (adjusted $\beta = -3.865$; CIs not reported); significantly higher IQ score in normal area (97.77 ± 18.91) compared with medium (89.03 ± 12.99) and high (88.58 ± 16.01) areas.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: Subjects were selected from five villages in Makoo. The villages were stated to all be rural with similar general demographic and geographic characteristics and were comparable in terms of SES and parental occupations. Children were 6–11 years old. Age, gender, and education were taken into account in the analysis. No other characteristics were provided or discussed. Participation rates were not reported. There is indirect evidence that the populations were similar, and some possible differences were addressed.
 - Basis for rating: Probably low risk of bias based on indirect evidence that subjects were similar and recruited using the same methods during the same time frame.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: Age, gender, dental fluorosis intensity, and educational levels (child's and parents') were evaluated as potential confounders. Other potential confounders such as smoking were not discussed. Information was obtained from a detailed questionnaire. Lead was measured, but only found in low levels in the drinking water throughout the study regions. Iodine in the water was also stated to be measured and residents were receiving iodine-enriched salt. Arsenic was not addressed, but there is no evidence that arsenic levels would vary across villages in this area.
 - Potentially important study-specific confounders: All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and that key confounders including potential co-exposures were addressed or were not likely to be an issue in the study area.
- **Attrition:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Attrition was low if it occurred. It was noted that 293 out of 314 children living in the villages were recruited. It is not clear if 21 children were excluded based on exclusion criteria or if they refused to participate; however, this accounts for less than 10% of the population and results were available for all 293 subjects.

- *Basis for rating:* Definitely low risk of bias based on direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - *Rating:* Probably high risk of bias (-)
 - *Summary:* Exposure was primarily based on area of residence. Fluoride in the groundwater was analyzed by the SPADNS (Sulphophenylazo dihydroxynaphthalene-disulfonate) method, utilizing 4000 UV-Vis spectrophotometer (Hach Company, Germany) in the environmental health engineering laboratory of the Public Health School of Tehran University of Medical Sciences. Specific details were not provided on methods of collection, samples locations, or if these locations represented the primary sources of drinking water for the subjects. Villages were categorized into normal (0.5–1 ppm), moderate (3.1±0.9 ppm), and high (5.2±1.1 ppm) fluoride based on the mean fluoride content of all seasons presumably for the stated 12-year time period. Subjects were stated to be long-life residents of the village. Dental fluorosis was also measured and increased in severity with fluoride levels; however, all areas had some degree of dental fluorosis. Although authors used an average fluoride level in varying seasons over presumably 12 years, they used a less-established method without reporting reliability or validity, nor did they provide data to indicate that the mean was truly representative of the fluoride levels over time and throughout the village. Although dental fluorosis severity increased with increasing fluoride levels, the data could also indicate potential exposure misclassification.
 - *Direction/magnitude of effect:* The presence of dental fluorosis in all groups indicates that there may have been different exposure in some children at a younger age. Although there were only about 20 children in the “normal” fluoride group with very mild to mild dental fluorosis, this could bias the results toward the null because those children may have experienced a higher level of fluoride at some point. The other two fluoride groups were exposed to fluoride levels that likely exceeded those in the “normal” fluoride group.
 - *Basis for rating:* Probably high risk of bias based on indirect evidence that exposure was assessed using insensitive methods.
- **Outcome:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* Intelligence was evaluated using the Raven's Color Progressive Matrices. This is a well-established method. Although the study authors did not provide data to indicate that the methods were valid in this study population, the test is designed to be culturally diverse. (+ for methods). The study report stated that test administrators were blinded. (++) for blinding). Overall rating for methods and blinding = +.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that outcomes were blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Probably low risk of bias (+)

- Summary: All outcomes outlined in the abstract, introduction, and methods were reported. However, because they did not report the method for obtaining the betas in Table 4 of the study, it is not clear if these were adjusted or unadjusted betas.
 - Basis for rating: Probably low risk of bias based on direct evidence that all the study's measured outcomes were reported, but the results were not sufficiently reported.
 - **Other potential threats:**
 - Rating: Probably low risk of bias (+)
 - Summary:
 - Statistical analyses: Statistical comparisons between groups were reasonable (ANOVA), but consideration of homogeneity of variance was not reported. In addition, the methods for obtaining the betas were not reported.
 - Other potential concerns: None identified.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
 - **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding and outcome. Study strengths include addressing potential key confounders, but it was limited by the cross-sectional study design and the group-level exposure data.
-

Soto-Barreras *et al.* (2019)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 9–10 years
- **Study area:** Chihuahua, Mexico
- **Sample size:** 161 children
- **Data relevant to the review:** Water fluoride, urinary fluoride, exposure dose, and dental fluorosis index by IQ grade.
- **Reported association with fluoride exposure:** No: No significant associations between fluoride exposure and IQ grades.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: Subjects were selected using a multistage cluster sampling. During the first stage, 13 public elementary schools were randomly selected from a pool of 73 using a cluster sample design. Secondly, only fourth grade students were included. Authors stated that they wanted to keep the same grade level, but they were not specific as to why fourth graders were selected as opposed to any other grade. Lastly, only children whose parents or guardians attended and responded to the survey were included. There is no information provided on how the 13 schools selected may be similar or different from the 60 schools not selected. There is no information provided on the number of

children in the fourth grade to know participant rates. It was only noted that 245 children were examined, but 161 were included after the exclusion rules were applied. Inclusion and exclusion criteria are presented. Reasons for exclusion do not appear to be related to exposure or outcome. Characteristics of participants and non-participants are not compared; however, characteristics of the 161 included children were provided and any differences were taken into account in the analysis.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposed groups were similar and were recruited using similar methods during the same time frame.
- **Confounding:**
 - **Rating:** Probably high risk of bias (-)
 - **Summary:** No confounders was considered when evaluating fluoride associations with intelligence; they were only applied when evaluating fluoride levels and dental caries. Based on Table 4 of the study, there was no significant association between IQ grade and child's age, sex, parental education, or SES status. No other information was reported or considered. There is no information on potential co-exposures. Based on water quality maps, the arsenic prediction indicates a greater than 50% probability of exceeding the WHO guidelines for arsenic of 10 µg/L in areas of Chihuahua, Mexico.
 - **Potentially important study-specific confounders:** Arsenic.
 - **Direction/magnitude of effect:** The direction and magnitude of effects is unknown. There is potential for arsenic to occur in the study area, but it is not known how it relates to fluoride exposure. If they occur together in the water, it will bias away from the null; however, if they occurred in different areas, there is potential to bias toward the null.
 - **Basis for rating:** Probably high risk of bias based on indirect evidence that there is potential for exposure to arsenic that was not sufficiently addressed.
- **Attrition:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** A total of 161 of 245 children were included in the study. Exclusion criteria are presented and are unrelated to outcome or exposure. For the 161 children, there are no missing outcome data.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Probably low risk of bias (+); Probably high risk of bias (-)
 - **Summary:** **Urinary Fluoride (probably low risk of bias):** First morning void urine samples were collected based on NIOSH methods. Water samples were also stated to be collected, but it does not appear that methods followed any particular standard, and there is no indication that subjects were provided with collection containers. Analysis was based on a calibration curve using fluoride ion selective electrode. QC methods were mentioned. Based on results, there were values below detection limits, but LODs or % below LOD were not reported.

Daily fluoride exposure (probably high risk of bias): Daily fluoride exposure was based on the water fluoride level, drinking water consumption (based on parental report of how many glasses of water consumed), and body weight.

- *Direction/magnitude of effect:* Spot urine samples that did not account for dilution could have exposure misclassification. The misclassification is likely non-differential and is not likely to bias in any specific direction. Daily exposure was based partially on parental report of water consumption. The direction and magnitude of effect is unknown.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure. The daily fluoride exposure is probably high risk of bias because there is indirect evidence that the exposure was assessed using methods of unknown validity.
- **Outcome:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* Intellectual ability was evaluated using Raven's Colored Progressive Matrices by an independent examiner. Some details were provided, but it was not stated that the tests were assessed blind; however, there is no indication that subjects were from high fluoride areas and the assessor would not have knowledge of the urine or water fluoride levels. Results for children were converted into a percentile according to age (details not provided) and overall scores were assigned an intellectual grade of I to V as described in the report.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods were reported in sufficient detail.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:*
 - *Statistical analyses:* The main analysis was for dental caries. Although they make conclusions on fluoride and IQ, they do not use the same analytical methods for both outcomes. Table 4 of the study provides a p-value although it is not clear what the p-value represents; it is presumed to be the Kruskal Wallis p-value. It appears that a Kolmogorov-Smirnov test was used to determine variable distribution and a Kruskal Wallis test was used to compare among the groups with a Dunn's test if significant.
 - *Other potential concerns:* None identified.
 - *Basis for rating:* Probably low risk if bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.

- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in exposure and outcome. Study strengths include individual exposure measurements and outcomes blindly assessed, but is limited by the cross-sectional study design, lack of accounting for urine dilution, and by not addressing potential exposures to arsenic in the study area.

Sudhir et al. (2009)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 13–15 years
- **Study area:** Nalgonda district (Andhra Pradesh), India
- **Sample size:** 1,000 children
- **Data relevant to the review:** Mean IQ grade (not standard scores) or IQ distribution by water fluoride strata (<0.7, 0.7–1.2, 1.3–4.0, and >4.0 ppm).
- **Reported association with fluoride exposure:** Yes: Significantly increased number of intellectually impaired children with increasing drinking water fluoride levels.

Risk of Bias:

- **Author contacts:**
 - Authors were contacted in September of 2017 for additional information related to risk-of-bias evaluation, but no response was received.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Children were selected from the same general population during the same time frame and were then broken down into nearly equal exposure groups. A cross-sectional study was conducted among 13–15-year-old school children of Nalgonda district, Andhra Pradesh between August and October 2006. Data were collected from the school children who were life-long residents of Nalgonda district, Andhra Pradesh and who consumed drinking water from the same source during the first 10 years of life. A stratified random sampling technique was used. The entire geographical area of Nalgonda district was divided into four strata based on different levels of naturally occurring fluoride in the drinking water supply. Children were randomly selected from schools in the different strata. It was noted that the 1,000 selected children were equally divided among all four strata, however, each group did not have 250 children (but instead 243–267 in each group). Participation rates are not reported. Exclusion criteria included: children who had a history of brain disease and head injuries, children whose intelligence had been affected by congenital or acquired disease, children who had migrated or were not permanent residents, children with orthodontic brackets, and children with severe extrinsic stains on their teeth. Age and gender data are presented in Table 1 of the study, but this information is not presented by the different fluoride groups.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that subjects were similar and were recruited using the same methods during the same time frame.

- **Confounding:**

- Rating: Probably low risk of bias (+)
- Summary: Data were collected using a self-administered questionnaire and clinical examination. The self-administered questionnaire requested information on demographic data (appears to cover age and sex), permanent residential address, staple food consumed, liquids routinely consumed, and aids used for oral hygiene maintenance (fluoridated or nonfluoridated). SES was measured using the Kakkar socio-economic status scale (KSESS) with eight closed-ended questions related to parental education, family income, father's occupation, and other factors. All children were asked to fill out the form, and the answers obtained were scored using Kakkar socio-economic status scoring keys. Based on this scoring, children were divided into three groups—lower class, middle class, or upper class. Age, sex, and SES were not found to be significantly associated with IQ. Other confounders including smoking were not addressed. Co-exposures such as arsenic and lead were not addressed; however, there is no indication that lead is a co-exposure in this population and arsenic is not likely a major concern in this area based on water quality maps.
- Potentially important study-specific confounders: Key confounders age, gender, and measures of SES were similar between exposure groups; however, arsenic was not taken into account. Arsenic often occurs in the drinking water along with fluoride in some Indian populations; however, based on water quality maps, this does not appear to be an issue in the Nalgonda district of Andhra Pradesh. Iodine deficiencies are not mentioned.
 - Direction/magnitude of effect: The presence of arsenic would potentially bias away from the null if present with fluoride. Deficiencies in iodine would bias away from the null if present in areas of high fluoride, but toward the null if present in areas of non-high fluoride.
- Basis for rating: Probably low risk of bias based on indirect evidence that the key confounders are considered, co-exposure to arsenic is likely not an issue in this area, and methods used for collecting the information were valid and reliable.

- **Attrition:**

- Rating: Definitely low risk of bias (++)
- Summary: Results were available for the 1,000 children selected to participate.
- Basis for rating: Definitely low risk of bias based on direct evidence of no attrition.

- **Exposure:**

- Rating: Probably low risk of bias (+)
- Summary: Children were placed into one of four strata based on the level of fluoride in drinking water. Collection of water samples was done in the districts. The placement into strata was based on fluoride levels obtained from documented records of District Rural Water Works Department. Once the children were assigned to strata, it was confirmed that the fluoride level of their drinking water was within the strata assigned. This was done using the methodology followed in National Oral Health Survey and Fluoride Mapping 2002–2003. During the initial visits to the schools, the children were interviewed regarding their history of residence and source of drinking water from birth to 10 years. The first child meeting criteria was given a bottle for water collection and

the next child was only given a bottle for collection if the water source was different than that of a previous child. Children were asked to collect the sample of water from the source that was used in the initial 10 years of their life and was collected the next day. It was not reported if all bottles were returned. The water samples collected were subjected to water fluoride analysis using an ion-specific electrode, Orion 720A fluoride meter at District Water Works, Nalgonda to confirm the fluoride levels in the water before commencement of clinical examination. LOD and QA/QC details were not reported.

- *Direction/magnitude of effect:* There is some potential for exposure misclassification based on recall of the children on the source of water used in their first 10 years of life. The misclassification is likely non-differential and not likely to bias in any specific direction. Children who had changed water since birth were excluded, but it was not specifically noted that the fluoride in the water source was stable over the years.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - *Rating:* Probably high risk of bias (NR)
 - *Summary:* The Raven's standard progressive matrices (1992 edition) was used to assess IQ. Exams were carried out by a single examiner. Calibration of the examiner was done before the study and in the middle of the study, but it was not clear if this applied to the IQ evaluation or only to the clinical examination. This Raven's test is a standard test and although there is no information provided to indicate that the methods were reliable and valid in the study population, this test was created to be culturally fair (+ for methods). Blinding or other methods to reduce potential bias were not reported (NR for blinding). No response was received to an e-mail request for clarification in September 2017. Overall rating for methods and blinding = NR.
 - *Basis for rating:* Probably high risk of bias based on indirect evidence that the outcome was not assessed blind and could bias the results.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:*
 - *Statistical analyses:* Statistical analyses were appropriate and no other threats to internal validity were identified.
 - *Other potential concerns:* None identified.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.

- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding and exposure. Study strengths include verification of exposure measurements and the addressing of potential key confounders, but it was limited by the cross-sectional study design and lack of information on blinding during outcome assessment.

Till *et al.* (2020)

Study Details:

- **Study design:** Prospective cohort
- **Population:** MIREC participants (pregnant mothers and their children aged 3–4 years)
- **Study area:** 10 cities, Canada
- **Sample size:** 398 mother–child pairs (247 from non-fluoridated areas, 151 from fluoridated areas; 200 breastfed as infants, 198 formula-fed as infants)
- **Data relevant to the review:** Adjusted linear regression models evaluating associations between IQ with water fluoride concentration (with or without adjusting for maternal urine) in formula-fed or breast-fed infants or by fluoride intake from formula.
- **Reported association with fluoride exposure:** Yes: Significantly lower performance IQ with water fluoride (adjusted β s = -9.26 formula-fed, -6.19 breastfed) and fluoride intake from formula (adjusted β = -8.76); significantly lower full-scale IQ with water fluoride in formula-fed (adjusted β = -4.40); no significant changes in full-scale IQ for water fluoride in breastfed children or fluoride intake from formula-fed children; no significant changes in verbal IQ scores with fluoride exposure.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Pregnant women were recruited between 2008 and 2011 by the MIREC program from 10 cities across Canada. Inclusion and exclusion criteria were provided. Additional details were stated to be available in Arbuckle *et al.* (2013). A total of 610 children were recruited to participate in the developmental follow-up with 601 children completing all testing. The demographic characteristics of women included in the current analyses ($n = 398$) were not substantially different from the original MIREC cohort ($N = 1945$) or the subset without complete water fluoride and covariate data ($n = 203$). A table of characteristics of the study population is provided. Approximately half of the children lived in nonfluoridated cities and half lived in fluoridated cities.
 - Basis for rating: Definitely low risk of bias based on direct evidence that the exposed groups were similar and were recruited with the same methods during the same time frame.
- **Confounding:**
 - Rating: Probably low risk of bias (+)

- Summary: Covariates were selected a priori that have been associated with fluoride, breast feeding, and children's intellectual ability. Final covariates included child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and HOME score. City was considered but was excluded from the models. Confounders that were not assessed include: parental mental health, iodine deficiency/excess, parental IQ, and co-exposure to arsenic and lead. Co-exposure to arsenic is less likely an issue in this Canadian population and the lack of information is not considered to appreciably bias the results.
- Potentially important study-specific confounders: All key confounders were considered in this study.
 - Direction/magnitude of effect: Not applicable.
- Basis for rating: Probably low risk of bias based on direct evidence that key confounders were addressed and indirect evidence that the methods used to collect the information were valid and reliable and co-exposures were not an issue.
- **Attrition:**
 - Rating: Probably low risk of bias (+)
 - Summary: Of 610 children, 601 (98.5%) in the MIREC developmental study who were ages 3–4 years completed the neurodevelopment testing. Of the 601 children who completed the neurodevelopmental testing, 591 (99%) completed the infant feeding questionnaire and 398 (67.3%) reported drinking tap water. It was noted that the demographic characteristics were not substantially different from the original MIREC cohort or the 203 subjects without complete water fluoride or covariate data.
 - Basis for rating: Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - Rating: Probably low risk of bias (+)
 - Summary: Information on breastfeeding was obtained via questionnaire at 30–48 months. Fluoride concentration in the drinking water was assessed by daily or monthly reports provided by water treatment plants. Water reports were first linked with mothers' postal codes and the daily or weekly amounts were averaged over the first 6 months of each child's life. Additional details can be found in Till *et al.* (2018). Maternal urinary exposure was used to assess fetal fluoride exposure. Procedures can be found in Green *et al.* (2019).
 - Direction/magnitude of effect: There is not any specific direction or magnitude of bias expected. Urinary fluoride levels are reflective of recent exposure. The possibility of the exposure misclassification would be similar in all subjects and would be non-differential. For the fluoride intake from formula, exposure was based on the fluoride levels in the water at the residence and the proportion of time that the infant was not exclusively breastfed. This exposure misclassification would also be non-differential.
 - Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**

- o Rating: Probably low risk of bias (+)
- o Summary: Intelligence was tested using the Wechsler Preschool and Primary Scale of Intelligence III. This is appropriate for both the study population and age group. This is considered a gold standard test. It was not reported whether the evaluators were blind to the child's fluoride exposure status during the assessment. Although it is unlikely that the assessors had knowledge of the specific drinking water levels or maternal urine levels, there is potential that the outcome assessors had knowledge of the city the child lived in and if the city was fluoridated or non-fluoridated. Correspondence with the study authors on the outcome assessment for Green *et al.* (2019) indicated that it was unlikely that the testers had knowledge of the city's fluoridation. The same is assumed here. Specific measurements included were identified.
- o Basis for rating: Probably low risk of bias based on indirect evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: All outcomes outlined in the abstract, introduction, and methods were reported in sufficient details.
 - o Basis for rating: Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - o Rating: Probably low risk of bias (+)
 - o Summary:
 - *Statistical analyses:* Regression diagnostics were used to test assumptions for linearity, normality, and homogeneity. There were two potential influential observations (based on Cook's distance), and sensitivity analyses re-estimated the models without these two variables. Effect modification by breastfeeding status was evaluated. Interestingly, all regression coefficients were divided by 2 to represent change in IQ per 0.5-mg/L change in fluoride. One concern is posed by the lack of accounting for city in the regression models, ideally as a random effect. The authors explored including city as a covariate in the models; however, city was not included either because it was strongly multi-collinear with water fluoride concentration (VIF > 20) (model 1, with water fluoride concentration) or because fluoride intake from formula is a function of water fluoride concentration (assessed at the city level) and was therefore deemed redundant (model 2). However, the models use city-level water fluoride concentrations (and in sensitivity analyses, adjust for maternal urinary fluoride) which warrant exploration of city as a random effect rather than a fixed effect (as would be by just having it included as a covariate). Even including individual-level maternal urinary fluoride might not fully account for lack of city, given that the subjects were from six different cities, with half of them fully on fluoridated water. Hence, even individual-level exposures are likely to be correlated at the city level. Based on a previous analysis (Green *et al.* 2019), it is unlikely that

exclusion of city from models (as a fixed or random effect) would impact the effect estimates.

- **Other potential concerns:** None identified.
- **Basis for rating:** Probably low risk if bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements, prospective cohort design, and the addressing of potential key confounders.

Trivedi et al. (2012)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 12–13 years
- **Study area:** Kachchh, Gujarat, India
- **Sample size:** 84 children
- **Data relevant to the review:** Mean IQ scores and distribution by low and high fluoride villages.
- **Reported association with fluoride exposure:** Yes: Significantly lower IQ score in the high fluoride (92.53 ± 3.13) compared to the low fluoride (97.17 ± 2.54) areas in boys and girls combined (as well as separately). Villages with higher fluoride levels had a larger percentage of subjects with IQ scores of 70–79, while the lower fluoride villages had a greater percentage of IQ scores > 109.

Risk of Bias:

- **Author contacts:**
 - Authors were contacted in September of 2017 to obtain additional information for risk-of-bias evaluation.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** There is insufficient information provided on the sampling methods to determine if the populations were similar. Although it was noted that samples were obtained for groundwater quality from March to May of 2011, there is no indication that the children were selected at the same time or during a similar time frame. Correspondence with the author indicates that children were selected within a week of the water collection based on random selection of a school in the village. Study participants were selected from six different villages of the Mundra region of Gujarat, India. Subjects were grouped into high and low villages based on the level of fluoride in the drinking water of those villages. The number of subjects per village were not reported, but it was noted that there were 50 children in the low fluoride group and 34 children in the high fluoride group. It is not clear if the differences in numbers were based on different participation rates or if there were fewer children in the high fluoride villages. Recruitment methods including any exclusion criteria and participation rates

were not provided. SES was stated to be low and equal based on questionnaire information, but the results were not provided. It should also be noted that only regular students (having attendance more than 80%) of standard 6th and 7th grades were selected, but it was not noted if attendance varied by village. Correspondence with the study author indicated that there was an average of 20 students per class with an average of 40 students per village. It appears that keeping the requirement for 80% attendance was a limiting factor that caused different numbers of children by area; however, this was applied similarly to both groups.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that subjects were similar and recruited using the same methods during the same time frame.

- **Confounding:**

- **Rating:** Probably low risk of bias (+)
- **Summary:** Children were stated to be students of the 6th and 7th standard grades. Age was not addressed, but the children would all be of similar age based on the grades included. Results were reported for males and females separately as well as combined. SES and iodine consumption were stated to be analyzed via a questionnaire and were standardized on the basis of the 2011 census of India. Although it was noted in the abstract that the SES was equal (no data provided), the study report did not mention the iodine results. Although the study authors did not address arsenic or lead, they did provide physicochemical analyses for the water samples from the six different villages. Information on arsenic in the water is not provided, but based on water quality maps, arsenic is not expected to be a major concern in this study area.
- **Potentially important study-specific confounders:** Key confounders age, gender, and measures of SES were similar between exposure groups; however, arsenic was not taken into account. Arsenic often occurs in the drinking water along with fluoride in some Indian populations; however, based on water quality maps, arsenic does not appear to be an issue in the study area.
 - **Direction/magnitude of effect:** Presence of arsenic would potentially bias away from the null if present with fluoride or toward the null if present in the reference group.
- **Basis for rating:** Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and reliable, that potential co-exposures were not an issue, and that key confounders were addressed.

- **Attrition:**

- **Rating:** Definitely low risk of bias (++)
- **Summary:** Results were provided for 84 children, but the methods do not indicate how many children were initially selected to participate nor were any exclusion criteria provided. It was noted in the results that 84 children had their groundwater and urine tested, but it was not noted if analyses were restricted to these children or if exposures were assessed in all the children who had IQ measurements. Correspondence with the study author indicated that the main reason for exclusion was a <80% attendance rate, with fluoride and IQ measured on all 84 children who met the criteria.
- **Basis for rating:** Definitely low risk of bias based on direct evidence of no attrition.

- **Exposure:**

- o Rating: Probably low risk of bias (+)
- o Summary: Children in villages were grouped based on fluoride levels that were assessed in groundwater (low F villages versus high F villages). The average concentration of these levels was considered to be the levels in the drinking water with confirmation using urinary fluoride levels. The groundwater samples were selected to cover major parts of the taluka and represent overall groundwater quality. Ten samples were obtained from each village. Fluoride was measured in the groundwater using ion exchange chromatography. Although urine levels were also significantly higher in the high fluoride village, no information was provided on how or when the urinary samples were obtained or how they were measured. However, correspondence with the study author indicated that the groundwater and urine fluoride levels were available for all 84 children indicating that the urine measures were available for the children that had IQ measures. The urine samples were stated to be collected at the same time that the second water sample was collected.
 - Direction/magnitude of effect: Fluoride levels were measured in both the drinking water and urine. Although there is some variability in the measurements, there is no overlap between the two groups and the urine and drinking water levels in the children support each other. Any potential exposure misclassification would be non-differential and direction and magnitude are unknown.
- o Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Outcome methods were only noted to be reported in Trivedi *et al.* (2007), which was scored as follows: IQ was measured in the children of both areas using a questionnaire prepared by Professor JH Shah, copyrighted by Akash Manomapan Kendra, Ahmedabad, India, and standardized on the Gujarati population with 97% reliability rate in relation to the Stanford-Binet Intelligence Scale (+ for methods). Blinding or other methods to reduce bias are not reported, but correspondence with the study author indicated that the teachers were blind to the status of fluoride. The teachers administered the tests in the presence of a research fellow. It is not completely clear who scored the tests, but it is assumed the teachers. (+ for blinding). Overall rating for methods and blinding = +.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that the outcomes were blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
 - o Basis for rating: Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**

- o Rating: Probably low risk of bias (+)
- o Summary:
 - *Statistical analyses:* Statistical analyses were reasonable (paired sample T-test), but consideration of homogeneity of variance was not reported.
 - *Other potential concerns:* No other threats to internal validity were identified.
- o Basis for rating: Probably low risk of bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements and the addressing of potential key confounders but was limited by the cross-sectional study design.

Valdez Jimenez *et al.* (2017)

Study Details:

- **Study design:** Prospective cohort
- **Population:** Infants aged 3–15 months
- **Study area:** Durango City and Lagos de Moreno, Jalisco, Mexico
- **Sample size:** 65 infants
- **Data relevant to the review:** The Bayley Scales of Infant Development II was used to assess Mental Development Index Scale and the Psychomotor Development Index scale in children 3 to 15 month and evaluated for associations with first and second trimester maternal urine fluoride.
- **Reported association with fluoride exposure:** Yes: Significant correlation between maternal urinary fluoride and MDI score during first trimester (adjusted $\beta = -19.05$; SE = 8.9) and second trimester (adjusted $\beta = -19.34$; SE = 7.46).

Risk of Bias:

- **Author contacts:**
 - o Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Subjects were recruited from two endemic areas in Mexico. The study authors do not provide information on the similarities or differences between the two areas nor do they indicate if there were different participation rates. However, recruitment methods were the same. Women receiving prenatal care in health centers located in Durango City and Lagos de Moreno, Jalisco, Mexico were recruited in 2013–2014. Participation rates are not likely to be an issue as characteristics were similar between those who participated and those who did not. Although they did not provide characteristics by area, the characteristics provided do not indicate any differences that may be biased by the selection. Considering the age range for the non-participants, the mean age for non-participants appears to be incorrect (or the age range is incorrect);

however, there does not appear to be a difference that would potentially indicate selection bias.

- **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited with the same methods in the same time frame, with no evidence of differences or issues with participation/response rates.
- **Confounding:**
 - **Rating:** Probably high risk of bias (-)
 - **Summary:** Questionnaires were used to obtain information about sociodemographic factors, prenatal history, mother's health status before pregnancy (e.g., use of drugs, vaccines, diseases) and the type of water for drinking and cooking. The marginalization index (MI) was obtained from the National Population Council (CONAPO). Two additional surveys were conducted during the 2nd and 3rd trimester of pregnancy to get information about the mother's health, pregnancy evolution, and sources of water consumption. A survey was also conducted to get information about childbirth (type of birth, week of birth, weight and length of the baby at birth, Apgar and health conditions of the baby during the first month of life). This information was corroborated with the birth certificate. Linear regression models included gestational age, children's age, marginality index, and type of drinking water. Bivariate analysis was conducted on the other factors including child's gender prior to conducting multivariable regression models. Some important confounders were not considered, including parental mental health, IQ, smoking, and potential co-exposures.
 - **Potentially important study-specific confounders:** Arsenic is a potential co-exposure in this area of Mexico.
 - *Direction/magnitude of effect:* If arsenic were present as a co-exposure it would bias the results away from the null.
 - **Basis for rating:** Probably high risk of bias based on indirect evidence that there is a potential for co-exposure with arsenic that was not addressed.
- **Attrition:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Out of the 90 women selected for inclusion in the study, 65 approved the participation of their infants. The authors provide a table of characteristics between women who consented to their children's cognitive evaluation and those that only participated in biological monitoring. There were no significant differences between the groups. There were fewer women who provided urine during the second and third trimesters. All specified children are included in the relevant analyses.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Fluoride exposure is assessed through morning urine samples and water fluoride levels collected from the children's homes. Sampling methodology is appropriately documented, and water levels were quantified through specific

ion-sensitive electrode assays. QC was described and accuracy was >90%. Urinary fluoride was corrected by specific gravity.

- *Direction/magnitude of effect:* Not applicable.

- *Basis for rating:* Definitely low risk of bias based on direct evidence that exposure was consistently assessed using well-established methods that directly measured exposure.

- **Outcome:**

- *Rating:* Definitely low risk of bias (++)

- *Summary:* Neurodevelopment was assessed with the Bayley Scales of Infant Development II (BSDI-II) that was noted to be reliable and valid for evaluating children from 3 months to 5 years of age. The average age of children assessed was 8 months, with a range of 3–15 months) (++) for methods). The study report stated that a trained psychologist who was blinded about the mother’s fluoride exposure evaluated the infants at home (++) for blinding). Overall rating for methods and blinding = ++.

- *Basis for rating:* Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.

- **Selective Reporting:**

- *Rating:* Probably low risk of bias (+)

- *Summary:* All outcomes outlined in the abstract, introduction, and methods were reported. Table 4 of the study only displays data for trimesters 1 and 2. Although 3rd trimester data were collected, they were not reported, likely because data were only available for 29 subjects. No discussion of this was provided.

- *Basis for rating:* Probably low risk of bias because, although it appears some data were not reported, it is likely because there were insufficient data and not because the authors were selectively reporting the results.

- **Other potential threats:**

- *Rating:* Definitely low risk of bias (++)

- *Summary:*

- *Statistical analyses:* Statistical analyses used were appropriate for the study.
- *Other potential concerns:* No other potential concerns were identified. In the peer-review report, NASEM (2020) cited the following as potential concerns: “the large difference in numbers of males and females in the offspring (20 males, 45 females), and apparently incorrect probabilities were reported for age differences between participants and nonparticipants, high rates of cesarean deliveries and premature births among participants (degree of overlap not reported), and incorrect comparisons of observed prematurity rates with national expected rates.” However, these concerns were taken in consideration in other domains (**Selection, Confounding**).

- *Basis for rating:* Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.

- **Basis for classification as lower risk-of-bias study overall:** Definitely low risk-of-bias ratings in exposure and outcome. Study strengths include individual exposure measurements and

outcome blindly assessed, but it is limited by the cross-sectional study design and lack of accounting for potential co-exposures to arsenic.

Wang *et al.* (2012)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 8–13 years (possibly the same population as Xiang *et al.* (2003a))
- **Study area:** Wamiao and Xinhuai villages located in Sihong County, Jiangsu Province, China
- **Sample size:** 526 school children
- **Data relevant to the review:** Mean IQ and % low IQ (< 80) by total fluoride intake.
- **Reported association with fluoride exposure:** Yes: Significantly lower mean IQ in the high fluoride village (92.02 ± 13.00) compared to the control village (100.41 ± 13.21); when high exposure group was broken into 4 exposure groups, a dose-dependent decrease in IQ and increase in % with low IQ observed; significant correlation between total fluoride intake and IQ ($r = -0.332$); OR for IQ<80 per increase in total fluoride intake=1.106; 95% CI 1.052–1.163).

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** The study appears to be the same population as Xiang *et al.* (2003a) and Xiang *et al.* (2011); however, the study does not cite these studies as providing additional information and numbers of children differ; therefore, it may be a separate analysis on the same villages. The years of testing were not provided so it cannot be determined if study subjects are the same. Two villages, Wamiao and Xinhuai, located 64 km apart in Sihong County, Jiangsu Province were selected for the study. Wamiao is a village in a region with severe endemic fluorosis and Xinhuai is a village in a non-endemic fluorosis region. Neither village has fluoride pollution from coal or industrial sources. Villages were stated to be similar in terms of annual per capita income, transportation, education, medical conditions, the natural environment, and lifestyle. All primary students ages 8–13 years currently in school in either village were surveyed with exclusions noted. Of 243 children from Wamiao, 236 (97.12%) were included, and of 305 children from Xinhuai, 290 (95.08%) were included. No table of subject characteristics was provided.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited using the same methods within the same time frame, with direct evidence that there was no difference in participation/response rates.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Logistic regression of low IQ rate and total fluoride intake adjusted for age and sex. Both villages had hand-pumped well water for drinking water, but the authors

do not mention if arsenic was also present in the drinking water. However, a publication by Xiang *et al.* (2013) on this study area indicates that Xinhuai (the low fluoride area) had significantly higher arsenic levels compared to Wamiao (the endemic fluorosis area), which would bias toward the null. Areas were stated to be similar in annual per capita income, transportation, education, medical conditions, the natural environment, and lifestyle; however, no details were provided. This study did not address other co-exposures, but other studies on populations in these villages (Xiang *et al.* 2011, Xiang *et al.* 2003a) indicate that iodine and lead are not concerns.

- **Potentially important study-specific confounders:** Arsenic often occurs in the drinking water along with fluoride in some Chinese populations; however, based on information provided in Xiang *et al.* (2013), arsenic concentrations were higher in the low fluoride area compared to the high fluoride area.
 - **Direction/magnitude of effect:** Presence of arsenic in this study population would potentially bias toward the null.
- **Basis for rating:** Probably low of risk bias because there is indirect evidence that the key confounders are take into account, methods used for collecting the information were valid and reliable, and co-exposures to arsenic and lead and iodine deficiency are not attributing to the effect observed in this area.
- **Attrition:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Data are reported for all 526 children noted to be included in the study. There is a slight discrepancy in the reported total number of children from the high-fluoride village and the number of participants from the high-fluoride village between this paper (236 participated of 243 total children) and the 2003 and 2011 publications on the same study population (222 of 238). This discrepancy is not explained but is not expected to appreciably bias the results.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - **Rating:** Probably low risk of bias (+); Probably high risk of bias (-)
 - **Summary:** **Water fluoride (+ probably low risk of bias):** Exposure was based on drinking water levels and fluoride intake. Residents in the Wamiao village were divided into five groups based on fluoride levels in the drinking water. Clean, dry polyethylene bottles were used to collect 50 mL of drinking water from each student's household and fluoride content was measured.

Total fluoride intake (- probably high risk of bias): Six families from each of the five Wamiao groups were randomly selected as dietary survey households. Intakes of various foods by each person at each meal and intakes of unboiled water, boiled water, and tea were surveyed for four consecutive days. Methods for food collection were described. Five representative households from each village were selected based on geographic location, population distribution, housing structure, and other conditions. Indoor air samples were collected once daily for five consecutive days; outdoor air was sampled at two points once daily for five days. Methods for determining fluoride

content in samples were noted to follow specific guidelines. Calculation of total fluoride intake was stated to follow Appendix A of the People's Republic of China Health Industry Standard with some details provided. Although it is assumed the method is valid, it was not detailed how each fluoride determination was made for each subject, and it appears that total fluoride intake was determined based on data from select subjects and not all subjects.

- *Direction/magnitude of effect:* There is potential for exposure misclassification based on calculating fluoride intake based on measurements from a few select subjects rather than all subjects. The direction and magnitude of effect cannot be assessed based on the information provided.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure. The intake is probably high risk of bias because there is indirect evidence that the exposure was assessed using methods of unknown validity.
- **Outcome:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* IQ of each child was measured with the Combined Raven's Test for Rural China (CRT-RC) (++) for methods). The test was stated to be administered to the children independently in a school classroom under the supervision of three exam proctors. Testing methods, testing language, and testing conditions were all in strict accordance with the CRT-RC guidebook. Major testing personnel received necessary training by the Psychology Department of East China Normal University. The children undergoing IQ testing and the test scorers were kept double-blinded throughout the testing process. (++) for blinding). Overall rating= ++.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:*
 - *Statistical analyses:* Although it was noted that a logistic regression was used to determine the odds of having low IQ with increasing fluoride intake, no details were provided on any of the other tests conducted. Because this is the same population evaluated in Xiang *et al.* (2003a) and Xiang *et al.* (2011), it is assumed that the same methods were used even if this study population consisted of different children.
 - *Other potential concerns:* None identified.

- ***Basis for rating:*** Probably low risk if bias based on indirect evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements with blinding at outcome assessment but is limited by the cross-sectional study design and not using individual measurements to calculate fluoride intake. All key confounders were accounted for in the study design or analysis, but there is potential for the presence of arsenic to bias toward the null.

Wang *et al.* (2020a)

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** School children aged 7–13 years
- ***Study area:*** Tongxu County, China
- ***Sample size:*** 325 school children
- ***Data relevant to the review:*** Associations between ADHD and other measures of learning disability with urine fluoride concentrations.
- ***Reported association with fluoride exposure:*** Yes: Significant correlation between psychosomatic problems and urinary fluoride (adjusted $\beta = 4.01$ [95% CI: 2.74, 5.28]) and increased risk of a T-score > 70 with increasing urinary fluoride (adjusted OR = 1.97 [95% CI: 1.19, 3.27]). No significant associations with ADHD or other measures of learning disability.

Risk of Bias:

- ***Author contacts:***
 - Authors were contacted in July of 2020 to obtain additional information for risk-of-bias evaluation. No response was received.
- ***Population selection:***
 - ***Rating:*** Probably low risk of bias (+)
 - ***Summary:*** Subjects were recruited in 2017 from Tongxu County, China. Children were selected from four randomly selected primary schools in the area. Selection was based on specified inclusion rules. It was noted that the living habits and diets of the participants from the four schools were well matched, but details were not provided. The area did not have industrial pollution within 1 km of the living environment of the children, and it was noted that the children were not exposed to other neurodevelopmental toxicants (lead, cadmium, arsenic, or mercury). A table of subject characteristics was provided in the study, but not by school or exposure. This is a pilot study, and it is not explicitly stated if all eligible subjects participated in the study. There is no information on participation rates or if they varied by school.
 - ***Basis for rating:*** Probably low risk of bias based on indirect evidence that the exposed groups were recruited using similar methods during the same time frame and that any differences between the exposed groups were considered in the statistical analyses.

- **Confounding:**

- Rating: Probably low risk of bias (+)
- Summary: It was noted that subjects were well matched in terms of living habits and diets, but there were no specifics provided. It was noted that there was no industrial exposure or exposure to other neurotoxins such as lead, cadmium, arsenic, or mercury. Covariates were collected using a standardized and structured questionnaire completed by the children and their guardians under the direction of investigators, but reliability or validity of the questionnaire was not reported. Information collected included age, gender, weight, height, parental education level, and parental migration (or work as migrant workers). IQ scores evaluated by the Combined Raven's Test-the Rural in China were used to represent basic cognitive function. Models were adjusted for age, BMI, gender, mother and father migration, and urinary creatinine. Adjustments were not made for parental education, race/ethnicity, maternal demographics (e.g., maternal age, BMI), parental behavioral and mental health disorders (e.g., ADHD, depression), smoking (e.g., maternal smoking status, secondhand tobacco smoke exposure), reproductive factors (e.g., parity), iodine deficiency/excess, maternal (and paternal) IQ, quantity and quality of caregiving environment (e.g., HOME score), or SES other than parental migration. There is no evidence to suggest that SES would differ substantially among the four rural schools in the same area of China that were randomly selected.
- Potentially important study-specific confounders: SES.
 - Direction/magnitude of effect: Direction and magnitude is unknown. It was noted that the subjects were matched in terms of living habits and diet and this could be an indication that SES was not different among the groups, but details were not provided.
- Basis for rating: Probably low risk of bias because there is indirect evidence that the key confounders are considered, that the methods for collecting the information were valid and reliable, and that co-exposure to arsenic is not an issue in this area.

- **Attrition:**

- Rating: Definitely low risk of bias (++)
- Summary: Data are complete. It was noted that there were 325 subjects included and results were available on all subjects.
- Basis for rating: Definitely low risk of bias based on direct evidence that there was no attrition.

- **Exposure:**

- Rating: Probably low risk of bias (+)
- Summary: Spot urine samples were collected from each child in the early morning into cleaned polyethylene tubes. Fluoride concentrations were measured using fluoride ion-selective electrode (with reference to Ma *et al.* (2017); however, that reference cites Zhou *et al.* (2012). Therefore, no QC methods or LODs were available. Fluoride concentrations were creatinine-adjusted.
 - Direction/magnitude of effect: Spot urine samples only account for recent exposure. Although this could cause there to be some exposure misclassification, the number of subjects should help dilute any issues with the non-differential misclassification.

- *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using acceptable methods that provide individual levels of exposure.
- **Outcome:**
 - *Rating:* Probably high risk of bias (NR)
 - *Summary:* Children's behavior was assessed by the Chinese version of the Conners' Parent Rating Scale-Revised (CPRS-48). The homogeneity reliability of Cronbach α in the Chinese version of CPRS-48 was 0.932; the correlation of Spearman-brown split-half was 0.900; and the retest reliability of total score was 0.594. Raw scores for each subscale are converted into sex- and age-adjusted T-scores within a mean $\pm$ standard deviation (SD) of 50 $\pm$ 10. The guardians independently completed the CPRS-48 according to the instruction manual under the direction of trained investigators (++ for methods). Blinding is not reported. Although it is unlikely that the outcome assessors were aware of the fluoride levels in the urine, it is unclear if subjects were selected based on areas with endemic fluoride or if parents were aware of fluoride concentrations in the areas. (NR for blinding). Overall rating for methods and blinding = NR.
 - *Basis for rating:* Probably high risk of bias based on no information provided to indicate that the outcome was blindly assessed.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes in the abstract, introduction, and methods are reported in sufficient details.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:*
 - *Statistical analyses:* Multiple linear regression models were used to assess the fluoride association with each behavioral outcome. Logistic regression was used to assess the risk of behavioral problems due to fluoride exposure, but what they used to delineate a behavioral problem was not specified. Sensitivity analyses were performed.
 - *Other potential concerns:* None identified.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that the statistical analyses were appropriate and no other potential threats to risk of bias were identified.
- **Basis for classification as lower risk-of-bias study overall:** Probably low risk-of-bias ratings in confounding and exposure. Study strengths include individual exposure measurements, but it is limited by the cross-sectional study design and lack of details on blinding of the outcome assessment. All key confounders were considered in the study design or analysis.

Study Details:

- **Study design:** Cross-sectional
- **Population:** School children aged 7–13 years
- **Study area:** Tianjin City, China (possibly a subset of the children from Yu *et al.* (2018))
- **Sample size:** 571 school children
- **Data relevant to the review:** IQ scores by urine and water fluoride levels.
- **Reported association with fluoride exposure:** Yes: Significant correlations between IQ score and water fluoride (adjusted $\beta = -1.587$ per 1-mg/L increase) and urinary fluoride (adjusted $\beta = -1.214$ per 1-mg/L increase).

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Subjects were from a cross-sectional study conducted in 2015, but no citation was provided on this cohort (presumably the Yu *et al.* (2018) cohort). It was noted that the subjects in that cohort were from districts with historically high or normal fluoride levels. Subjects for this study were selected by using a stratified and multistage random sampling approach. Brief description was provided. The study area consisted of three historically high fluoride areas and four nonendemic areas. A flow diagram was provided for inclusion and exclusion, but this detail was given for all children and not by area. Therefore, it cannot be determined if the participation differed by area. However, there was a 93% recruitment rate, and the 13 excluded due to missing data are not likely excluded due to exposure. Detailed characteristics of the study population are provided. Exclusion criteria included: "children who had congenital or acquired diseases affecting intelligence, or a history of cerebral trauma and neurological disorders, or those with a positive screening test history (like hepatitis B virus infection, Treponema palladium infection and Down's syndrome) and adverse exposures (smoking and drinking) during maternal pregnancy, prior diagnosis of thyroid disease, and children who had had missing values of significant factors (2.2%) were also excluded."
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that the exposed groups were recruited using similar methods during the same time frame and that any differences between the exposed groups were accounted for in the statistical analyses.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Study authors noted that the study areas are not exposed to other neurotoxins such as lead, arsenic, or mercury nor were they iodine-deficient. Final models included child's age, child's gender, child's BMI, maternal and paternal education, household income, and low birth weight. Other potential confounders that were considered is unclear as they only noted that the confounders were selected based on current literature. Reasons for exclusion included history of disease affecting intelligence, history of trauma or neurological disorders, positive screening test history,

or exposures such as smoking or drinking during pregnancy. Information was obtained by questionnaire or measurements. Variables such as parental BMI, behavioral and mental health disorders, IQ, and quantity and quality of the caregiving environment were not addressed.

- o Potentially important study-specific confounders: All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
- o Basis for rating: Probably low risk of bias because there is direct evidence that the key confounders are taken into account, indirect evidence that the methods for collecting the information were valid and reliable, and co-exposure to arsenic is not an issue in this area.
- **Attrition:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: A detailed chart of the recruitment process is presented. The study had a 93% recruitment rate and only 2.2% of subjects with missing data for certain covariates were excluded.
 - o Basis for rating: Definitely low risk of bias based on direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- **Exposure:**
 - o Rating: Probably low risk of bias (+)
 - o Summary: Children provided spot urine samples, presumably at the time of examination. Water samples were randomly collected from public water supplies in each village. Fluoride concentrations were analyzed using fluoride ion-selective electrode according to the national standardized method in China. There is no indication if the urine samples accounted for dilution.
 - *Direction/magnitude of effect:* Not accounting for dilution could cause there to be some exposure misclassification. The direction and magnitude would depend on where the differences occurred.
 - o Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using acceptable methods that provide individual levels of exposure.
- **Outcome:**
 - o Rating: Definitely low risk of bias (++)
 - o Summary: Assessments of IQ scores were conducted by graduate students at the School of Public Health, Tongji Medical College at the Huazhong University of Science and Technology. Each team member was assigned a single task, meaning that only one person would have conducted the IQ tests. A Combined Raven's Test for Rural China was used. Therefore, the test was appropriate for the study population (++) for method). It was note that the examiner was trained and blind to the exposure (++) for blinding). Overall = ++
 - o Basis for rating: Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.

- **Selective Reporting:**
 - Rating: Definitely low risk of bias (++)
 - Summary: All outcomes in the abstract, introduction, and methods are reported in sufficient details.
 - Basis for rating: Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - Rating: Definitely low risk of bias (++)
 - Summary:
 - *Statistical analyses:* Statistical analyses were appropriate and no other threats to internal validity were identified. Logistic and multivariate regression models accounting for potential confounders were used. Results are presented as betas or odds ratios and 95% confidence intervals. Regression diagnostics were conducted for all models, including examination of multicollinearity, heteroscedasticity, and influential observations. Mediation and interaction analyses were appropriate. The stratified and multistage random sampling approach for subject selection and the fact that selected villages are similar in population and general demographic characteristics helps to ensure that there was no need to account for village-level effects even when the analysis used water samples from the village.
 - *Other potential concerns:* None identified.
 - Basis for rating: Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and no other potential threats to risk of bias were identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements but is limited by the cross-sectional study design and lack of accounting for urine dilution. All key confounders were considered in the study design or analysis.

Xiang *et al.* (2003a)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 8–13 years
- **Study area:** Wamiao and Xinhuai villages located in Sihong County, Jiangsu Province, China
- **Sample size:** 512 school children
- **Data relevant to the review:** Comparison of IQ (mean and distribution) between Wamiao County (a severe endemic fluorosis area) and Xinhuai County (non-endemic fluorosis area); additional breakdown of the Wamiao area into 5 water fluoride exposure groups.
- **Reported association with fluoride exposure:** Yes: Significant dose-related effect of drinking water fluoride on IQ score based on quintile levels with significantly lower IQ scores observed with water fluoride levels of 1.53 mg/L or higher. Pearson correlation coefficient of -0.164 with urinary fluoride. IQ scores for children in the non-endemic region (100.41 ± 13.21) were

significantly higher than the endemic region (92.02 ± 13.00). The lower-bound confidence limit benchmark concentration (BMCL) of 1.85 mg/L was calculated.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: Two villages, Wamiao and Xinhuai, located 64 km apart in Sihong County, Jiangsu Province were selected for this study, which was conducted between September and December 2002. Wamiao is located in a severe fluorosis endemic area, and Xinhuai is located in a non-endemic fluorosis area. Neither village has fluoride pollution from burning coal or other industrial sources. All eligible children in each village were included; children who had been absent from either village for 2 years or longer or who had a history of brain disease or head injury were excluded. In Wamiao, 93% of the children (222 out of 238) were included for the study, while in Xinhuai, 95% were included (290 out of 305). The children in Wamiao were divided into five subgroups according to the level of fluoride in their drinking water: <1.0 mg/L (group A), 1.0–1.9 mg/L (group B), 2.0–2.9 mg/L (group C), 3.0–3.9 mg/L (group D), and >3.9 mg/L (group E). Children in Xinhuai (0.18–0.76 mg F/L in the drinking water) served as a control group (group F). Demographic characteristics are not presented, and statistical analyses are not adjusted, but mean IQ scores are stratified by child's age, child's gender, family income, and parental education.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited using the same methods within the same time frame, with direct evidence that there was no difference in participation/response rates.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: Although information was stated to be collected on personal characteristics, medical history, education levels of the children and parents, family SES, and lifestyle, only child's gender, child's age, family income, and parental education were addressed. Other potential co-exposures, such as arsenic, were not addressed. A separate publication in 2003 [(Xiang *et al.* 2003b), letter to the editor], indicated that blood lead levels were not significantly different between the two areas. Although arsenic was not addressed specifically in this publication, Xiang *et al.* (2013) measured both fluoride and arsenic in the Wamiao and Xinhuai areas. Xinhuai (the low fluoride area) had significantly higher arsenic levels compared to Wamiao (the endemic fluorosis area). This is likely to bias toward the null; however, the study observed a significantly lower IQ score in the endemic fluorosis area. Iodine was tested in a subset of the children and found not to be significantly different between the two groups.
 - Potentially important study-specific confounders: Arsenic often occurs in the drinking water along with fluoride in some Chinese populations; however, based on information provided in Xiang *et al.* (2013), arsenic concentrations were higher in the low fluoride area compared to the high fluoride area.

- *Direction/magnitude of effect:* Presence of arsenic in this study population would potentially bias towards the null.
 - *Basis for rating:* Probably low risk of bias because there is indirect evidence that the key confounders are taken into account, methods used for collecting the information were valid and reliable, and co-exposures to arsenic and lead and iodine deficiency are not attributing to the effect observed in this area.
- **Attrition:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* Data are complete. IQ results were reported for all 512 children included in the study (222 in the endemic area and 290 in the nonendemic area).
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that there was no attrition.
- **Exposure:**
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* Exposure was based on drinking water and urinary levels of fluoride. The two study areas were selected to reflect a severe endemic area and a nonendemic area. Drinking water was collected from wells and early-morning spot urine samples were collected from a randomly-selected subsample of children. Both water and urine samples were measured using fluoride ion-selective electrode, but no quality control was discussed. Both absolute and creatinine-adjusted urine results were reported.
 - *Direction/magnitude of effect:* There is potential for exposure misclassification because only current levels were assessed. Migration of subjects in or out of the area was not assessed, but the study authors noted that, if the children had been absent from the village for 2 or more years, they were excluded. Misclassification would likely be non-differential, which could bias the results in either direction.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* The IQ of each child was measured with the Combined Raven's Test for Rural China (CRT-RC) (++) for methods). The test was stated to be administered to the children independently in a school classroom, in a double-blind manner, under the supervision of an examiner and two assistants, and in accordance with the directions of the CRT-RC manual regarding test administration conditions, instructions to be given, and test environment. (++) for blinding). Overall rating= ++
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.

- **Basis for rating:** Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:**
 - **Statistical analyses:** Data were stated to be analyzed using SAS without reporting the tests conducted. Results provided in the tables indicate that a t-test was conducted, but it was not reported that homogeneity of variance was tested or confirmed. In addition, correlations were tested with Pearson's correlation.
 - A potential concern raised by the NASEM (2020) peer review was the lack of accounting for relationships in exposure between persons from the same village. However, only two villages were included, and the analyses consisted of village-level comparisons; hence, accounting for clustering was not possible. Without controlling for village effects and given the large differences in fluoride concentrations and IQ between villages, the apparent dose-response relationship could be due to a village effect in addition to a fluoride effect. However, the dose-response relationship is still present within the “exposed” village, diminishing the concern for a village-only effect.
 - **Other potential concerns:** None identified.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that statistical analyses were appropriate and that there were no other threats to risk of bias.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements and outcomes blindly assessed but is limited by the cross-sectional study design and lack of accounting for urine dilution. All key confounders were considered in the study design or analysis, but there is potential for the presence of arsenic to bias toward the null.

Xiang *et al.* (2011)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 8–13 years (same population as Xiang *et al.* (2003a))
- **Study area:** Wamiao and Xinhuai villages located in Sihong County, Jiangsu Providence, China
- **Sample size:** 512 school children
- **Data relevant to the review:** Mean IQ scores and odds ratio for having an IQ < 80 presented by serum fluoride quartiles.
- **Reported association with fluoride exposure:** Yes: Significant trend on association between quartiles of serum fluoride and children's IQ score < 80 (adjusted ORs for Q1 and Q2; Q1 and Q3; and Q1 and Q4, respectively: 1; 2.22 [95% CI: 1.42, 3.47]; and 2.48 [95% CI: 1.85, 3.32]); significant effects at ≥ 0.05 ppm fluoride.

Risk of Bias:

- **Author contacts:**
 - Authors were not contacted for additional information because it was not necessary.
- **Population selection:**
 - Rating: Probably low risk of bias (+)
 - Summary: The study population is the same as that was used in the Xiang *et al.* (2003a) study, but a few more measurements were available and different analyses were conducted. The comparison population is considered the same as previously based on the study populations being recruited from similar populations, using similar methods, during the same time frame. Demographic characteristics were not provided.
 - Basis for rating: Probably low risk of bias based on indirect evidence that the exposure groups were similar and were recruited using the same methods within the same time frame, with direct evidence that there was no difference in participation/response rates.
- **Confounding:**
 - Rating: Probably low risk of bias (+)
 - Summary: As was noted in the 2003 publication, information was collected on personal characteristics, medical history, education levels in the children and parents, family SES, and lifestyle. In the logistic regression model, age and gender were adjusted in the analysis. In the previous report, no significant associations were observed between groups for family income and parents' education. Urinary iodine and blood lead levels were also stated to be measured and were noted not to be significantly different between the groups. Although the iodine levels were reported in the previous publication, the lead levels were not reported nor were the methods. Lead information is reported in a letter to the editor (Xiang *et al.* (2003b)) and was not significantly different between the areas. Although arsenic was not addressed specifically in this publication, Xiang *et al.* (2013) measured both fluoride and arsenic in the Wamiao and Xinhuai areas. Xinhuai (the low fluoride area) had significantly higher arsenic levels compared to Wamiao (the endemic fluorosis area). This is likely to bias toward the null; however, the study observed a significantly lower IQ score in the endemic fluorosis area and with increasing serum fluoride.
 - Potentially important study-specific confounders: Arsenic often occurs in the drinking water along with fluoride in some Chinese populations; however, based on information provided in Xiang *et al.* (2013), arsenic concentrations were higher in the low fluoride area compared to the high fluoride area.
 - Direction/magnitude of effect: Presence of arsenic in this study population would potentially bias toward the null.
 - Basis for rating: Probably low of risk bias because there is indirect evidence that the key confounders are taken into account, methods used for collecting the information were valid and reliable, and co-exposures to arsenic and lead and iodine deficiency are not attributing to the effects observed in this area.
- **Attrition:**
 - Rating: Definitely low risk of bias (++)
 - Summary: Data are reported for all 512 children noted to be included in the study.
 - Basis for rating: Definitely low risk of bias based on direct evidence that there was no attrition.

- **Exposure:**

- Rating: Probably low risk of bias (+)
- Summary: Fluoride levels were measured in serum with a fluoride ion-selective electrode. A fasting venous blood sample was used. No details are provided on validation (including correlation with drinking water levels) or QA. Children who did not reside in their village for at least 2 years were excluded. Results were provided in quartiles, but they combined the lower two quartiles with results ranging from <0.05 mg/L to >0.08 mg/L.
 - *Direction/magnitude of effect:* Serum fluoride may not be the best estimate for exposure. There is potential for exposure misclassification because only current levels were assessed. Migration of subjects in or out of the area was not assessed, but the study authors noted that, if the children had been absent from the village for 2 or more years, they were excluded. Misclassification would likely be non-differential, which could bias results in either direction.
- Basis for rating: Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.

- **Outcome:**

- Rating: Definitely low risk of bias (++)
- Summary: IQ was assessed as part of the 2003 evaluation. IQ was measured with the Combined Raven's Test for Rural China which is appropriate for this population (++ for methods). Although this study does not provide details, the original study article from 2003 provides specific details. The study authors indicate in the 2003 publication that the tests were conducted in a double-blind manner and these are the same results and population (++ for methods). Overall rating=++
- Basis for rating: Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.

- **Selective Reporting:**

- Rating: Definitely low risk of bias (++)
- Summary: All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.
- Basis for rating: Definitely low risk of bias based on direct evidence that all measured outcomes were reported.

- **Other potential threats:**

- Rating: Definitely low risk of bias (++)
- Summary:
 - *Statistical analyses:* Statistical analyses conducted were appropriate for the study. Chi square tests were used to compare categorical variables, and logistic regression was used to evaluate the association between serum fluoride levels and risk of low IQ. A potential concern raised by the NASEM (2020) peer review was the lack of accounting for relationships in exposure between persons from the same village. However, only two villages were included, and the analyses consisted of village-level comparisons; hence, accounting for clustering was not possible. Without controlling for village effects and given the large differences in

fluoride concentrations and IQ between villages, the apparent dose-response relationship could be due to a village effect in addition than a fluoride effect. However, the dose-response relationship is still present within the “exposed” village, diminishing the concern for a village-only effect.

- **Other potential concerns:** None identified.
- **Basis for rating:** Definitely low risk if bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements with blinding at outcome assessment but is limited by the cross-sectional study design and use of serum concentrations. All key confounders were considered in the study design or analysis, but there is potential for the presence of arsenic to bias toward the null.

Yu et al. (2018)

Study Details:

- **Study design:** Cross-sectional
- **Population:** Children aged 7–13 years
- **Study area:** Tianjin City, China
- **Sample size:** 2,886 school children
- **Data relevant to the review:** IQ for normal (≤ 1 mg/L) versus high (> 1 mg/L) water fluoride; betas for IQ score by water and urine fluoride groupings; ORs by IQ category using water and urine fluoride levels.
- **Reported association with fluoride exposure:** Yes: Significant difference ($p = 0.036$) in mean IQ scores in high (106.4 ± 12.3) versus normal (107.4 ± 13.0) water fluoride areas. Distribution of IQ scores was also significantly different ($p = 0.003$); every 0.5-mg/L increase in water fluoride (between 3.40 and 3.90 mg/L) was associated with an IQ score 4.29 points lower (95% CI: $-8.09, -0.48$).

Risk of Bias:

- **Author contacts:**
 - Authors were contacted in September 2018 to obtain additional information for the risk-of-bias evaluation.
- **Population selection:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** School children (2,886), aged 7–13 years, were recruited from the rural areas of Tianjin City, China. After exclusion, 1,636 children were assigned to the "normal-fluoride" exposure group and 1,250 were assigned to the "high-fluoride" exposure group based on a cut-off water fluoride level of 1.0 mg/L. A multi-stage random sampling technique, stratified by area, was performed to select representative samples among local children who were permanent residents since birth. Detailed characteristics of the study population are provided. Exclusion criteria included: 1) children who had

congenital or acquired diseases affecting intelligence, 2) children with a history of cerebral trauma and neurological disorders, 3) children with a positive screening test history (like hepatitis B virus infection, Treponema palladium infection and Down's syndrome), and 4) children with adverse exposures (smoking and drinking) during maternal pregnancy. A table of characteristics was provided by fluoride level with differences adjusted in the analysis.

- **Basis for rating:** Definitely low risk of bias based on direct evidence that the exposed groups were recruited using similar methods during the same time frame and that any differences between the exposed groups were considered in the statistical analyses.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Demographic data were collected by trained investigators during a face-to-face interview with the recruited children and their parents. Questionnaires were not stated to be validated. The developmental status of the children was further assessed by calculation of BMI, and all measurements were conducted by nurses based on recommended standard methods. Variables that presented differential distribution between the normal-fluoride and high-fluoride exposure groups were adjusted in the linear regression analysis of IQ data and included age, sex, paternal and maternal education levels, and low birth weight. Children exposed to smoking in utero were excluded from the study. Sensitivity analyses were conducted by modifying covariates adjusted in multivariable models among demographics (age and sex); development (BMI); socioeconomics (maternal education, paternal education, and household income); history of maternal disease during pregnancy (gestational diabetes, malnutrition, and anemia); and delivery conditions (hypoxia, dystocia, premature birth, post-term birth, and low birth weight). None of the study sites selected were in areas endemic for iodine deficiency disorders nor were other potential neurotoxins like lead, arsenic, and mercury present. Variables such as parental BMI and behavioral and mental health disorders were not addressed.
 - **Potentially important study-specific confounders:** All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that methods of obtaining the information were valid and reliable and direct evidence that all key confounders and co-exposures were addressed.
- **Attrition:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** There were 1,636 children assigned to the "normal-fluoride" exposure group based on water fluoride, and 1,250 children were assigned to the "high-fluoride" exposure group. Exclusion from the original group of 2,886 children was adequately described. A total of 2,380 children provided urine samples. There is no indication that the data presented excludes any additional children or urine samples, but results do not indicate a sample size for all results.

- *Basis for rating:* Probably low risk of bias based on indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
- ***Exposure:***
 - *Rating:* Probably low risk of bias (+)
 - *Summary:* According to the annual surveillance data from the CDC, the drinking water sources and water fluoride concentrations in each village had remained at stable levels over the past decade. During the investigation, water samples were collected randomly from the public water supplies in each village. Spot (early-morning) urine samples from every child and water samples from each village were collected in pre-cleaned, labeled polythene tubes and transported to the lab within 24 hours while frozen. Samples were stored at –80°C until analysis. Concentrations of fluoride ions (mg/L) were analyzed using the national standardized ion-selective electrode method in China; the detection limit was 0.01 mg/L. Samples were diluted with an equal volume of total ionic strength adjusted buffer (TISAB) of pH 5–5.5 for optimal analysis. Double-distilled deionized water was used throughout the experiment. There is no reporting of any QC methods.
 - *Direction/magnitude of effect:* Spot urine samples may lead to non-differential exposure misclassification. The large population size likely dilutes any potential effects of occasional misclassification. Because the drinking water sources of fluoride had been noted to be stable for the past decade and the children were 13 years or younger, there would only be exposure misclassification if there was a lot of migration between areas.
 - *Basis for rating:* Probably low risk of bias based on indirect evidence that exposure was consistently assessed using well-established methods that directly measured exposure.
- ***Outcome:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* IQ scores were measured using the second edition of Combined Raven's Test-The Rural in China (CRT-RC2) for children aged 7–13 years (++ for methods). The test was completed by each participant within 40 minutes according to the instruction manual. For each test, 40 children were randomly allocated to one classroom to take the test independently under the supervision of four trained professionals. There is no mention of whether the evaluators were blinded to the fluoride group of each child (normal vs. high fluoride) or whether there were steps taken to ensure consistency in scoring across the evaluators. It is also not clear if the 40 children randomly assigned to the classroom were specific to the village or if a local center was used. Correspondence with the study authors indicated that the four professionals worked together throughout the examination without knowledge of the child's fluoride exposure (++ for blinding).
 - *Basis for rating:* Definitely low risk of bias based on the direct evidence that the outcome was blindly assessed using instruments that were valid and reliable.
- ***Selective Reporting:***
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All outcomes outlined in the abstract, introduction, and methods are reported in sufficient detail.

- o *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- ***Other potential threats:***
 - o *Rating:* Definitely low risk of bias (++)
 - o *Summary:*
 - *Statistical analyses:* Statistical analyses used were appropriate for the study.
 - *Other potential concerns:* None identified.
 - o *Basis for rating:* Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- ***Basis for classification as lower risk-of-bias study overall:*** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements with blinding at outcome assessment but is limited by the cross-sectional study design and lack of accounting for urine dilution. All key confounders including potential co-exposures were considered in the study design or analysis.

Zhang *et al.* (2015b)

Study Details:

- ***Study design:*** Cross-sectional
- ***Population:*** Children aged 10–12 years
- ***Study area:*** Tianjin City, China
- ***Sample size:*** 180 children
- ***Data relevant to the review:*** IQ by control and high fluoride groups; IQ correlations with water, serum, or urinary fluoride levels; betas for IQ with urinary fluoride levels (by genotypes)
- ***Reported association with fluoride exposure:*** Yes: Significant correlation between IQ score and serum fluoride ($r = -0.47$) and urinary fluoride ($r = -0.45$); significant difference in IQ score for high-fluoride area (>1 mg/L; 102.33 ± 13.46) compared with control area (<1 mg/L; 109.42 ± 13.30).

Risk of Bias:

- ***Author contacts:***
 - o Authors were not contacted for additional information because it was not necessary.
- ***Population selection:***
 - o *Rating:* Definitely low risk of bias (++)
 - o *Summary:* Subjects were similar and recruited during the same time frame using the same methods. Authors recruited schoolchildren from a high fluoride area (1.40 mg/L) and a control area (0.63 mg/L) in Tianjin City, China. In accordance with the principles of matching social and natural factors such as educational standard, economic situation, geological environments as much as possible, two areas with different fluoride concentrations in the groundwater were selected by a stratified cluster random sampling of this region. A total of 180 5th grade children aged 10 to 12 years from two primary schools located 18 km apart in the Jinnan District were recruited—Gegu Second

Primary School (from an endemic fluorosis area) and Shuanggang Experimental Primary School (from a non-endemic fluorosis area). The areas are not affected by other drinking water contaminants, such as arsenic or iodine. All subjects were unrelated ethnic Han Chinese and residents in Tianjin with similar physical and mental health status. The authors excluded subjects with known neurological conditions including pervasive developmental disorders and epilepsy. Descriptive statistics of the study population are presented by exposure group in Table 1 of the study. A number of potential differences are taken into account in the statistical analyses.

- **Basis for rating:** Definitely low risk of bias based on direct evidence that the exposure groups were similar and recruited using similar methods during the same time frame.
- **Confounding:**
 - **Rating:** Probably low risk of bias (+)
 - **Summary:** Covariates included in the statistical models were child's age, child's gender, educational levels of parents, drinking water fluoride (mg/L), and levels of thyroid hormones (T3, T4, and TSH). Authors report that the study areas are not affected by other contaminants such as arsenic or iodine and residents were of similar physical and mental health status. Other important confounders (maternal demographics, smoking, reproductive health) were not considered. Covariate data were obtained from a study questionnaire.
 - **Potentially important study-specific confounders:** All key confounders were considered in this study.
 - *Direction/magnitude of effect:* Not applicable.
 - **Basis for rating:** Probably low risk of bias based on indirect evidence that the methods used to collect the information were valid and reliable and direct evidence that key confounders including potential co-exposures were addressed.
- **Attrition:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Results are complete for the 180 children selected for the study.
 - **Basis for rating:** Definitely low risk of bias based on direct evidence that there was no attrition.
- **Exposure:**
 - **Rating:** Definitely low risk of bias (++)
 - **Summary:** Drinking water samples (10 mL) were collected from the tube wells of each child's household. Three fasting venous blood samples were also collected. Urine samples were collected in the early morning before breakfast. Fluoride contents in drinking water (W-F), serum (S-F), and urine (U-F) were measured using an ion analyzer EA940 with a fluoride ion-selective electrode (Shanghai constant magnetic electronic technology Co, Ltd, China) according to the China standard GB 7484-87. All reference solutions for the fluoride determinations were double-deionized water. Parallel samples were set for determination and averages were taken. The quantitation limits of this method for W-F, S-F, and U-F were 0.2, 0.012, and 0.5 mg/L, respectively. Recovery rates for this method were in the range of 94.3%–106.4%. The intra- and inter-assay coefficients of variation for fluoride were 2.7% and 6.7%, respectively. Dilution of the urinary fluoride was not addressed.

- *Direction/magnitude of effect:* Not applicable.
- *Basis for rating:* Definitely low risk of bias based on direct evidence that the exposure was consistently assessed using well-established methods that directly measured exposure.
- **Outcome:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* A Combined Raven's Test for Rural China (CRT-RC) was taken to evaluate the IQ of each child (++) for methods). The study report stated that all tests were administered at school by a trained examiner who was masked to participants' drinking water fluoride levels (++) for blinding). Overall rating for methods and blinding=++.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that the outcome was blindly assessed using instruments that were valid and reliable in the study population.
- **Selective Reporting:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:* All results outlined in the abstract, introduction, and methods sections were reported in sufficient detail.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that all measured outcomes were reported.
- **Other potential threats:**
 - *Rating:* Definitely low risk of bias (++)
 - *Summary:*
 - *Statistical analyses:* Statistical methods are very well-documented including testing for normality of the data.
 - *Other potential concerns:* None identified.
 - *Basis for rating:* Definitely low risk of bias based on direct evidence that the statistical analyses were appropriate and there were no other potential threats to risk of bias identified.
- **Basis for classification as lower risk-of-bias study overall:** Definitely or probably low risk-of-bias ratings in confounding, exposure, and outcome. Study strengths include individual exposure measurements, outcomes blindly assessed, and assessment of potential key confounders including potential co-exposures.

Appendix 5. Results of Fluoride Meta-analyses

What is the strength of the relationship between exposure to fluoride and children's IQ?

Aim 1. To update existing meta-analyses with additional studies

Approach

The approach used to perform a meta-analysis of the associations between exposure to fluoride and children's IQ levels was outlined in the associated protocol (<https://ntp.niehs.nih.gov/go/785076>). Details are presented below.

The mean-effect meta-analysis included studies that reported effect estimates as mean outcome measures and included measures of uncertainty such as standard deviation (SD), standard error (SE), 95% CI, and number of subjects (N) for at least one exposed and one reference exposure group. If results from multiple exposure groups were reported within a single study, the highest exposure group was considered the "exposed" group and the lowest exposure group was considered the "reference" group. A sensitivity analysis was performed to evaluate the impact of using any exposed group compared to the reference group (**Figure A-25**). This was accomplished by combining the information from the exposure groups using the approach outlined in the Cochrane Handbook for Systematic Reviews (Higgins *et al.* 2019).

When results were not reported for gender-specific groups or age-specific subgroups (<10, ≥10), they were calculated (if possible) by combining groups, following the approach outlined in the Cochrane Handbook for Systematic Reviews (Higgins *et al.* 2019). Similarly, when only mean effects, Ns, and p-values for differences between groups are reported (Lin *et al.* 1991), SDs were calculated using the SE and t-statistic (assuming equal variances) (Higgins *et al.* 2019).

The meta-analysis pooled the standardized mean difference and corresponding 95% CI using a random-effects model. Heterogeneity was assessed by Cochran's Q test (Cochran 1954) and the I² statistic. Forest plots were used to display results and to examine possible heterogeneity between studies. Potential publication bias was assessed by developing funnel plots and performing Egger regression on the estimates of effect size (Begg and Mazumdar 1994, Egger *et al.* 2008, Egger *et al.* 1997). If publication bias was believed to be present, trim-and-fill methods (Duval and Tweedie 2000a, b) were used to estimate the number of missing studies affected by publication bias, assess the effect of those studies on the effect estimate, and predict the impact of the hypothetical "missing" studies. To investigate sources of heterogeneity, subgroup analyses were performed by risk-of-bias evaluation, gender, age group, country, type of intelligence assessment, and type of exposure.

There were 46 studies included in the mean-effect meta-analysis (see **Table A5-1**). **Table A-2** presents information on the studies excluded from the analysis because of missing information on the number of subjects and/or the mean or variance of the outcome. Other studies were excluded because of overlapping study populations. For studies with overlapping populations (i.e., multiple studies that use the same cohort), results were selected with the most information considering the following factors: exposure metric, exposure range, exposure period, number of subjects, and statistical adjustment for potential confounders. Other studies were excluded from the mean-effect meta-analysis because they reported individual-level effects.

Summary Results

Table A5-1. Pooled SMDs and 95% CIs for Children's IQ Score and Exposures to Fluoride				
Analysis	Number of Studies	SMD (95% CI)	Heterogeneity	
			p-value	I ²
Overall Effect	46	-0.50 (-0.61, -0.39)	<0.001	89%
Subgroup Analyses				
Risk of Bias				
Lower	9	-0.31 (-0.52, -0.10)	<0.001	87%
Higher	37	-0.56 (-0.68, -0.43)	<0.001	88%
Gender ¹				
Males	12	-0.78 (-0.99, -0.56)	<0.001	75%
Females	11	-0.65 (-0.85, -0.45)	0.001	66%
Age Group				
<10 years ¹	10	-0.55 (-0.79, -0.30)	<0.001	83%
≥ 10 years	11	-0.58 (-0.78, -0.38)	<0.001	76%
Country				
China	31	-0.44 (-0.54, -0.33)	<0.001	86%
India	9	-1.02 (-1.54, -0.51)	<0.001	93%
Iran	4	-0.68 (-0.99, -0.38)	0.077	56%
Assessment Type				
CRT-RC tests	23	-0.36 (-0.47, -0.26)	<0.001	81%
Non-CRT-RC tests	23	-0.67 (-0.87, -0.47)	<0.001	90%
Raven's tests	10	-0.76 (-1.10, -0.43)	<0.001	91%
Other tests	13	-0.62 (-0.88, -0.35)	<0.001	90%
Exposure Type				
Water fluoride	28	-0.45 (-0.57, -0.34)	<0.001	85%
Dental fluorosis	7	-0.99 (-1.57, -0.41)	<0.001	96%
Other exposures ²	11	-0.47 (-0.67, -0.27)	<0.001	85%
Sensitivity Analysis				
Any exposure vs. reference	46	-0.46 (-0.58, -0.35)	<0.001	92%
Previous Meta-analyses				
Duan <i>et al.</i> (2018)	26	-0.52 (-0.62, -0.42)	<0.001	69%
Choi <i>et al.</i> (2012)	27	-0.45 (-0.56, -0.34)	<0.001	80%

Notes:

CI = confidence interval; CRC-RC = Combined Raven's Test–The Rural edition in China; SMD = standardized weighted mean difference

¹An *et al.* (1992) includes 10-year-old children in the <10 age group (7–10 years reported).

²Includes iodine (Ren *et al.* 1989 [translated in Ren *et al.* 2008], Lin *et al.* 1991, Wang *et al.* 2001); arsenic (Zhang *et al.* 1998, Wang *et al.* 2007); aluminum (Sun *et al.* 1991); and non-drinking water fluoride (i.e., fluoride from coal burning (Guo *et al.* 1991 [translated in Guo *et al.* 2008a], Li *et al.* 1994 [translated in Li *et al.* 2008b], Li *et al.* 1995, Wang *et al.* 1996 [translated in Wang *et al.* 2008b], Wang *et al.* 2005, Li *et al.* 2009, Bai *et al.* 2014)).

Overall Effect (Main Analysis)

For the group-level exposure meta-analysis, a comparison on the mean outcome measure (IQ score) was conducted across two exposure groups (“exposed” and “reference”). The random-effects pooled SMD estimated from the 46 studies included in the meta-analysis was -0.50 (95% CI: $-0.61, -0.39$). There was evidence of heterogeneity ($I^2 = 89\%$, $p < 0.001$; [Table A5-1](#) and [Figure A5-1](#)) and publication bias (funnel plot and Egger’s test $p < 0.001$, Begg’s test $p = 0.08$; [Figure A5-2](#) and [Figure A5-3](#)). Eliminating publication bias through trim-and-fill analysis continued to support the finding that exposure to fluoride is associated with lower IQ in children, with an adjusted pooled effect estimate of -0.42 (95% CI: $-0.54, -0.30$) ([Figure A5-4](#) and [Figure A5-5](#)).

Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017) studies were excluded from the main analysis due to uncertainties about the way IQ assessments for children were performed in those studies. A sensitivity analysis was conducted that included these studies ([Figure A-35](#)).

Subgroup Analyses

Risk of Bias

Subgroup analysis by risk-of-bias evaluation showed that exposure to fluoride is associated with lower IQ scores in children for both higher and lower risk-of-bias studies ([Figure A5-6](#)), with a more severe effect for the higher risk-of-bias studies. The funnel plots and Egger’s and Begg’s tests of publication bias showed evidence of publication bias only among higher risk-of-bias studies ([Figure A-1](#), [Figure A-2](#)). Eliminating publication bias through trim-and-fill analysis continued to support that exposure to fluoride is associated with lower IQ scores in children, with an adjusted pooled effect estimate of -0.35 (95% CI: $-0.50, -0.21$) ([Figure A-4](#)). There was no evidence of publication bias among lower risk-of-bias studies.

Gender

Subgroup analysis by gender showed that exposure to fluoride is associated with lower IQ scores in both males and females ([Figure A5-11](#)). There was a slight suggestion of publication bias in the Egger’s test for males, but not females ([Figure A-5](#) and [Figure A-6](#)). Eliminating publication bias through trim-and-fill analysis continued to support that exposure to fluoride is associated with lower IQ scores in males, with an adjusted pooled SMD estimate of -0.68 (95% CI: $-0.90, -0.46$) ([Figure A-8](#)).

Age Group

Subgroup analysis by age group showed that exposure to fluoride is associated with lower IQ scores in children regardless of age group (<10 years or ≥ 10 years) ([Figure A5-12](#)). The funnel plots and Egger’s and Begg’s tests of publication bias showed evidence of publication bias in children younger than 10 years old ([Figure A-9](#) and [Figure A-10](#)). Eliminating publication bias through trim-and-fill analysis for studies in children younger than 10 years old continued to support that exposure to fluoride is associated with lower IQ in children, with an adjusted pooled effect estimate of -0.55 (95% CI: $-0.79, -0.30$) ([Figure A-10](#)). There was no suggestion of publication bias in the subgroup analyses for children 10 years old and older.

Country

Subgroup analysis by country showed that exposure to fluoride is associated with lower IQ scores in children in China, India, and Iran ([Figure A5-13](#)), with the largest effect in India. A funnel plot with the SEs of the SMD plotted against the SMD from each study showed slight evidence of publication bias in India ([Figure A-11](#)). In addition, Egger’s and Begg’s tests of publication bias revealed evidence of publication bias for studies in India ($p < 0.001$, [Figure A-12](#)). Eliminating publication bias through trim-and-fill analysis for studies in India continued to support that exposure to fluoride is associated with

lower IQ in children, with an adjusted pooled effect estimate of -1.49 (95% CI: $-2.15, -0.83$) (Figure A-13). There was no suggestion of publication bias in the subgroup analyses for China or Iran.

Assessment Type

Subgroup analysis by assessment type showed that exposure to fluoride is associated with lower IQ scores in children tested using non-CRT-RC tests than using CRT-RC tests (Figure A5-14). The funnel plots and Egger's and Begg's tests of publication bias showed evidence of publication bias only among non-CRT-RC and Raven's tests (Figure A-15 and Figure A-16). Eliminating publication bias through trim-and-fill analysis for studies with Raven's tests continued to support that exposure to fluoride is associated with lower IQ scores in children, with an adjusted pooled SMD estimate of -1.22 (95% CI: $-1.68, -0.75$) (Figure A-19 and Figure A-20). There was no suggestion of publication bias in the subgroup analysis for studies using CRT-RC or other types of tests.

Exposure Type

Subgroup analysis by exposure type showed that exposure to fluoride is associated with lower IQ scores in children in studies that reported mean effects by fluoride exposure type (Figure A5-15). The funnel plots and Egger's test of publication bias showed evidence of publication bias for water fluoride and dental fluorosis (Figure A-21 and Figure A-22). Eliminating publication bias through trim-and-fill analysis continued to support that exposure to fluoride in water is associated with lower IQ scores in children, with an adjusted pooled SMD estimate of -0.42 (95% CI: $-0.53, -0.30$) (Figure A-23 and Figure A-24). There was no suggestion of publication bias in the subgroup analysis for studies with other exposures or non-drinking water fluoride exposures.

Overall Analysis

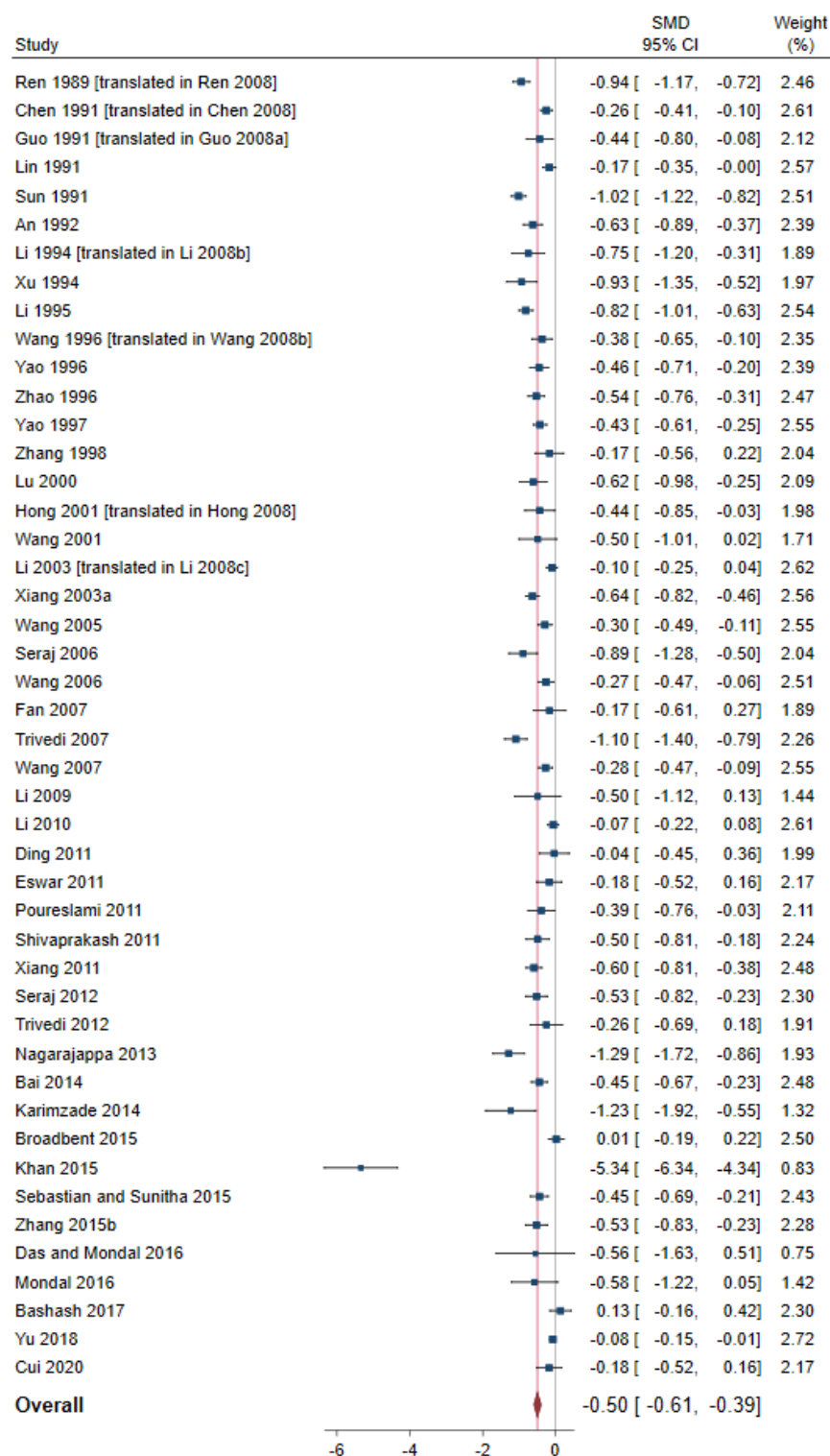


Figure A5-1. Association Between Fluoride Exposure and IQ Scores in Children: Overall Analysis

SMDs for individual studies are shown with solid boxes representing the weight, and the random-effects pooled SMD is shown as a solid diamond. Horizontal lines represent 95% CIs for the study-specific SMDs.

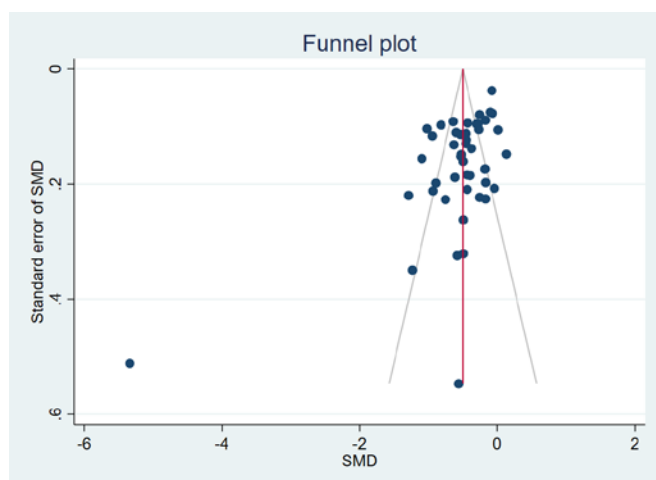


Figure A5-2. Funnel Plot of Included Studies

This funnel plot shows individual studies included in the analysis according to random-effect standardized weighted mean difference (SMD) estimates (x-axis) and the standard error (SE) of each study-specific SMD (y-axis). The solid vertical line indicates the pooled SMD estimate for all studies combined and the dashed lines indicated pseudo 95% confidence limits around the pooled SMD estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -3.21
      SE of beta1 =    0.649
           z =      -4.95
      Prob > |z| =    0.0000

Begg's test for small-study effects

Kendall's score =   -185.00
      SE of score =   105.617
           z =      -1.76
      Prob > |z| =    0.0815
```

Figure A5-3. Test for Publication Bias

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right			
Iteration	Number of studies =		50
Model: Random-effects	observed =		46
Method: DerSimonian-Laird	imputed =		4
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.502	-0.611	-0.393
Observed + Imputed	-0.419	-0.537	-0.301

Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left			
Iteration	Number of studies =		56
Model: Random-effects	observed =		46
Method: DerSimonian-Laird	imputed =		10
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.502	-0.611	-0.393
Observed + Imputed	-0.643	-0.776	-0.511

Figure A5-4. Trim-and-fill Analysis

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in pooled SMD).

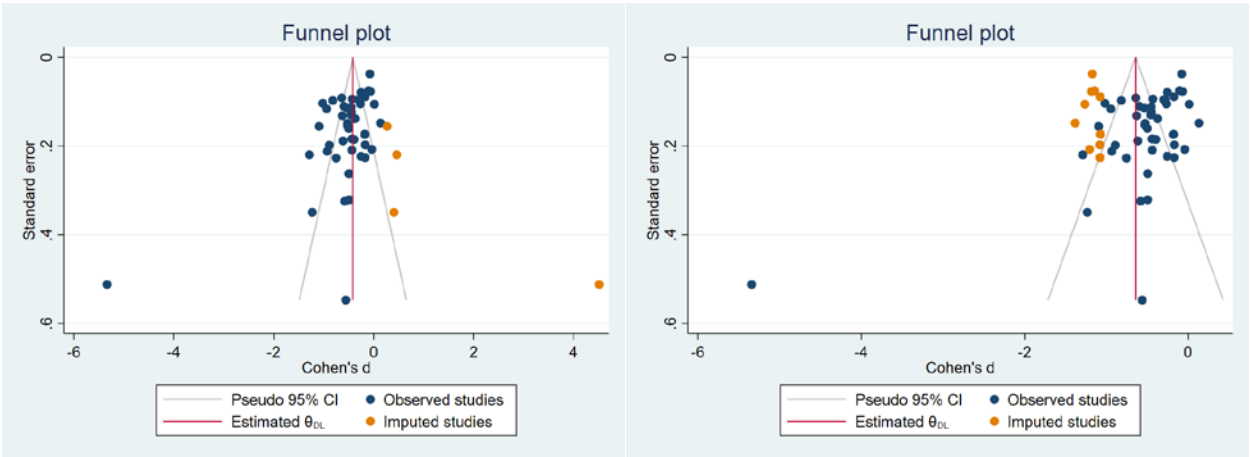


Figure A5-5. Filled-in Funnel Plots to Eliminate Publication Bias

Left panel shows the funnel plot filled in to the right using a run estimator (the linear estimator to the right showed no change in pooled SMD); right panel shows the funnel plot filled in to the left using a linear estimator (the run estimator to the left showed no change in pooled SMD).

Risk-of-bias Subgroup Analysis

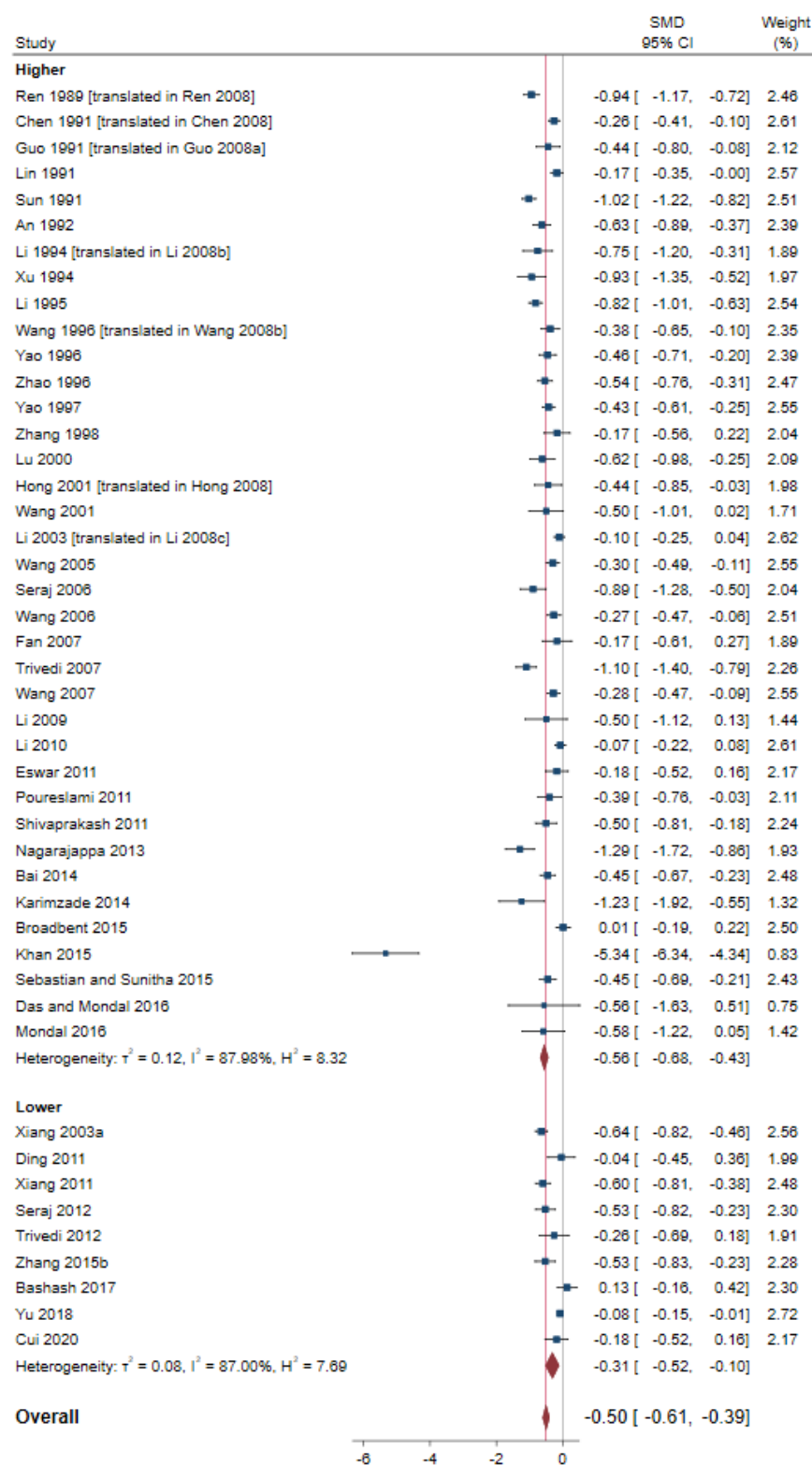


Figure A5-6. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Risk of Bias

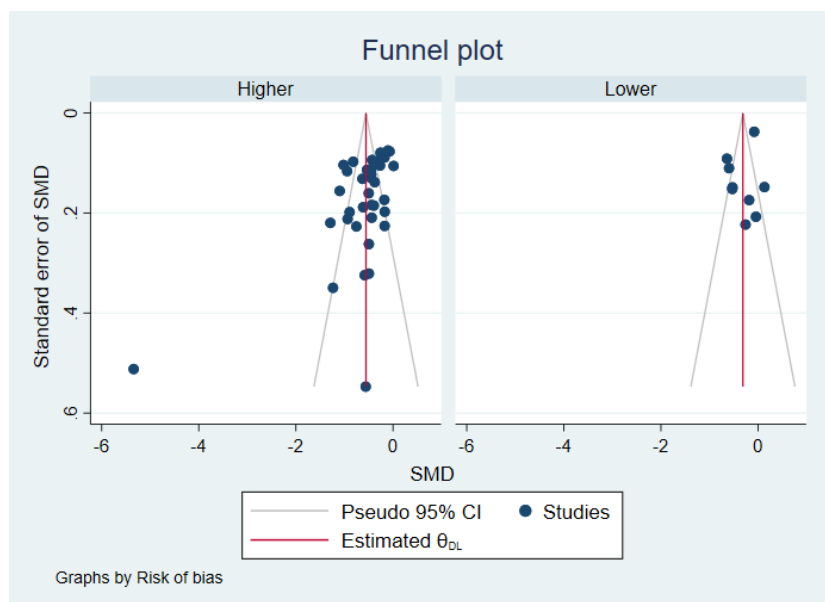


Figure A5-7. Funnel Plot by Risk-of-bias Evaluation

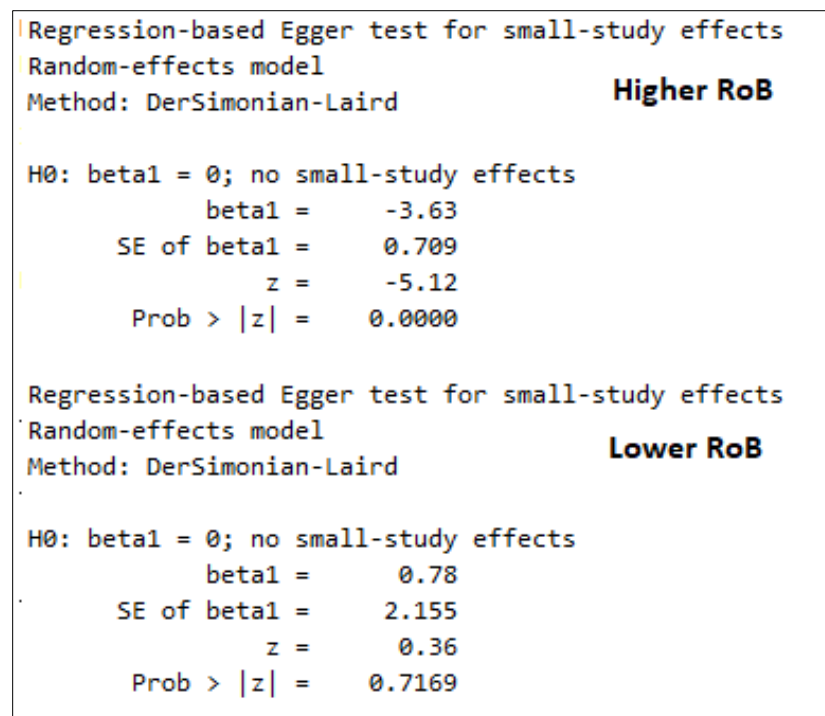


Figure A5-8. Test for Publication Bias by Risk of Bias

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left					
Iteration		Number of studies =		46	Iteration		Number of studies =		44
Model: Random-effects		observed =		37	Model: Random-effects		observed =		37
Method: DerSimonian-Laird		imputed =		9	Method: DerSimonian-Laird		imputed =		7
Pooling					Pooling				
Model: Random-effects					Model: Random-effects				
Method: DerSimonian-Laird					Method: DerSimonian-Laird				
Studies		Cohen's d		[95% Conf. Interval]	Studies		Cohen's d		[95% Conf. Interval]
Observed		-0.556		-0.684 -0.428	Observed		-0.556		-0.684 -0.428
Observed + Imputed		-0.354		-0.498 -0.210	Observed + Imputed		-0.684		-0.831 -0.537

Figure A5-9. Trim-and-fill Analysis for Higher Risk-of-bias Studies

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in the pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in the pooled SMD).

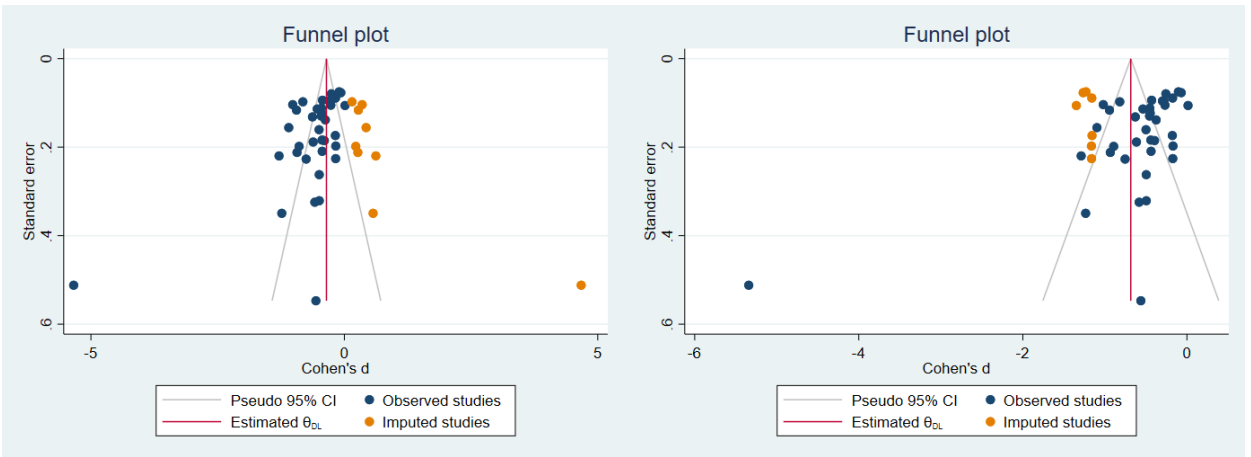


Figure A5-10. Filled-in Funnel Plots to Eliminate Publication Bias for Higher Risk-of-bias Studies

Left panel shows funnel plot filled in to the right using a run estimator (the linear estimator to the right showed no change in the pooled SMD); right panel shows the funnel plot filled in to the left using a linear estimator (the run estimator to the left showed no change in the pooled SMD).

Gender Subgroup Analysis

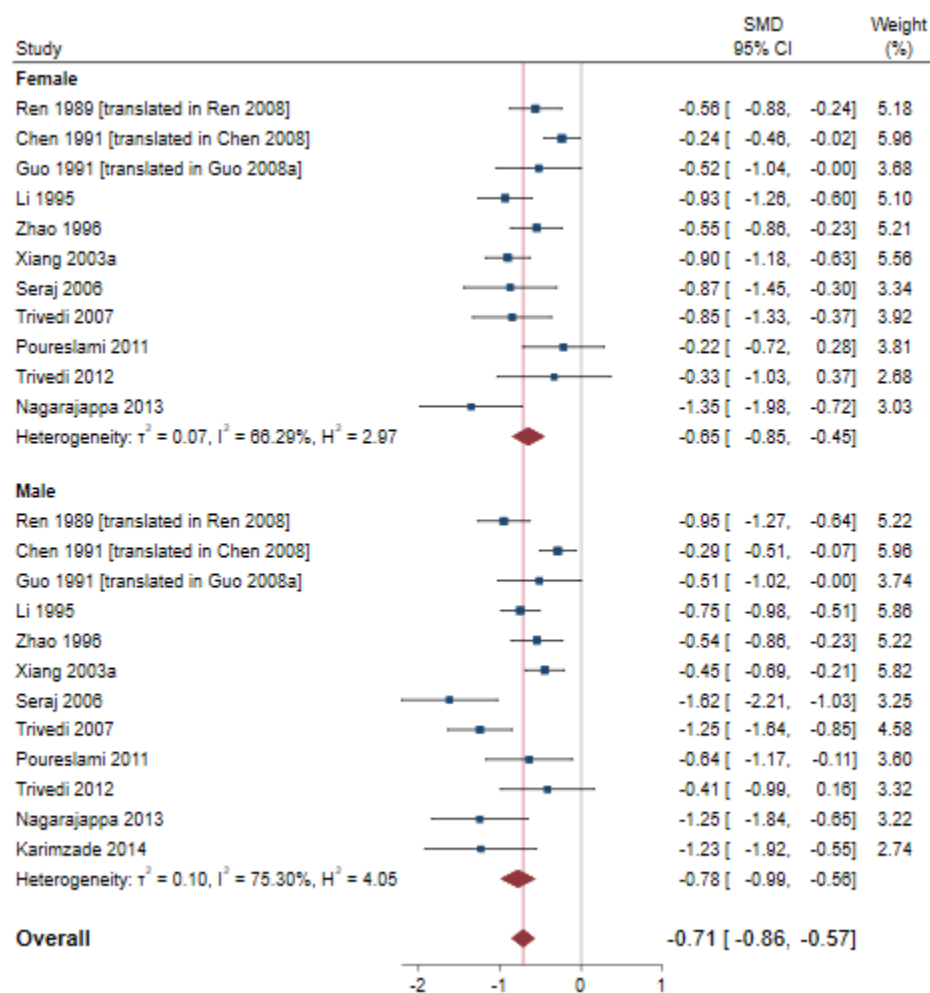


Figure A5-11. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Gender

Age Group Subgroup Analysis

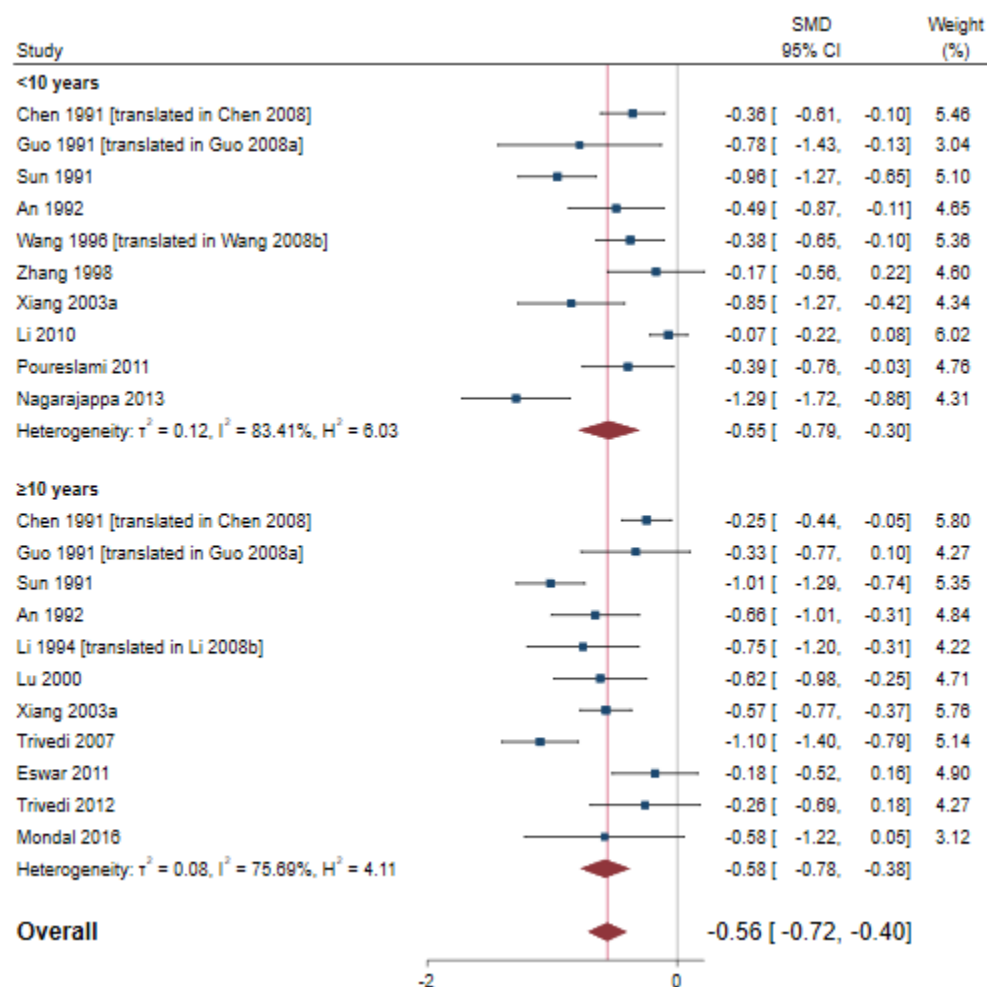


Figure A5-12. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Age Group

Country Subgroup Analysis

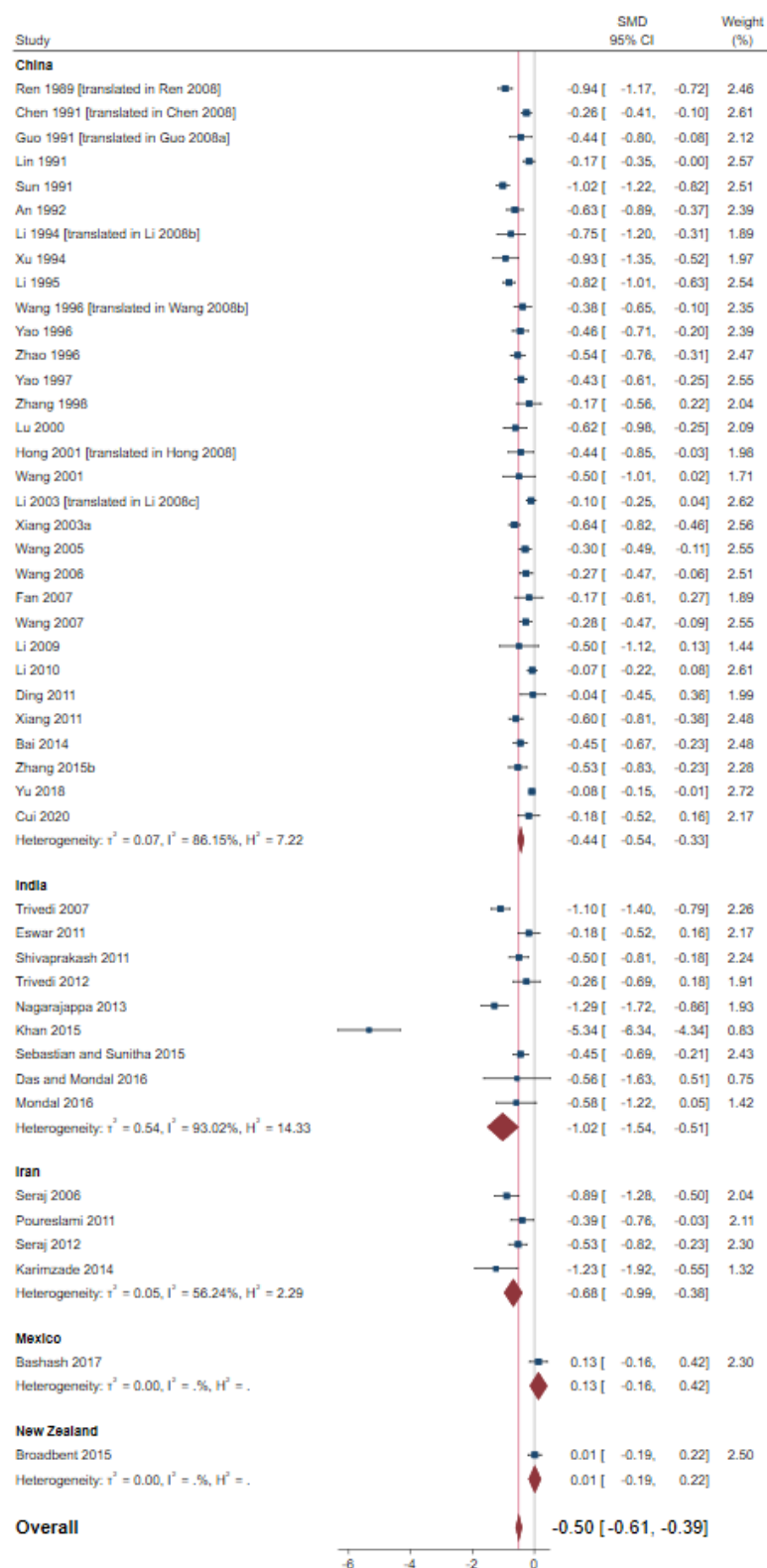


Figure A5-13. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Country

Assessment Type Subgroup Analysis

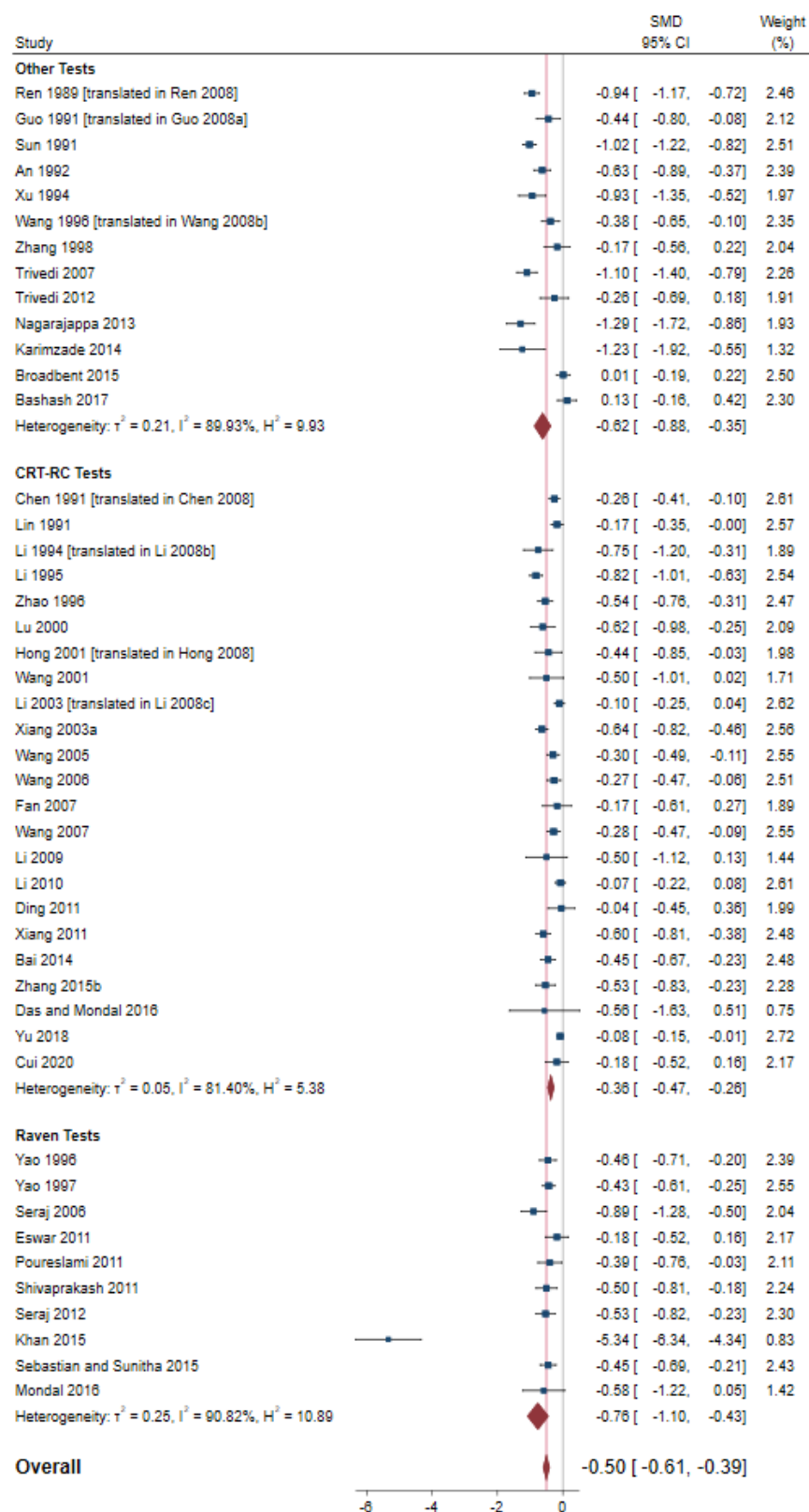


Figure A5-14. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type

Exposure Type Subgroup Analysis

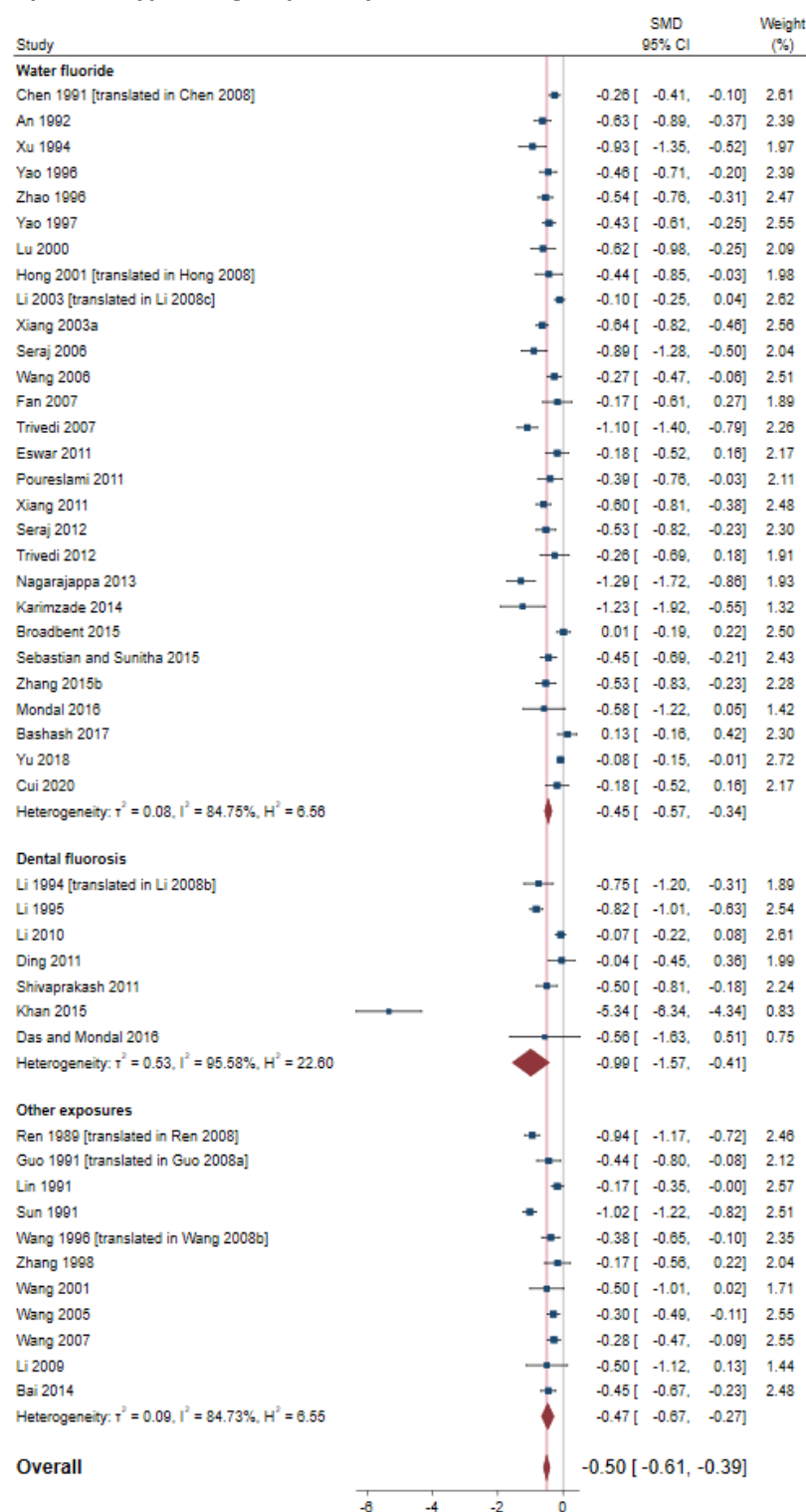


Figure A5-15. Association Between Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type

Exposure types include water, dental fluorosis, and other exposures (iodine, arsenic, aluminum, and fluoride from coal burning).

Aim 2. To conduct new meta-analyses using individual-level exposure data

Approach

The individual-effect meta-analysis included studies that reported effect estimates as betas and included 95% CIs or SEs (see [Table B-1](#)). Adjusted effect estimates were used in the meta-analysis. If results from multiple models were reported within a single study, the most adjusted results were selected. The study outcomes were evaluated with respect to a 1-mg/L unit increase in exposure. To ensure consistent units across studies, units of exposure were transformed to mg/L as needed. For Bashash *et al.* (2017), Yu *et al.* (2018), and Till *et al.* (2020), units of exposure were transformed to levels ranging from 0.5 to 1 mg/L. For Cui *et al.* (2018), units of exposure were transformed from 1 log mg/L to 1 mg/L. Cui *et al.* (2018) reported an association between IQ and log-transformed exposure. A sensitivity analysis was performed to evaluate the impact of using Cui *et al.* (2018), since the relationship between IQ and exposure evaluated in this study was not linear (as in the other studies included). Yu *et al.* (2018) reported estimates from piecewise linear regression models, with three estimated ranges for urinary fluoride exposure (low 0.01–1.60 mg/L, medium 1.60–2.50 mg/L, and high 2.50–5.54 mg/L) and two estimated ranges for water fluoride exposure (low 0.20–3.40 mg/L and high 3.40–3.90 mg/L). Because these piecewise effect estimates are likely correlated, study-specific pooled effect estimates were used for urinary and water fluoride exposures for the overall effect meta-analysis. A sensitivity analysis was performed to evaluate the impact of using the pooled estimate rather than the piecewise estimates from Yu *et al.* (2018).

Yu *et al.* (2018) and Wang *et al.* (2020b) used the same study cohort of children recruited in 2015 from the rural areas of Tianjin City, China. Only results from Yu *et al.* (2018) were included in the meta-analysis since Wang *et al.* (2020b) used a subset ($n = 571$) of the original study population from Yu *et al.* (2018) ($n = 2,668$). A sensitivity analysis was conducted to evaluate the impact of using the effect estimate from Wang *et al.* (2020b) rather than the pooled effect estimate from Yu *et al.* (2018).

Green *et al.* (2019) and Till *et al.* (2020) used the same cohort of 398 mother-child dyads in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort that reported drinking tap water in 10 Canadian cities. Both studies reported effect estimates for maternal urinary fluoride (MUF) and water fluoride concentrations. In the Green *et al.* (2019) study, 512 mother-child pairs had MUF data (and all covariates) compared to 398 pairs in Till *et al.* (2020). Water fluoride levels were available for 420 pairs in Green *et al.* (2019) compared to 398 pairs in Till *et al.* (2020). Both references reported effect estimates adjusted for maternal education, maternal race, child's sex, HOME total score, and secondhand smoking status in the child's residence. In addition, Till *et al.* (2020) adjusted for child's age at IQ testing. The age range for study subjects was 3–4 years old. For the main analysis, results from Green *et al.* (2019) were included. A sensitivity analysis was conducted using the water fluoride result for formula-fed children and the MUF result from Till *et al.* (2020) since these are most adjusted compared to Green *et al.* (2019). For fluoride intakes, estimates from both studies were used including total fluoride intake from Green *et al.* (2019) and infant formula intake from Till *et al.* (2020).

In the overall effect analysis, for studies reporting multiple measures of fluoride exposure, results associated with measured or estimated individual-level exposures, biomarker levels (such as urinary fluoride), or fluoride intake were prioritized over results associated with water fluoride concentrations. Subgroup analyses were performed that considered all exposure types. All studies used in these analyses with individual-level effects were lower risk of bias.

The overall effect based on studies with individual-level measures of exposure showed that a 1-unit increase in fluoride exposure was associated with a significantly lower IQ score (beta = -1.40; 95% CI: -2.33, -0.47) ([Table A5-2](#)). A 1-mg/day increase in fluoride intake resulted in significantly lower IQ score (beta = -3.31; 95% CI: -6.12, -0.50). A 1-mg/L increase in water fluoride also resulted in significantly lower IQ score (beta = -4.77; 95% CI: -9.10, -0.45). The results for fluoride intake and water fluoride, however, are based on two studies and should be interpreted with caution.

There was evidence of moderate heterogeneity ($I^2 = 46\%$, $p = 0.101$; [Table A5-2](#), [Figure A5-16](#), and [Figure A5-17](#)) in studies with individual-level urinary exposure levels. Eliminating publication bias through trim-and-fill analysis continued to support that 1-mg/L increases in individual-level urinary or water fluoride were associated with lower IQ scores, with an adjusted pooled effect estimate of -0.82 (95% CI: -1.81, 0.17) ([Figure A5-19](#)).

A sensitivity analysis to evaluate the impact of using the piecewise estimates from Yu *et al.* (2018) revealed no significant change in the pooled effect estimate (-1.37; 95% CI: -2.38, -0.37) ([Figure B-1](#)). A sensitivity analysis to evaluate using estimates from Wang *et al.* (2020b) rather than Yu *et al.* (2018) study also revealed no significant change in the pooled effect estimate (-1.24; 95% CI: -1.94, -0.54) ([Figure B-6](#)). A sensitivity analysis using the water fluoride result for formula-fed children and the MUF result from Till *et al.* (2020) (rather than Green *et al.* (2019)) suggested no significant change in the overall pooled effect estimate (-1.50; 95% CI: -2.44, -0.57) ([Figure B-11](#)).

Summary Results

Summary Results

Table A5-2. Pooled Effect Estimates and 95% CIs for Children’s IQ Scores and Individual-level Exposures to Fluoride				
Analysis	Number of Studies	Beta (95% CI)	Heterogeneity	
			p-value	I ²
Overall Effect				
Full-scale IQ	6	−1.40 (−2.33, −0.47)	0.101	46%
Verbal IQ	6	−1.36 (−2.28, −0.45)	0.110	44%
Performance IQ	6	−1.33 (−2.25, −0.42)	0.117	43%
Subgroup Analyses				
Gender				
Males	2	−2.23 (−5.45, 0.99)	0.092	65%
Females	3	−1.64 (−4.80, 1.51)	0.045	68%
Country				
Canada	1	−1.95 (−5.18, 1.29)	NA	
China	4	−0.84 (−1.39, −0.30)	0.342	10%
Mexico	1	−5.00 (−8.53, −1.47)	NA	
Assessment Type				
CRT-RC tests	4	−0.84 (−1.39, −0.30)	0.342	10%
Non-CRT-RC tests	2	−3.39 (−6.37, −0.41)	0.212	36%
Exposure Type				
Urinary fluoride	6	−1.40 (−2.33, −0.47)	0.101	46%
Intake	2	−3.31 (−6.12, −0.50)	0.746	0%
Water fluoride	2	−4.77 (−9.09, −0.45)	0.707	0%

Notes:

CI = confidence interval; NA = not applicable

Overall Analysis

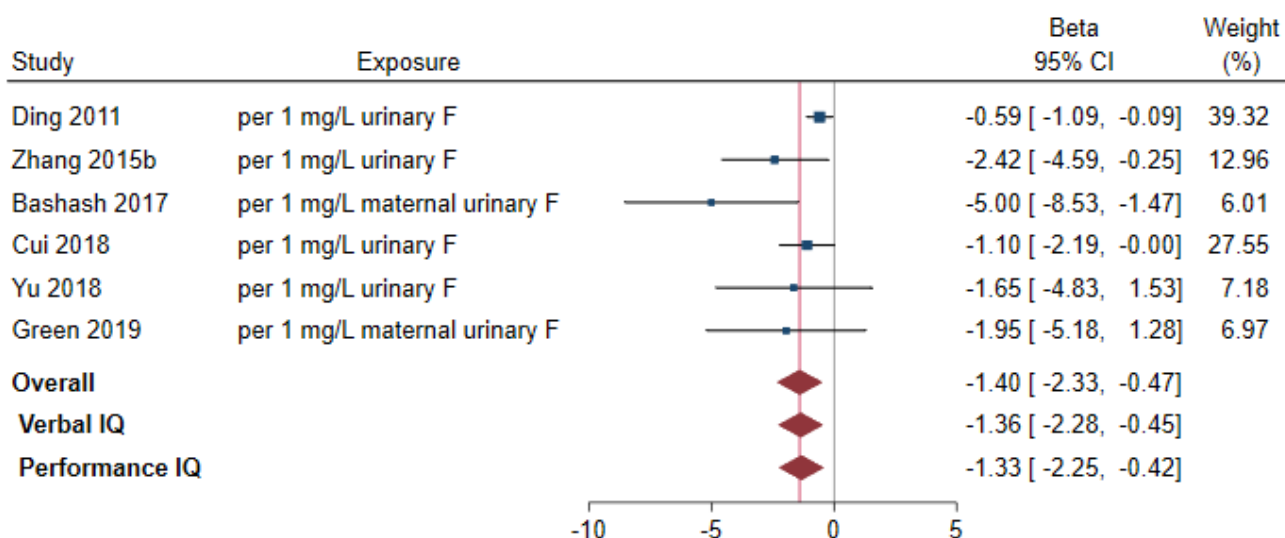


Figure A5-16. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Overall Analysis

Estimates (betas) for individual studies are shown with solid boxes representing the weight, and the pooled estimate is shown as a solid diamond. Horizontal lines represent 95% CIs for the study-specific betas.

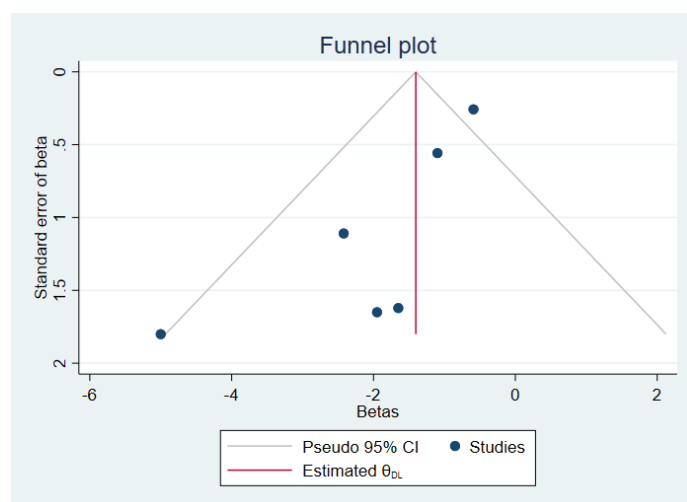


Figure A5-17. Funnel Plot of Included Studies with Individual-level Exposures

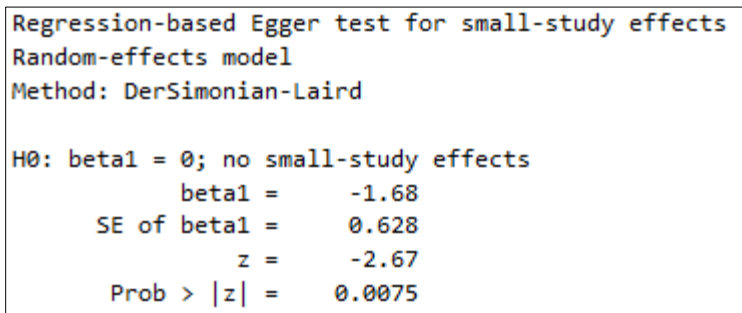


Figure A5-18. Test for Publication Bias for Studies with Individual-level Exposures

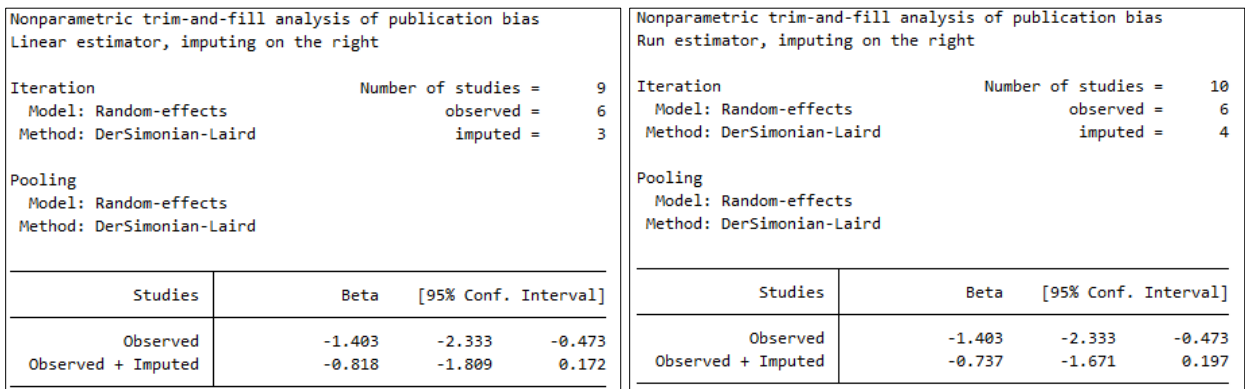


Figure A5-19. Trim-and-fill Analysis for Studies with Individual-level Exposures

Left panel shows the random-effects pooled effect estimate after filling in to the right using a liner estimator; right panel shows random-effects pooled effect estimate after filling in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled slope.

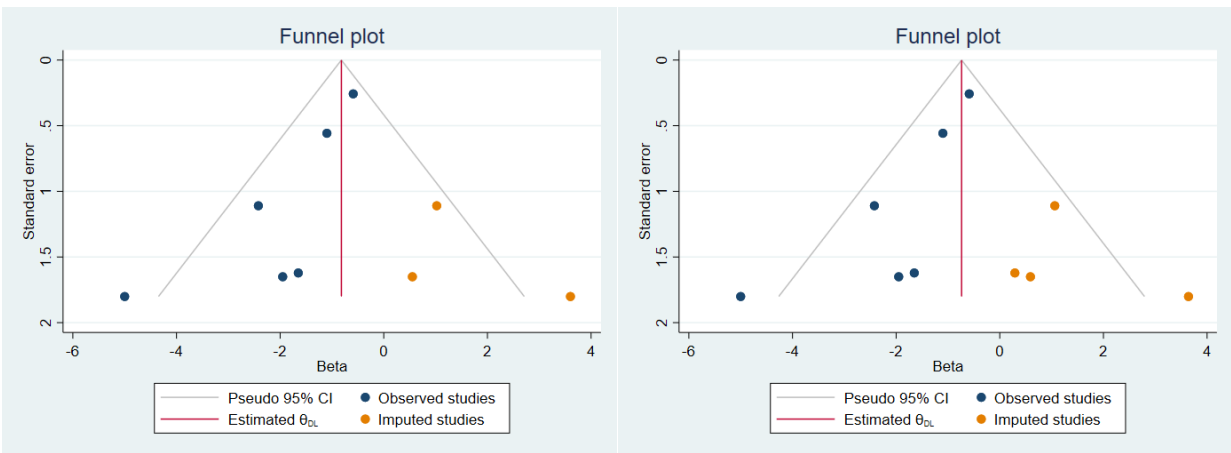


Figure A5-20. Filled-in Funnel Plots to Eliminate Publication Bias for Studies with Individual-level Exposures

Left panel shows funnel plot filled in to the right using a linear estimator; right panel shows the funnel plot filled in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

Exposure Type Subgroup Analysis

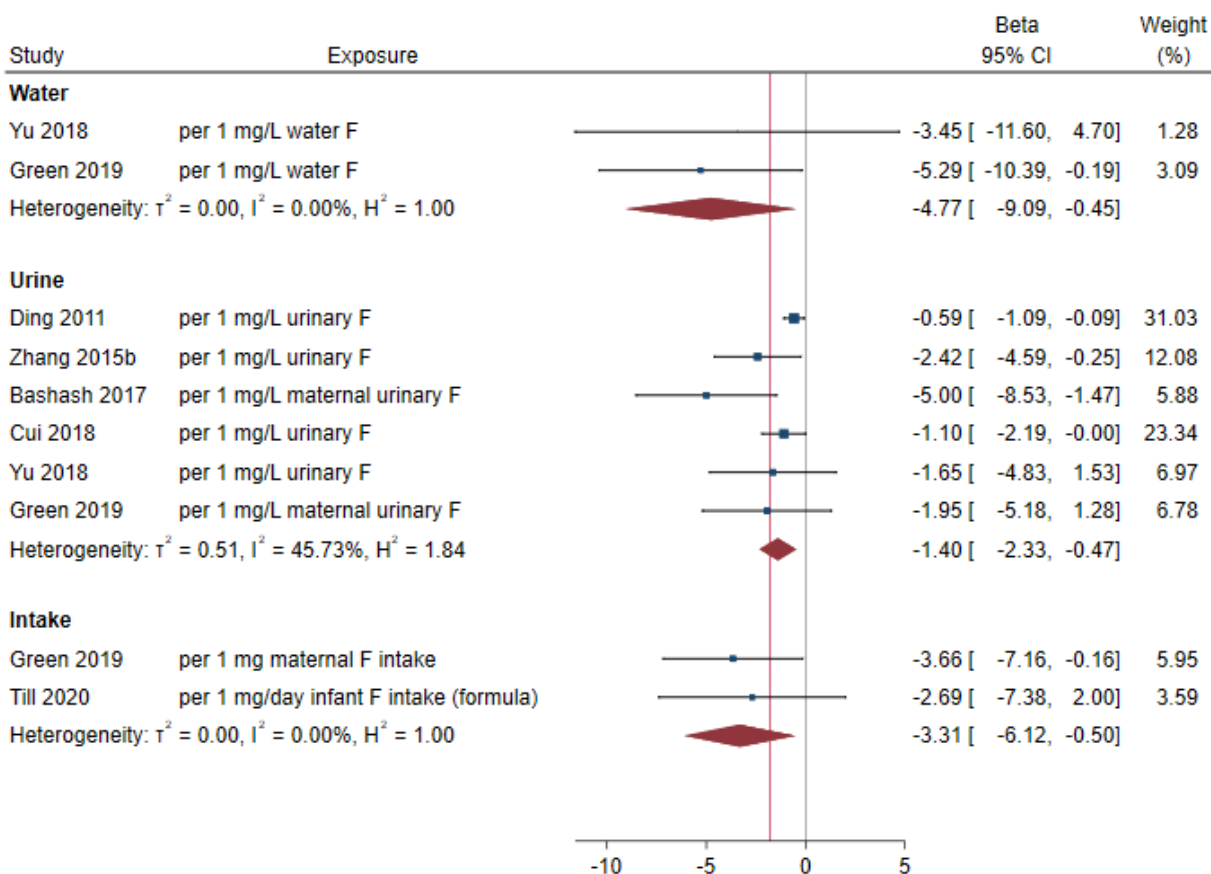


Figure A5-21. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Exposure Type

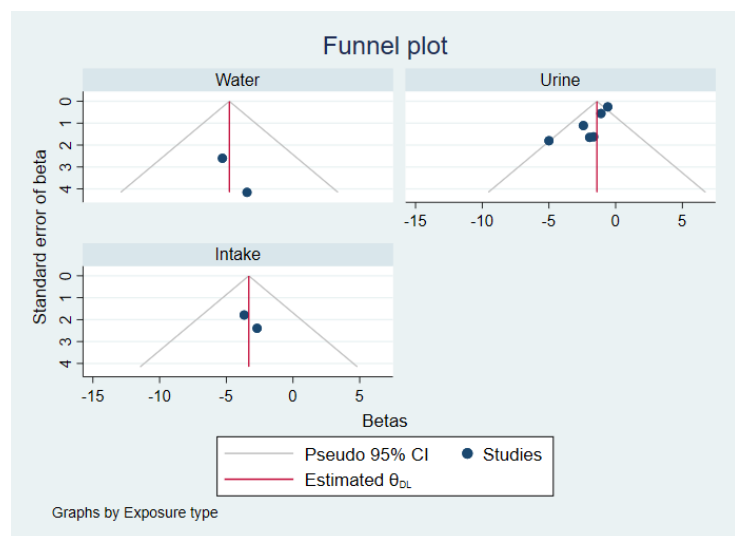


Figure A5-22. Funnel Plot of Included Studies

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analyses. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Country Subgroup Analysis

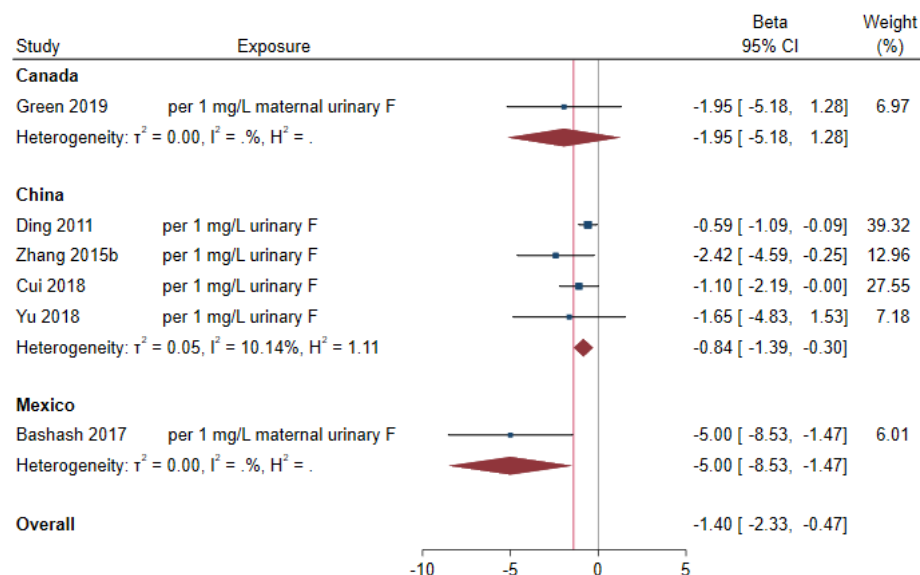


Figure A5-23. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Country

Note: The analyses for publication bias for studies from China, Canada, and Mexico rely on a very small number of studies each and are not shown.

Assessment Type Subgroup Analysis

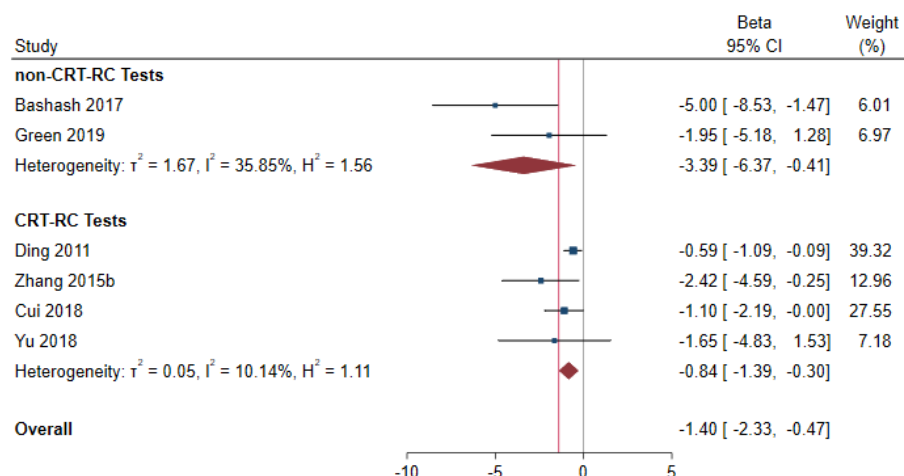


Figure A5-24. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Assessment Type

Note: The analyses for publication bias for CRT-RC studies and non-CRT-RC studies include only four and two studies, respectively, and are not shown.

Gender Subgroup Analysis

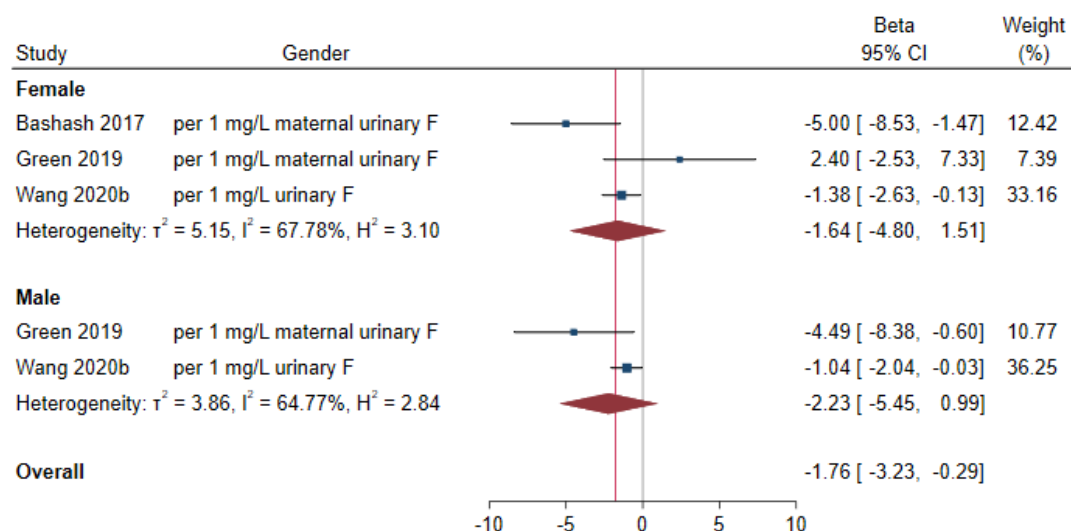


Figure A5-25. Association Between Individual-level Fluoride Exposure and IQ Scores in Children: Effect by Gender

Note: The analysis for publication bias by gender relies on two or three studies each and are not shown.

Dose-response meta-analyses using mean-effect estimates

Approach

For the dose-response meta-analysis using the mean-effect estimates, a one-step approach developed in the protocol (<https://ntp.niehs.nih.gov/go/785076>) and Crippa *et al.* (2018) was used. The approach uses linear mixed models to analyze all available data, including studies with one nonreference group. For each study, the median or mean fluoride intake for each exposure group was assigned to its corresponding effect estimate. If median or mean intakes by exposure group were not provided, the midpoint of the upper and lower boundaries in every category was assigned as the average intake. If the upper boundary for the highest exposure group was not reported, the boundary was assumed to have the same amplitude as the nearest category. For each study, the SMDs and corresponding SEs are used to compare the differences in mean IQ between the exposed and reference groups. The corresponding SMD for the reference group is set to zero for this analysis. The SMDs and corresponding variances are used to estimate a pooled dose-response curve using a restricted maximum likelihood estimation method. To examine a potential nonlinear relationship between exposure to fluoride and children's IQ levels, quadratic terms and restricted cubic splines were created, and a potential departure from a linear trend was assessed by testing the coefficient of the quadratic term and a second spline equal to zero. Models were compared and best model fit was determined based on the Akaike information criterion (AIC) (Müller *et al.* 2013).

A dose-response meta-analysis using the effect estimates reported in studies with individual-level exposure was considered. However, because of the small number of studies ($n = 10$), the various types of exposure metrics, and the different types of reported effect estimates that could not be combined, a dose-response meta-analysis of these studies could not be conducted.

Summary Results

Characteristics of the studies that compared mean IQ scores among groups of children with different levels of fluoride exposure are shown in [Table A-1](#).

The meta-analysis combining data from 31 studies with fluoride levels in drinking water showed a significantly lower children's IQ score with increasing exposure ([Table A5-3](#)). Based on the AIC, the best model fit was achieved when restricted cubic splines with three knots were added to the linear model. However, given the small difference in AICs between the different models, and for ease of interpretability, the linear model results were chosen for the purposes of discussion although results from all models are presented in [Table A5-3](#). Based on the linear model, the decrease in mean SMD between exposed and reference groups was -0.14 (95% CI: -0.19 , -0.08) ([Table A5-3](#)). When the analysis was restricted to studies with the "high" group exposed to < 1.5 mg/L fluoride in drinking water ($n = 9$; 2 lower risk-of-bias studies and 7 higher risk-of-bias studies), the mean SMD became positive and nonsignificant (0.32 ; 95% CI: -0.57 , 1.20). However, when including groups exposed to < 2 mg/L fluoride in drinking water, the mean SMD in children's IQ scores was both negative and statistically significant (SMD = -0.27 ; 95% CI: -0.36 , -0.17) ($n = 9$; 2 lower risk-of-bias studies and 7 higher risk-of-bias studies).

The meta-analysis combining data from 9 studies with fluoride levels in urine showed a significantly lower children's IQ with increasing exposure (SMD = -0.18 ; 95% CI: -0.31 , -0.05) ([Table A5-3](#)). Based on AIC, the best model fit was the linear model ([Table A5-3](#)). There was no improvement in the fit of the model when a quadratic term or restricted cubic splines were added to the linear model ([Table A5-3](#)). When the analyses were restricted to studies with the "high" group with < 1.5 mg/L fluoride in urine ($n = 4$; 2 lower risk-of-bias studies and 2 higher risk-of-bias studies), the direction of the effect did not

change, but it was no longer statistically significant (SMD = -0.13; 95% CI: -0.29, 0.03). When the dose-response meta-analysis was extended to include exposed groups with < 2 mg/L urinary fluoride (n = 6; 3 lower risk-of-bias studies and 3 higher risk-of-bias studies), the mean SMD remained negative and not statistically significant (-0.25; 95% CI: -0.71, 0.22).

Dose-Response Meta-analysis Using Mean Effects—Model Selection

Table A5-3. Model Comparison for Dose-response Meta-analysis for Children's IQ Scores (SMDs) and Exposures to Fluoride: Parameter Estimates and Model Fit¹				
Analysis	No. of Studies/ No. of Observations	Linear Model²	Quadratic Model³	Restricted Cubic Splines Model⁴
Water Fluoride				
All data	31/49	-0.14 (-0.19, -0.08) 113.6	-0.23 (-0.32, -0.14) 0.02 (0.01, 0.03) 110	-0.24 (-0.40, -0.08) 0.38 (-0.06, 0.81) 101.7
<1.5 mg/L	9/12	0.32 (-0.57, 1.20) 26.1	1.97 (-0.98, 4.92) -1.26 (-3.23, 0.71) 28.8	0.81 (-0.37, 1.99) -19.37 (-42.19, 3.44) 22.4
<2 mg/L	9/17	-0.27 (-0.36, -0.17) 44.6	0.64 (-1.04, 2.32) -0.40 (-1.09, 0.29) 31.6	0.23 (-0.71, 1.17) -4.63 (-12.47, 3.21) 27.6
<4 mg/L	24/38	-0.17 (-0.25, -0.09) 81.7	-0.28 (-0.64, 0.08) 0.03 (-0.10, 0.16) 79.5	-0.26 (-0.48, -0.03) 0.36 (-1.06, 1.79) 73.9
Urinary Fluoride				
All data	9/22	-0.18 (-0.31, -0.05) 61.1	-0.17 (-0.46, 0.12) -0.004 (-0.05, 0.04) 71.6	-0.12 (-0.31, 0.07) -0.11 (-0.35, 0.13) 68.7
<1.5 mg/L	4/7	-0.13 (-0.29, 0.03) -0.3	-0.63 (-1.28, 0.01) 0.31 (-0.06, 0.68) 4.7	-0.30 (-0.55, -0.04) 5.09 (-1.00, 11.18) -0.9
<2 mg/L	6/11	-0.09 (-0.22, 0.03) -2.3	-0.25 (-0.71, 0.22) 0.07 (-0.13, 0.27) 5.8	-0.13 (-0.34, 0.09) 0.25 (-0.87, 1.37) 2.9

Notes:

AIC = Akaike information criterion; SMD = standardized mean difference

¹Parameter estimates are changes in SMDs (beta [95% CI]); model fit is represented by the AIC.

²The estimates represent change in SMD for the linear model and AIC, respectively.

³The estimates represent change in SMD for the linear term, change in SMD for quadratic term, and AIC, respectively.

⁴The estimates represent change in SMD for the first spline term, change in SMD for the second spline term, and AIC, respectively.

Attachment A. Subgroup and Sensitivity Analyses (Aim 1)

Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Ren <i>et al.</i> (1989) [translated in Ren <i>et al.</i> 2008]	China	8–14	No fluoride measurement High fluoride and low iodine village/low iodine village	Not specified	Wechsler Intelligence Scale for Children	Higher	Gender; iodine
Chen <i>et al.</i> (1991) [translated in Chen <i>et al.</i> 2008] ^w	China	7–14	Drinking water Endemic fluorosis village/nonendemic village	0.89 mg/L (nonendemic); 4.55 mg/L (endemic)	Chinese Standardized Raven Test	Higher	Age; gender
Guo <i>et al.</i> (1991) [translated in Guo <i>et al.</i> 2008a]	China	7–13	Serum Coal burning-related fluoride endemic area/control area using wood	0.1044 ± 0.0652 mg/L (control); 0.1483 ± 0.0473 mg/L (endemic)	Chinese Binet Intelligence Test	Higher	Age; gender; SES
Lin <i>et al.</i> (1991) ^{w*}	China	7–14	Drinking water High fluoride and low iodine village/low iodine village/control area with iodine supplementation	0.34 mg/L (low iodine village); 0.88 mg/L (high fluoride, low iodine village)	Combined Raven's Test for Rural China	Higher	SES
Sun <i>et al.</i> (1991)	China	6.5–12	No fluoride measurement Endemic (aluminum-fluoride endemic toxicosis)/nonendemic	Fluorosis: 98.36% (endemic)	Japan's Shigeo Kobayashi's 50-point scoring method	Higher	Age
An <i>et al.</i> (1992) ^w	China	7–16	Drinking water High fluoride/nonhigh fluoride area	0.6–1.0 mg/L (nonhigh); 2.1–7.6 mg/L (high)	Wechsler Intelligence Scale for Children-Revised	Higher	Age; race; SES
Li <i>et al.</i> (1994) [translated in Li <i>et al.</i> 2008b]	China	12–13	Grain (cooked by burning high-fluoride coal) High fluoride group III (dental fluorosis present)/high fluoride group II (dental fluorosis present)/high fluoride group I (no dental fluorosis)/control group (no dental fluorosis)	0.5 mg/kg (reference); 4.7 mg/kg (group I); 5.2 mg/kg (group II); 31.6 mg/kg (group III)	Proofing test	Higher	Age; gender; SES

Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Xu <i>et al.</i> (1994) ^{w*}	China	8–14	Drinking water Low- and high-fluoride and iodine regions/control region	0.8 mg/L (reference); 0.8 mg/L (low iodine); 0.5 mg/L (low fluoride, low iodine); 0.38 mg/L (low fluoride); 0.5 mg/L (low fluoride, high iodine); 2.0 mg/L (high fluoride, low iodine); 1.8 mg/L (high fluoride); 3.9 mg/L (high fluoride, high iodine);	Binet-Simon Scale	Higher	–
Li <i>et al.</i> (1995) ^u	China	8–13	Urine Dental fluorosis index (DFI) Fluorosis area due to soot from coal burning/nonfluorosis area	1.02 mg/L; DFI: <0.4 (nonfluorosis area); 1.81 mg/L; DFI: 0.8 (slight fluorosis area); 2.01 mg/L; DFI: 2.5 (medium fluorosis area); 2.69 mg/L; DFI: 3.2 (severe fluorosis area)	China Rui Wen Scaler for Rural Areas	Higher	Gender
Wang <i>et al.</i> (1996) [translated in Wang <i>et al.</i> 2008b] ^w	China	4–7	Drinking water (well) High fluoride region/low fluoride region	0.58–1.0 mg/L (low); >1.0–8.6 mg/L (high)	Wechsler Preschool and Primary Scale of Intelligence	Higher	Age; gender
Yao <i>et al.</i> (1996) ^w	China	8–12	Drinking water Endemic fluorosis area/nonendemic area	1 mg/L (nonendemic); 2 mg/L (slightly endemic); 11 mg/L (severely endemic)	Raven Test – Associative Atlas	Higher	Iodine; SES
Zhao <i>et al.</i> (1996) ^w	China	7–14	Drinking water High fluoride village (Sima)/low fluoride village (Xinghua)	0.91 mg/L (low) 4.12 mg/L (high)	China Rui Wen Scaler for Rural Areas	Higher	Age; SES
Yao (1997) ^{w*}	China	7–12	Drinking water Fluorosis area without water improvements/fluorosis area with water improvements/nonfluorosis area	0.4 mg/L (nonfluorosis area); 0.33 mg/L (fluorosis area with water improvement); 2 mg/L (fluorosis area without water improvement)	Raven’s Standard Progressive Matrices (China’s Rural Version)	Higher	Iodine; SES

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Zhang <i>et al.</i> (1998) ^{w*}	China	4–10	Drinking water High fluoride and high arsenic group/high fluoride group/reference	0.58 mg/L (reference); 0.8 mg/L (high fluoride, high arsenic); 0.8 mg/L (high fluoride)	Shigeo Kobayashi 50-pt. test	Higher	Age; arsenic
Lu <i>et al.</i> (2000) ^{w,u}	China	10–12	Urine, drinking water High fluoride area/low fluoride area	0.37 ± 0.04 mg/L drinking water (low); 1.43 ± 0.64 mg/L urine (low); 3.15 ± 0.61 mg/L drinking water (high); 4.99 ± 2.57 mg/L urine (high)	Chinese Combined Raven Test-C2	Higher	SES
Hong <i>et al.</i> (2001) [translated in Hong <i>et al.</i> 2008] ^{w*}	China	8–14	Drinking water High fluoride and iodine regions/reference	0.75 mg/L (reference); 2.90 mg/L (high fluoride); 2.85 mg/L (high fluoride, high iodine); 2.94 mg/L (high fluoride, low iodine); 0.48 mg/L (low fluoride, low iodine)	Chinese Standardized Raven Test	Higher	Iodine; SES; demographics
Wang <i>et al.</i> (2001) ^w	China	8–12	Drinking water Investigative point (high fluoride)/control point (low fluoride)	0.5 mg/L (low); 2.97 mg/L (high)	Combined Raven's Test for Rural China	Higher	–
Li <i>et al.</i> (2003) [translated in Li <i>et al.</i> 2008c]	China	6–13	No fluoride measurement Endemic fluorosis areas/reference	Not specified	Chinese Standardized Raven Test	Higher	–

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Xiang <i>et al.</i> (2003a) ^{w*}	China	8–13	Drinking water Endemic fluorosis areas/nonendemic fluorosis area	0.36 ± 0.15 mg/L (reference); 0.75 ± 0.14 mg/L (endemic fluorosis area group A); 1.53 ± 0.27 mg/L (endemic fluorosis area group B); 2.46 ± 0.3 mg/L (endemic fluorosis area group C); 3.28 ± 0.25 mg/L (endemic fluorosis area group D); 4.16 ± 0.22 mg/L (endemic fluorosis area group E); 2.47 ± 0.79 mg/L (high fluoride)	Combined Raven's Test for Rural China	Lower	Age; gender; iodine; lead; SES
Wang <i>et al.</i> (2005)	China	8–12	Drinking water High fluoride group/reference	0.48 mg/L (reference); 8.31 mg/L (high)	Chinese Combined Raven Test-C2	Higher	SES
Seraj <i>et al.</i> (2006) ^w	Iran	7–11	Drinking water High fluoride area/low fluoride area	0.4 ppm (low); 2.5 ppm (high area)	Raven Test	Higher	Gender
Wang <i>et al.</i> (2006) ^w	China	8–12	Drinking water Area severely affected by fluorosis/reference	0.73 ± 0.28 mg/L (reference); 5.54 ± 3.88 mg/L (high)	Combined Raven's Test for Rural China	Higher	–
Fan <i>et al.</i> (2007) ^w	China	7–14	Drinking water High fluoride area/low fluoride area	1.03 mg/L (low); 3.15 mg/L (high)	Chinese Combined Raven Test-C2	Higher	–
Trivedi <i>et al.</i> (2007) ^w	India	12–13	Drinking water High fluoride area/low fluoride area	2.01 ± 0.009 mg/L (low); 5.55 ± 0.41 mg/L (high)	questionnaire prepared by Professor JH Shah	Higher	Age; gender
Wang <i>et al.</i> (2007) ^w	China	8–12	Drinking water High fluoride area/reference	0.5 ± 0.2 mg/L (reference); 8.3 ± 1.9 mg/L (high)	Combined Raven's Test for Rural China	Higher	Age; gender; arsenic; SES

Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Li <i>et al.</i> (2009) ^{u*}	China	8–12	Urine Endemic fluorosis region caused by coal burning (severe/medium/mild/reference) Degree of dental fluorosis (severe/medium/mild/very mild/suspected/normal)	0.962 ± 0.517 mg/L (reference) 1.235 ± 0.426 mg/L (mild endemic region) 1.670 ± 0.663 mg/L (medium endemic region) 2.336 ± 1.128 mg/L (severe endemic region) 0.867 ± 0.233 mg/L (normal fluorosis) 1.094 ± 0.355 mg/L (suspected fluorosis) 1.173 ± 0.480 mg/L (very mild fluorosis) 1.637 ± 0.682 mg/L (mild fluorosis) 2.005 ± 0.796 mg/L (medium fluorosis) 2.662 ± 1.093 mg/L (severe fluorosis)	Combined Raven's Test for Rural China	Higher	Age; gender
Li <i>et al.</i> (2010)	China	7–10	No fluoride measurement Dental fluorosis children/nondental fluorosis children	Not specified	Combined Raven's Test for Rural China	Higher	Gender

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Ding <i>et al.</i> (2011) ^{u*}	China	7–14	Urine Dental fluorosis (questionable/moderate/mild/very mild/normal) Mean urinary fluoride levels (10 groups)	0.80 ± 0.55 mg/L (normal dental fluorosis); 1.11 ± 0.74 mg/L (very mild dental fluorosis); 1.31 ± 0.78 mg/L (mild dental fluorosis); 1.46 ± 0.79 mg/L (moderate dental fluorosis); 1.13 ± 0.73 mg/L (questionable dental fluorosis); 0.26 mg/L (group 1); 0.45 mg/L (group 2); 0.56 mg/L (group 3); 0.66 mg/L (group 4); 0.75 mg/L (group 5); 0.89 mg/L (group 6); 1.08 mg/L (group 7); 1.33 mg/L (group 8); 1.74 mg/L (group 9); 2.96 mg/L (group 10)	Combined Raven's Test for Rural China	Lower	Age; arsenic; iodine; lead; SES; demographics
Eswar <i>et al.</i> (2011) ^w	India	12–14	Drinking water High fluoride villages/low fluoride villages	0.29 mg/L (low); 2.45 mg/L (high)	Standard Progressive Matrices	Higher	Age; gender
Poureslami <i>et al.</i> (2011) ^w	Iran	7–9	Drinking water Endemic dental fluorosis city/reference city	0.41 mg/L (reference); 2.38 mg/L (endemic)	Persian version of Raven's Matrices Test	Higher	Gender
Shivaprakash <i>et al.</i> (2011) ^w	India	7–11	Drinking water Fluorosis severity groups (mild/moderate/severe)/all fluorosis/no fluorosis	<0.5 ppm (no fluorosis); 2.5–3.5 ppm (mild fluorosis); 2.5–3.5 ppm (moderate fluorosis); 2.5–3.5 ppm (severe fluorosis); 2.5–3.5 ppm (all fluorosis)	Raven's Colored Progressive Matrices	Higher	Health factors; SES
Xiang <i>et al.</i> (2011)	China	8–13	Serum Quartiles (Q4/Q3/Q2 and Q1)	<0.05 mg/L (Q1 and Q2 reference); 0.05–0.08 mg/L (Q3); >0.08 mg/L (Q4)	Combined Raven's Test for Rural China	Lower	Age; gender; iodine; lead; SES

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Seraj <i>et al.</i> (2012) ^w	Iran	6–11	Drinking water High/medium/low fluoride levels	0.8 ± 0.3 mg/L (normal); 3.1 ± 0.9 mg/L (medium); 5.2 ± 1.1 mg/L (high)	Raven's Colored Progressive Matrices	Lower	Age; gender; SES
Trivedi <i>et al.</i> (2012) ^w	India	12–13	Ground water High fluoride area/low fluoride area	0.84 ± 0.38 mg/L (low); 2.3 ± 0.87 mg/L (high)	questionnaire prepared by Professor JH Shah	Lower	Gender; SES
Nagarajappa <i>et al.</i> (2013) ^w	India	8–10	Drinking water High fluoride area/low fluoride area	0.5 mg/L (low); 2.4–3.5 mg/L (high)	Seguin Form Board Test	Higher	Gender; SES; demographics
Bai <i>et al.</i> (2014) ^{u*}	China	8–12	Urine Coal-burning-borne fluorosis areas (seriously-affected/lightly-affected/reference)	0.54 mg/L (reference); 0.81 mg/L (lightly-affected area); 1.96 mg/L (seriously-affected area)	Chinese Combined Raven Test-C2	Higher	SES
Karimzade <i>et al.</i> (2014) ^w	Iran	9–12	Drinking water High fluoride area/low fluoride area	0.25 mg/L (low); 3.94 mg/L (high)	Iranian version of the Raymond B Cattell test	Higher	Gender
Broadbent <i>et al.</i> (2015) ^{w*}	New Zealand	7–13	Drinking water Area with community water fluoridation (high)/area without community water fluoridation (low) Fluoride tablet use (ever/never) Fluoride toothpaste use (always/sometimes/never)	0.0–0.3 mg/L (low); 0.7–1.0 mg/L (high) 0 mg (never used fluoride tablets); 0.5 mg (ever used fluoride tablets) Range not specified for fluoride toothpaste use (always/sometimes/never)	Wechsler Intelligence Scale for Children-Revised	Higher	Gender; SES; low birth weight; breastfeeding
Khan <i>et al.</i> (2015)	India	6–11	Drinking water High fluoride areas (Unnao)/low fluoride areas (Tiwariganj) Fluorosis grades (normal/very mild/mild/moderate/severe)	0.19 ppm (Tiwariganj); 2.41 ppm (Unnao) Range not specified by fluorosis grades	Raven's Colored Progressive Matrices	Higher	Health factors; SES
Sebastian and Sunitha (2015) ^{w*}	India	10–12	Drinking water Low fluoride villages/normal fluoride villages/high fluoride villages	0.40 mg/L (low); 1.2 mg/L (normal); 2.0 mg/L (high)	Raven's Colored Progressive Matrices	Higher	Age; gender; SES

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Zhang <i>et al.</i> (2015b) ^{w*}	China	10–12	Urine, drinking water, serum High fluoride areas/reference	1.10 ± 0.67 mg/L urine; 0.63 (0.58–0.68)mg/L water; 0.06 ± 0.03 serum (reference); 2.40 ± 1.01 mg/L urine; 1.40 (1.23–1.57) mg/L water; 0.18 ± 0.11 serum (high)	Combined Raven’s Test for Rural China	Lower	Age; gender; arsenic; iodine; drinking water fluoride; SES; thyroid hormone levels; COMT genotype
Das and Mondal (2016) ^u	India	6–18	Urine, drinking water Dental fluorosis (severe/moderate/mild/very mild/normal)	2.91 ± 1.76 mg/L urine; 0.069 ± 0.021 mg/kg-d drinking water (normal dental fluorosis); 2.50 ± 2.39 mg/L urine; 0.064 ± 0.004 mg/kg-d drinking water (questionable dental fluorosis); 2.58 ± 1.31 mg/L urine; 0.060 ± 0.036 mg/kg-d drinking water (very mild dental fluorosis); 2.95 ± 1.44 mg/L urine; 0.060 ± 0.030 mg/kg-d drinking water (mild dental fluorosis); 4.82 ± 3.57 mg/L urine; 0.099 ± 0.063 mg/kg-d drinking water (moderate dental fluorosis); 3.81 ± 2.51 mg/L urine; 0.093 ± 0.040 mg/kg-d drinking water (severe dental fluorosis)	Combined Raven’s Test for Rural China	Higher	–
Mondal <i>et al.</i> (2016) ^w	India	10–14	Drinking water High fluoride areas/low fluoride areas	Not reported (low); 0.33–18.08 mg/L (high)	Raven Standard Theoretical Intelligence Test	Higher	SES

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Table A-1. Characteristics of Studies Included in the Mean-effect Meta-analysis							
Reference ¹	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Bashash <i>et al.</i> (2017) ^u	Mexico	6–12	Urine	<0.80 mg/L (reference); ≥0.80 mg/L (high)	Wechsler Abbreviated Scale of Intelligence	Lower	Age; gender; weight at birth; parity; gestational age; maternal characteristics (smoking history, marital status, age at delivery, IQ, education, cohort)
Yu <i>et al.</i> (2018) ^{u*,w}	China	7–13	Drinking water High fluoride/normal fluoride Urine (per 0.5-mg/L increment in each range) High/medium/low fluoride ranges	≤1 mg/L (normal); >1 mg/L (high) 0.01–1.60 mg/L (low range urinary); 1.60–2.50 mg/L (medium range urinary); 2.50–5.54 mg/L (high range urinary)	Combined Raven’s Test for Rural China	Lower	Age; gender; health factors; SES
Cui <i>et al.</i> (2020) ^u	China	7–12	Urine High/medium/low fluoride levels	<1.6 mg/L (low); 1.6–2.5 mg/L (medium); ≥2.5 mg/L (high)	Combined Raven’s Test	Lower	Gender; arsenic; iodine

Notes:

COMT = catechol-O-methyltransferase; RoB = risk of bias; SES = socioeconomic status

¹A “w” superscript indicates studies included in the mean effect dose-response meta-analysis using fluoride in water; a “u” superscript indicates studies included in the mean effect dose-response meta-analysis using fluoride in urine; “*” indicates studies included in the mean effect dose-response meta-analysis at levels < 1.5 mg/L.

Table A-2. Studies Excluded from Mean-effect Meta-analysis	
Reference, Country	Reason for Exclusion
Qin <i>et al.</i> (1990)[translated in Qin <i>et al.</i> 2008], China	Missing mean or SD of outcome measure
Yang <i>et al.</i> (1994) [translated in Yang <i>et al.</i> 2008], China	Overlapping population with Wang <i>et al.</i> (2001); Table 2 in Yang <i>et al.</i> (1994) seemed incomplete
Wang <i>et al.</i> (2005b) [translated in Wang <i>et al.</i> 2008a], China	Missing mean or SD of outcome measure
Rocha-Amador <i>et al.</i> (2007), Mexico	Missing mean or SD of outcome measure
Liu <i>et al.</i> (2000) [translated in Liu <i>et al.</i> 2008], China	Overlapping population with Lu <i>et al.</i> (2000)
Sudhir <i>et al.</i> (2009), India	Missing mean or SD of outcome measure
He and Zhang (2010), China	Missing mean or SD of outcome measure
Kang <i>et al.</i> (2011), China	Missing mean or SD of outcome measure
Saxena <i>et al.</i> (2012), India	Missing mean or SD of outcome measure
Wang <i>et al.</i> (2012), China	Overlapping population with Xiang <i>et al.</i> (2003a); used in individual-level meta-analysis
Singh <i>et al.</i> (2013), India	Missing mean or SD of outcome measure
Wei <i>et al.</i> (2014), China	Missing mean or SD of outcome measure
Choi <i>et al.</i> (2015), China	Cognitive functions other than IQ
Kundu <i>et al.</i> (2015), India	Unusual IQ scores; used only for sensitivity analysis
Aravind <i>et al.</i> (2016), India	Unusual IQ scores; used only for sensitivity analysis
Razdan <i>et al.</i> (2017), India	Unusual IQ scores; used only for sensitivity analysis
Cui <i>et al.</i> (2018), China	Missing mean or SD of outcome measure; used in individual-level meta-analysis
Green <i>et al.</i> (2019), Canada	Missing mean or SD of outcome measure; used in individual-level meta-analysis
Soto-Barreras <i>et al.</i> (2019), Mexico	Missing mean or SD of outcome measure
Zhao <i>et al.</i> (2019), China	Overlapping population with Yu <i>et al.</i> (2018), but smaller sample size
Zhou <i>et al.</i> (2019), China	Overlapping population with Yu <i>et al.</i> (2018), but smaller sample size
Till <i>et al.</i> (2020), Canada	Missing mean or SD of outcome measure; used in individual-level meta-analysis
Wang <i>et al.</i> (2020b), China	Missing mean or SD of outcome measure; used in individual-level meta-analysis
Zhao <i>et al.</i> (2020), China	Overlapping population with Yu <i>et al.</i> (2018), but smaller sample size

Notes:

SD = standard deviation

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Table A-3. Characteristics of Studies Included in the Individual-level Meta-analysis							
Reference	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Ding <i>et al.</i> (2011)	China	7–14	Urine	0.10–3.55 mg/L	Combined Raven’s Test for Rural China	Lower	Age; arsenic; iodine; lead; SES; demographics
Zhang <i>et al.</i> (2015b)	China	10–12	Urine High fluoride area/reference	1.10 ± 0.67 mg/L (reference); 2.40 ± 1.01 mg/L (high fluoride area)	Combined Raven’s Test for Rural China	Lower	Age; gender; arsenic; iodine; drinking water fluoride; SES; thyroid hormone levels; COMT genotype
Bashash <i>et al.</i> (2017)	Mexico	6–12	Urine	0.18–2.8 mg/L	Wechsler Abbreviated Scale of Intelligence	Lower	Age; gender; weight at birth; parity; gestational age; maternal characteristics (smoking history, marital status, age at delivery, IQ, education, cohort)
Cui <i>et al.</i> (2018)	China	7–12	Urine	0.8–2.0 mg/L	Combined Raven’s Test for Rural China	Lower	Age; maternal education; smoking in family member; stress; anger; dopamine receptor-2 polymorphism
Yu <i>et al.</i> (2018)	China	7–13	Urine, drinking water	0.01–5.54 mg/L (urine) 0.20–3.90 mg/L (water)	Combined Raven’s Test for Rural China	Lower	Age; gender; maternal education; paternal education; low birth weight
Green <i>et al.</i> (2019)	Canada	3–4	Maternal urine, maternal fluoride intake, drinking water	0.51 ± 0.36 mg/L (urine) 0.54 ± 0.44 mg/day (maternal daily fluoride intake) 0.31 ± 0.23 mg/L (water)	Wechsler Primary and Preschool Scale of Intelligence-III	Lower	Gender; city; maternal education; race/ethnicity; HOME score; prenatal secondhand smoke exposure

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Table A-3. Characteristics of Studies Included in the Individual-level Meta-analysis							
Reference	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric, Exposure Groups)	Range			
Till <i>et al.</i> (2020)	Canada	3–4	Residence, maternal urine, infant fluoride intake from formula, drinking water Fluoridated/nonfluoridated areas	0.64–0.70 (fluoridated), 0.38–0.42 mg/L (nonfluoridated) (urine) 0.12–0.34 (fluoridated), 0.02–0.08 mg/day (nonfluoridated) (infant formula fluoride intake) 0.58 (fluoridated), 0.13 (nonfluoridated) (water)	Wechsler Primary and Preschool Scale of Intelligence-III	Lower	Age; gender; maternal education; maternal race; HOME total score; secondhand smoke status in the child's house
Wang <i>et al.</i> (2020b)	China	7–13	Urine, drinking water	0.01–5.54 mg/L (urine) 0.20–3.90 mg/L (water)	Combined Raven's Test for Rural China	Lower	Age; gender; body mass index; maternal education; paternal education; household income; low birth weight

Notes:

COMT = catechol-O-methyltransferase; RoB = risk of bias; SES = socioeconomic status; HOME = Home Observation for Measurement of the Environment

Effects by Risk-of-bias Evaluation

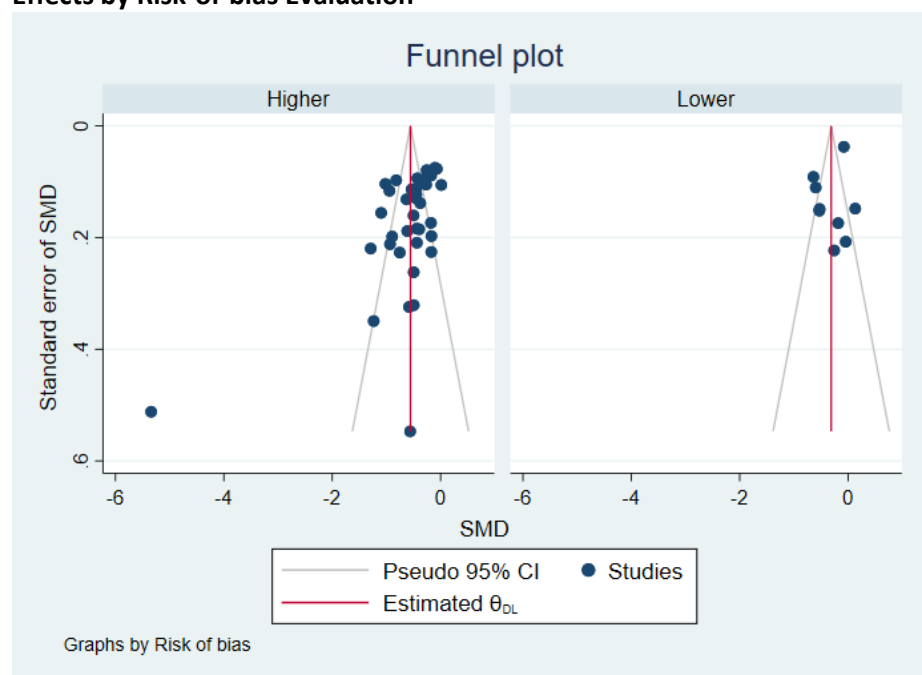


Figure A-1. Funnel Plot by Risk-of-bias Evaluation

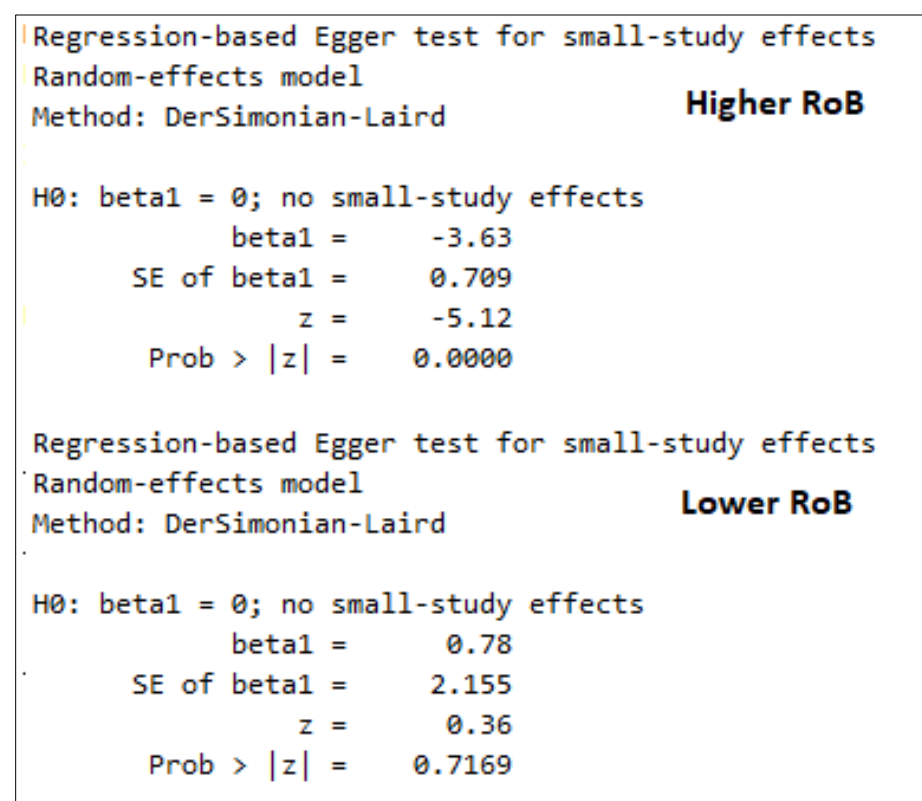


Figure A-2. Test for Publication Bias by Risk of Bias

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left					
Iteration		Number of studies =		46	Iteration		Number of studies =		44
Model: Random-effects		observed =		37	Model: Random-effects		observed =		37
Method: DerSimonian-Laird		imputed =		9	Method: DerSimonian-Laird		imputed =		7
Pooling					Pooling				
Model: Random-effects					Model: Random-effects				
Method: DerSimonian-Laird					Method: DerSimonian-Laird				
Studies		Cohen's d		[95% Conf. Interval]	Studies		Cohen's d		[95% Conf. Interval]
Observed		-0.556		-0.684 -0.428	Observed		-0.556		-0.684 -0.428
Observed + Imputed		-0.354		-0.498 -0.210	Observed + Imputed		-0.684		-0.831 -0.537

Figure A-3. Trim-and-fill Analysis for High Risk-of-bias Studies

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

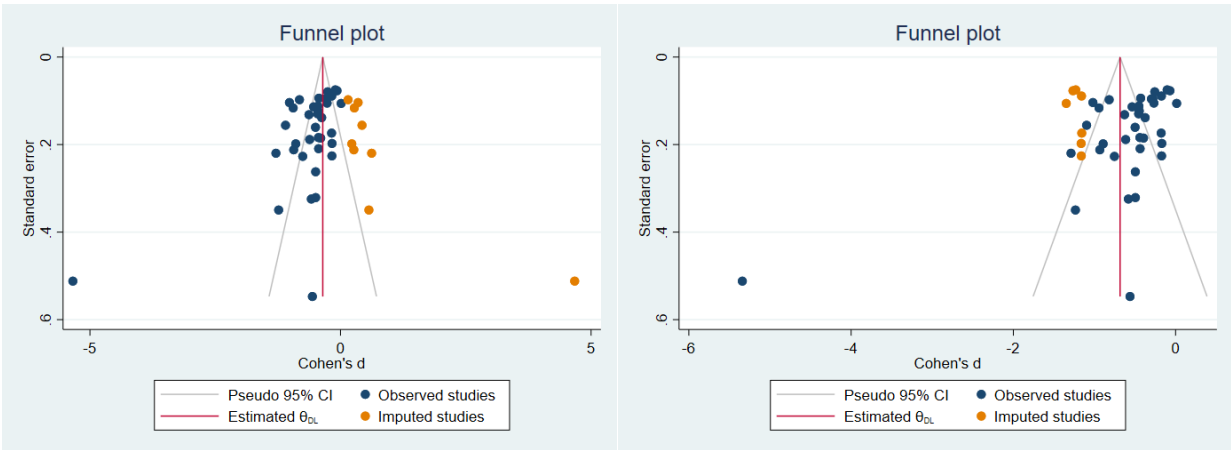


Figure A-4. Filled-in Funnel Plots for High Risk-of-bias Studies

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in the pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in the pooled SMD).

Effects by Gender

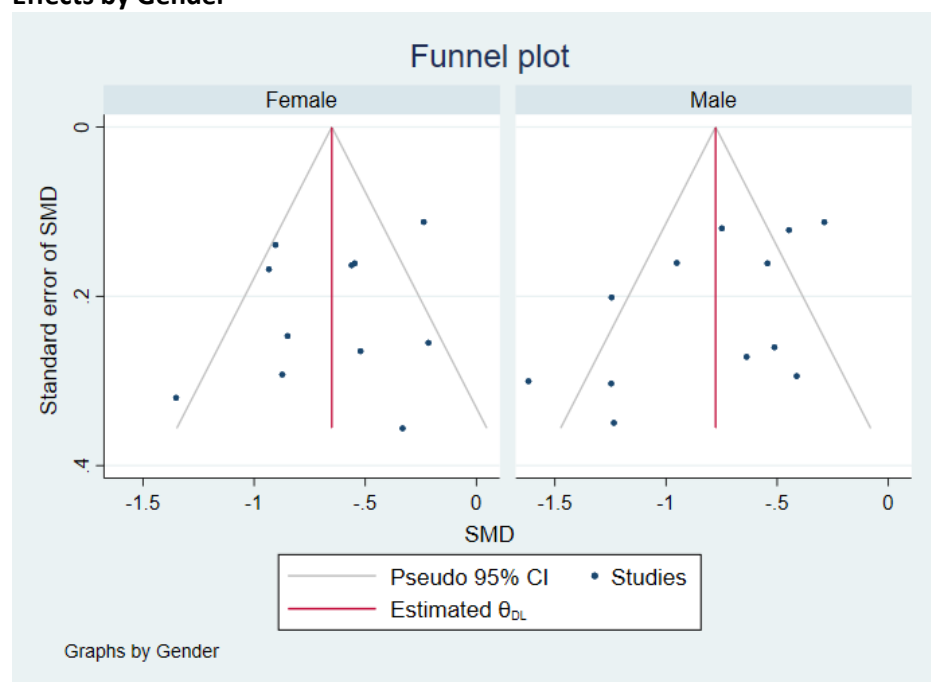


Figure A-5. Funnel Plots by Gender

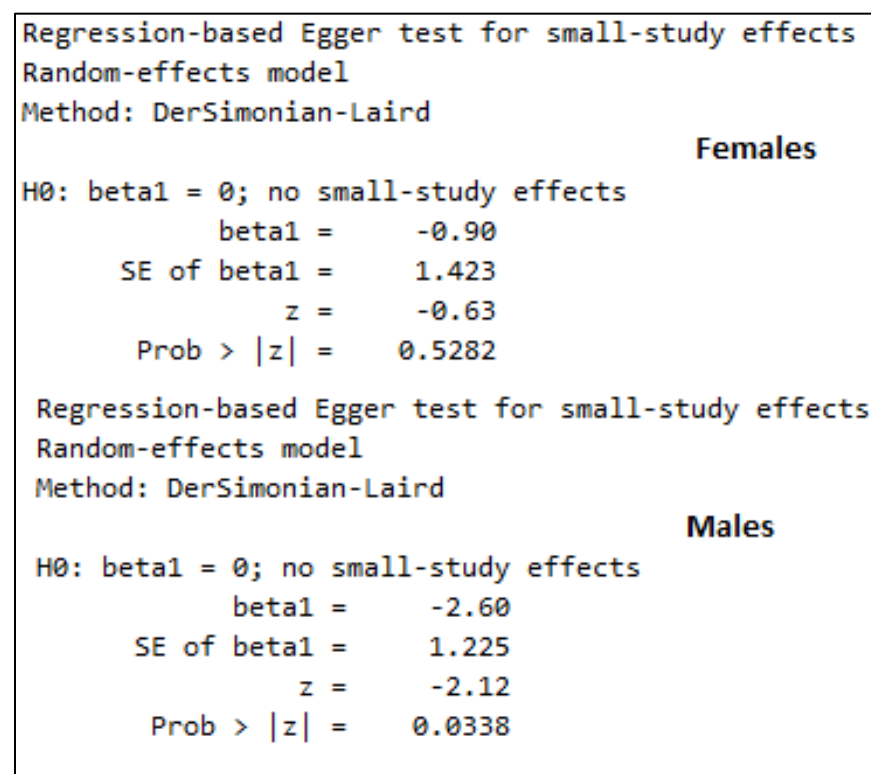


Figure A-6. Test for Publication Bias by Gender

Nonparametric trim-and-fill analysis of publication bias			
Linear estimator, imputing on the right			
Iteration	Number of studies =		14
Model: Random-effects	observed =		12
Method: DerSimonian-Laird	imputed =		2
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.777	-0.994	-0.560
Observed + Imputed	-0.681	-0.900	-0.461

Figure A-7. Trim-and-fill Analysis for Studies in Boys Using Linear and Run Estimators

Filling in to the right using a run estimator or to the left using a linear or a run estimator showed no change in the pooled SMD.

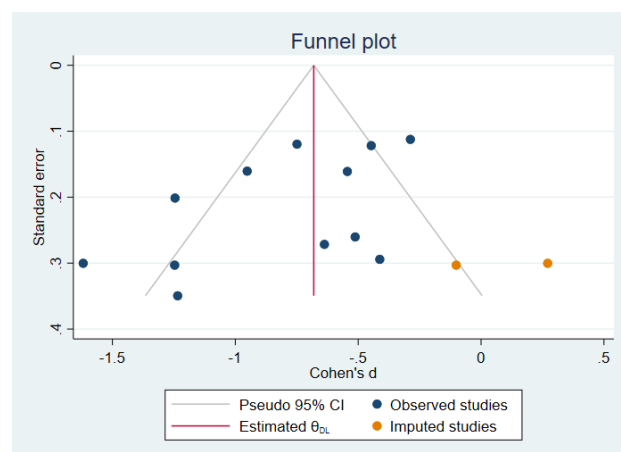


Figure A-8. Filled-in Funnel Plots for Studies in Boys

Panel shows funnel plot filled in to the right using a linear estimator. Filling in to the right using a run estimator or to the left using a linear or a run estimator showed no change in the pooled SMD.

Effects by Age Group

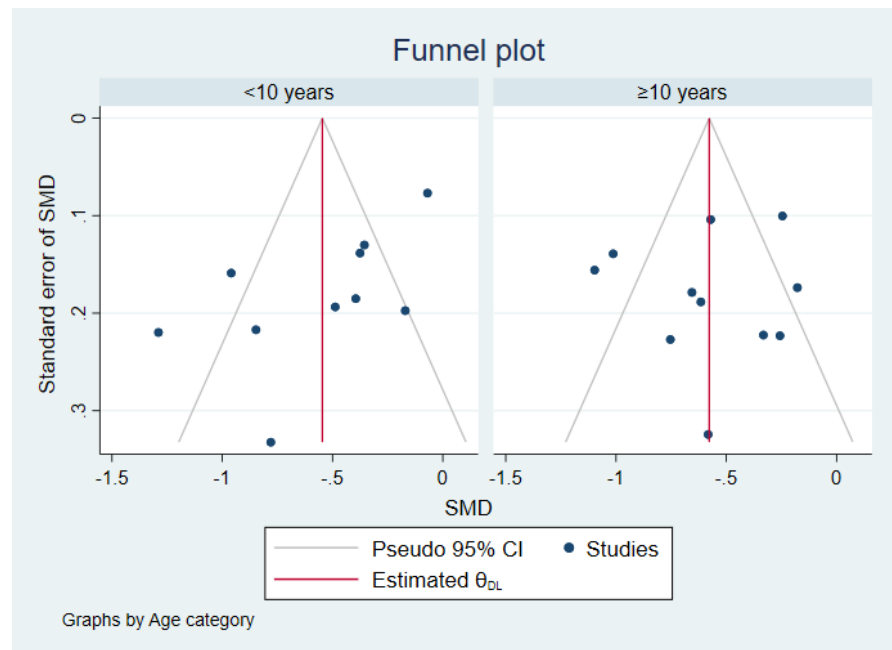


Figure A-9. Funnel Plot by Age Group

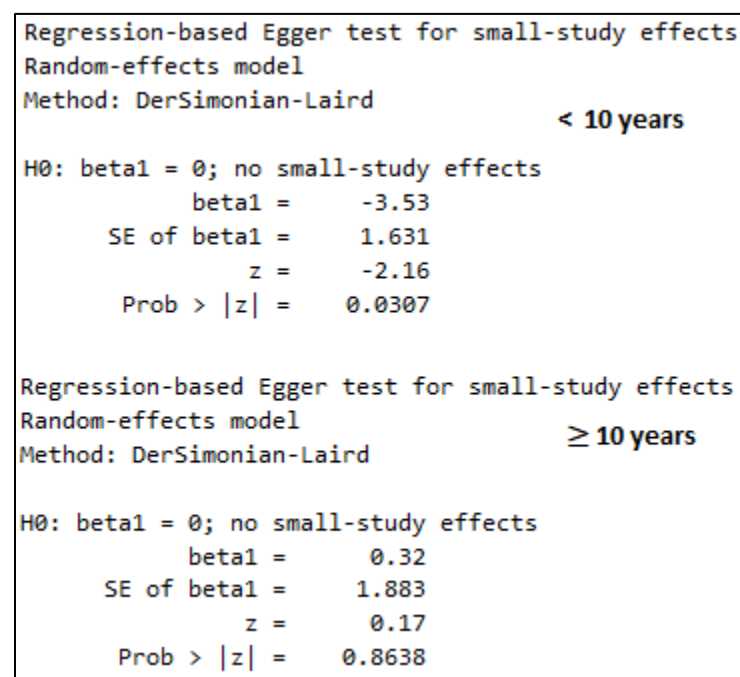


Figure A-10. Test for Publication Bias by Age Group

Note: Although suggestive of publication bias in the less-than-10 age group, filling in to the right or left using a linear or run estimator showed no change in the pooled SMD.

Effects by Country

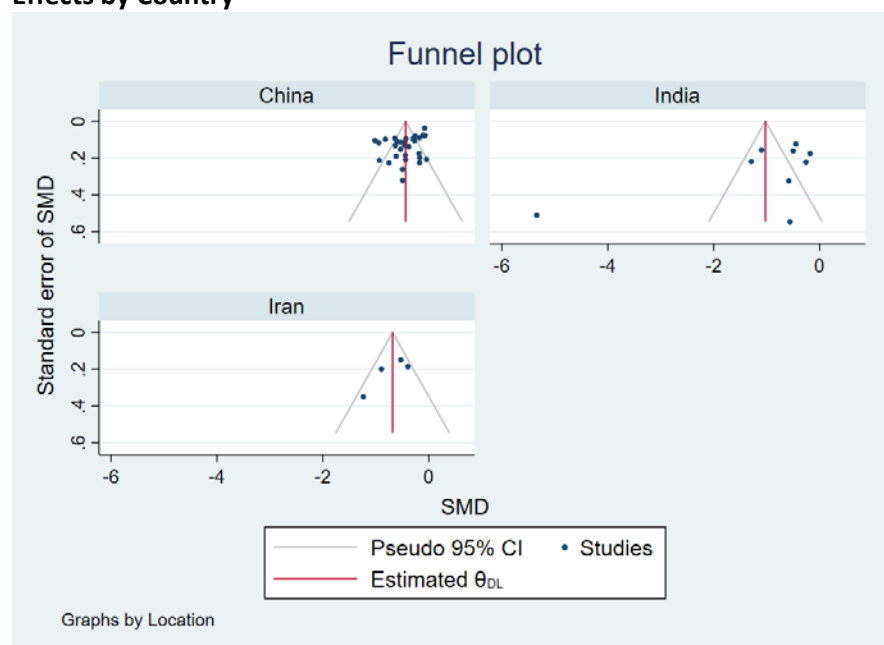


Figure A-11. Funnel Plot by Country

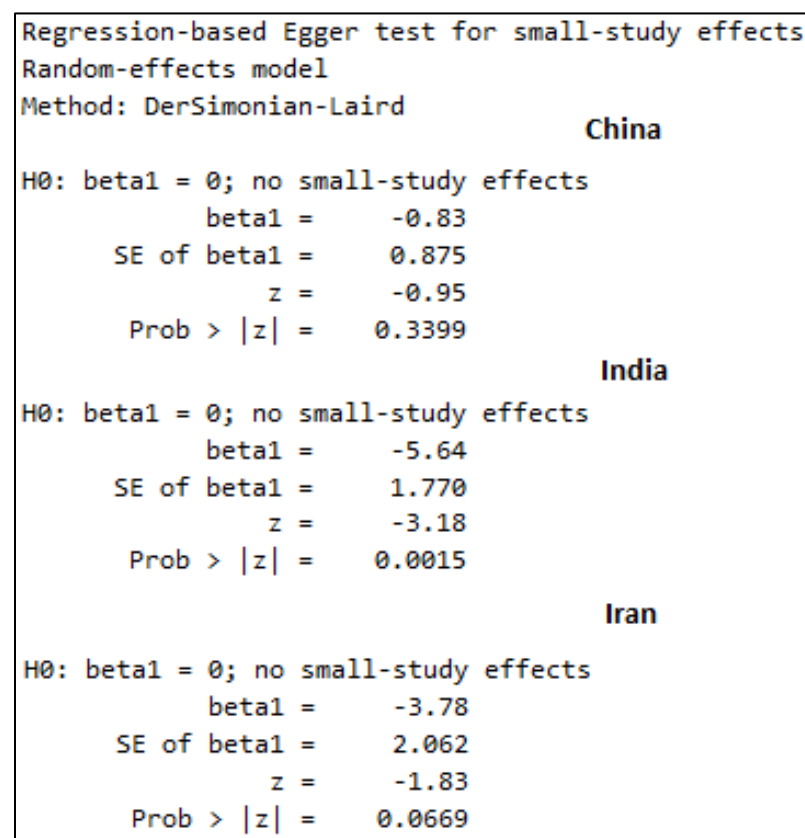


Figure A-12. Test for Publication Bias by Country

Nonparametric trim-and-fill analysis of publication bias			India
Linear estimator, imputing on the left			
Iteration	Number of studies =	12	
Model: Random-effects	observed =	9	
Method: DerSimonian-Laird	imputed =	3	
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-1.023	-1.540	-0.506
Observed + Imputed	-1.491	-2.154	-0.828

Figure A-13. Trim-and-fill Analysis for Studies in India

Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

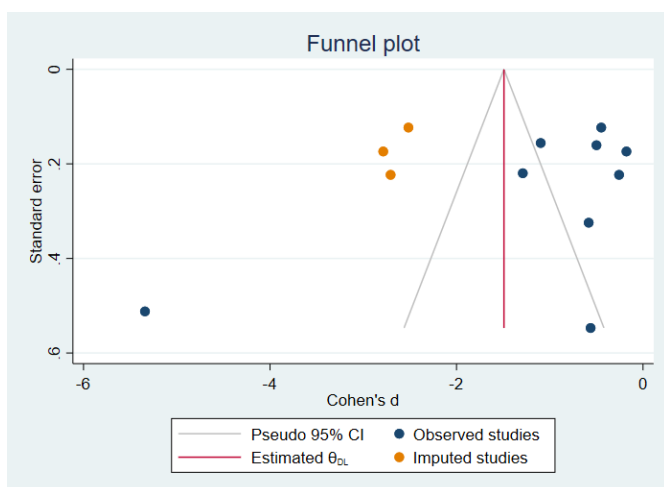


Figure A-14. Filled-in Funnel Plot for Studies in India

Panel shows funnel plot filled in to the left using a linear estimator. Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

Effect by Assessment Type

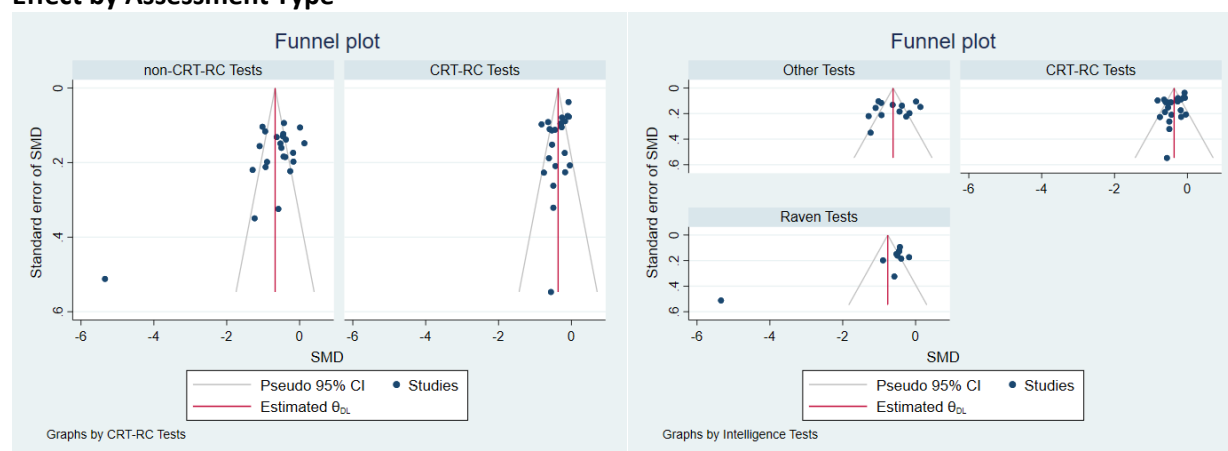


Figure A-15. Funnel Plot by CRT-RC-type Test

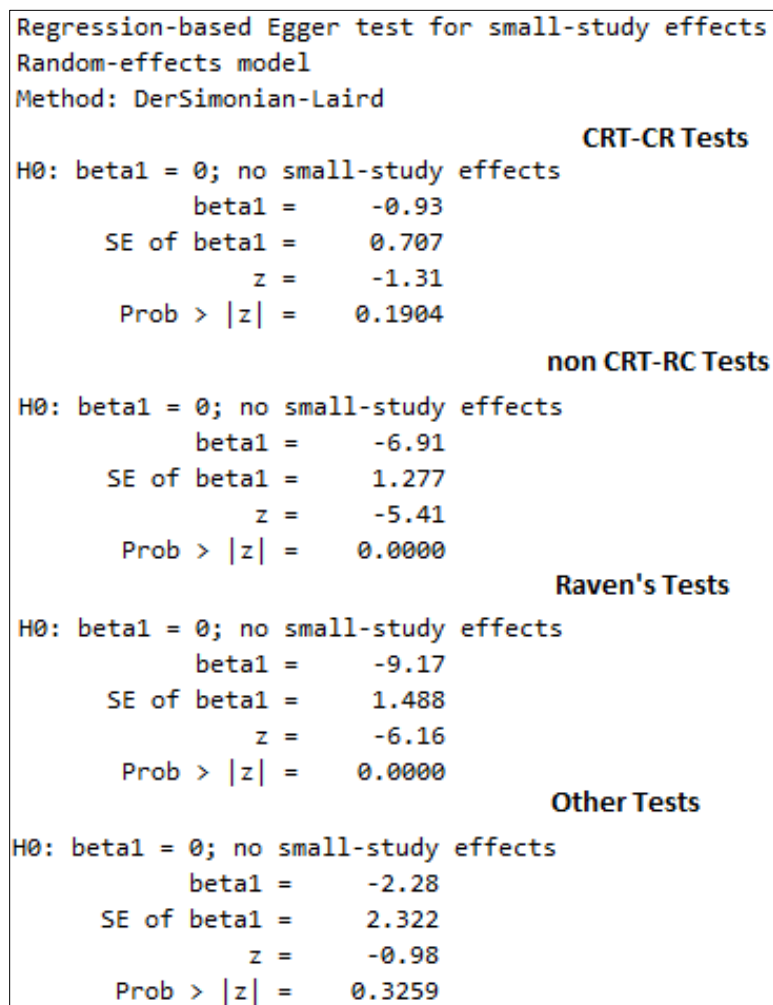


Figure A-16. Test for Publication Bias by Assessment Type

Nonparametric trim-and-fill analysis of publication bias			
Linear estimator, imputing on the left			
Iteration	Number of studies =	30	
Model: Random-effects	observed =	23	
Method: DerSimonian-Laird	imputed =	7	
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.672	-0.874	-0.469
Observed + Imputed	-0.920	-1.152	-0.687

Figure A-17. Trim-and-fill Analysis in Non-CRT-RC Tests

Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

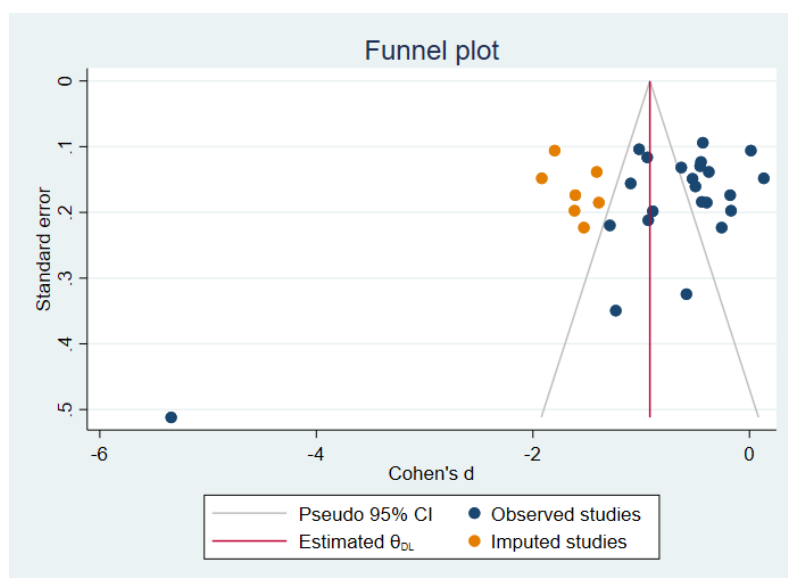


Figure A-18. Filled-in Funnel Plot to Eliminate Publication Bias in Non-CRT-RC Tests

Panel shows funnel plot filled in to the left using a linear estimator. Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

Nonparametric trim-and-fill analysis of publication bias			
Linear estimator, imputing on the left			
Iteration	Number of studies =		14
Model: Random-effects	observed =		10
Method: DerSimonian-Laird	imputed =		4
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.763	-1.098	-0.428
Observed + Imputed	-1.215	-1.676	-0.754

Figure A-19. Trim-and-fill Analysis for Raven-type Tests

Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

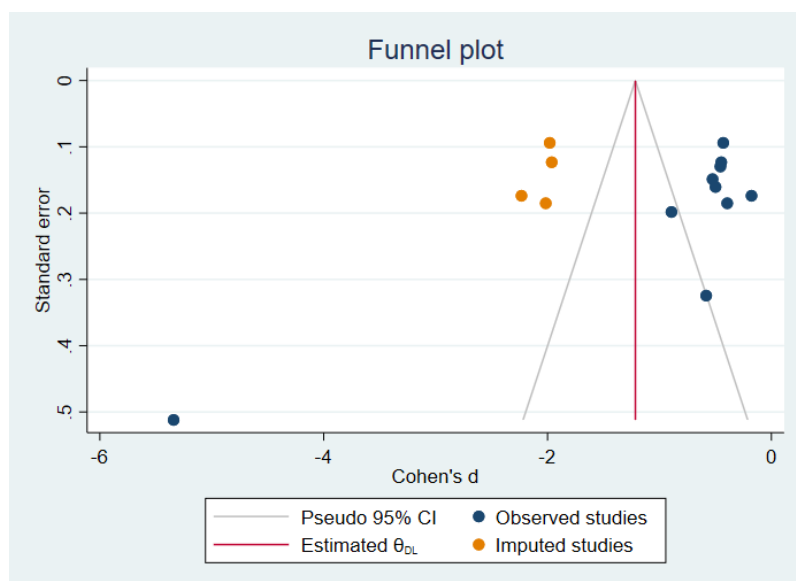


Figure A-20. Filled-in Funnel Plot to Eliminate Publication Bias for Raven-type Tests

Panel shows funnel plot filled in to the left using a linear estimator. Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

Effect by Exposure Type

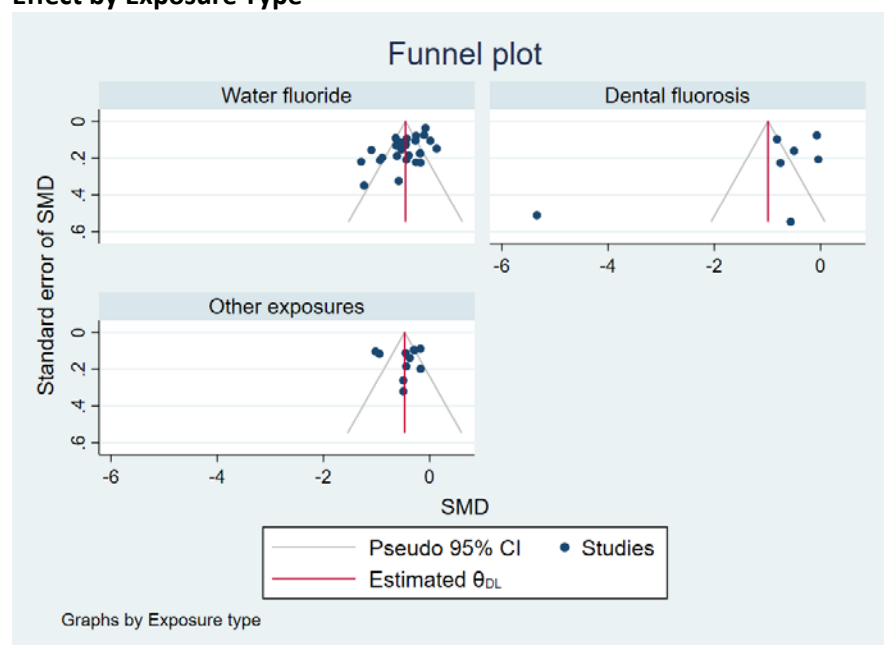


Figure A-21. Funnel Plot by Exposure Type

Regression-based Egger test for small-study effects	
Random-effects model	
Method: DerSimonian-Laird	
Water fluoride	
H0: $\beta_1 = 0$; no small-study effects	
beta1 =	-2.44
SE of beta1 =	0.837
z =	-2.92
Prob > z =	0.0035
Dental fluorosis	
H0: $\beta_1 = 0$; no small-study effects	
beta1 =	-5.81
SE of beta1 =	1.649
z =	-3.52
Prob > z =	0.0004
Other exposures	
H0: $\beta_1 = 0$; no small-study effects	
beta1 =	0.21
SE of beta1 =	1.609
z =	0.13
Prob > z =	0.8954

Figure A-22. Test for Publication Bias by Exposure Type

Nonparametric trim-and-fill analysis of publication bias			
Run estimator, imputing on the right			
Water fluoride			
Iteration	Number of studies =	30	
Model: Random-effects	observed =	28	
Method: DerSimonian-Laird	imputed =	2	
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.455	-0.573	-0.336
Observed + Imputed	-0.415	-0.533	-0.296
Dental fluorosis			
Nonparametric trim-and-fill analysis of publication bias			
Linear estimator, imputing on the left			
Iteration	Number of studies =	9	
Model: Random-effects	observed =	7	
Method: DerSimonian-Laird	imputed =	2	
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.989	-1.566	-0.412
Observed + Imputed	-1.510	-2.467	-0.553

Figure A-23. Trim-and-fill Analysis for Water Fluoride and Dental Fluorosis Exposures

For water fluoride, filling in to the right using a linear estimator or to the left using a linear or a run estimator showed no change in the pooled SMD. For dental fluorosis, filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

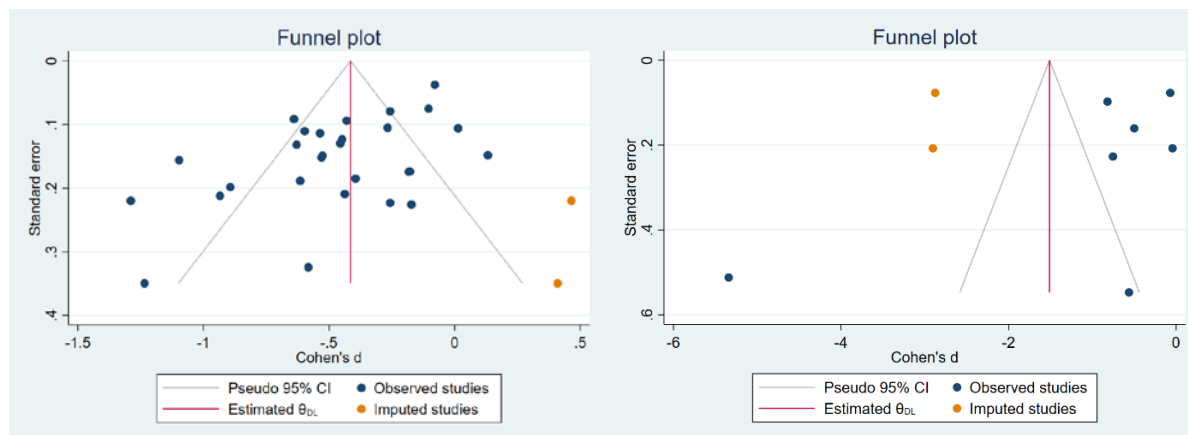


Figure A-24. Filled-in Funnel Plots to Eliminate Publication Bias for Water Fluoride (Left Panel) and Dental Fluorosis (Right Panel) Studies

For water fluoride, panel shows funnel plot filled in to the right using a run estimator. Filling in to the right using a linear estimator or to the left using a linear or a run estimator showed no change in the pooled SMD. For dental fluorosis, panel shows funnel plot filled in to the left using a linear estimator. Filling in to the right using a linear or a run estimator or to the left using a run estimator showed no change in the pooled SMD.

Sensitivity Analysis: Any Exposure Group Compared to Reference Group

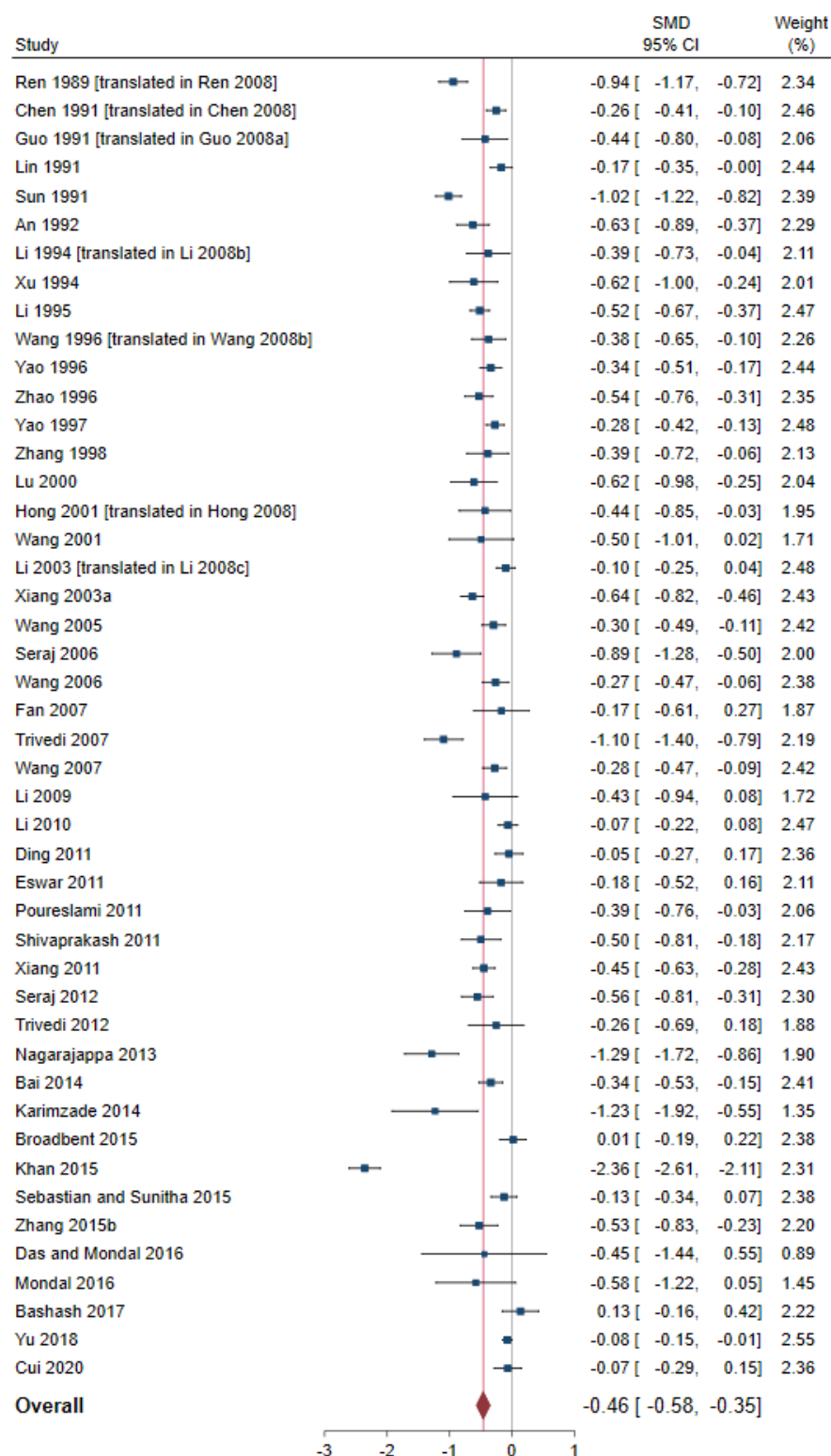


Figure A-25. Association Between Fluoride Exposure and IQ Scores in Children Using Any Exposure Versus Reference

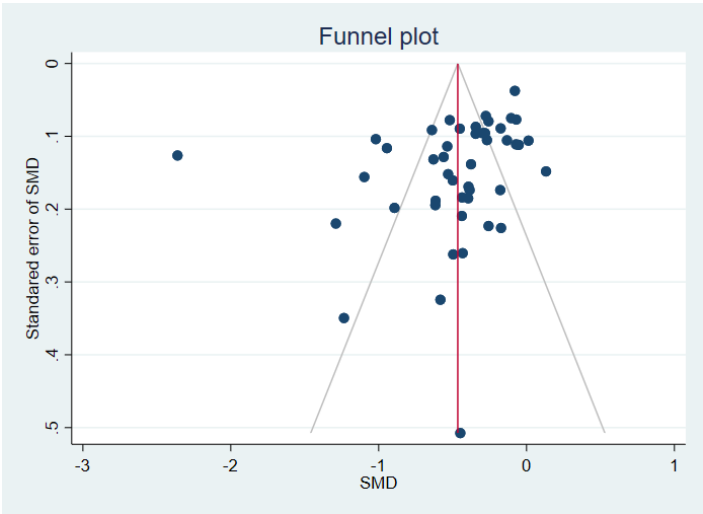


Figure A-26. Funnel Plot in Sensitivity Analysis Using Any Exposure Versus Reference

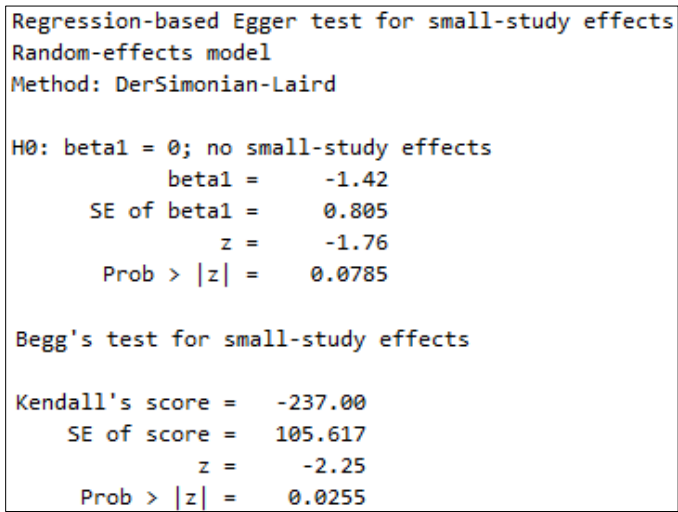


Figure A-27. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left			
Iteration		Number of studies =		52	Iteration		Number of studies =
Model: Random-effects		observed =		46	Model: Random-effects		observed =
Method: DerSimonian-Laird		imputed =		6	Method: DerSimonian-Laird		imputed =
Pooling					Pooling		
Model: Random-effects					Model: Random-effects		
Method: DerSimonian-Laird					Method: DerSimonian-Laird		
Studies	Cohen's d	[95% Conf. Interval]			Studies	Cohen's d	[95% Conf. Interval]
Observed	-0.465	-0.580	-0.349		Observed	-0.465	-0.580 -0.349
Observed + Imputed	-0.340	-0.475	-0.206		Observed + Imputed	-0.608	-0.738 -0.479

Figure A-28. Trim-and-fill Analysis in Sensitivity Analysis Using Any Exposure Versus Reference

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

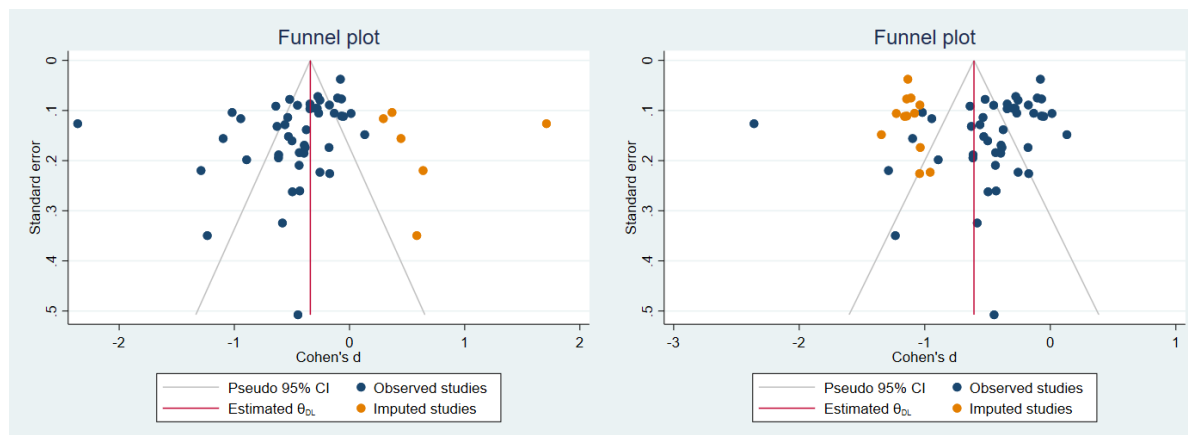


Figure A-29. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator (the linear estimator to the right showed no change in the pooled SMD); right panel shows random-effects pooled SMD after filling in to the left using a linear estimator (the run estimator to the left showed no change in the pooled SMD).

Sensitivity Analysis: Any Exposure Group Compared to Reference Group Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)

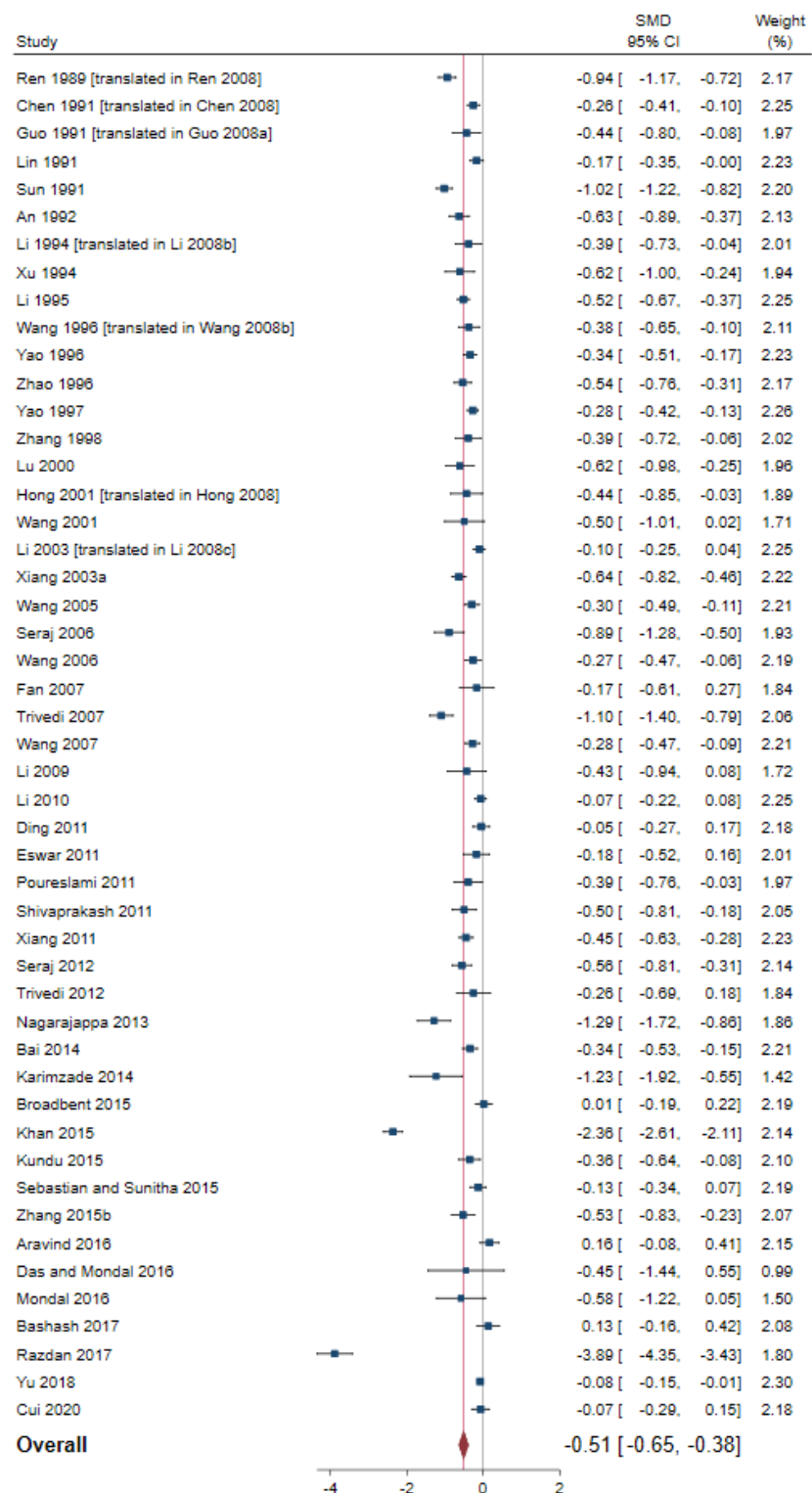


Figure A-30. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Any Exposure Group Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

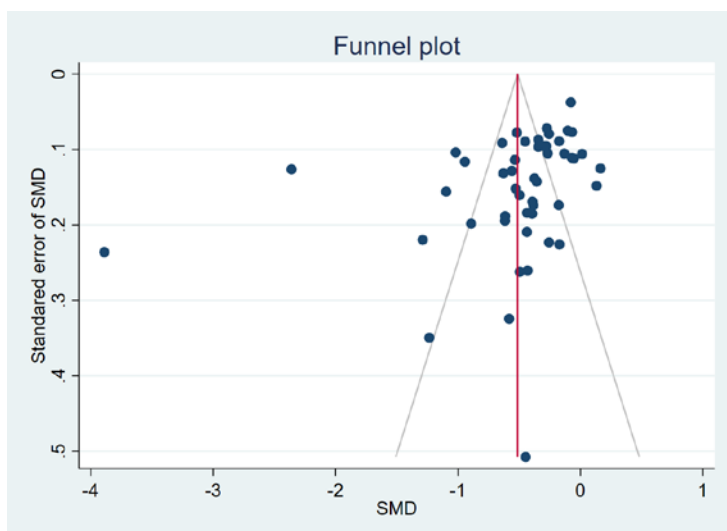


Figure A-31. Funnel Plot in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -2.46
      SE of beta1 =    0.890
              z =      -2.77
      Prob > |z| =    0.0056
```

Figure A-32. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left			
Iteration	Number of studies = 56			Iteration	Number of studies = 65		
Model: Random-effects	observed = 49			Model: Random-effects	observed = 49		
Method: DerSimonian-Laird	imputed = 7			Method: DerSimonian-Laird	imputed = 16		
Pooling				Pooling			
Model: Random-effects				Model: Random-effects			
Method: DerSimonian-Laird				Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]		Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.514	-0.645	-0.383	Observed	-0.514	-0.645	-0.383
Observed + Imputed	-0.329	-0.485	-0.173	Observed + Imputed	-0.730	-0.880	-0.579

Figure A-33. Trim-and-fill Analysis in Sensitivity Analysis Using Any Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

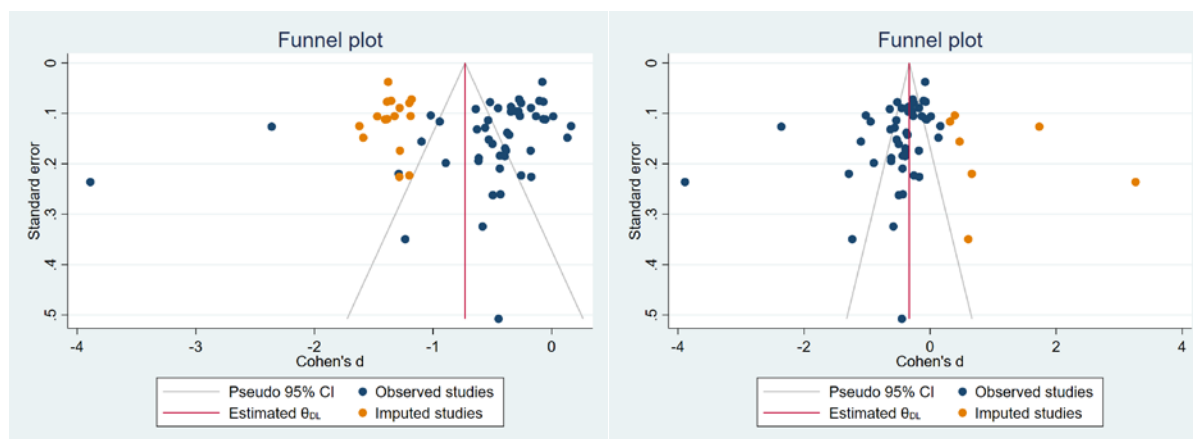


Figure A-34. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator; right panel shows random-effects pooled SMD after filling in to the left using a linear estimator. Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

Sensitivity Analysis: Highest Exposure Group Compared to Reference Group Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)

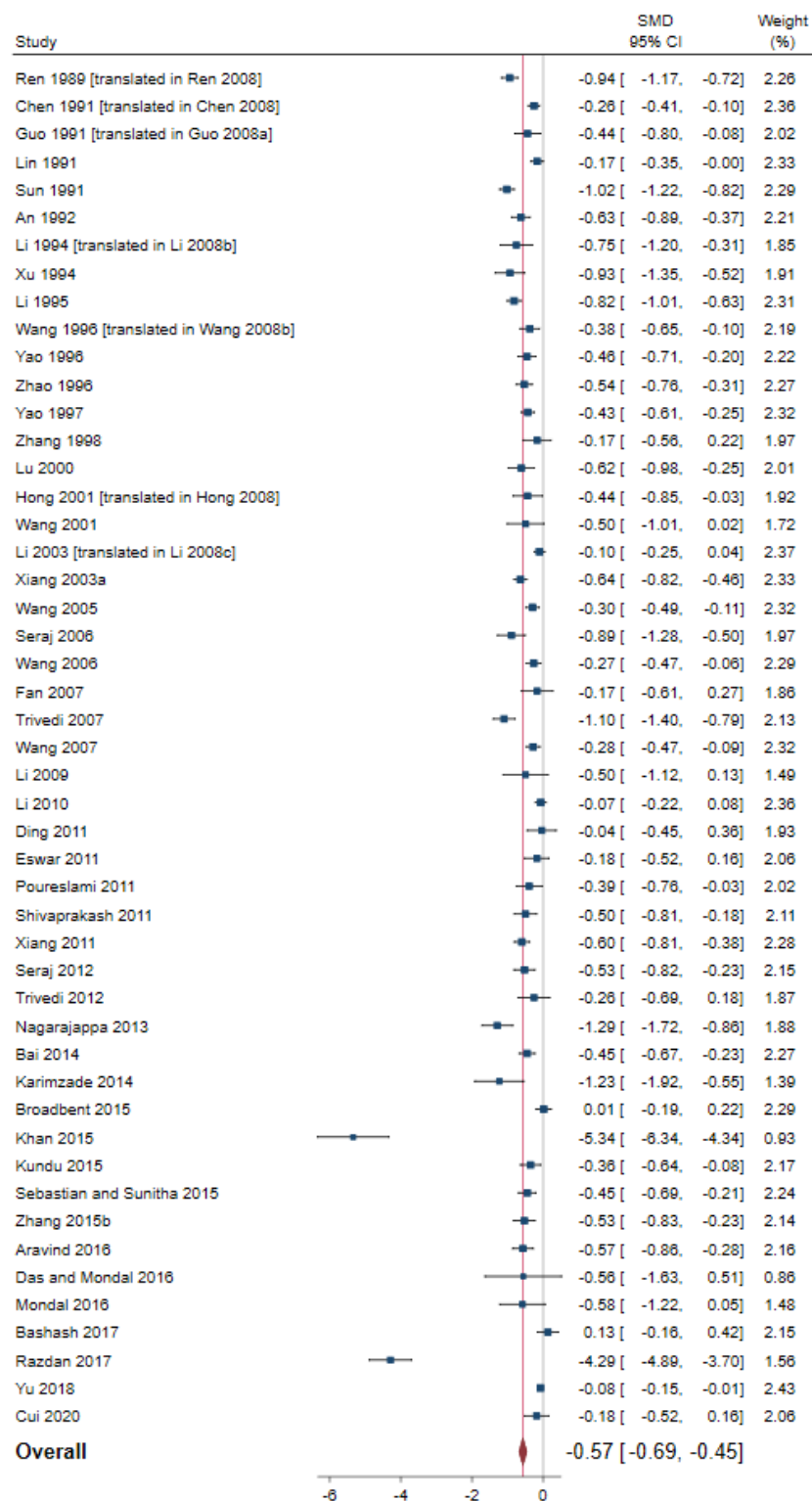


Figure A-35. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

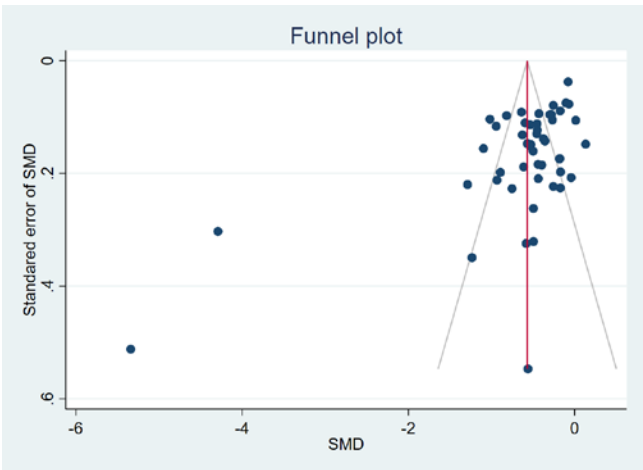


Figure A-36. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

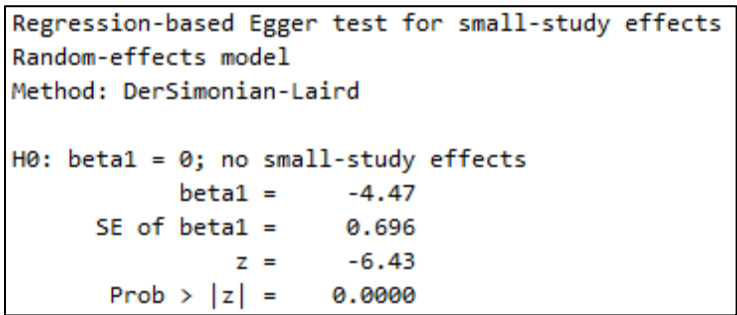


Figure A-37. Test for Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left							
Iteration		Number of studies =		54	Iteration		Number of studies =		66		
Model: Random-effects		observed =		49	Model: Random-effects		observed =		49		
Method: DerSimonian-Laird		imputed =		5	Method: DerSimonian-Laird		imputed =		17		
Pooling				Pooling							
Model: Random-effects				Model: Random-effects							
Method: DerSimonian-Laird				Method: DerSimonian-Laird							
Studies		Cohen's d		[95% Conf. Interval]		Studies		Cohen's d		[95% Conf. Interval]	
Observed		-0.570		-0.693 -0.447		Observed		-0.570		-0.693 -0.447	
Observed + Imputed		-0.422		-0.563 -0.281		Observed + Imputed		-0.838		-0.999 -0.676	

Figure A-38. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

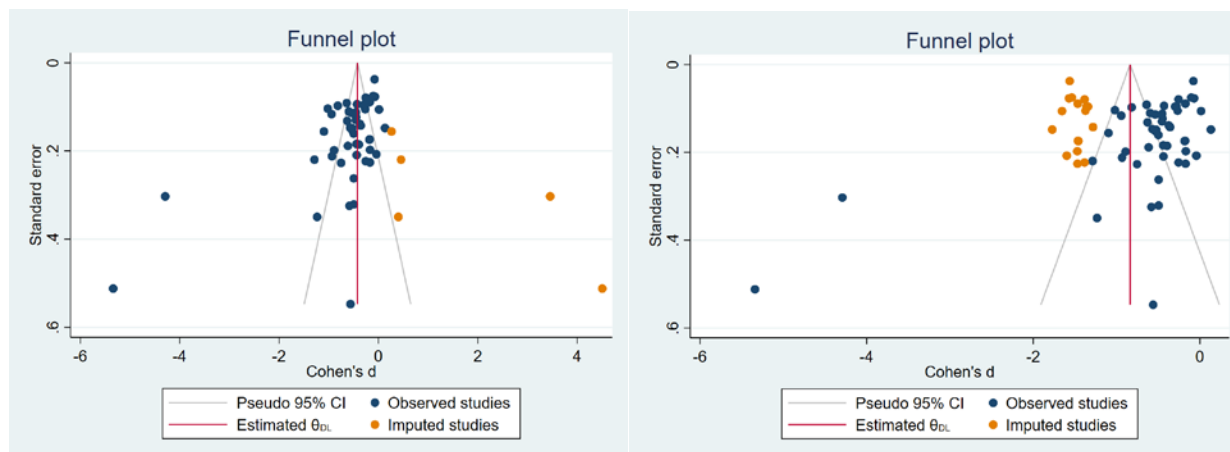


Figure A-39. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Including Aravind *et al.* (2016), Kundu *et al.* (2015), and Razdan *et al.* (2017)]

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator; right panel shows random-effects pooled SMD after filling in to the left using a linear estimator. Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

Sensitivity Analysis: Excluding Lin *et al.* (1991)¹

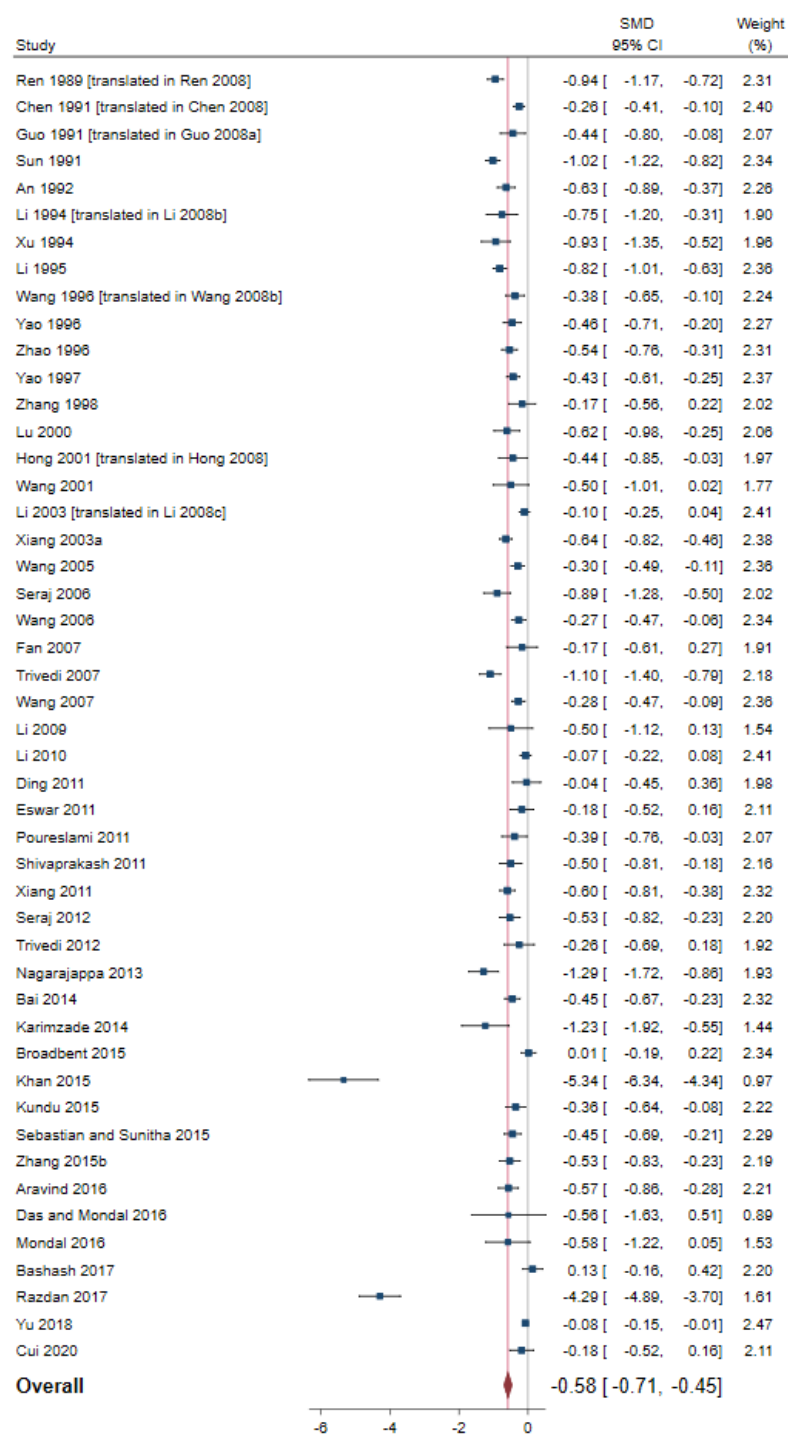


Figure A-40. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Excluding Lin *et al.* (1991)]

¹Lin *et al.* (1991): ICF calculated standard errors based on p-values.

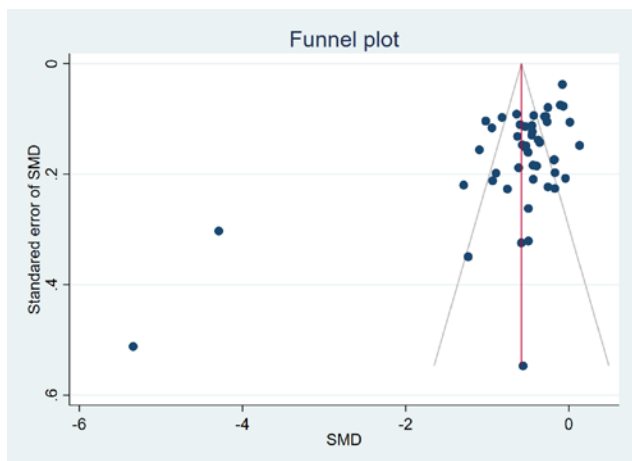


Figure A-41. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin *et al.* (1991)]

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -4.47
      SE of beta1 =    0.711
              z =     -6.29
      Prob > |z| =    0.0000
```

Figure A-42. Test for Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin *et al.* (1991)]

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the left			
Iteration	Number of studies = 53			Iteration	Number of studies = 65		
Model: Random-effects	observed = 48			Model: Random-effects	observed = 48		
Method: DerSimonian-Laird	imputed = 5			Method: DerSimonian-Laird	imputed = 17		
Pooling				Pooling			
Model: Random-effects				Model: Random-effects			
Method: DerSimonian-Laird				Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]		Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.581	-0.707	-0.454	Observed	-0.581	-0.707	-0.454
Observed + Imputed	-0.429	-0.573	-0.284	Observed + Imputed	-0.855	-1.021	-0.689

Figure A-43. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin *et al.* (1991)]

Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

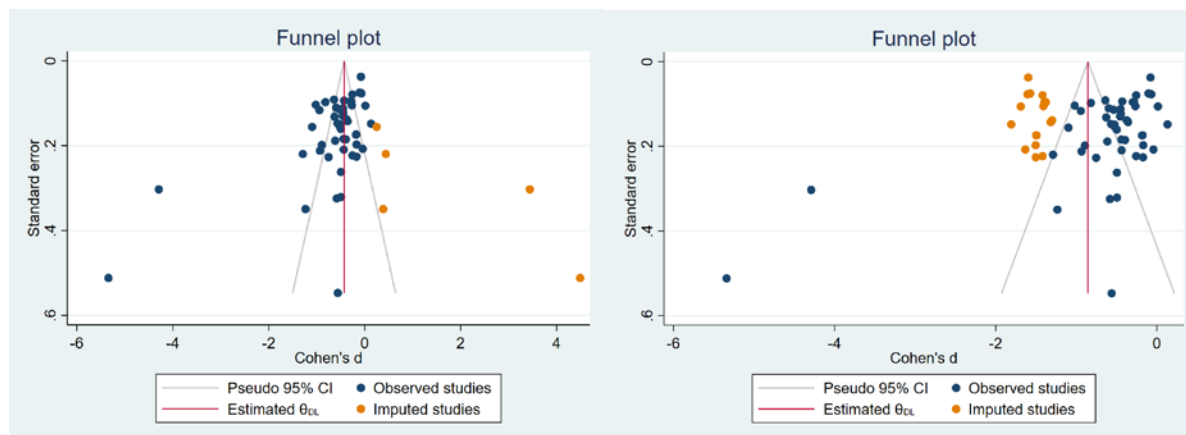


Figure A-44. Filled-in Funnel Plots to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Lin *et al.* (1991)]

Left panel shows the random-effects pooled SMD after filling in to the right using a run estimator; right panel shows random-effects pooled SMD after filling in to the left using a linear estimator. Filling in to the right using a linear estimator or to the left using a run estimator showed no change in the pooled SMD.

Sensitivity Analysis: Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)

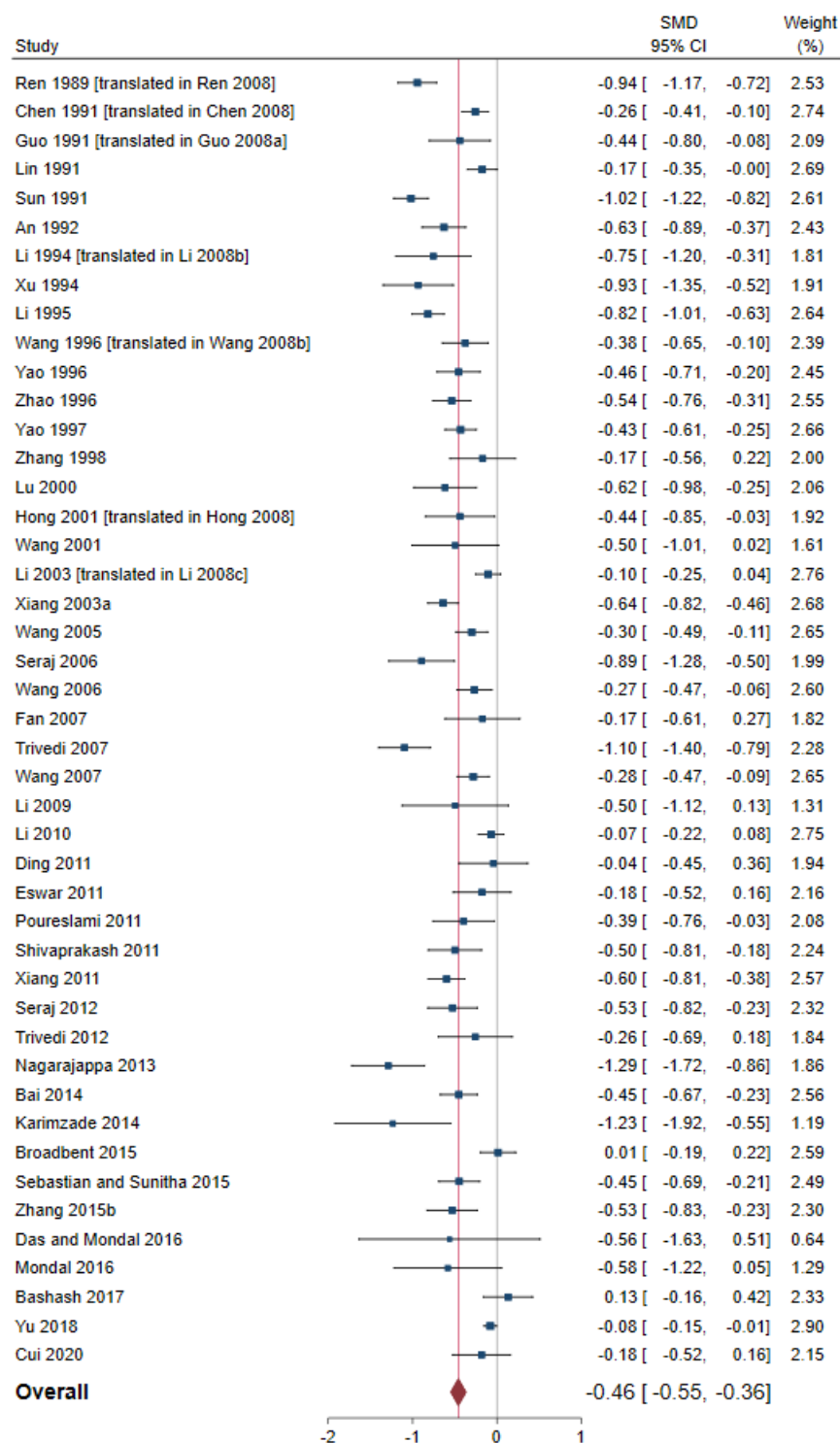


Figure A-45. Association Between Fluoride Exposure and IQ Scores in Children in Analysis Using Highest Exposure Versus Reference [Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)]

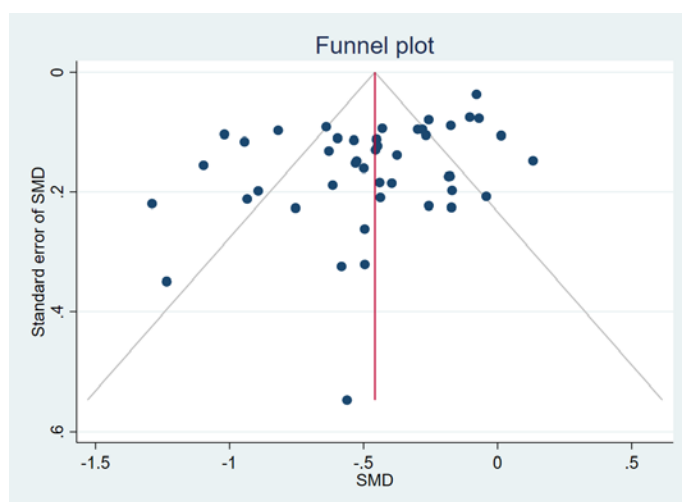


Figure A-46. Funnel Plot in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)]

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -1.30
      SE of beta1 =    0.659
      z =      -1.98
      Prob > |z| =    0.0481
```

Figure A-47. Test for Publication Bias in Sensitivity Analysis Using Any Exposure Versus Reference [Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)]

Nonparametric trim-and-fill analysis of publication bias			
Run estimator, imputing on the right			
Iteration	Number of studies =		48
Model: Random-effects	observed =		45
Method: DerSimonian-Laird	imputed =		3
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Cohen's d	[95% Conf. Interval]	
Observed	-0.458	-0.554	-0.361
Observed + Imputed	-0.417	-0.514	-0.319

Figure A-48. Trim-and-fill Analysis in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)]

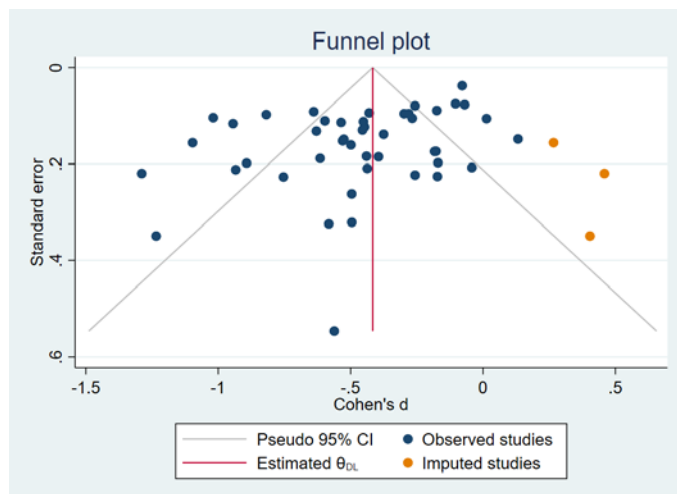


Figure A-49. Filled-in Funnel Plot to Eliminate Publication Bias in Sensitivity Analysis Using Highest Exposure Versus Reference [Excluding Aravind *et al.* (2016), Kundu *et al.* (2015), Razdan *et al.* (2017), and Khan *et al.* (2015)]

Panel shows the random-effects pooled SMD after filling in to the right using a run estimator. Filling in to the right using a linear estimator or to the left using a linear or a run estimator showed no change in the pooled SMD.

Attachment B. Subgroup and Sensitivity Analyses (Aim 2)

Table B-1. Characteristics of Studies Included in the Individual-level Meta-analysis							
Reference	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric)	Range			
Ding <i>et al.</i> (2011)	China	7–14	Urine	0.10–3.55 mg/L	Combined Raven's Test for Rural China	Lower	Age; arsenic; iodine; lead; SES; demographics
Zhang <i>et al.</i> (2015b)	China	10–12	Urine	1.10 ± 0.67 mg/L (reference); 2.40 ± 1.01 mg/L (high fluoride area)	Combined Raven's Test for Rural China	Lower	Age; gender; arsenic; iodine; drinking water fluoride; SES; thyroid hormone levels; COMT genotype
Bashash <i>et al.</i> (2017)	Mexico	6–12	Urine	0.18–2.8 mg/L	Wechsler Abbreviated Scale of Intelligence	Lower	Age; gender; weight at birth; parity; gestational age; maternal characteristics (smoking history, marital status, age at delivery, IQ, education, and cohort)
Cui <i>et al.</i> (2018)	China	7–12	Urine	0.8–2.0 mg/L	Combined Raven's Test for Rural China	Lower	Age; maternal education; smoking in family member; stress; anger; dopamine receptor-2 polymorphism
Yu <i>et al.</i> (2018)	China	7–13	Urine, drinking Water	0.01–5.54 mg/L (urine) 0.20–3.90 mg/L (water)	Combined Raven's Test for Rural China	Lower	Age; gender; maternal education; paternal education; low birth weight

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Table B-1. Characteristics of Studies Included in the Individual-level Meta-analysis							
Reference	Study Location	Age Range (Years)	Fluoride Exposure		Intelligence Assessment	Overall RoB Rating	Confounders Considered
			Assessment (Metric)	Range			
Green <i>et al.</i> (2019)	Canada	3–4	Maternal urine, maternal fluoride intake, drinking water	0.51 ± 0.36 mg/L (urine) 0.54 ± 0.44 mg/day (maternal daily fluoride intake) 0.31 ± 0.23 mg/L (water)	Wechsler Primary and Preschool Scale of Intelligence-III	Lower	Gender; city; maternal education; race/ethnicity; HOME score; prenatal secondhand smoke exposure
Till <i>et al.</i> (2020)	Canada	3–4	Residence (fluoridated/nonfluoridated cities), maternal urine, infant fluoride intake from formula, drinking water	0.64–0.70 mg/L (fluoridated), 0.38–0.42 mg/L (nonfluoridated) (urine) 0.12–0.34 mg/day (fluoridated), 0.02–0.08 mg/day (nonfluoridated) (infant formula fluoride intake) 0.58 mg/L (fluoridated), 0.13 mg/L (nonfluoridated) (water)	Wechsler Primary and Preschool Scale of Intelligence-III	Lower	Age; gender; maternal education; maternal race; HOME total score; second-hand smoke status in the child's house
Wang <i>et al.</i> (2020b)	China	7–13	Urine, drinking water	0.01–5.54 mg/L (urine) 0.20–3.90 mg/L (water)	Combined Raven's Test for Rural China	Lower	Age; gender; body mass index; maternal education; paternal education; household income; low birth weight

Sensitivity Analysis for Individual-level Studies: No Pooling for Yu *et al.* (2018)

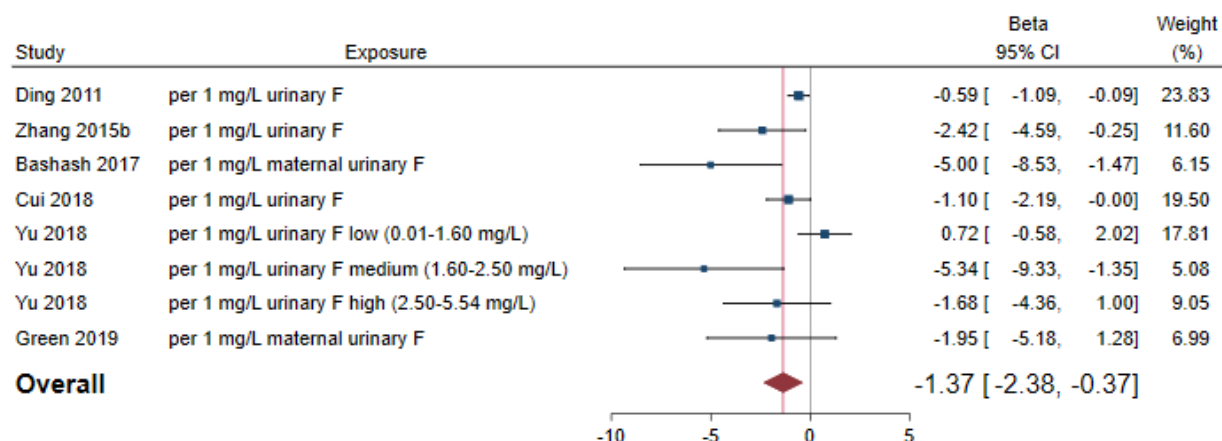


Figure B-1. Association Between Individual-level Fluoride Exposure and IQ Scores in Children [No Pooling for Yu *et al.* (2018)]

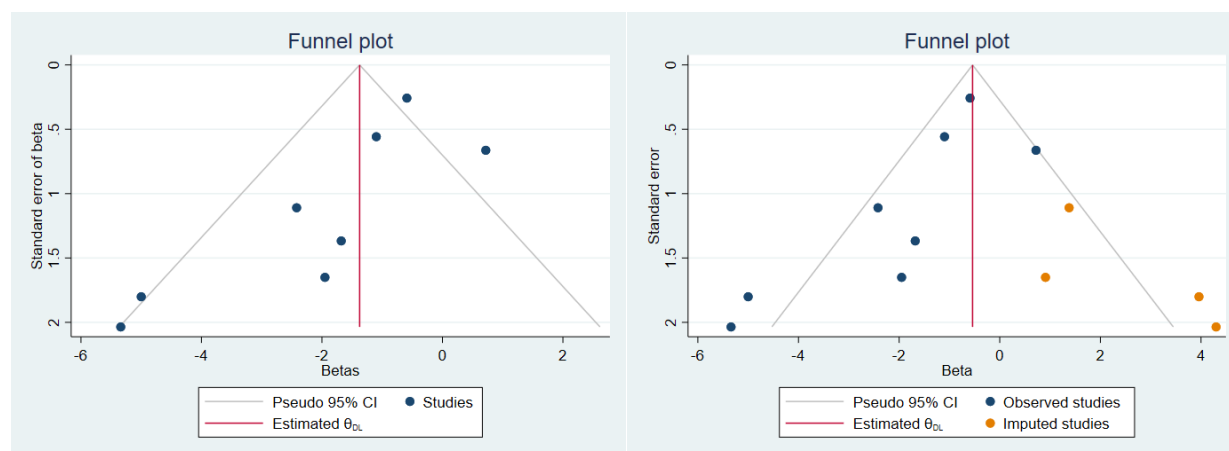


Figure B-2. Funnel Plots of Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [No Pooling for Yu *et al.* (2018)]

Right panel shows funnel plot filled in to the right using a linear estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =    -2.21
SE of beta1 =    0.801
          z =    -2.75
Prob > |z| =    0.0059
```

Figure B-3. Test for Publication Bias for Studies with Individual-level Exposures

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Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right					
Iteration		Number of studies =		12	Iteration		Number of studies =		9
Model: Random-effects		observed =		8	Model: Random-effects		observed =		8
Method: DerSimonian-Laird		imputed =		4	Method: DerSimonian-Laird		imputed =		1
Pooling				Pooling					
Model: Random-effects				Model: Random-effects					
Method: DerSimonian-Laird				Method: DerSimonian-Laird					
Studies		Beta		[95% Conf. Interval]	Studies		Beta		[95% Conf. Interval]
Observed		-1.374		-2.379 -0.369	Observed		-1.374		-2.379 -0.369
Observed + Imputed		-0.540		-1.567 0.486	Observed + Imputed		-1.188		-2.220 -0.155

Figure B-4. Trim-and-fill Analysis for Studies with Individual-level Exposures

Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

Sensitivity Analysis for Individual-level Studies: Effect by Exposure Type, No Pooling for Yu *et al.* (2018)

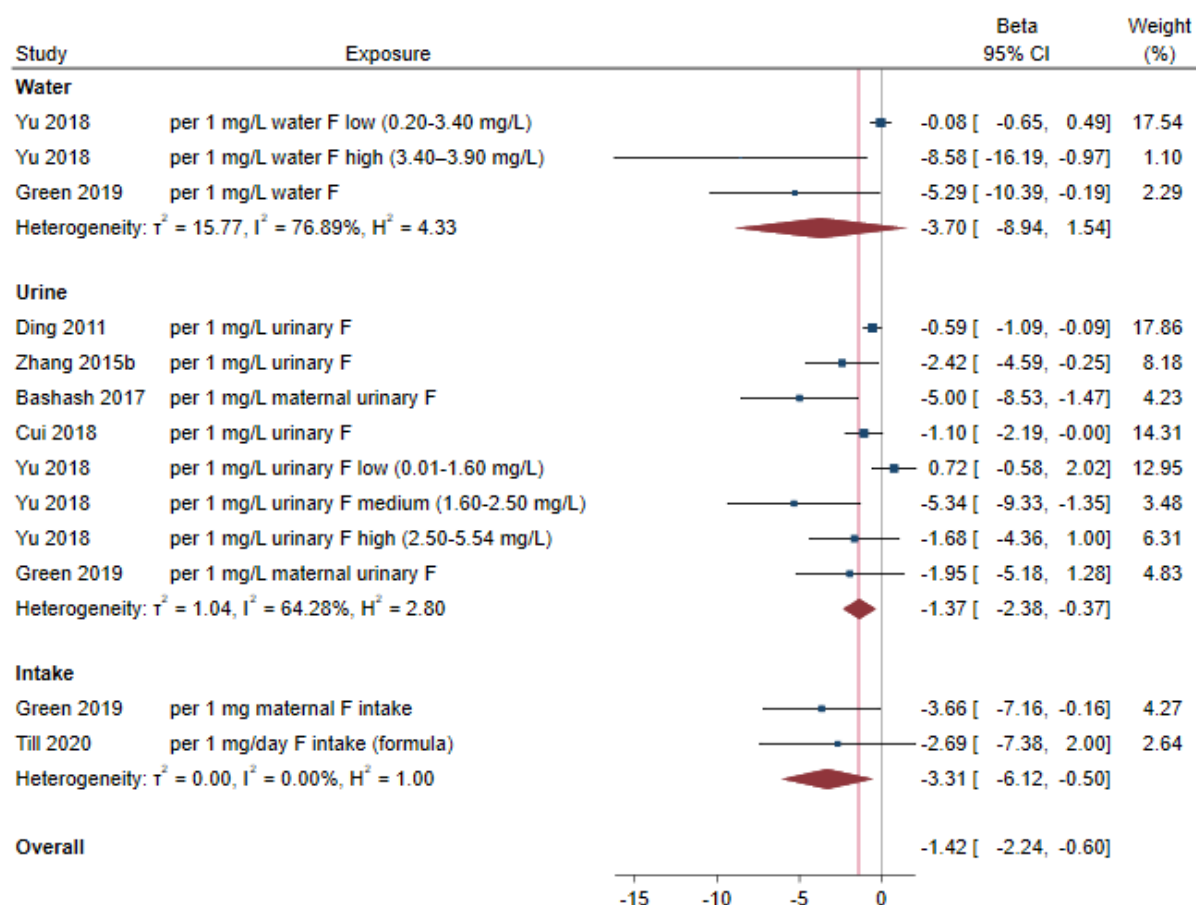


Figure B-5. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [No Pooling for Yu *et al.* (2018)]

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analyses. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Sensitivity Analysis for Individual-level Studies: Using Wang *et al.* (2020b) Versus Yu *et al.* (2018)

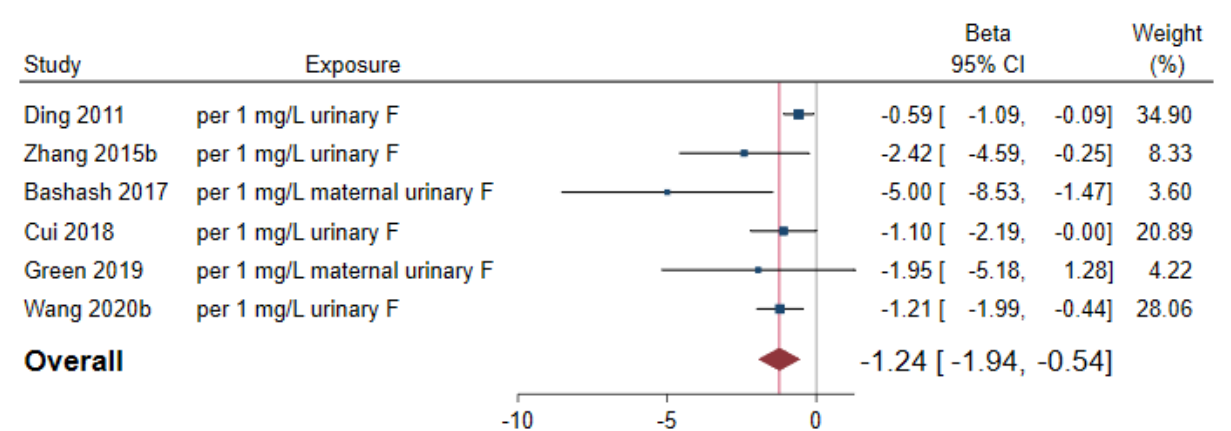


Figure B-6. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [Using Wang *et al.* (2020b) Estimates in Place of Yu *et al.* (2018) Estimates]

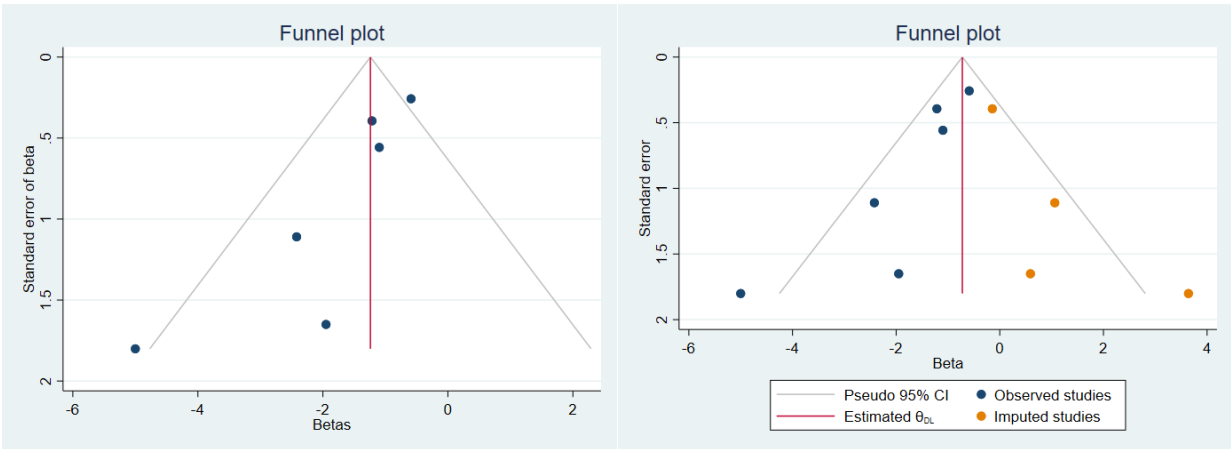


Figure B-7. Funnel Plot of Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Wang *et al.* (2020b) Estimates in Place of Yu *et al.* (2018) Estimates]

Right panel shows funnel plot filled in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

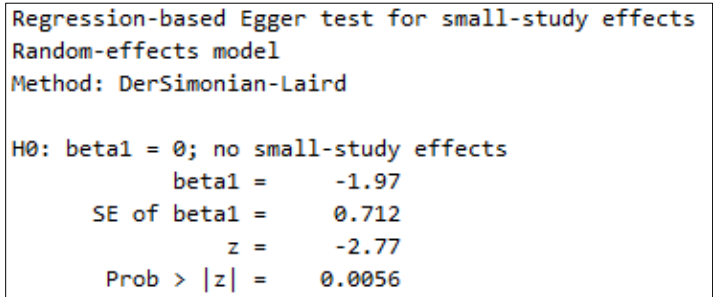


Figure B-8. Test for Publication Bias for Studies with Individual-level Exposures [Using Wang *et al.* (2020b) Estimates in Place of Yu *et al.* (2018) Estimates]

Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the right					Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				
Iteration		Number of studies =		9	Iteration		Number of studies =		10
Model: Random-effects		observed =		6	Model: Random-effects		observed =		6
Method: DerSimonian-Laird		imputed =		3	Method: DerSimonian-Laird		imputed =		4
Pooling					Pooling				
Model: Random-effects					Model: Random-effects				
Method: DerSimonian-Laird					Method: DerSimonian-Laird				
Studies		Beta		[95% Conf. Interval]	Studies		Beta		[95% Conf. Interval]
Observed		-1.240		-1.939 -0.540	Observed		-1.240		-1.939 -0.540
Observed + Imputed		-0.900		-1.676 -0.123	Observed + Imputed		-0.722		-1.411 -0.034

Figure B-9. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Wang *et al.* (2020b) Estimates in Place of Yu *et al.* (2018) Estimates]

Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

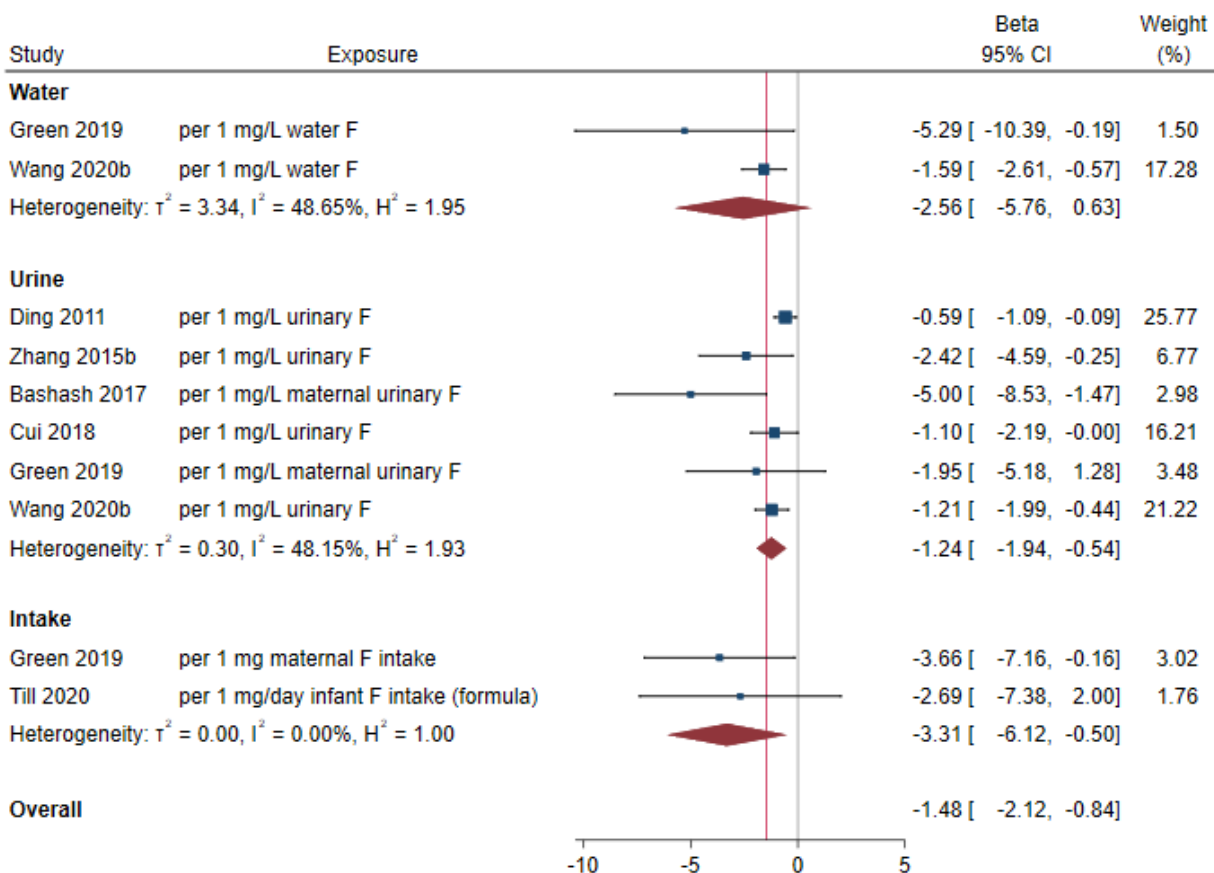


Figure B-10. Association Between Fluoride Exposure and IQ Scores in Children by Exposure for Individual-level Exposures [Using Wang *et al.* (2020b) Estimates in Place of Yu *et al.* (2018) Estimates]

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analysis. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Sensitivity Analysis for Individual-level Studies: Using Till *et al.* (2020) Versus Green *et al.* (2019)

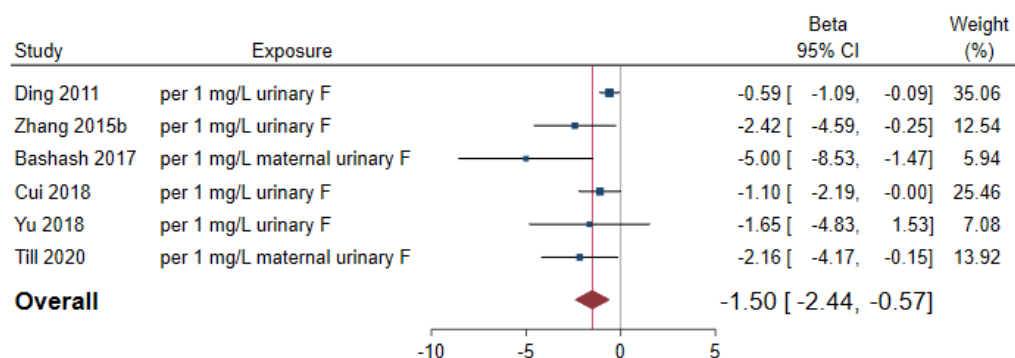


Figure B-11. Association Between Fluoride Exposure and IQ Scores in Children for Individual-level Exposures [Using Till *et al.* (2020) Estimates in Place of Green *et al.* (2019) Estimates]

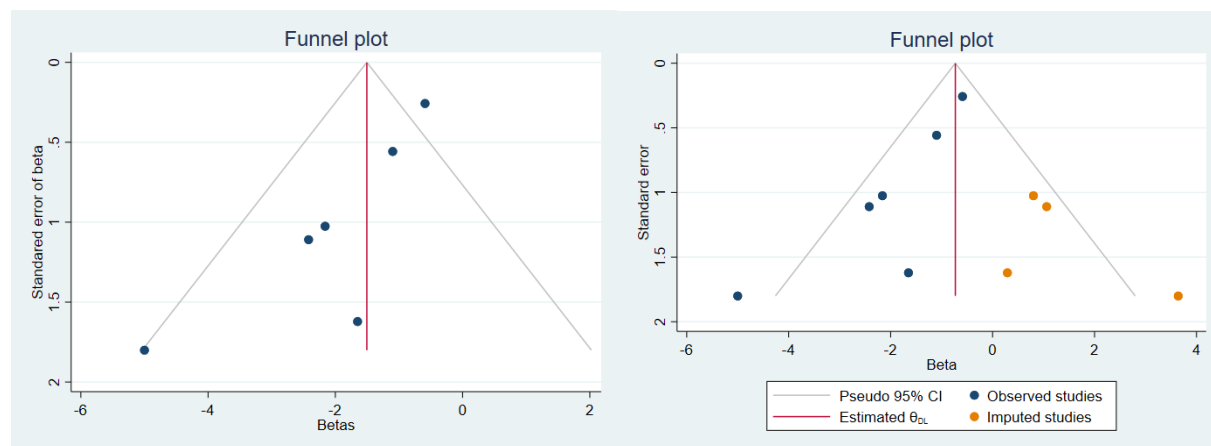


Figure B-12. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Till *et al.* (2020) Estimates in Place of Green *et al.* (2019) Estimates]

Right panel shows funnel plot filled in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -1.94
      SE of beta1 =    0.655
              z =     -2.96
      Prob > |z| =    0.0031
```

Figure B-13. Test for Publication Bias for Studies with Individual-level Exposures [Using Till *et al.* (2020) Estimates in Place of Green *et al.* (2019) Estimates]

Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the right					Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				
Iteration		Number of studies =		9	Iteration		Number of studies =		10
Model: Random-effects		observed =		6	Model: Random-effects		observed =		6
Method: DerSimonian-Laird		imputed =		3	Method: DerSimonian-Laird		imputed =		4
Pooling					Pooling				
Model: Random-effects					Model: Random-effects				
Method: DerSimonian-Laird					Method: DerSimonian-Laird				
Studies		Beta [95% Conf. Interval]			Studies		Beta [95% Conf. Interval]		
Observed		-1.504	-2.439	-0.570	Observed		-1.504	-2.439	-0.570
Observed + Imputed		-0.808	-1.774	0.159	Observed + Imputed		-0.730	-1.649	0.188

Figure B-14. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Till *et al.* (2020) Estimates in Place of Green *et al.* (2019) Estimates]

Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

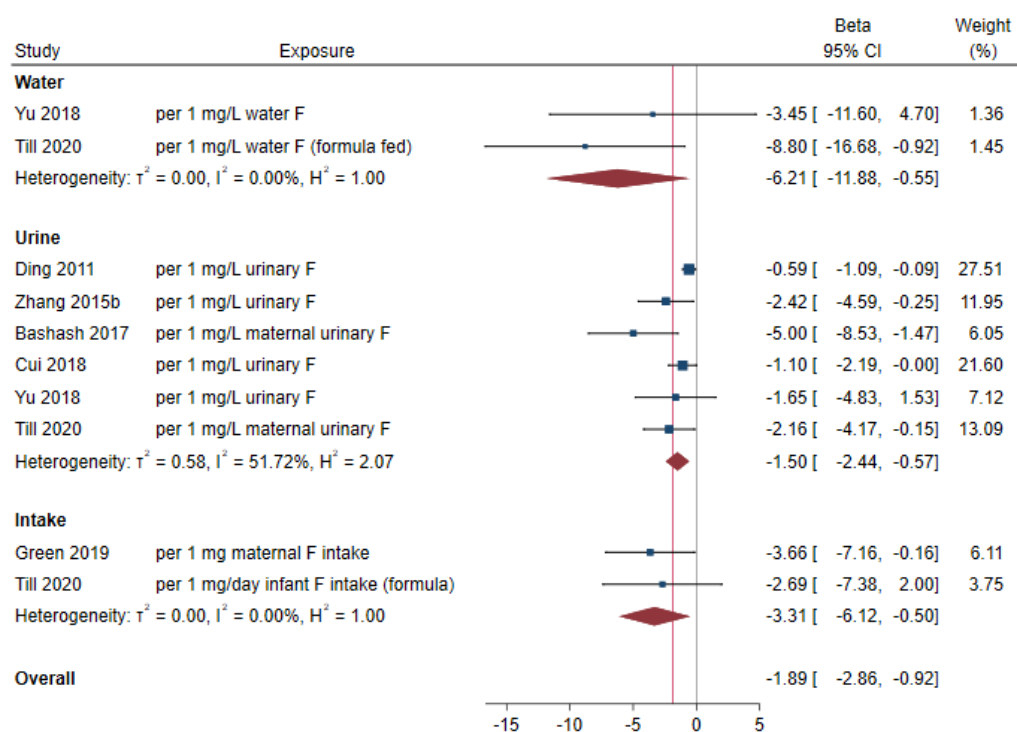


Figure B-15. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type for Individual-level Exposures [Using Till *et al.* (2020) Estimates in Place of Green *et al.* (2019) Estimates]

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analysis. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Sensitivity Analysis for Individual-level Studies: Verbal IQ

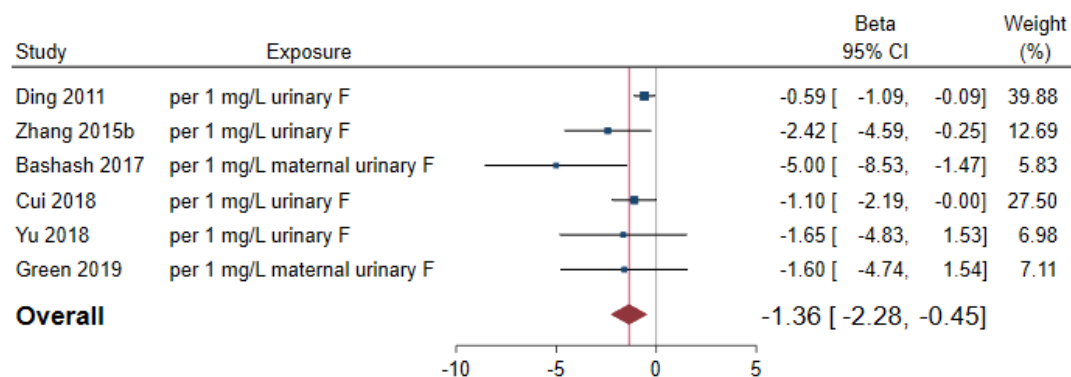


Figure B-16. Association between Fluoride Exposure and IQ Scores in Children Using Verbal IQ Score for Green *et al.* (2019)

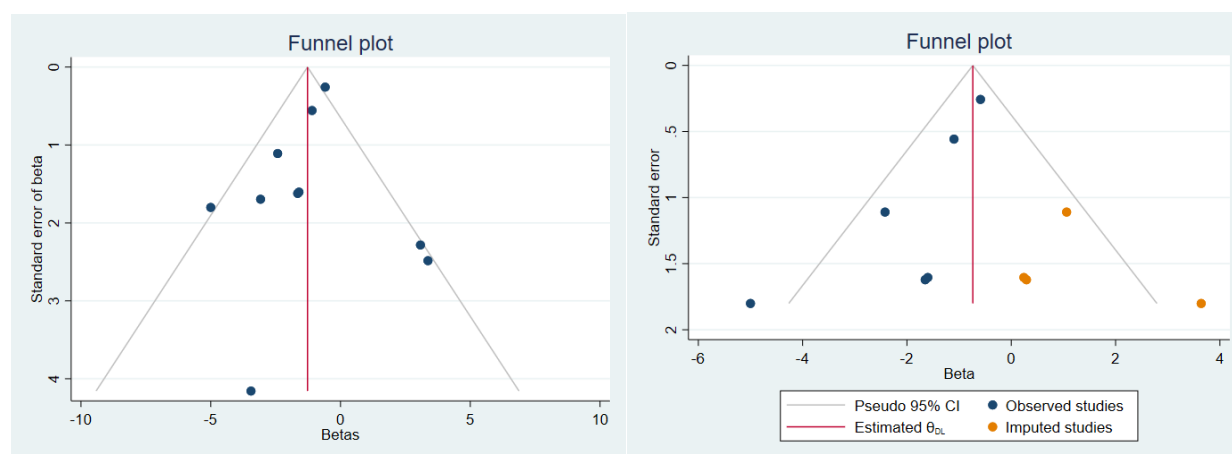


Figure B-17. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Verbal IQ Score for Green *et al.* (2019)]

Right panel shows funnel plot filled in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -1.62
SE of beta1 =      0.629
      z =      -2.58
Prob > |z| =      0.0098
```

Figure B-18. Test for Publication Bias for Studies with Individual-level Exposures [Using Verbal IQ Score for Green *et al.* (2019)]

Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the right				Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right			
Iteration	Number of studies =			Iteration	Number of studies =		
Model: Random-effects	observed =			Model: Random-effects	observed =		
Method: DerSimonian-Laird	imputed =			Method: DerSimonian-Laird	imputed =		
Pooling				Pooling			
Model: Random-effects				Model: Random-effects			
Method: DerSimonian-Laird				Method: DerSimonian-Laird			
Studies	Beta [95% Conf. Interval]			Studies	Beta [95% Conf. Interval]		
Observed	-1.365 -2.278 -0.452			Observed	-1.365 -2.278 -0.452		
Observed + Imputed	-0.814 -1.788 0.159			Observed + Imputed	-0.737 -1.654 0.180		

Figure B-19. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Verbal IQ Score for Green *et al.* (2019)]

Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

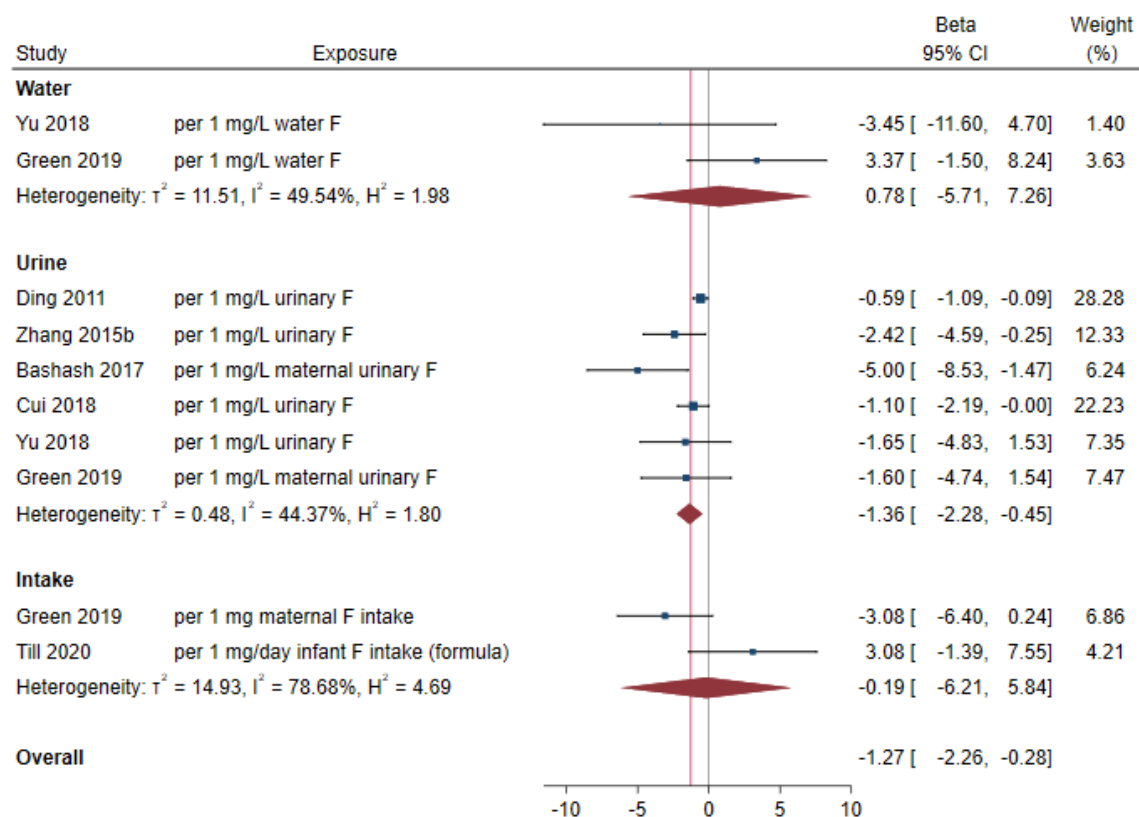


Figure B-20. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type Using Verbal IQ Score for Green *et al.* (2019)

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analysis. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Sensitivity Analysis for Individual-level Studies: Performance IQ

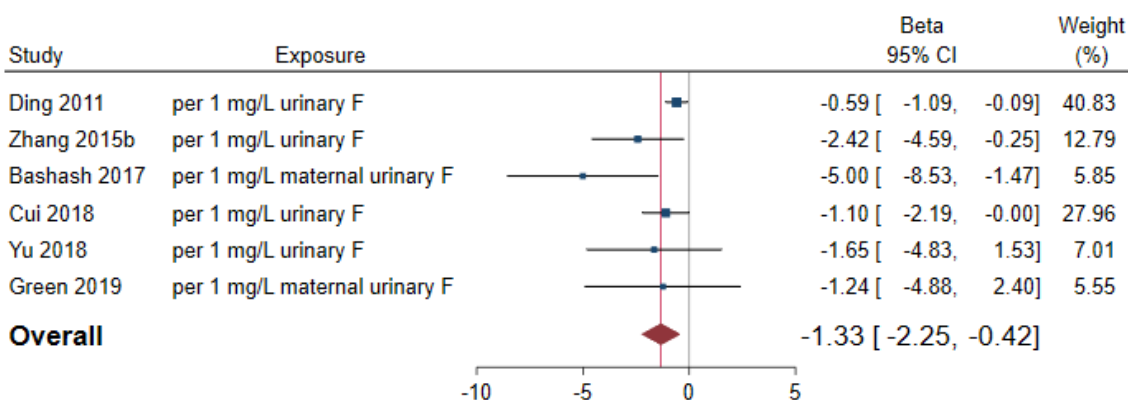


Figure B-21. Association Between Fluoride Exposure and IQ Scores in Children Using Performance IQ Score for Green *et al.* (2019)

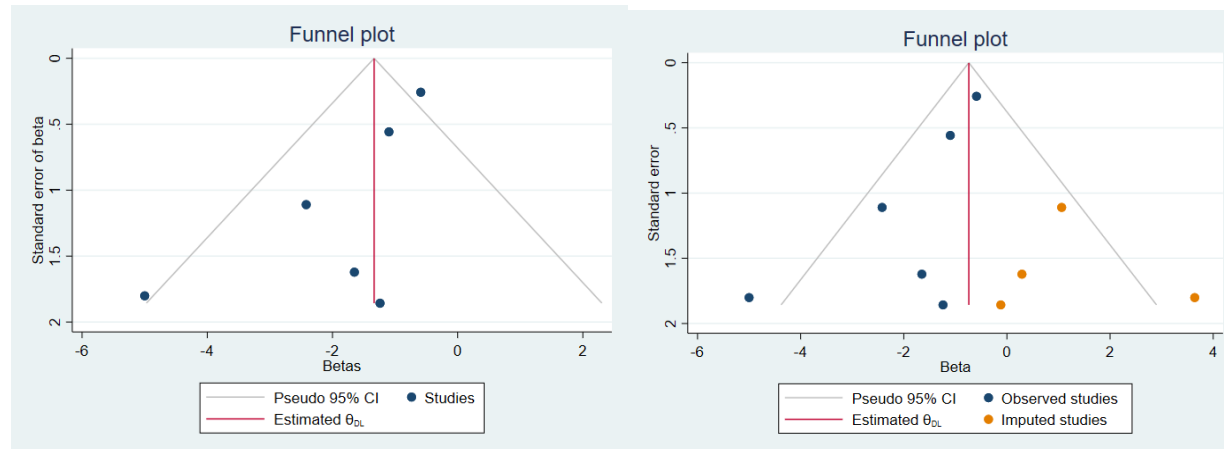


Figure B-22. Funnel Plot of Included Studies with Individual-level Exposures and Filled-in Funnel Plot to Eliminate Publication Bias [Using Performance IQ Score for Green *et al.* (2019)]

Right panel shows funnel plot filled in to the right using a run estimator. Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

```
Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -1.52
SE of beta1 =      0.623
      z =      -2.44
Prob > |z| =      0.0147
```

Figure B-23. Test for Publication Bias for Studies with Individual-level Exposures [Using Performance IQ Score for Green *et al.* (2019)]

Nonparametric trim-and-fill analysis of publication bias Linear estimator, imputing on the right				
Iteration		Number of studies =		9
Model: Random-effects		observed =		6
Method: DerSimonian-Laird		imputed =		3
Pooling				
Model: Random-effects				
Method: DerSimonian-Laird				
Studies	Beta [95% Conf. Interval]			
Observed	-1.335	-2.248	-0.421	
Observed + Imputed	-0.777	-1.759	0.204	

Nonparametric trim-and-fill analysis of publication bias Run estimator, imputing on the right				
Iteration		Number of studies =		10
Model: Random-effects		observed =		6
Method: DerSimonian-Laird		imputed =		4
Pooling				
Model: Random-effects				
Method: DerSimonian-Laird				
Studies	Beta [95% Conf. Interval]			
Observed	-1.335	-2.248	-0.421	
Observed + Imputed	-0.739	-1.662	0.184	

Figure B-24. Trim-and-fill Analysis for Studies with Individual-level Exposures [Using Performance IQ Score for Green *et al.* (2019)]

Filling in to the left using a linear or a run estimator showed no change in the pooled effect estimate.

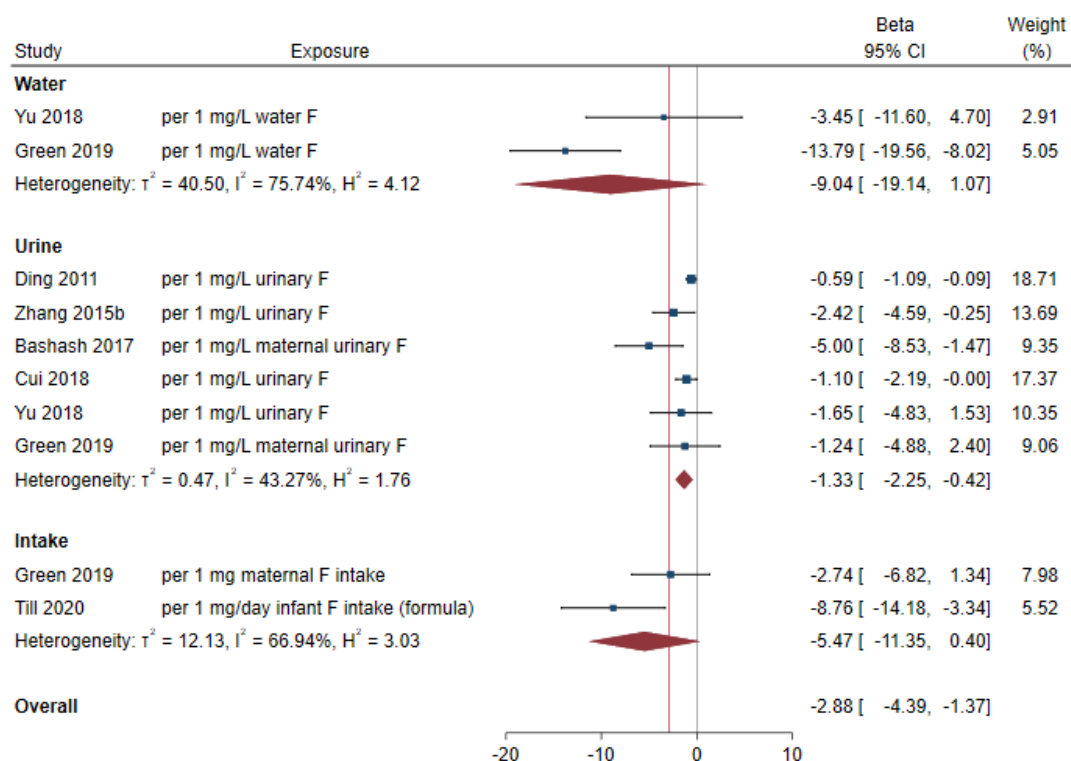


Figure B-25. Association Between Fluoride Exposure and IQ Scores in Children by Exposure Type Using Performance IQ Score for Green *et al.* (2019)

Note: The analysis for publication bias for studies with fluoride in urine is identical to the overall analysis. The analyses for publication bias for studies with fluoride in water or fluoride intake rely on two studies each and are not shown.

Sensitivity Analysis for Individual-level Studies: Excluding Cui *et al.* (2018)

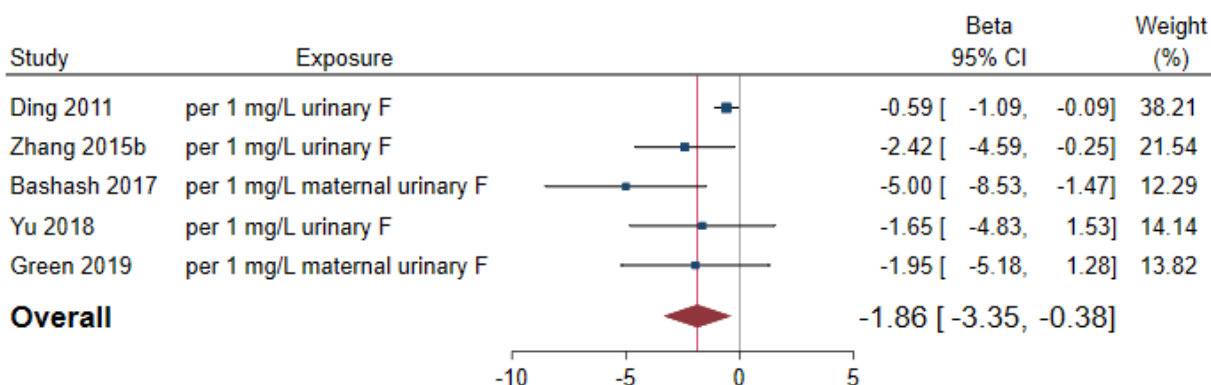


Figure B-26. Association Between Fluoride Exposure and IQ Scores in Children [Excluding Cui *et al.* (2018)]

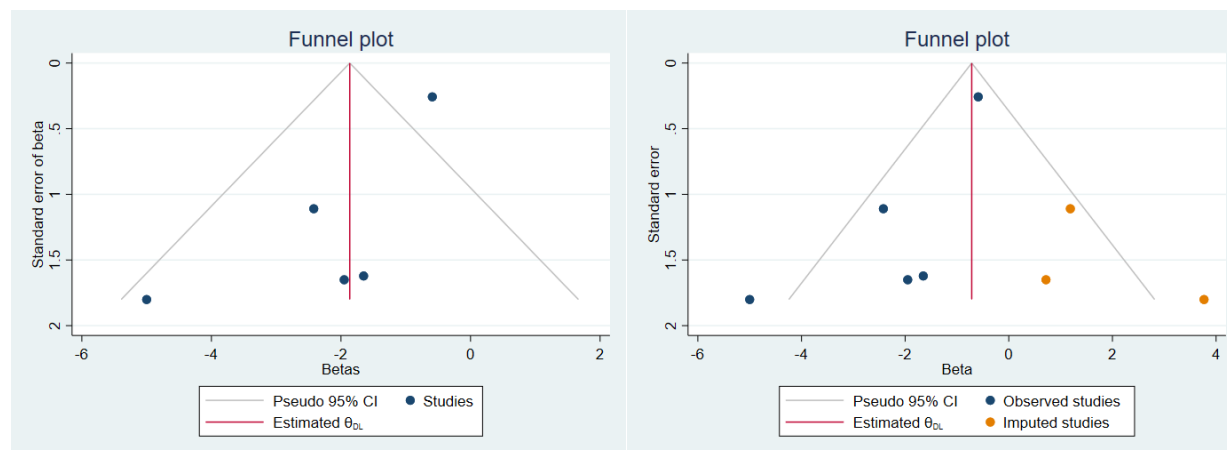


Figure B-27. Funnel Plot and Filled-in Funnel Plot to Eliminate Publication Bias of Included Studies with Individual-level Exposures [Excluding Cui *et al.* (2018)]

Right panel shows filling in to the right using a linear estimator. Filling in to the right using a run estimator or to the left using a linear or run estimator showed no change in the pooled effect estimate.

```

Regression-based Egger test for small-study effects
Random-effects model
Method: DerSimonian-Laird

H0: beta1 = 0; no small-study effects
      beta1 =      -1.68
      SE of beta1 =    0.638
              z =     -2.63
      Prob > |z| =    0.0085
    
```

Figure B-28. Test for Publication Bias for Studies with Individual-level Exposures [Excluding Cui *et al.* (2018)]

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Nonparametric trim-and-fill analysis of publication bias			
Linear estimator, imputing on the right			
Iteration	Number of studies =		8
Model: Random-effects	observed =		5
Method: DerSimonian-Laird	imputed =		3
Pooling			
Model: Random-effects			
Method: DerSimonian-Laird			
Studies	Beta	[95% Conf. Interval]	
Observed	-1.864	-3.351	-0.377
Observed + Imputed	-0.715	-2.056	0.625

Figure B-29. Trim-and-fill Analysis for Studies with Individual-level Exposures [Excluding Cui *et al.* (2018)]

Filling in to the right using a run estimator or to the left using a linear or run estimator showed no change in the pooled effect estimate.



Green Bay

Reasons to VOTE “NO” Fluoridation

**As a dentist, I promoted fluoridation.
Five reasons I changed.**

*Bill Osmunson DDS, MPH
Aesthetic and Comprehensive Dentistry
Neuromuscular Dental Practitioner,
Educator, Author, and Nutritionist
Bellevue, WA 98357*

*[www. IAOMT.org](http://www.IAOMT.org) www.fluoridealert.org
www.slweb.org www.washingtonsafewater.com*



CONFIDENCE:

1. Freedom — Other sources of fluoride if desired.
2. Swallowing F is NOT FDA Approved
3. Many are Swallowing too much Fluoride
4. Fluoridation is no longer effective.
5. Fluoridation is NOT SAFE

CONGRESS DEFINED *DRUGS*:

*“Articles **intended** for use in the
... prevention of disease ...”*

21 USC 321 (g)(1)(B)

***Intent** of use determines regulatory oversight, not whether it is
natural or artificial, and regardless of concentration or efficacy.*

Fluoride is exempt from poison laws when regulated under drug or pesticide laws

FDA testified to Congress that fluoride is a drug.

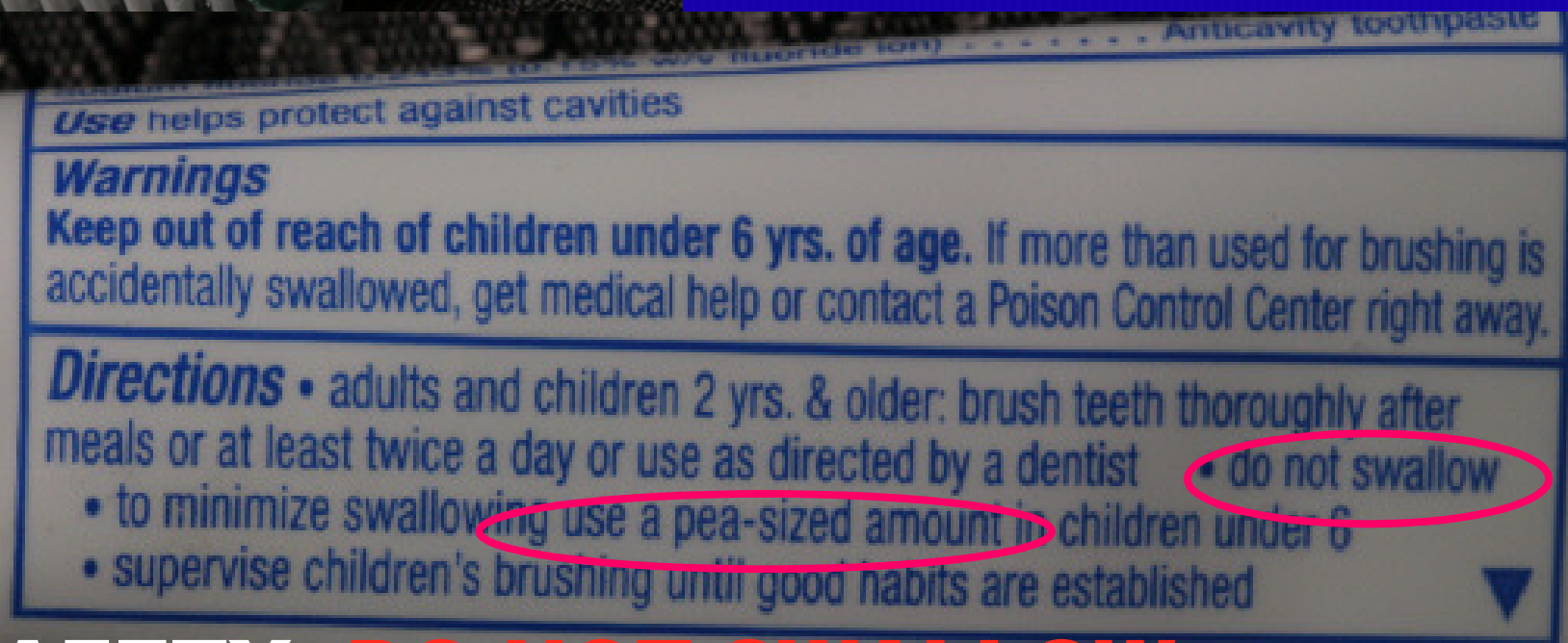
Congressional Investigation 2001



A Pea Size of
Tooth Paste has
0.25 mg of F -
The same as 1 glass
of Fluoridated Water.



<http://www.cdc.gov/mmwr/PDF/rr/rr5014.pdf>



FDA SAFETY: DO NOT SWALLOW.

“Flexible language”, FDA

<http://www.cdc.gov/mmwr/PDF/rr/rr5014.pdf>

Stream of evidence.

EPA

SDWA: “No national primary drinking water regulation may require the addition of any substance for preventive health care purposes unrelated to contamination of drinking water. ”

[42 USC 300g-1\(b\)\(11\):](#)

“The Safe Drinking Water Act prohibits the deliberate addition of any substance to drinking water for health-related purposes other than disinfection of the water.”

FOIA Request HQ-FOI-01418-10

Stream of evidence.

EPA Scientists say “NO” to Fluoridation

"In summary, we hold that fluoridation is an unreasonable risk. That is, the toxicity of fluoride is so great and the purported benefits associated with it are so small - if there are any at all – that requiring every man, woman and child in America to ingest it borders on criminal behavior on the part of governments."

-Dr. J. William Hirzy, Senior Vice-President, Headquarters Union,

-US Environmental Protection Agency, March 26, 2001





After 70 years of Fluoridation
and still no gold standard
“Prospective Randomized Controlled Trials”
on effectiveness.

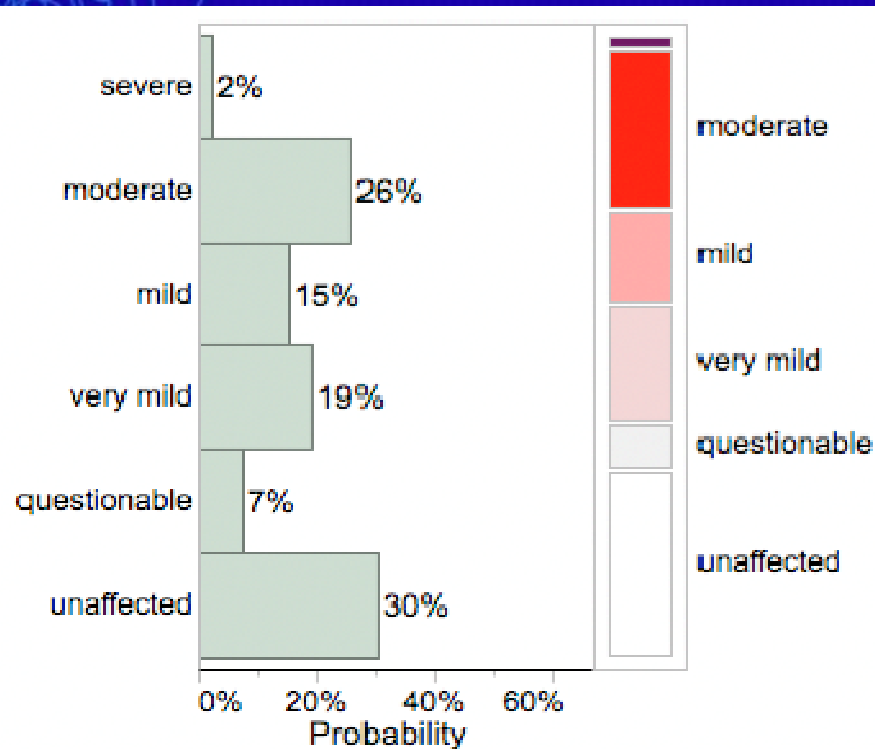
FDA says the “Final Manufacturer”
is Responsible for Research
to Gain FDA Approval.
(City/Water District)

HUGE INCREASES IN FLUOROSIS

1950's, promised not to exceed 15%

2004 Increased to 41%

2012 Increased to 70%



30% UNAFFECTED

NHANES 2012

Meta-analyses of water fluoridation and dental fluorosis

🔔 “infant formula consumption was associated with a higher prevalence of enamel fluorosis in the permanent dentition” Hujoel et al, JADA:2009,140:849 (17 studies)

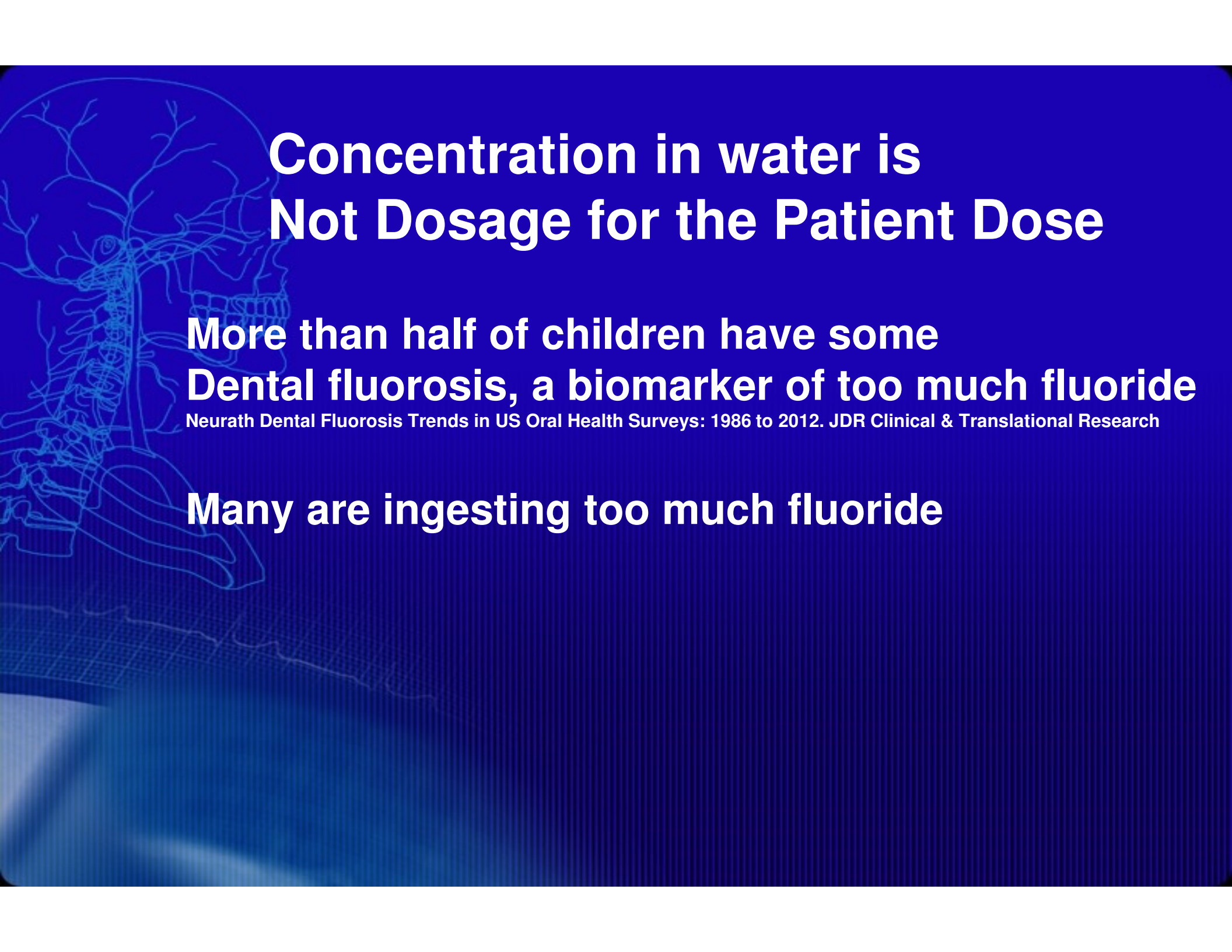
🔔 “where the fluoride level in water is 0.7 ppm, there is a chance of around 12% of people having dental fluorosis that may cause concern about how their teeth look.”
Cochrane review 2015 (90 studies)

FLUORIDE CHEMICAL RESEARCH IS INCOMPLETE.

WITHOUT QUALITY EVIDENCE, INGESTION IS AN EXPERIMENT

- A. Not one Study corrects for Unknown Confounding Factors
- B. Not one Prospective Randomized Controlled Trial
- C. Socioeconomic status usually not controlled
- D. Inadequate size
- E. Difficulty in diagnosing decay
- F. Delay in tooth eruption not controlled
- G. Diet: Vitamin D, calcium, strontium, sugar, fresh and frozen year round vegetables and fruit consumption not controlled.
- H. Total exposure of Fluoride not determined
- I. Oral hygiene not determined
- J. Not evaluating Life time benefit
- K. Estimating or assuming subject actually drinks the fluoridated water.
- L. Dental treatment expenses not considered
- M. Breast feeding and infant formula excluded
- N. Fraud, gross errors, and bias not corrected.
- O. Genetics not considered

Stream of evidence.



Concentration in water is Not Dosage for the Patient Dose

**More than half of children have some
Dental fluorosis, a biomarker of too much fluoride**

Neurath Dental Fluorosis Trends in US Oral Health Surveys: 1986 to 2012. JDR Clinical & Translational Research

Many are ingesting too much fluoride

WHO

"Dental and Public health administrators should be aware of the total fluoride exposure in the population before introducing any additional fluoride program for caries prevention."

WHO (1994). Fluorides and Oral Health. WHO Technical Report Series 846.

"Estimation of the amount of fluoride ingested from all environmental and dietary sources is important so that rational and scientifically sound decisions can be made when guidelines for the use of fluorides are reviewed periodically and modified."

Pang D, et al. (1992). Journal of Dental Research 71: 1382-1388.

Stream of evidence.

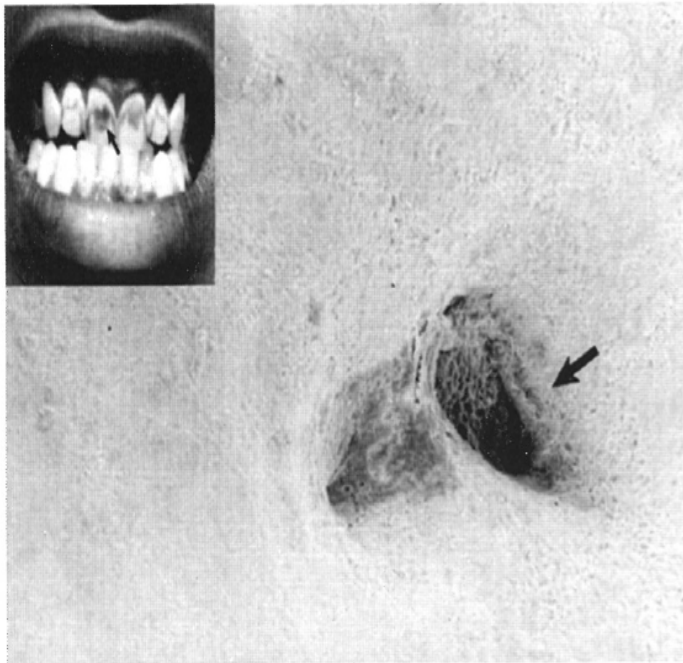
CDC “Dental fluorosis only occurs when younger children consume too much fluoride, . . . when teeth are developing under the gums.”

http://www.cdc.gov/fluoridation/safety/dental_fluorosis.htm#a2 Accessed 10 15

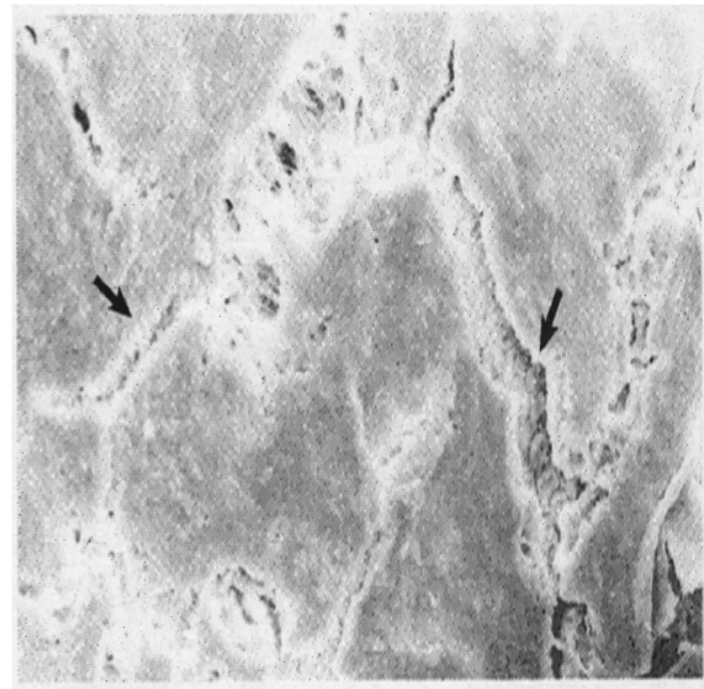


\$12,000 Treatment
Average 15 year

Dental Fluorosis Viewed by Scanning Electron Microscope



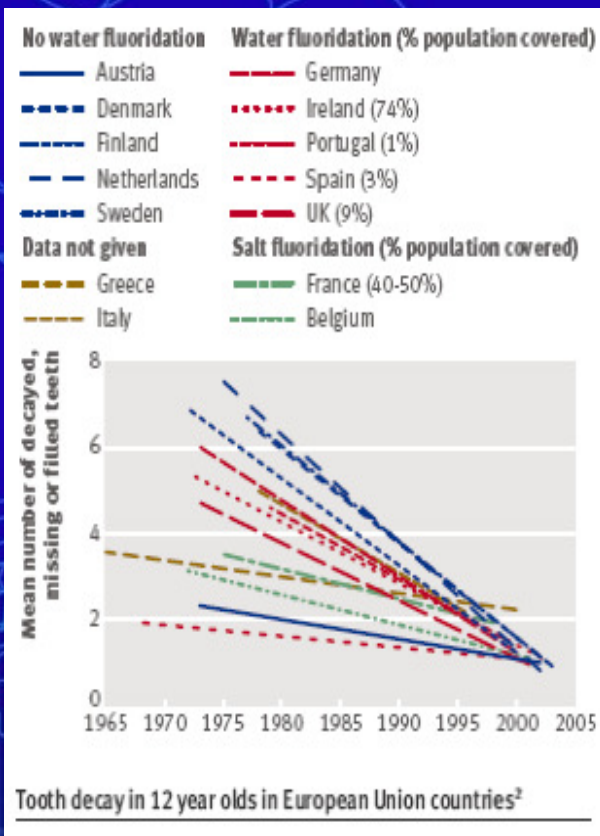
Pits in enamel



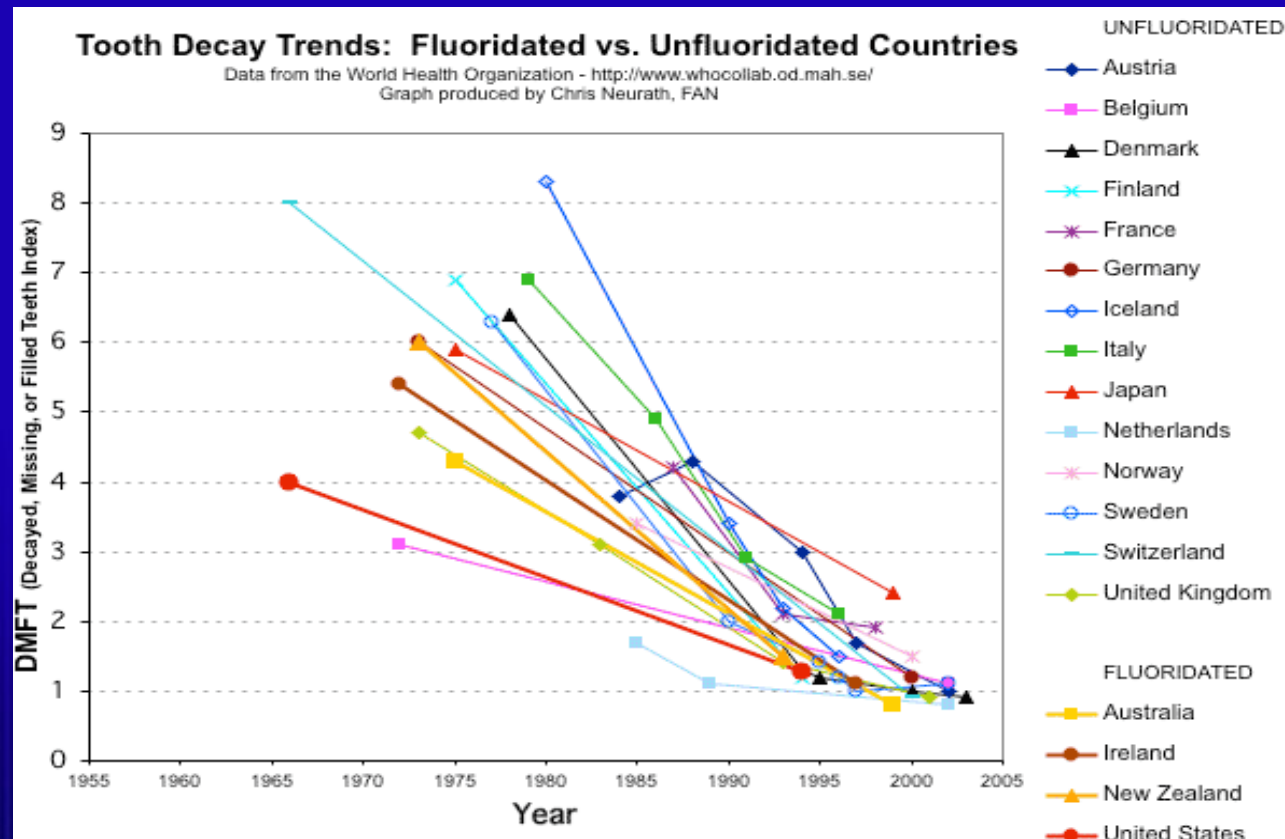
Cracks and Fissures
in enamel



Fluoride Bomb



Chen et al, BMJ 5 October 2007



Neurath Fluoride Research 2006

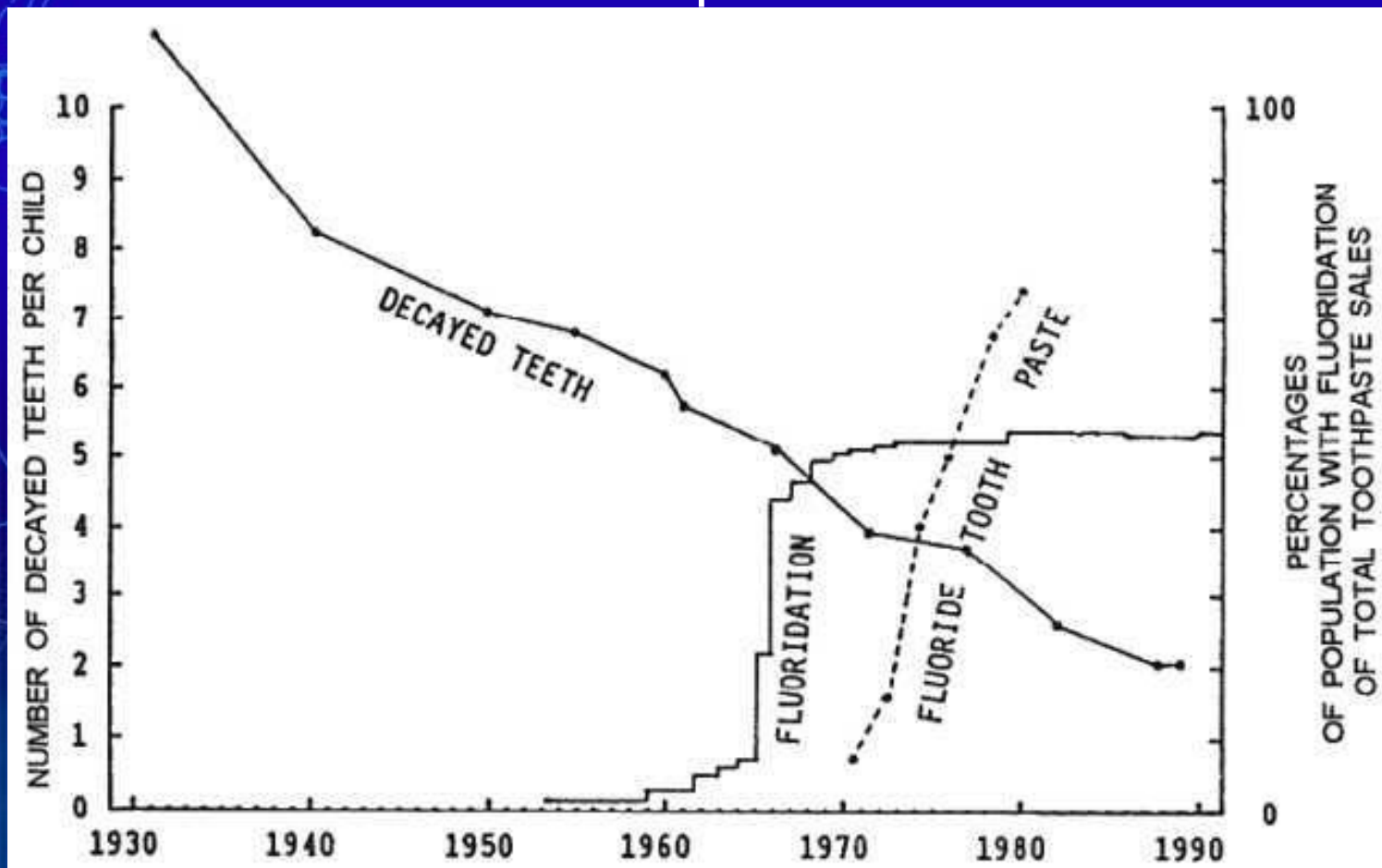
Fluoridated vs. Unfluoridated Countries.

Tooth Decay Trends for 12 Year Olds: Data from World Health Organization. (Graph by Chris Neurath).

<http://www.fluoridealert.org/health/teeth/caries/who-dmft.html>

Just because a child has fewer cavities than their parents, does not prove fluoridation is effective.

What caused the decline in caries prior to fluoridation?

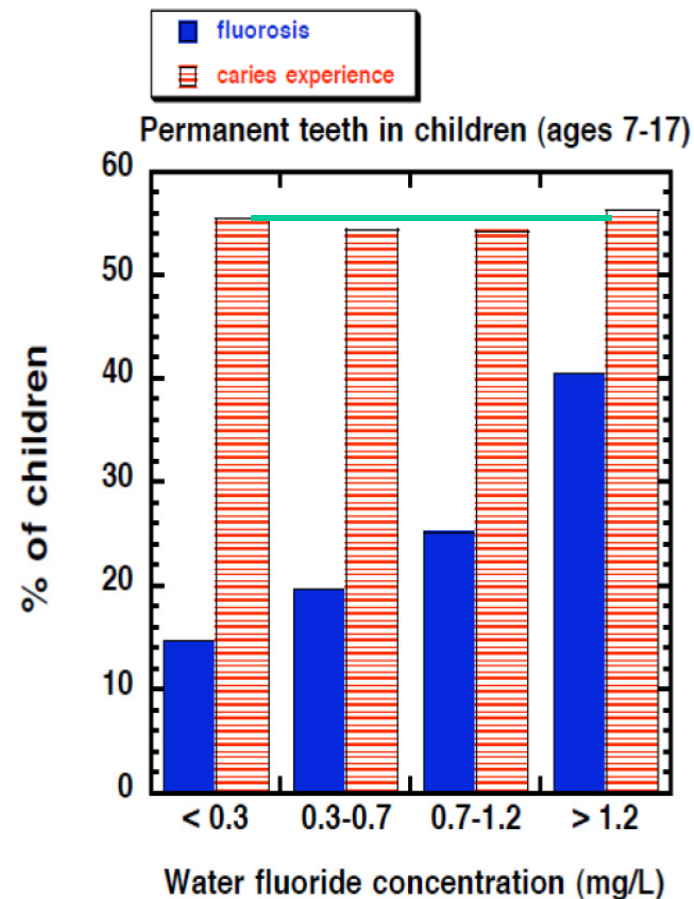


<http://www.fluoride-journal.com/98-31-2/312103-f.htm>

Colquhoun 1997 ISFR Published 1998

The harm from fluoride is far more expensive than the theoretical benefit.

lida, H., and Kumar, J.V. 2009. The association between enamel fluorosis and dental caries in U.S. schoolchildren. JADA 140:855-862.



Blue lines = Dental Fluorosis
Red lines = Caries



INFANT

Mother's Milk: most samples,
F not detected

Mean 0.004 ppm F NRC p. 33



Early Childhood Caries (ECC), is not fluoride deficiency
Bad Diet: sleeping with a bottle of milk, juice, etc.





The Claim:

“For every dollar spent on fluoride chemicals, \$38 of treatment is saved,” is SPECULATION based on estimates of assumptions - - not measured evidence.

**\$3 per person per year for a best-case scenario,
but this savings is eliminated by the estimated
cost of treating dental fluorosis.**

Ko (2015) Int J Occup Environ Health

Realistic estimates of the cost of fluoridation

Estimates usually do NOT include the cost of

- 🔔 other chemicals added because HFSA is used
- 🔔 F testing, record keeping and reporting
- 🔔 extra hazmat precautions and training
- 🔔 F equipment maintenance, upgrades & replacement
- 🔔 fluoridation promotion
- 🔔 added liability insurance and legal fees
- 🔔 holding fluoridation plebiscites
- 🔔 HFSA spills and fluoridation overfeeds
- 🔔 avoiding fluoride in families sensitive to fluoride
- 🔔 treating objectionable fluorosis
- 🔔 treating other fluoride-related health problems



Claims of top 10 public health achievement of the 20th Century is “marketing” — not “science.”

ADA awarded Kentucky with “50 Year Award” for (100%) fluoridation 2003

42% had no teeth, #1 in USA (2002 Mortality Weekly Report)

Connecticut

Detroit

Boston report a caries crisis and for years all have had fluoride chemicals in their water.

<http://www.fortwayne.com/mid/newssentinel/7521679.htm?template=contentModules/printstory.jsp>

http://www.enquirer.com/editions/2002/10/06/loc_special_report.html

<http://www.fluoridealert.org/f-boston.htm>

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=13678102&query hl=1

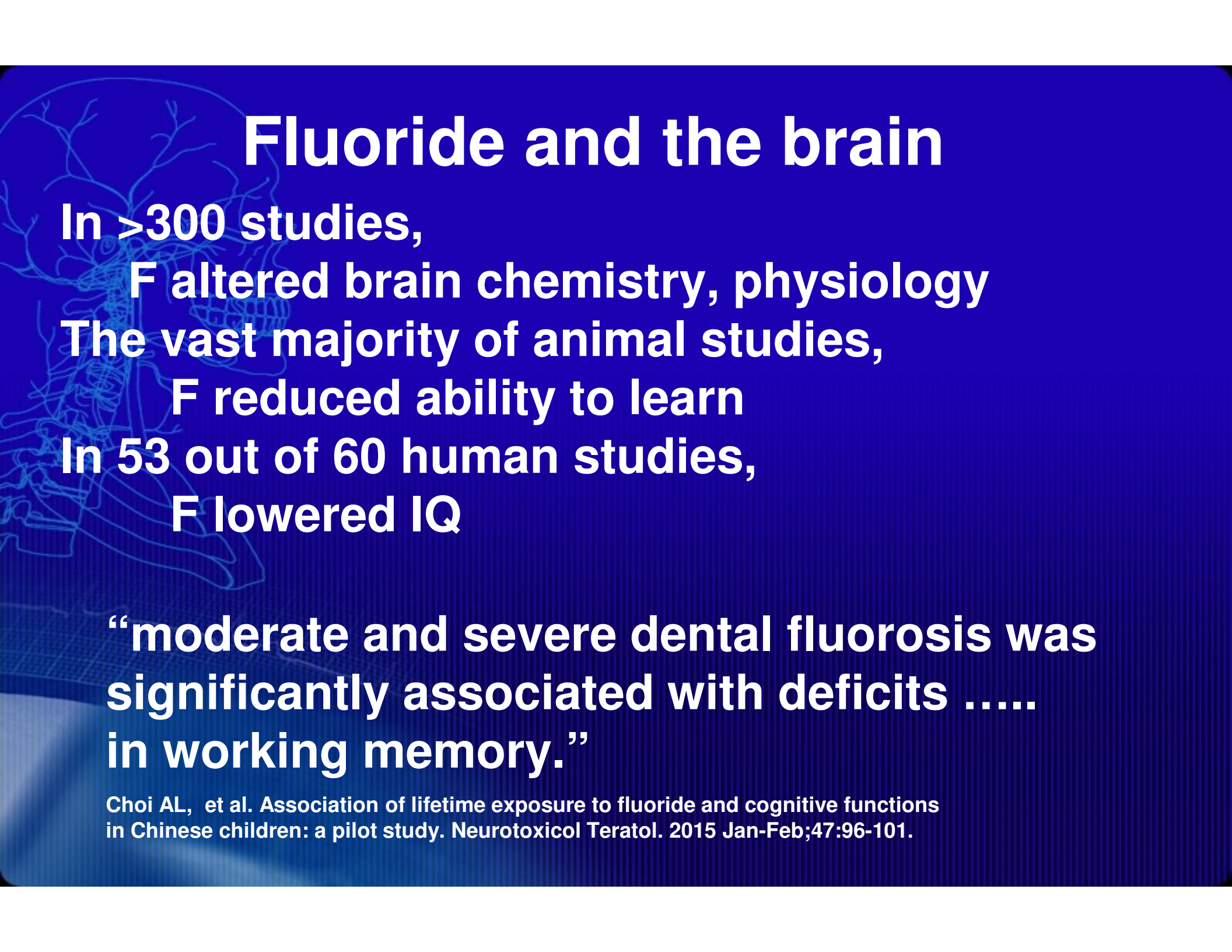
http://www.nhregister.com/site/news.cfm?newsid=14472801&BRD=1281&PAG=461&dept_id=517515&rfi=8&xb=kasan

Claim: "All reputable public health agencies support fluoridation."

Except 97% of European governments and dental associations China, Israel, and Japan do not.

Austria	REJECTED: "toxic fluorides" NOT added
Belgium	REJECTED: encourages self-determination — those who want fluoride should get it themselves.
Finland	STOPPED: "...do not favor or recommend fluoridation of drinking water. There are better ways of providing the fluoride our teeth need." A recent study found ... <u>"no indication of an increasing trend of caries..."</u>
Germany	STOPPED: A recent study found <u>no evidence of an increasing trend of caries</u>
Denmark	REJECTED: "...toxic fluorides have never been added to the public water supplies in Denmark."
Norway	REJECTED: "...drinking water should not be fluoridated"
Sweden	BANNED: "not allowed". No safety data available!
Netherlands	REJECTED: Inevitably, whenever there is a court decision against fluoridation, the dental lobby pushes to have the judgment overturned on a technicality or they try to get the laws changed to legalize it. Their tactics didn't work in the vast majority of Europe.
Hungary	STOPPED: for technical reasons in the '60s. However, despite technological advances, Hungary remains unfluoridated.
Japan	REJECTED: "...may cause health problems...." The 0.8 -1.5 mg regulated level is for calcium-fluoride, not the hazardous waste by-product which is added with artificial fluoridation.
<u>Israel</u>	SUSPENDED mandatory fluoridation until the issue is reexamined from all aspects.: June 21, 2006 "The labor, welfare and health Knesset committee"
China	BANNED: "not allowed"
<u>France</u>	REDUCED: Was 50% now 30% fluoridated Salt
<u>Ireland</u>	74% Fluoridated
<u>UK</u>	9% Fluoridated

Most European dental associations no longer recommend fluoride supplements.



Fluoride and the brain

In >300 studies,

F altered brain chemistry, physiology

The vast majority of animal studies,

F reduced ability to learn

In 53 out of 60 human studies,

F lowered IQ

**“moderate and severe dental fluorosis was
significantly associated with deficits
in working memory.”**

**Choi AL, et al. Association of lifetime exposure to fluoride and cognitive functions
in Chinese children: a pilot study. Neurotoxicol Teratol. 2015 Jan-Feb;47:96-101.**

The Lillie Center for Energy and Health Studies Inc.

Fluoridegate Unraveling

Freedom of Information Act Request document: From
CDC Oral Health Division Director William Maas, in an
email with American Dental Assn officials:

“If there is kidney disease, then more fluoride
stays in the body and is deposited in the
bones...a person with chronic kidney
disease...with 1ppm fluoride in water might
have bones that have the fluoride content of a
person...with 4ppm fluoride...”

Journal of Public Health Dentistry, Fall 2009,
Concerning Fluid Consumption Fluoride

- “There was substantial variation in the estimated amount of fluoride ingestion [in children] depending on ... race, gender, and race/ethnicity.”
- “Conclusion: Our results raise concerns that some children are ingesting significantly more fluoride than others depending on sociodemographic factors and fluid consumption patterns.”

Quotes from Dental Literature Unseen by Government Leaders

- “It is estimated that 84% of [cavities] in the 5-17 year-old population involves tooth surfaces with pits and fissures” (the back molars)
- “Pit and fissure cavities aren’t considered to be preventable by fluorides, they are prevented by sealants.”
- Dentists do not openly share that fluorides don’t work where the vast majority of cavities occur!

• Sources: Schelle R. (1984). JADA 108:448 and Gray, AS (1987) Journal of the Canadian Dental Association 10:763-765

After it swallowed 215M gallons of polluted water, Mosaic sinkhole finally corked

Tampa Bay Times

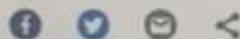
NEWS SPORTS OPINION LIFE & CULTURE FOOD LONG READS



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NEWS

Two years after it swallowed 215M gallons of polluted water, Mosaic sinkhole finally corked



Nearly two years after a massive sinkhole opened up at a Mosaic phosphate processing plant in Mulberry and drained the polluted water from phosphogypsum stack, Mosaic says the chasm is nearly filled in. [Courtesy of Mosaic]

By Craig Pittman

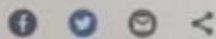


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NEWS

Mosaic plant sinkhole dumps 215 million gallons of reprocessed water into Floridan Aquifer (w/video)



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CERTIFIED TO NSF / ANSI 60

SECTION 1		PRODUCT AND COMPANY IDENTIFICATION	
TRADE NAME:	Hydrofluosilicic Acid		
CHEMICAL NAME:	Hydrofluosilicic Acid		
CAS NUMBER:	16961-83-4		
CHEMICAL FAMILY:	Inorganic Fluorides		
SYNONYMS:	Fluorosilicic Acid, Hexafluosilicic Acid, HFS, FSA		
PRIMARY USE:	Industrial Chemical		
COMPANY INFORMATION:	The Mosaic Company Atria Corporate Center Suite E490 3033 Campus Drive Plymouth, MN 55441 www.mosaicco.com For non-emergency questions, phone numbers are 8 AM to 5 PM Central Time US 800-918-8270 or 763-577-2700		
EMERGENCY TELEPHONE:	EMERGENCY OVERVIEW 24 Hour Emergency Telephone Number: <u>For Chemical Emergencies:</u> Spill, Leak, Fire or Accident Call CHEMTREC (CCN 201871) North America: (800) 424-9300 Others: (703) 527-3887 (collect)		
SECTION 2		HAZARD IDENTIFICATION	
EMERGENCY OVERVIEW :	Health Hazards:	Corrosive to the skin, eyes and mucous membranes through direct contact, inhalation or ingestion. May cause severe irritation and burns, which may not be immediately apparent. Handle with extreme care.	
	Physical Hazards:	Not applicable	
	Physical Form:	Liquid	
	Appearance:	Water white to straw yellow liquid	
	Odor:	Pungent	



CERTIFIED TO NSF / ANSI 60

	NFPA HAZARD CLASS		HMIS HAZARD CLASS		WHMIS HAZARD CLASS	
	Health:	3	Health:	3	Symbol	
	Flammability:	0	Flammability:	0	Classification	E
	Instability:	1	Physical Hazard:	0	Sub Class	
	Special Hazard:	Corrosive	PPE:	Section 8		
POTENTIAL HEALTH EFFECTS:	Eye:		Corrosive. Contact may cause severe irritation, eye burns, and permanent eye damage.			
	Skin:		Corrosive. Contact may cause severe irritation, skin burns, and permanent skin damage.			
	Inhalation (Breathing)		Corrosive. Harmful if inhaled. May cause severe irritation and burns of the nose, throat, and respiratory tract.			
	Ingestion (Swallowing)		Corrosive. Harmful or fatal if swallowed. May cause severe irritation and burns of the mouth, throat and digestive tract.			
	Signs and Symptoms:		Effects of overexposure may include severe irritation and burns of the mouth, nose, throat, respiratory and digestive tract. Symptoms of overexposure may include ulceration of the nose and throat, coughing, salivation, headache, fatigue, dizziness, nausea, shock, and pulmonary edema (accumulation of fluid around the lungs). May lead to coma or death. Onset of symptoms may be delayed.			
	Cancer:		The ingredient(s) of this product is (are) not classified as carcinogenic by NTP, IARC, or OSHA			
	Target Organs:		No data available for this material (see Other Comments below).			
	Developmental:		No data available for this material			

	Other Comments:	Prolonged or repeated overexposure to fluoride compounds may cause fluorosis. Fluorosis is characterized by skeletal changes, consisting of osteosclerosis (hardening or abnormal density of bone) and osteomalacia (softening of bones) and by mottled discoloration of the enamel of teeth (if exposure occurs during enamel formation). Symptoms may include bone and joint pain and limited range of motion. Conditions aggravated by exposure may include skin and respiratory (asthma-like) disorders.	
	Pre-Existing Medical Conditions:	Conditions aggravated by exposure may include skin and respiratory (asthma-like) disorders.	
POTENTIAL ENVIRONMENTAL EFFECTS:	May be hazardous to the environment and aquatic organisms.		
SECTION 3	COMPOSITION INFORMATION ON INGREDIENTS		
FORMULA:	H ₂ SiF ₆		
COMPOSITION:	Hydrofluosilicic Acid	CAS No. 16961-83-4	20-25%
	Water		75-80%
SECTION 4	FIRST AID MEASURES		
FIRST AID PROCEDURES:	Eyes:	Immediately flush with plenty of water for at least 15 minutes. Get medical attention immediately.	
	Skin:	Immediately flush with plenty of water. Remove contaminated clothing. Discard contaminated clothing properly. Get medical attention if irritation occurs or persists.	
	Inhaled:	Move to fresh air. Administer oxygen. Treat symptomatically. Get medical attention promptly. Observe for possible delayed reaction.	
	Ingestion:	Do Not induce vomiting. Give large quantities of milk or water to patient if conscious. Seek medical attention promptly.	
NOTE TO PHYSICIAN:	None		
SECTION 5	FIRE FIGHTING MEASURES		
Flammable Properties:	Flash Point:	Not applicable	
	OSHA Flammability Class:	Not applicable	
	LEL/UEL:	Not applicable	
	Auto-Ignition Temperature:	Not applicable	



CERTIFIED TO NSF / ANSI 60

SECTION 16	OTHER INFORMATION
Disclaimer:	The information in this document is believed to be correct as of the date issued. HOWEVER, NO WARRANTY OF MERCHANTABILITY, FITNESS FOR ANY PARTICULAR PURPOSE, OR ANY OTHER WARRANTY IS EXPRESSED OR IS TO BE IMPLIED REGARDING THE ACCURACY OR COMPLETENESS OF THIS INFORMATION, THE RESULTS TO BE OBTAINED FROM THE USE OF THIS INFORMATION OR THE PRODUCT, THE SAFETY OF THIS PRODUCT, OR THE HAZARDS RELATED TO ITS USE. This information and product are furnished on the condition that the person receiving them shall make their own determination as to suitability of the product for their particular purpose and on the condition that they assume the risk of their use thereof. The conditions and use of this product are beyond the control of Mosaic, and Mosaic disclaims any liability for loss or damage incurred in connection with the use or misuse of this substance.
Preparation:	The preparation of this MSDS was in accordance with ANSI Z400.1-2010.
Revision Date:	January 3, 2014
Sections Revised:	2, 12
MSDS Number	MOS200011.02
References:	OSHA 29CFR1910.1000, NFPA 704, ACGIH TLV, NIOSH ICSC1233

Hydrofluosilicic Acid, 20 - 30 %
WHMIS Number: 00060388

Brenntag Canada Inc.
Date of Revision: 2006 January 12
Page 2

- . Skin Absorption: Skin absorption is a secondary concern to the continual destruction of tissue while the product is in contact with the skin.
- . Eye Contact: Extremely corrosive! This product causes corneal scarring and clouding. Glaucoma, cataracts and permanent blindness may occur.
- . Ingestion: Corrosive! This product causes severe burning and pain in the mouth, throat and abdomen. Vomiting, diarrhea and perforation of the esophagus and stomach lining may occur.

Other Health Effects: Corrosive effects on the skin and eyes may be delayed, and damage may occur without the sensation or onset of pain. Strict adherence to first aid measures following any exposure is essential.

May cause pulmonary oedema, fluorosis, exostoses, hypocalcemia, shock, central nervous system (CNS) depression, coma and death. CNS depression is characterized by headache, dizziness, drowsiness, nausea, vomiting and incoordination. Severe overexposures may lead to coma and possible death due to respiratory failure. Pulmonary oedema is the build-up of fluid in the lungs that might be fatal. Symptoms of pulmonary oedema, such as shortness of breath, may not appear until several hours after exposure and are aggravated by physical exertion. (4)

Fluoride is a bone seeker, and excessive amounts will produce weakening and degeneration of the bone structure. Chronic exposure may cause excess accumulation of fluorine (fluorosis) in the teeth and bones. Severe fluorosis in children weakens tooth enamel resulting in surface pitting. After prolonged high intake in adults bony changes occur characterized by hardening or abnormal density of bone (osteosclerosis), benign bony growths projecting outward from the surface of the bone (exostoses) and calcification of ligaments, tendons, and muscle attachments to bone. Ingestion and skin contact may cause an abnormal reduction of blood calcium (hypocalcemia) and kidney damage since fluorides precipitate calcium stored in the body. There may also be heart, asthma, nerve, intestinal and rheumatism problems. (1,3,4)

Brenntag Canada Inc.

BRENNTAG

MATERIAL SAFETY DATA SHEET

HYDROFLUOSILICIC ACID, 20 - 30 %

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Brenntag Canada Inc.
43 Jutland Road.
Toronto, Ontario
M9E 2G6
(416) 259-8231

WHMIS Number: 00060388
Index: GCD1379/06A
Effective Date: 2006 January 12
Date of Revision: 2006 January 12
Website: <http://www.brenntag.ca>

EMERGENCY TELEPHONE NUMBERS (FOR EMERGENCIES INVOLVING CHEMICAL SPILLS OR RELEASE)

Toronto, ON (416) 226-6117	Montreal, QC (514) 861-1211	Winnipeg, MB (204) 943-8827
Edmonton, AB (780) 424-1754	Calgary, AB (403) 263-8660	Vancouver, BC (604) 685-5036

PRODUCT IDENTIFICATION

Product Name: Hydrofluosilicic Acid 20 - 30 %.
Chemical Name: Hydrofluosilicic Acid.
Synonyms: Fluosilicic Acid; Hexafluosilicic Acid; Hydrogen Hexafluosilicate;
Hydrosilicofluoric Acid; Silicofluoric Acid; Silicon Hexafluoride Dihydride; Sand Acid;
Fluorosilicic Acid.
Chemical Family: Inorganic Acid.
Molecular Formula: H_2SiF_6 .
Product Use: Glass manufacturing. Chemical intermediate. Laboratory reagent.
CAS #: 16961-83-4.
WHMIS Classification / Symbol: D-1B: Toxic (acute effects), E: Corrosive.



READ THE ENTIRE MSDS FOR THE COMPLETE HAZARD EVALUATION OF THIS PRODUCT.

2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW: Corrosive! May be fatal if inhaled or swallowed. Causes severe skin and eye burns. Vapours are extremely irritating to eyes and respiratory tract. At elevated temperatures may cause irritation of the eyes and respiratory tract. High vapour concentrations may cause drowsiness. See "Other Health Effects" Section. Can decompose at high temperatures forming toxic gases. Contents may develop pressure on prolonged exposure to heat.

POTENTIAL HEALTH EFFECTS

- Inhalation:** Corrosive! Product may cause severe irritation of the nose, throat and respiratory tract. Repeated and/or prolonged exposures may cause productive cough, running nose, bronchopneumonia, pulmonary oedema (fluid build-up in lungs), and reduction of pulmonary function. Mist or spray may be irritating to the nose, throat and respiratory tract. See "Other Health Effects" Section.
- Skin Contact:** Corrosive! Burns can occur if not promptly removed. Concentrated solutions may cause pain and deep and severe burns to the skin. Prolonged and repeated exposure to dilute solutions often causes irritation, redness, pain and drying and cracking of the skin. Toxic effects may be delayed.

WATER FLUORIDATION IN ENGLAND LINKED TO HIGHER RATES OF UNDERACTIVE THYROID

Source: MedicalXpress.com | February 24th, 2015 | Provided by British Medical Journal

Location: United Kingdom, England

Water fluoridation above a certain level is linked to 30 per cent higher than expected rates of underactive thyroid (hypothyroidism) in England, suggests research published online in the *Journal of Epidemiology and Community Health*.

The findings prompt the researchers to call for a rethink of public health policy to fluoridate the water to protect the nation's tooth health.

In England, around 10 per cent of the population (6 million) live in areas with a naturally or artificially fluoridated supply of 1 mg fluoride per litre of drinking water.



Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint



Full length article

Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth



Julia K. Riddell^{a,*}, Ashley J. Malin^b, David Flora^a, Hugh McCague^c, Christine Till^a

^a Faculty of Health, York University, Ontario, Canada

^b Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States

^c Institute for Social Research, York University, Ontario, Canada

ARTICLE INFO

Keywords:

Community water fluoridation
Urinary fluoride
Attention deficit hyperactivity disorder (ADHD)
Canadian Health Measures Survey (CHMS)

ABSTRACT

Background: Exposure to fluoride has been linked with increased prevalence of attention deficit hyperactivity disorder (ADHD) in the United States and symptoms of inattention in Mexican children. We examined the association between fluoride exposure and attention outcomes among youth living in Canada.

Method: We used cross-sectional data collected from youth 6 to 17 years of age from the Canadian Health Measures Survey (Cycles 2 and 3). Urinary fluoride concentration adjusted for specific gravity (UFGS) was available for 1877 participants. Water fluoride concentration measured in tap water samples was available for 980 participants. Community water fluoridation (CWF) status was determined by viewing reports on each city's website or contacting the water treatment plant. We used logistic regression to test the association between the three measures of fluoride exposure and ADHD diagnosis. Linear regression was used to examine the relationship between the three measures of fluoride exposure and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

Results: UFGS did not significantly predict ADHD diagnosis or hyperactive/inattentive symptoms. A 1 mg/L increase in tap water fluoride level was associated with a 6.1 times higher odds of an ADHD diagnosis (95% CI = 1.60, 22.8). A significant interaction between age and tap water fluoride level ($p = .03$) indicated a stronger association between tap water fluoride and hyperactivity/inattention symptoms among older youth. A 1 mg/L increase in water fluoride level was associated with a 1.5 SDQ score increase (95% CI: 0.23, 2.68, $p = .02$) for youth at the 75th percentile of age (14 years old). Similarly, there was a significant interaction between age and CWF. At the 75th percentile of age (14 years old), those living in a fluoridated region had a 0.7

Community Water Fluoridation: *A Public Harm Policy*



*Evolving expert medical,
scientific, and legal opinion is
against CWF based on scientific
evidence of harm*

presented by:
Karen Favazza Spencer, M.A.
October 8, 2020
for Green Bay City Council



Blood is Thicker Than Water: Flaws in a National Toxicology Program Study

**Karen Favazza Spencer, M.A.
Hardy Limeback, B.Sc., Ph.D., D.D.S.**

Medical Hypotheses
Volume 121, December 2018, Pages 160-163
<https://doi.org/10.1016/j.mehy.2018.09.031>

Honest Broker

Analyst Role

- ☒ Digs for Data
- ☒ Documents Facts
- ☒ Determines Agendas
- ☒ Advises Decision Makers



Organized Bullying



KSpencer

I prefer learning science from actual science rather than from 1960s Peter Seller comedies. That the dental community and other fluoridationists bring up that old Cold War satire at every opportunity does make me wonder where they learn their science.

Science plus Legal Opinion

1. 2015 letter to Institute of Medicine from Erin Brockovich, American Academy of Environmental Medicine, et. al: <http://momsagainstfluoridation.org/erin-brockovich-and-signers-put-health-agencies-notice-april-2015>
2. 2014 legal analysis by Prof. Rita Barnett-Rose: http://works.bepress.com/rita_barnett/3/
3. 2014 Peel Canada legal memo and scientific affidavit: <http://momsagainstfluoridation.org/sites/default/files/Fluoridation-Legal-Opinion-June-24-14.pdf>

Like Reply



Steve Slott

a

Jun 14, 2015

Like Reply



DrJohnnyJohnson

Who advocates against the Proven Safe and Effective Public Health Measure of Community Water Fluoridation?

Apr 5, 2015

- a. Conspiracy Theorists....."ooh, follow the money; ooh, The Commies are trying to take over the U.S.; ooh, Hitler used it in the Concentration Camps to dumb down the Jews; ooh, we're having our rights taken away from us by Big Brother....Just follow the Money"
- b. Fear Mongers: "It causes Autism, IQ, Thyroid, In-grown toenails...."
- c. People who don't like the financially disadvantaged: "Why should I have to drink it? If they want it, they can get it from a fluoride pill; a tanker of hydrofluorosilicic acid (yes J.Wille, that's your all time favorite); yada, yada, yada.



Steven Slott

Wholewheat

Oh, gee, yet another uninformed antfluoridationist chimes in with a load of hogwash. Tell you what, WW, why don't you provide valid, peer-reviewed scientific evidence of any "dangers" of optimal level fluoride?

Your inevitable inability to do so will be taken as your admission that you are intentionally seeking to mislead the citizens of your community, to the detriment of the health and well-being of everyone.

Steven D. Slott, DDS

Communications Officer

American Fluoridation Society

June 2017

Deceptive Percentages v. Actual Data

Figure 1

Tooth decay in fluoridated (F), partially fluoridated (PF), and non-fluoridated (NF) areas: Permanent Teeth.

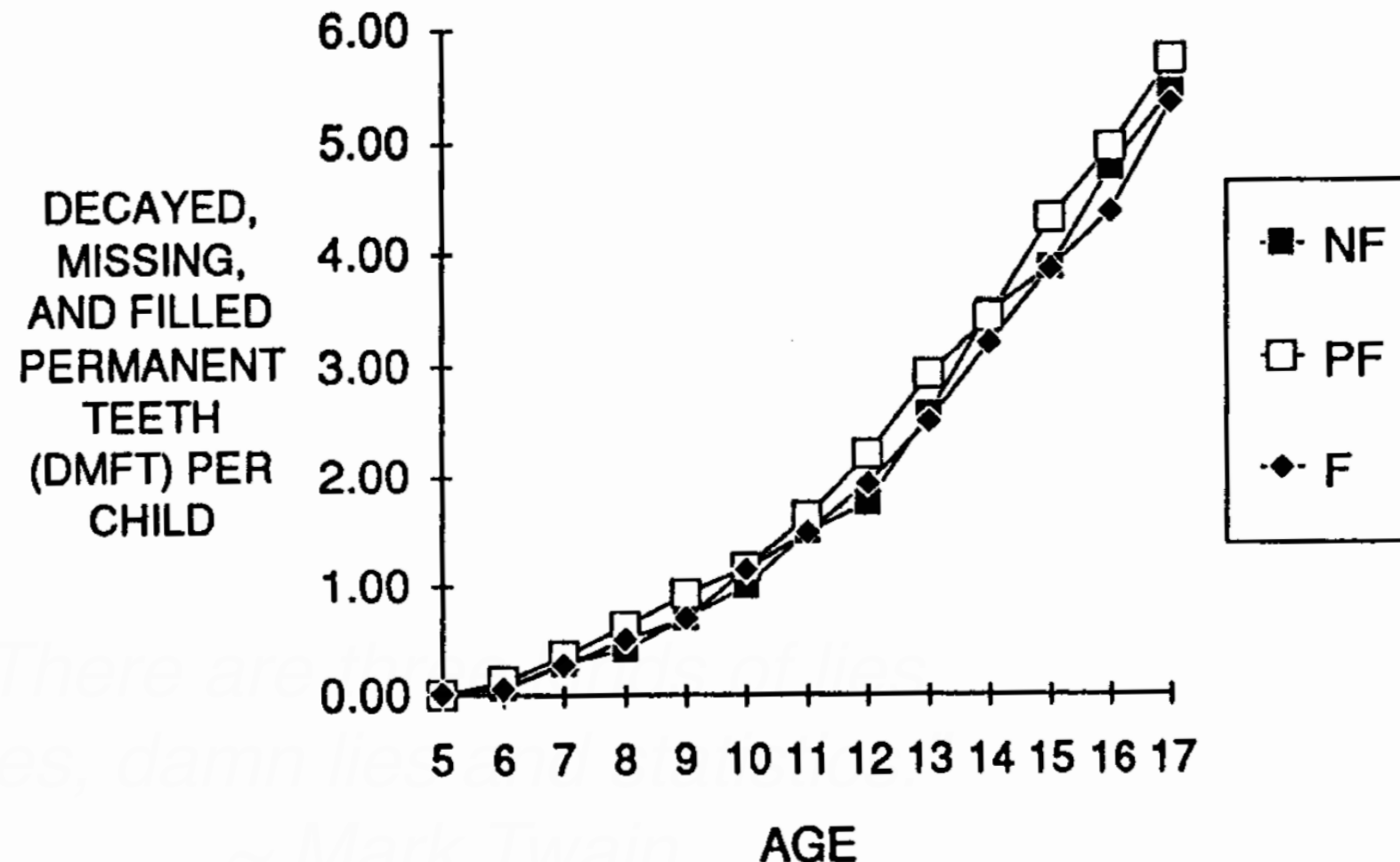


Table 2

Average-age-adjusted DMFT rates for 39,207 U.S. schoolchildren and 17,336 life-long resident schoolchildren in 84 areas throughout the United States. Standard deviations are given in parentheses.

Source: Water Fluoridation & Tooth Decay: Results from the 1986-1987 National Survey of U.S. Children. John A. Yiamouyiannis. Fluoride. Vol 23. No 2. April 1990.

Zealous Advocacy

Suspect Science

Calgary Study: "...Some of the coverage was positive and accurate, but in other cases the study findings were mis-reported and the conclusions overstated; for example, suggesting that 'cavities spiked since fluoridation was stopped'. There was no spike but rather a gradual increase, and the trend observed was **not** since fluoridation was stopped, but rather over a time period during which cessation occurred: 2004/05 to 2013/14 (cessation occurred in 2011)." - Lindsay McLaren, PhD on (Fall 2017 in [MOSAIC](#))

Why Juneau AK Medicaid study failed to show effect of fluoridation cessation

- only 2 time points chosen; before (2003) and after (2012) the year fluoridation ended (2006)
- almost a decade between points: too long (anything could have happened)
- year to year variation was not known –the increase seen could have occurred during fluoridation
- 6 yrs of fluoridation cessation did not affect > 7 yr olds. That was plenty of time to see an effect
- other explanations:
 - dentists were NOT blinded to fluoridation status and could have treated more aggressively because fluoridation halted
 - dentists could have been maximizing dental treatment in Medicaid patients to maintain income and Medicaid reimbursement could have increased
 - decline in oral home care in the younger children (older children not affected)
 - worsening of sugar abuse (this seems to be worldwide trend)
 - there could have been more Medicaid fraud (it happened in Anchorage)

Critique by Dr. Hardy Limeback BSc, DDS, PhD
December 2018 on Meyer et al. 2018

Calgary Quiz: Cessation Study (McLaren et al. 2016)
Choose the best answer for each problem

- a) cherry picked data
- b) scientific fraud
- c) flawed study design
- d) author bias and scientific advocacy
- e) all of the above

Problem 1: Study compares data from 2004/05 to 2013/14 to claim that dental decay increased after fluoridation ended, although fluoridation ended in 2011 and a comparison of data from 2004/05 to 2009/10, the year before fluoridation ended, shows that most of the increased decay was before fluoridation ended.

Problem 2: The number of primary teeth examined in the 2004/05 sample was quite unequal, 599 for Calgary and 6,445 for Edmonton.

Problem 3: Study omits data that showed a decrease of cavities in permanent teeth for the children in the no-fluoride community and instead mentions "non-significant" trend towards increase in a subset of that data.

Problem 4: Study advocates for an optional medical intervention affecting millions, ignoring many larger studies of longer duration with different conclusions as well as multiple studies proving harm.

Problem 5: Study author was a proponent of fluoridation who fought removal. Study featured in near identical articles in multiple Canadian newspapers the day it was published.

Evolving Medical Opinion

Opposes CWF as Harmful

ADA shrinking CWF “endorsers” list

COMPENDIUM

National and International Organizations That Recognize the Public Health Benefits of Community Water Fluoridation for Preventing Dental Decay

Academy of Dentistry International
Academy of General Dentistry
Academy for Sports Dentistry

Alzheimer's Association

America's Health Insurance Plans
American Academy of Family Physicians
American Academy of Nurse Practitioners
American Academy of Oral and Maxillofacial Pathology
American Academy of Orthopaedic Surgeons
American Academy of Pediatrics
American Academy of Pediatric Dentistry
American Academy of Periodontology
American Academy of Physician Assistants
American Association for Community Dental Programs
American Association for Dental Research
American Association for Health Education
American Association for the Advancement of Science
American Association of Endodontists
American Association of Oral and Maxillofacial Surgeons
American Association of Orthodontists
American Association of Public Health Dentistry
American Association of Women Dentists
American Cancer Society
American College of Dentists
American College of Physicians–American Society of Internal Medicine
American College of Preventive Medicine
American College of Prosthodontists
American Council on Science and Health
American Dental Assistants Association
American Dental Association
American Dental Education Association
American Dental Hygienists' Association
American Dietetic Association
American Federation of Labor and Congress of Industrial Organizations
American Hospital Association
American Legislative Exchange Council
American Medical Association
American Nurses Association
American Osteopathic Association
American Pharmacists Association
American Public Health Association
American School Health Association
American Society for Clinical Nutrition
American Society for Nutritional Sciences
American Student Dental Association

American Veterinary Medical Association

American Water Works Association
Association for Academic Health Centers
Association of American Medical Colleges
Association of Clinicians for the Underserved
Association of Maternal and Child Health Programs
Association of State and Territorial Dental Directors

Association of State and Territorial Health Officials
Association of State and Territorial Public Health Nutrition Directors
British Fluoridation Society
Canadian Dental Association
Canadian Dental Hygienists Association
Canadian Medical Association
Canadian Nurses Association
Canadian Paediatric Society
Canadian Public Health Association
Child Welfare League of America
Children's Dental Health Project
Chocolate Manufacturers Association
Consumer Federation of America
Council of State and Territorial Epidemiologists
Delta Dental Plans Association
FDI World Dental Federation
Federation of American Hospitals
Hispanic Dental Association
Indian Dental Association (U.S.A.)
Institute of Medicine
International Association for Dental Research
International Association for Orthodontics
International College of Dentists
March of Dimes Birth Defects Foundation
National Association of Community Health Centers
National Association of County and City Health Officials
National Association of Dental Assistants
National Association of Local Boards of Health

National Association of Social Workers

National Confectioners Association
National Council Against Health Fraud
National Dental Assistants Association
National Dental Association
National Dental Hygienists' Association

National Down Syndrome Congress

National Down Syndrome Society

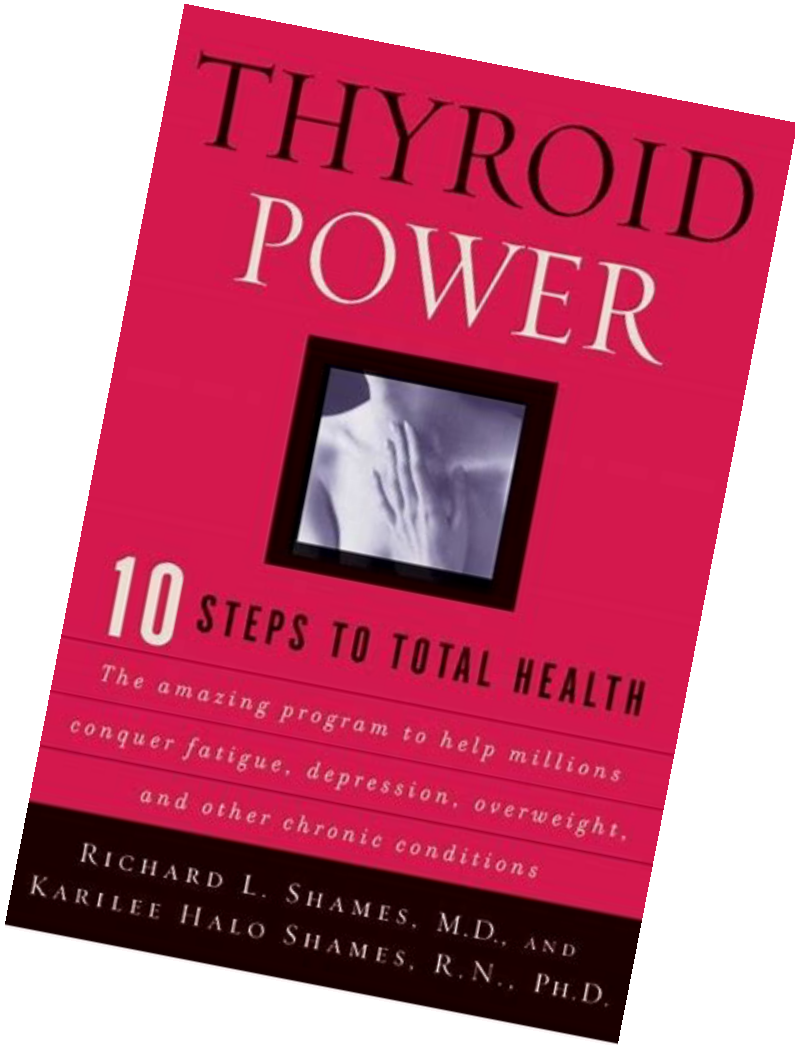
National Eating Disorders Association
National Foundation of Dentistry for the Handicapped
National Head Start Association
National Health Law Program
National Healthy Mothers, Healthy Babies Coalition

National Infertility Foundation

Oral Health America
Robert Wood Johnson Foundation
Society for Public Health Education
Society of American Indian Dentists
Special Care Dentistry
Academy of Dentistry for Persons with Disabilities
American Association of Hospital Dentists
American Society for Geriatric Dentistry
The Children's Health Fund
The Dental Health Foundation (of California)
U.S. Department of Defense
U.S. Department of Veterans Affairs
U.S. Public Health Service
Centers for Disease Control and Prevention (CDC)
National Institute of Dental and Craniofacial Research (NIDCR)
World Federation of Orthodontists
World Health Organization

The list above was current at the time Fluoridation Facts went to press. As organizations and entities continue to be added to the Compendium, the most current Compendium can be viewed on ADA.org at <http://www.ada.org/goto/ffcompendium>.

Permission is hereby granted to reproduce and distribute this Fluoridation Facts Compendium in its entirety, without modification. To request any other copyright permission please contact the American Dental Association at 1-312-440-2879.



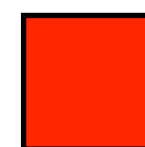
NTP Confirmation

Fluoride exposure can harm brains

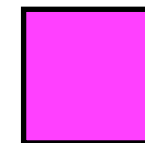
“NTP’s conclusion that fluoride is *presumed to be a cognitive neurodevelopmental hazard to humans* is based on consistent evidence from 26 lower risk-of-bias studies that evaluated fluoride exposure and effects on children’s IQ and other cognitive effects.” - *National Toxicology Program “Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects”* (Sept 16, 2020)

“A few studies also support the possibility of **heightened sensitivities to the detrimental cognitive effects of fluoride exposures in individuals** with certain polymorphisms in dopamine receptor D2, or catechol-O-methyltransferase (Cui *et al.* 2018, Zhang *et al.* 2015b), impacting dopamine catabolism and receptor sensitivity. Differential exposures to fluoride and **genetic susceptibilities of children to fluoride** appear to warrant further research.” - *National Toxicology Program “Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects”* (Sept 16, 2020)

“based on scientific judgement as to the **robustness** of the **body of evidence** that supports moderate confidence in the human data and consideration of the potential impact of additional studies” - NTP 2019



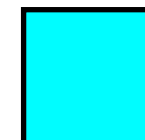
Known



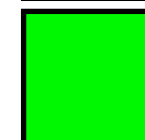
Presumed



Suspected



Not classifiable



Not identified

Public Harm Policy

Medical assault on vulnerable consumers

It would be a crime if you didn't stop fluoridation now and realized in a few years that your delay caused permanent harm to the brains and bodies of your constituents.

Karen Favazza Spencer

Gloucester, MA

Follow me on [Twitter](#)

Subscribe on [YouTube](#)

Publications with Citations:

2019 [We Too Letter](#)

2018 [Published Study](#)

2018 [Summary of Harm](#)

2016 [Appeal to Governors](#)

More power to you if fluoridation doesn't bother you, but not the power to assume it's safe for your neighbor with kidney disease, his pregnant wife or their diabetic daughter!

Fluoridation is Assault

Medical procedure without individual informed consent is assault. Municipal fluoridation is the distribution of a drug - a patently immoral and illegal medical procedure.

Many consumers have conditions that are worsened by fluoride exposure. Others may have statuses that make fluoridation ill-advised, i.e. pregnant women for whom fluoride consumption is associated with increased risks of pre-term birth and cognitive-behavioral effects in offspring and the elderly for whom fluoride consumption is associated with increased risks of neurological disorders and arthritis.

Community Water Fluoridation: A Public Harm Policy

Testimony to Green Bay, WI City Council

My name is Karen Favazza Spencer. I live in Gloucester MA. I am an analyst and co-author of a [peer-reviewed paper](#) concerning fluoride science and the political impact of zealous advocates who influence the public, politicians and government agencies. ([You Tube version](#))

Prior to my fluoridation activism, I was an analyst and project manager in Corporate America where my job involved digging for data, documenting facts, and determining stakeholder agendas. I served as an **honest broker** to decision makers.

When I first became involved because of my own health which was worsened by this 'public health' program, I was unaware of deceptive pro-fluoridation lobbying.

I was shocked when Johnny Johnson from Florida and Steven Slott from North Carolina along with other proponents showed up on my city paper where they aggressively denigrated locals who opposed fluoridation.

(See my story with citations here: <http://fluoridealert.org/wp-content/uploads/SalemState2016.09.07.pdf>)

Although it is necessary to acknowledge fluoridationist propaganda, it is exhausting. Let me just point to a few items.

1. When fluoridationists insist that fluoridation reduces cavities by 25%, that is a disingenuous misrepresentation that originated in a 1980s follow up to the New York state fluoridation trials. When researchers looked at ~1,500 children, they found absolutely no difference in cavities in the 5th graders, 4th graders, 3rd graders, or 2nd graders. In the first grade, researchers found no difference except among the handful of the poorest children - an average of 2 cavities in the unfluoridated group and one and a half cavities in the fluoridated group. A half cavity difference in just a **handful** of kids out of 1,500.
* 25% of 2 cavities = a half cavity in **just** the lowest SES & youngest group, a misleading "scientific artifact"
(See <http://www.slweb.org/NIDR.html> and http://www.nofluoride.com/Chemical_&_Engr_News.cfm and http://www.fluorideresearch.org/232/files/FJ1990_v23_n2_p055-067.pdf)
2. Most science finds cavity reduction is between insignificant & imaginary, but pro-fluoridation studies use flawed design, false logic, and manipulated data to misrepresent fact. Most recently, the Calgary and Juneau studies were further corrupted by the media. But this isn't about cavities or fake news. (See <http://onlinelibrary.wiley.com/doi/10.1111/cdoe.12329/abstract>)
3. Many thyroid doctors and kidney doctors have long advised their patients avoid fluoridated water. In recent years, many pediatricians and obstetricians began advising the same to pregnant women and mothers of bottle fed infants.
4. Many organizations have quietly asked the ADA to remove their name from the list of endorsers, including the Alzheimers Association in 2019.

The National Toxicology Program wrote in September that studies suggest that due to genetics, **some people have heightened sensitivities to the adverse effects of fluoride**. My experience with fluoride illnesses, some of which are shared by others in my extended Italian family, is supportive of that science.

I believe Johnny Johnson said it would be a shame if you stopped fluoridation and regretted it in ten years. Let me say, it would be a **crime** if you didn't stop fluoridation now and realized in a few years that your delay caused permanent harm to the brains and bodies of your constituents.

The Neurotoxic Risks of Fluoride **Far outweigh any Benefit to Teeth**

Paul Connett, PhD

Director, Fluoride Action Network

Fluoride**ALERT**.org

GREEN BAY, Wisconsin

Oct 8, 2020

My name is Paul Connett

- I reside in Binghamton, NY
- I am a retired professor of chemistry, who specialized in environmental chemistry and toxicology.
- I have spent the last 24 years researching fluoride's toxicity

- Water fluoridation has NEVER been SCIENCE-based - it is "Authority-based" or "Belief in Authority-Based."
- Saying that fluoridation is "safe and effective" over and over again doesn't make it so!

I will argue-

- That the evidence that Fluoride poses a RISK to the fetal and infant BRAIN is far stronger –and more significant from a public health point of view - than any evidence that ingesting fluoride BENEFITS teeth

It cannot be denied

- That there has never been a single **Randomized Control Trial** to demonstrate that swallowing fluoride lowers tooth decay
- There have been 70 RCTs demonstrating that **fluoridated toothpaste** lowers tooth decay

It cannot be denied

The vast majority of countries worldwide do NOT fluoridate their water supplies

And yet according to WHO figures there is little to no difference in tooth decay among 12 –year-olds between fluoridated and non-fluoridated countries

Undeniable facts

- The placental membrane does not protect the fetus from fluoride –
- **RESULT:** the highest dosage of fluoride (mg/kg bodyweight/ day) goes to the fetus –
- The blood brain barrier is not fully protective until 6 months of age –
- The next highest dosage goes to the bottle-fed infant

**The level of fluoride in Mothers' milk
is 0.004 ppm (NRC, 2006, p.40)**



**The level of fluoride in Mothers' milk
is 0.004 ppm (NRC, 2006, p.40)**



**In effect, mothers' milk protects
the infant from fluoride exposure**

Water fluoridation removes that protection when babies are bottle-fed



Range of F in USA, 0.7 – 1.2 ppm
= 175 - 300 x level in mothers' milk

Between 1990 and 2017

- Many animal and human studies showed that fluoride had the potential to damage the brain
- BUT the bombshells have come since 2017

SINCE 2017

Two Rigorous NIH funded studies

- SHOWED that Fluoride exposure to women during pregnancy is associated with IQ loss in offspring (Bashash, 2017 and Green, 2019)

In 2020 Another Rigorous NIH
funded study showed

Children who were Bottle-fed as
babies in **fluoridated communities**
in Canada had lower IQ than
children who were Bottle-fed in **non-**
fluoridated communities (Till,
2020) (a **9 IQ point difference**)

Conclusion

Even if a very small benefit to teeth accrues during fetal or infant development, it would be a VERY POOR public health policy to seek such a benefit at the expense of damaging the fetal and infant brain.

These IQ studies are being reviewed in two different arena

- 1) In a systematic Review conducted by the US National Toxicology Program (NTP)
- 2) In US Federal Court in TSCA lawsuit brought against US EPA by the Fluoirde Action Network and others

Until these reviews are complete

- 1) It would be wise to put a moratorium on any further fluoridation in Green Bay.

More details on Key Studies

www.FluorideALERT.org



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TRENDING TOPICS

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FLUORIDE & IQ - THE 63 STUDIES

FAN has described each study

STUDIES FINDING ASSOCIATION BETWEEN FLUORIDE & REDUCED IQ:

IQ Study #64 (Till 2019)

Citation:	Till C, Green R, Flora D, Hornung R, Martinez-Miller EA, Blazer M, Farmus L, Ayotte P, Muckle G, Lanphear B. (2019). Fluoride exposue from infant formula and child IQ in a Canadian birth cohort. <i>Environment International</i> 134:105315.
Location of Study:	In fluoridated and non-fluoridated cities in Canada.
Size of Study:	398 mother-child pairs
Age of Subjects:	Fetus and Infants up to 3-4 year-olds
Source of Fluoride:	Fluoride in drinking water for (1) Fetal fluoride exposure and (2) breast-fed versus formula-fed from both fluoridated and non-fluoridated cities.

Key Papers on Fluoride & Neurotoxicity

IQ studies

- 1) Xiang 2003**
- 2) Choi 2012 (review)**
- 3) Bashash 2017**
- 4) Green 2019**
- 5) Till 2020**

Key Papers on Fluoride & Neurotoxicity

ADHD studies

1. Malin 2015
2. Bashash 2018
3. Riddell 2019

Bashash 2017

The Bashash et al., 2017 study



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SEPTEMBER 2017 | VOLUME 125 | ISSUE 9



Altmetric 143

Environ Health Perspect; DOI:10.1289/EHP655

Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6–12 Years of Age in Mexico

Morteza Bashash,¹ Deena Thomas,² Howard Hu,¹ E. Angeles Martinez-Mier,³ Brisa N. Sanchez,² Niladri Basu,⁴ Karen E. Peterson,^{2,5,6} Adrienne S. Ettinger,² Robert Wright,⁷ Zhenzhen Zhang,² Yun Liu,² Lourdes Schnaas,⁸ Adriana Mercado-Garcia,⁹ Martha María Téllez-Rojo,⁹ and Mauricio Hernández-Avila⁹

Bashash, 2017

- This was a 12-year multi-million dollar study – funded by EPA, NIH and NIEHS.
- Authors came from many prestigious institutions (e.g. Universities of Toronto, McGill, Harvard, Indiana, Michigan, Mount Sinai and more)

Bashash, 2017

- Examined approximately 300 mother-offspring pairs.
- Both exposure and outcomes were determined on an individual basis.
- The mothers' exposure to fluoride during pregnancy was determined via analysis of their urine (a measure of total fluoride exposure regardless of source).

Bashash 2017

Many potential confounders adjusted for:

Child characteristics:

1. gestational age
2. weight at birth
3. sex
4. parity (being the first child)
5. age at outcome measurement

Maternal characteristics:

6. smoking history (ever smoked vs. nonsmoker)
7. marital status (married vs. others)
8. age at delivery
9. maternal IQ
10. education,
11. cohort (Cohort 3-Ca, Cohort 3- placebo and Cohort 2A)
12. **HOME score**
13. child's urine F at outcome assessment
14. SES (Socio-Economic Status)
15. maternal bone lead
16. maternal blood mercury
17. calcium supplement

Excluded from study if:

18. history of psychiatric disorders
19. high-risk pregnancies
20. gestational diabetes

reported current use of:

21. daily alcohol
22. illegal drugs
23. continuous prescription drugs

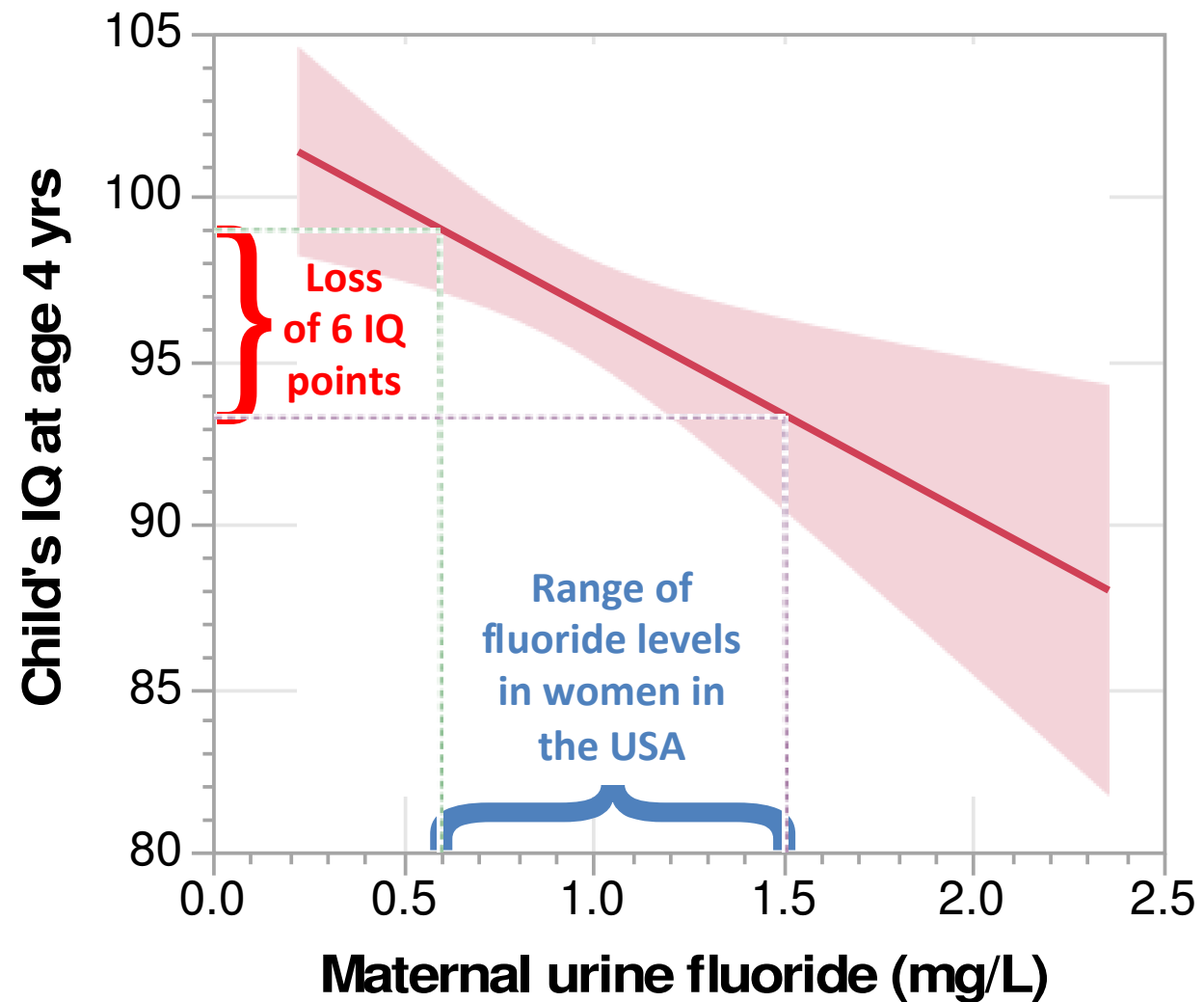
were diagnosed with:

24. preeclampsia
25. renal disease
26. circulatory diseases
27. hypertension
28. seizures during the index pregnancy

The study results

- The IQ of the women's children was measured at age 4 and again at 6-12 years
- For every 1 mg/L increase in the mother's urine F level the children lost an average of *5-6 IQ points*, a very large effect.

Relationship between fluoride and IQ found in new study (Bashash et al. 2017)



Bashash 2017

“Conclusion

In this study, higher levels of maternal urinary fluoride during pregnancy (a proxy for prenatal fluoride exposure) **that are in the range of levels of exposure in other general population samples of pregnant women as well as nonpregnant adults** were associated with lower scores on tests of cognitive function in the offspring at 4 and 6-12 y old.”

The American Dental Association's (ADA) response to this study

American Dental Association Response to Study Regarding Fluoride Intake in Mexico.
September 19.

The American Dental Association (ADA) examined a study in Environmental Health Perspectives based on fluoride intake in Mexico, and concludes the findings are not applicable to the U.S. The ADA continues to endorse fluoridation of public water as the most effective public health measure to prevent tooth decay...

Dr. Howard Hu (Toronto U.)



What the principle author of the study said:

... [The article quotes the lead investigator of the study, Dr Howard Hu:] "This is a very rigorous epidemiology study. You just can't deny it. It's directly related to whether fluoride is a risk for the neurodevelopment of children. So, to say it has no relevance to the folks in the U.S. seems disingenuous."

Green 2019

Green 2019

High quality, mother-offspring longitudinal cohort study; Canada.

Research

JAMA Pediatrics | [Original Investigation](#)

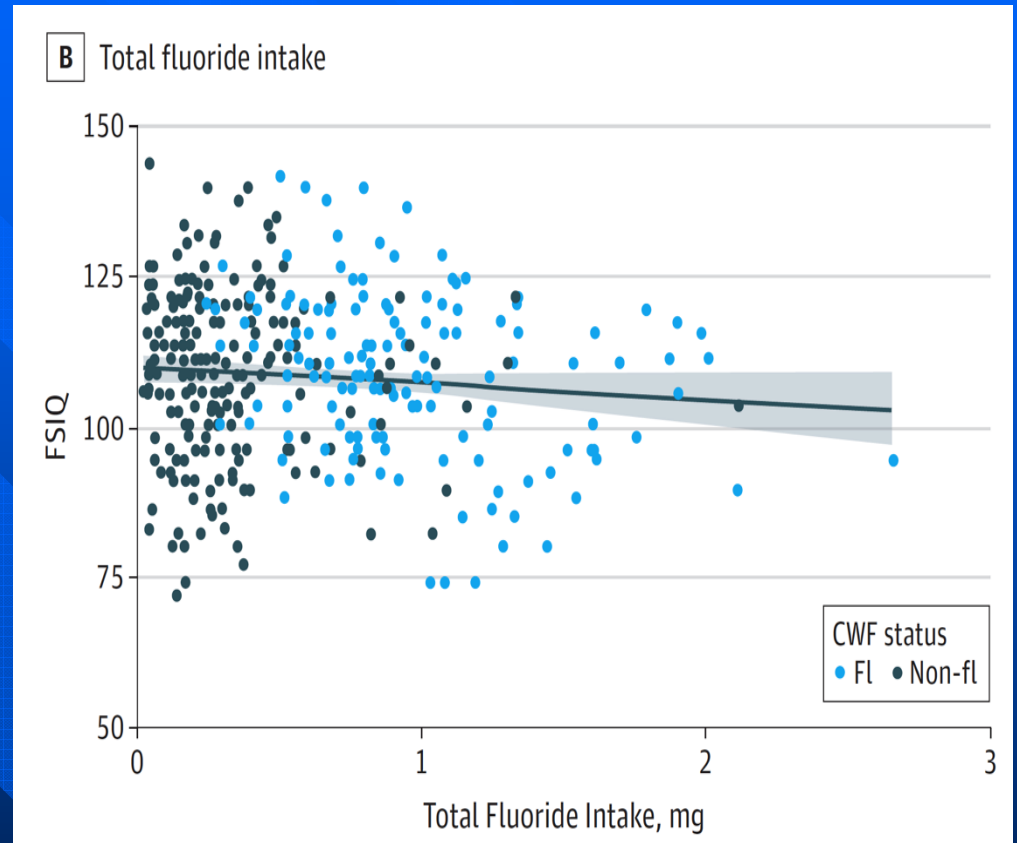
Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada

Rivka Green, MA; Bruce Lanphear, MD; Richard Homung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Raichel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD

Green 2019

- Second NIH-funded study of F developmental neurotoxicity.
- Found large, statistically significant effects on IQ.
- Average IQ loss of 4.5 points in **boys** for each 1 mg/L increase in mother's urine.

F and IQ



- **Average IQ loss of 3.7 points for each 1 mg/day increase in mother's F ingestion.**

Green, 2019:

***JAMA* Editor's Podcast**



Frederick P. Rivara, MD, MPH
Editor, *JAMA Networks Open*



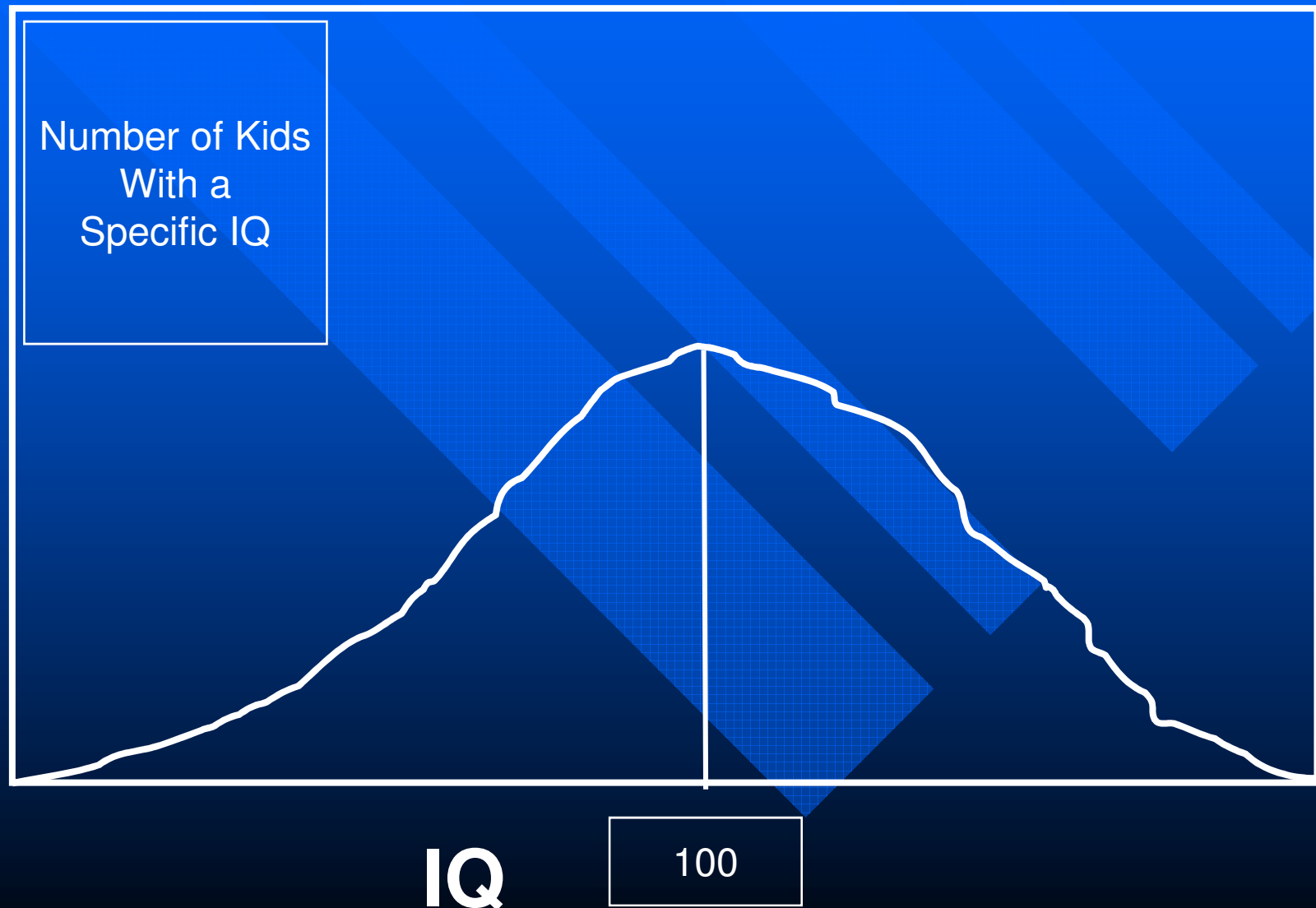
Dimitri A. Christakis, MD, MPH
Editor, *JAMA Pediatrics*

F neurotoxicity

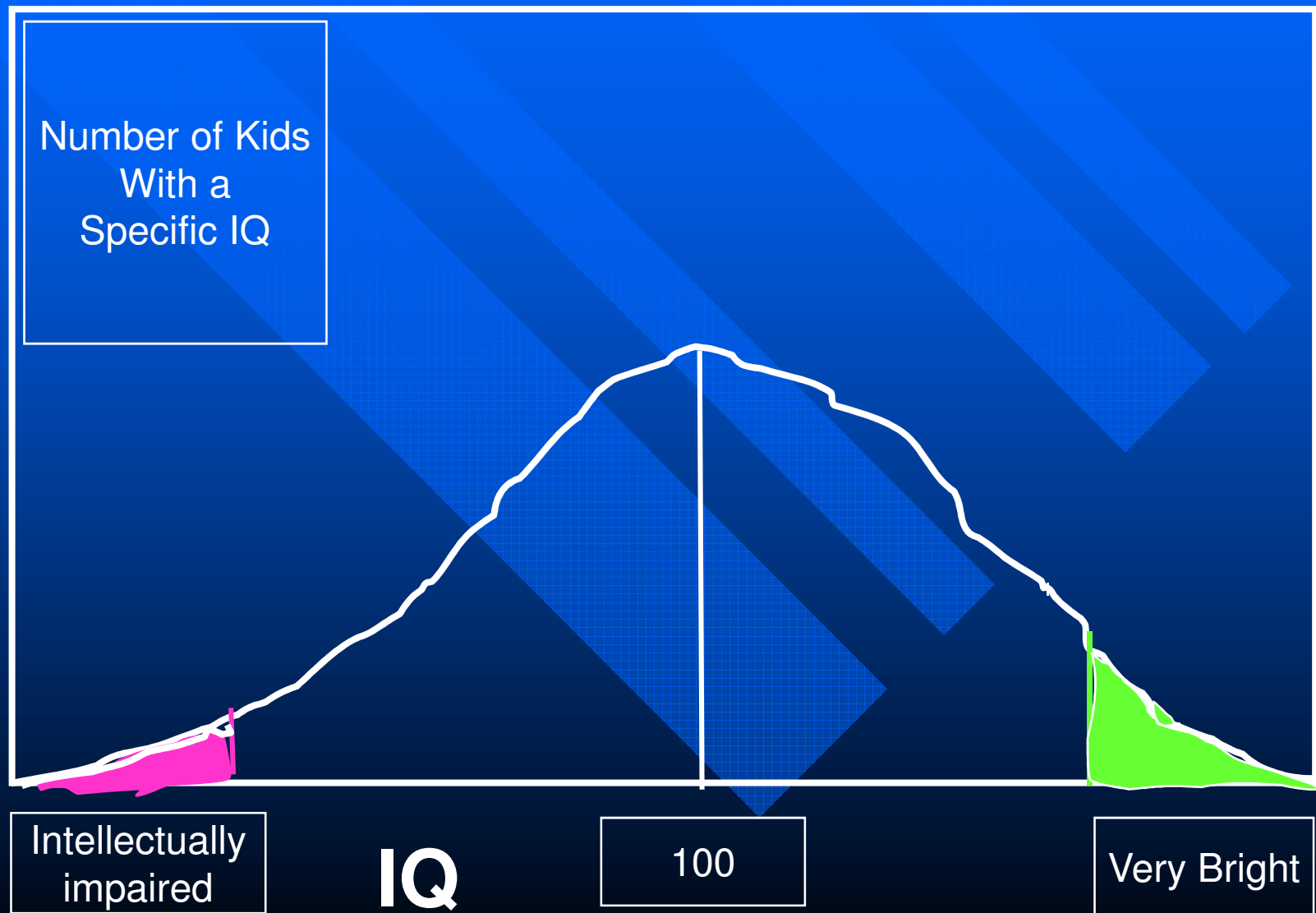
Editor's advice: Pregnant mothers should avoid fluoridated water



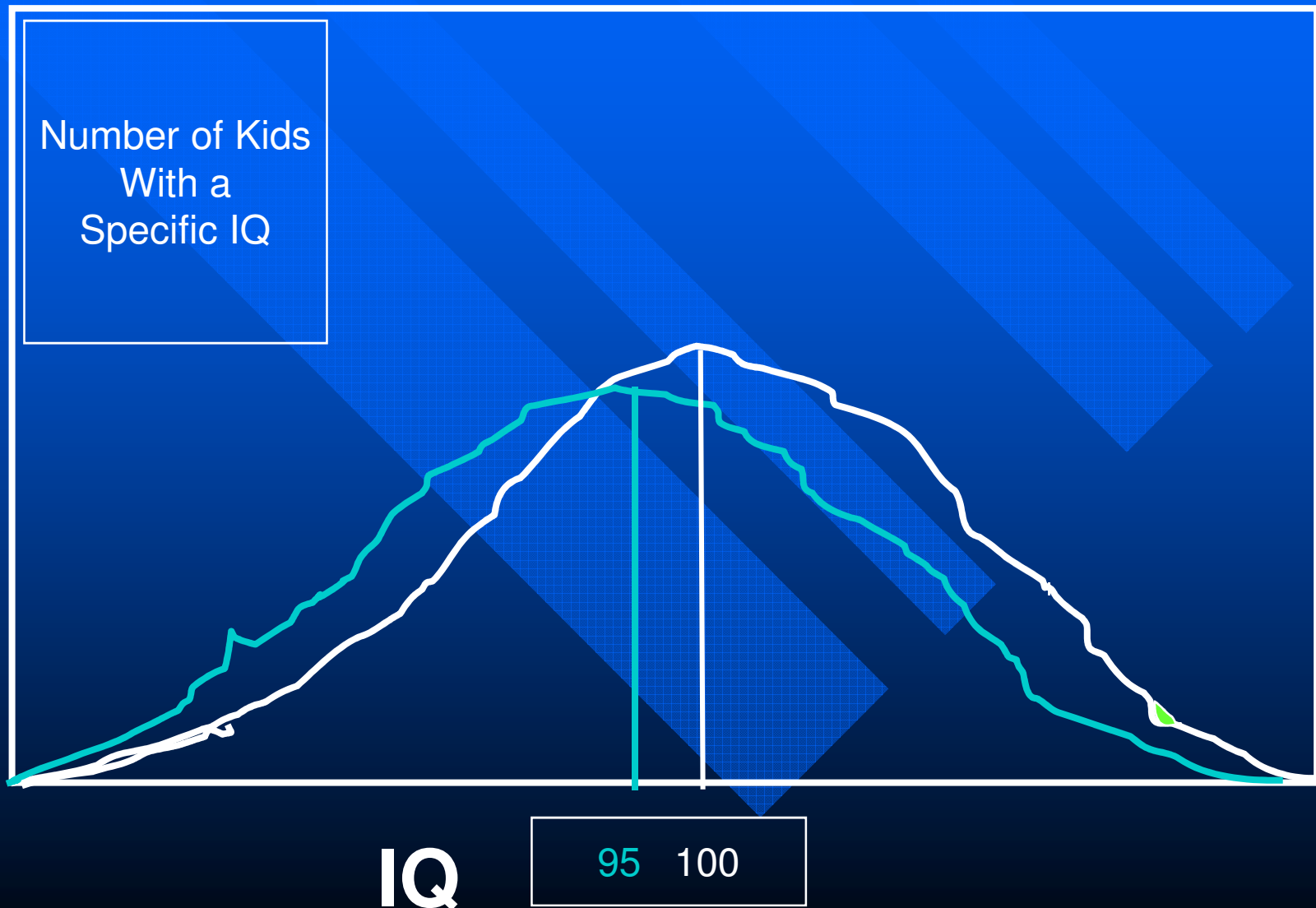
IQ and population



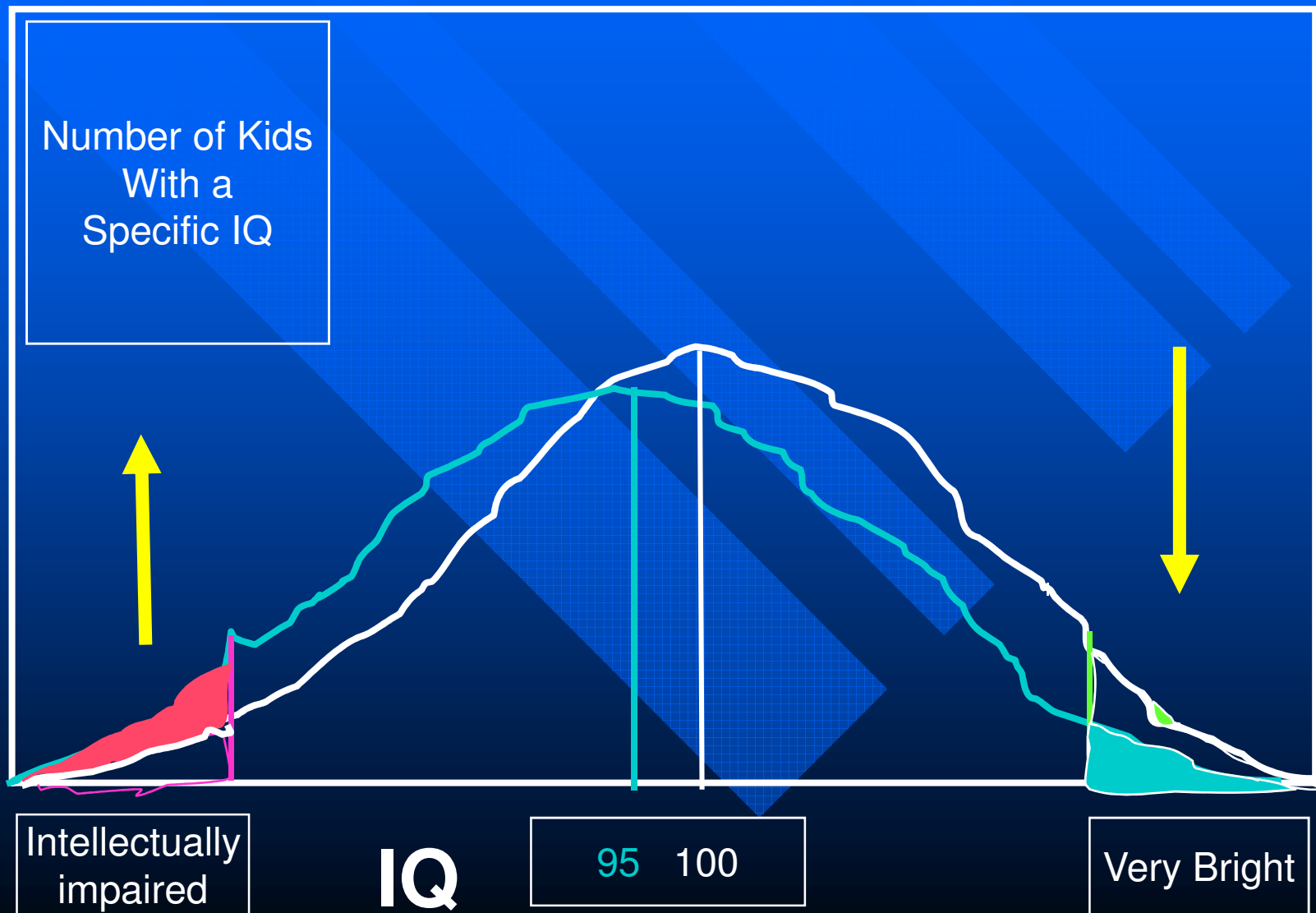
IQ and population



IQ and population



IQ and population



Till 2020

Till 2020

Environment International 134 (2020) 105315



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Environment International

journal homepage: www.elsevier.com/locate/envint





Check for updates

TiI 2020

High quality, mother-offspring
longitudinal cohort study;
F in infant formula;
Canada.

Dramatic lowering of IQ



**NEW STUDY:
FLUORIDATION LOWERS IQ OF FORMULA-FED BABIES**

Fluoride exposure from infant formula and child IQ in a Canadian birth cohort

Christine Till¹*, Rivka Green², David Flock³, Richard Herrang⁴, E. Angeles Martinez-Mier⁵, Maddy Blom⁶, Linda Fournier⁷, Pierre Ayotte^{8,9}, Gina Muckle¹⁰, Bruce Lanphear¹¹

¹Faculty of Health, York University, Toronto, Canada
²Department of Paediatrics, University of Toronto, Canada
³School of Medicine, Indiana University, USA
⁴Centre de Recherche en Santé de Québec, Université Laval, Québec, Canada
⁵Department of Social and Preventive Medicine, York University, Toronto, Canada
⁶School of Psychology, York University, Toronto, Canada
⁷Department of Psychology, York University, Toronto, Canada
⁸Department of Psychology, York University, Toronto, Canada
⁹Department of Psychology, York University, Toronto, Canada
¹⁰Department of Psychology, York University, Toronto, Canada
¹¹Department of Psychology, York University, Toronto, Canada



ABSTRACT

Background: Infant consumption of formula contaminated with fluoride (water) can lead to excessive fluoride exposure in infancy and childhood. We examined the association between fluoride exposure in infancy and childhood and IQ at 3-4 years. **Methods:** We examined 205 mother-child dyads in the National Longitudinal Survey of Children and Youth (NLSCY) who were born in 2001. We examined water fluoride concentration in the home during the first 12 months of life. We also examined the association between fluoride exposure and IQ at 3-4 years. **Results:** We found a significant association between fluoride exposure and IQ at 3-4 years. **Conclusion:** Fluoride exposure from infant formula is associated with lower IQ at 3-4 years.

NIH
National Institute of
Environmental
Health Sciences

Till 2020

Children who were formula-fed and lived in fluoridated areas as babies have dramatically lower IQ compared to those who lived in non-fluoridated areas.



NEW STUDY: FLUORIDATION LOWERS IQ OF FORMULA-FED BABIES

Fluoride exposure from infant formula and child IQ in a Canadian birth cohort

Christine Till^{1*}, Rivka Green², David Flock³, Richard Herrang⁴, E. Angeles Martinez-Mier⁵, Maddy Blomer⁶, Linda Farnius⁷, Pierre Ayotte^{8,9}, Gina Muckle^{10,11}, Bruce Lanphear¹²

¹Faculty of Health, York University, Toronto, Canada
²Professor and Endocrinologist, Health, Children's Hospital, Medical Center, OH, USA
³School of Dentistry, Indiana University, USA
⁴Centre de Recherche en Santé de Québec, Université Laval, Québec, Canada
⁵Department of Social and Preventive Medicine, Laval University, Québec, Canada
⁶School of Psychology, Laval University, Québec, Canada
⁷Faculty of Health Sciences, Saint Mary's University, British Columbia, Canada
⁸Department of Pediatrics, Université de Montréal, Québec, Canada
⁹Department of Pediatrics, Université de Montréal, Québec, Canada
¹⁰Department of Pediatrics, Université de Montréal, Québec, Canada
¹¹Department of Pediatrics, Université de Montréal, Québec, Canada
¹²Department of Pediatrics, Université de Montréal, Québec, Canada



ABSTRACT

Background: Infant consumption of formula contaminated with fluoride (water) can be a source of fluoride exposure in infancy and childhood. We examined the association between fluoride exposure in infancy and childhood and IQ in a Canadian birth cohort. **Methods:** We examined 205 mother-child dyads in the National Longitudinal Survey of Children and Youth (NLSCY) who were born in 1994. We examined water fluoride concentration in the household drinking tap water. We examined water fluoride concentration in the formula-fed versus formula-fed and the impact of water fluoride and formula consumption on child IQ. **Results:** Thirty-eight percent of mother-child dyads lived in a household with fluoride water. Fluoride concentration (ppm) in the household drinking tap water (median 0.7) corresponded to a 0.3- and 0.4-point decrease in performance IQ (mean 10.72, -0.37 and 0.47) and formula-fed children (mean 10.72, -0.37 and 0.47) and formula-fed children (mean 10.72, -0.37 and 0.47). A 0.5 mg/l increase in fluoride in the household drinking tap water corresponded to a 0.3- and 0.4-point decrease in performance IQ (mean 10.72, -0.37 and 0.47) and formula-fed children (mean 10.72, -0.37 and 0.47). **Conclusion:** Fluoride exposure in infancy and childhood is a source of fluoride exposure in infancy and childhood. Fluoride exposure in infancy and childhood is a source of fluoride exposure in infancy and childhood.



Till 2020

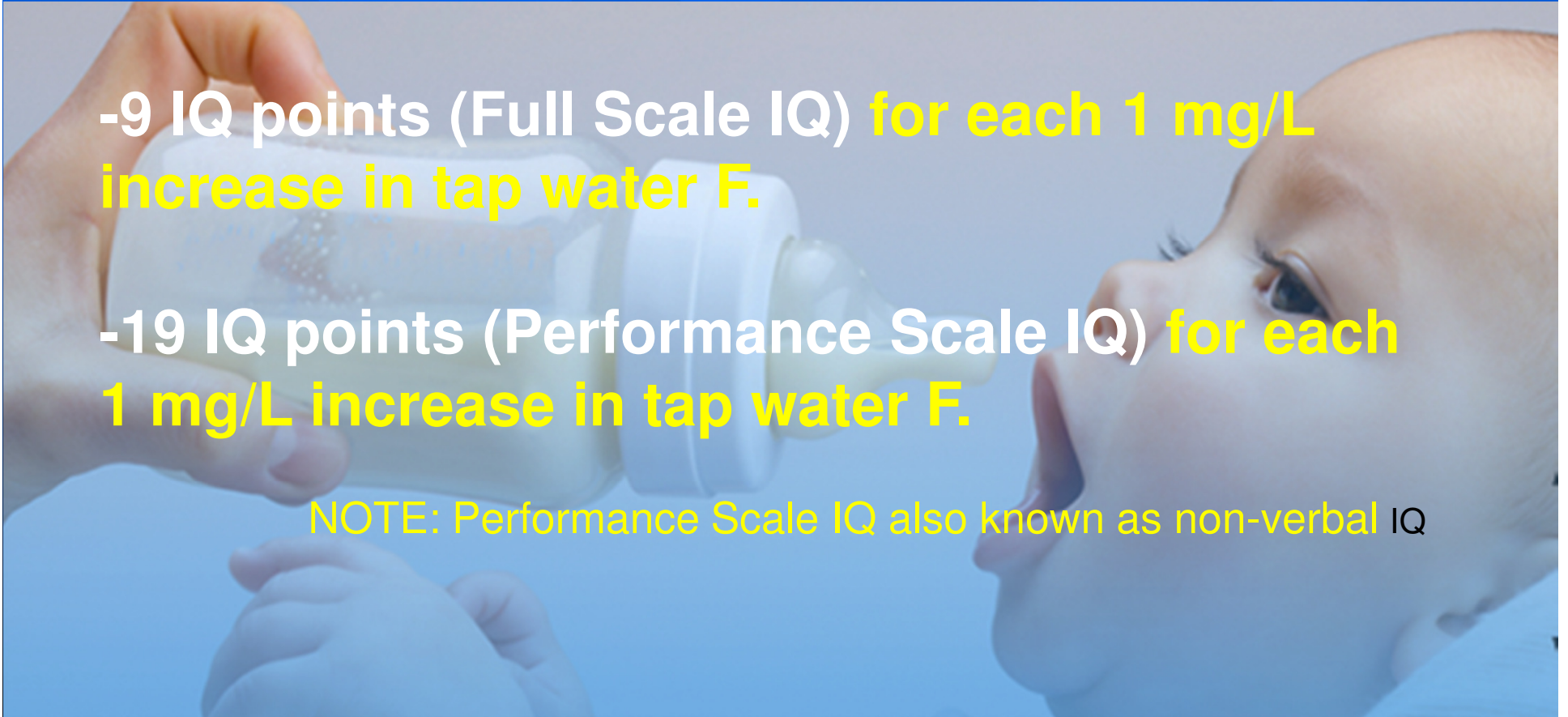
F and IQ

**Very large loss of IQ with increasing tap water
F for *formula-fed infants*:**

**-9 IQ points (Full Scale IQ) for each 1 mg/L
increase in tap water F.**

**-19 IQ points (Performance Scale IQ) for each
1 mg/L increase in tap water F.**

NOTE: Performance Scale IQ also known as non-verbal IQ



Till 2020

Recommendation: no fluoridated water for infants

“After adjusting for fetal exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children. In the absence of any [dental] benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water or water with lower fluoride content as a formula diluent.”

Fluoride and ADHD

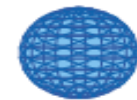
Malin and Till, 2015

F neurotoxicity

Malin and Till 2015

1st study of F and ADHD; ecological; USA.

Malin and Till *Environmental Health* (2015) 14:17
DOI 10.1186/s12940-015-0003-1



ENVIRONMENTAL HEALTH

RESEARCH

Open Access

Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association

Ashley J Malin* and Christine Till

Malin and Till 2015

F and ADHD

Dramatic rise in ADHD prevalence as percent of state fluoridated increased.

About 50% higher ADHD rate in states with most fluoridation compared to those with least.

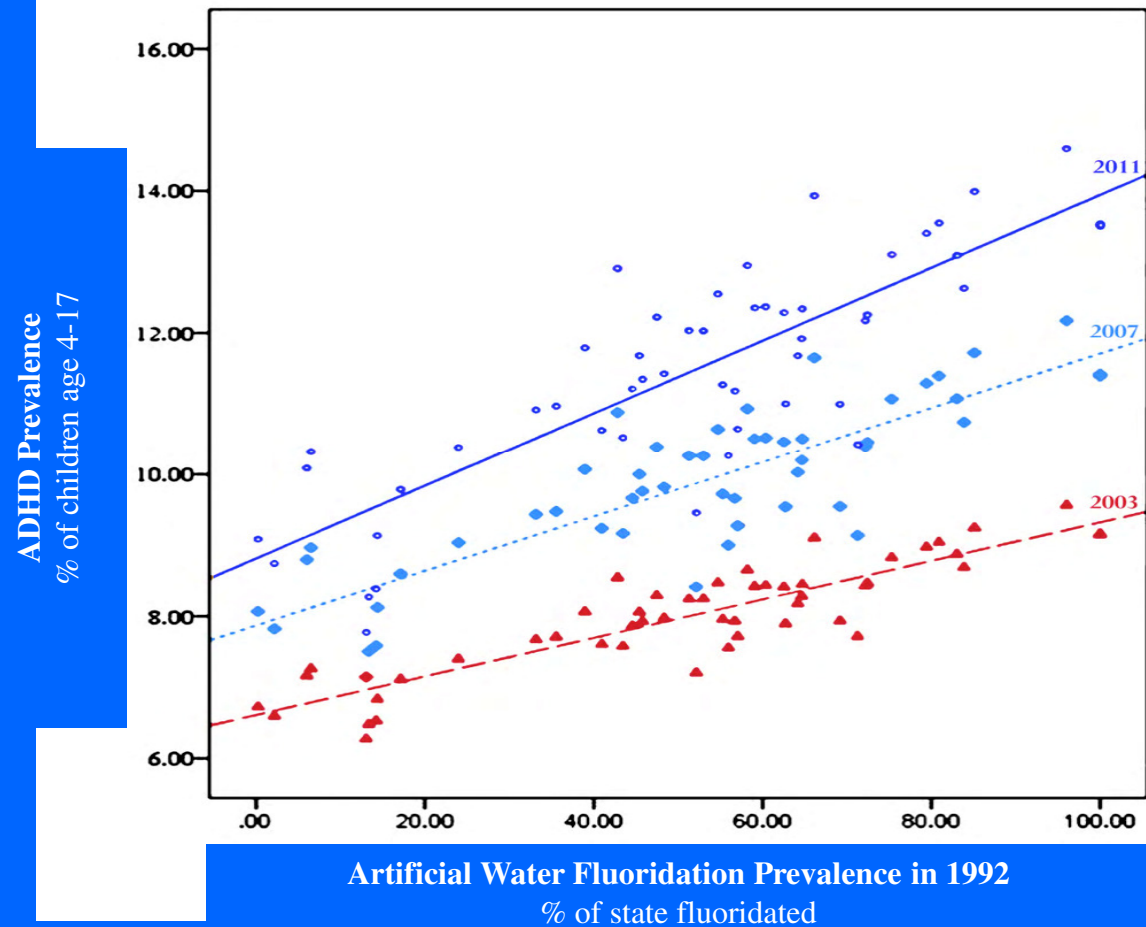


Figure 1. Artificial fluoridation prevalence predicting ADHD prevalence after adjusting for 1992 median household income, by state. For three survey years: 2003, 2007, 2011.

Bashash, 2018

Bashash 2018

1st high quality study of F and ADHD; Mexico.

Environment International 121 (2018) 658–666



Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint



Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in Mexico City



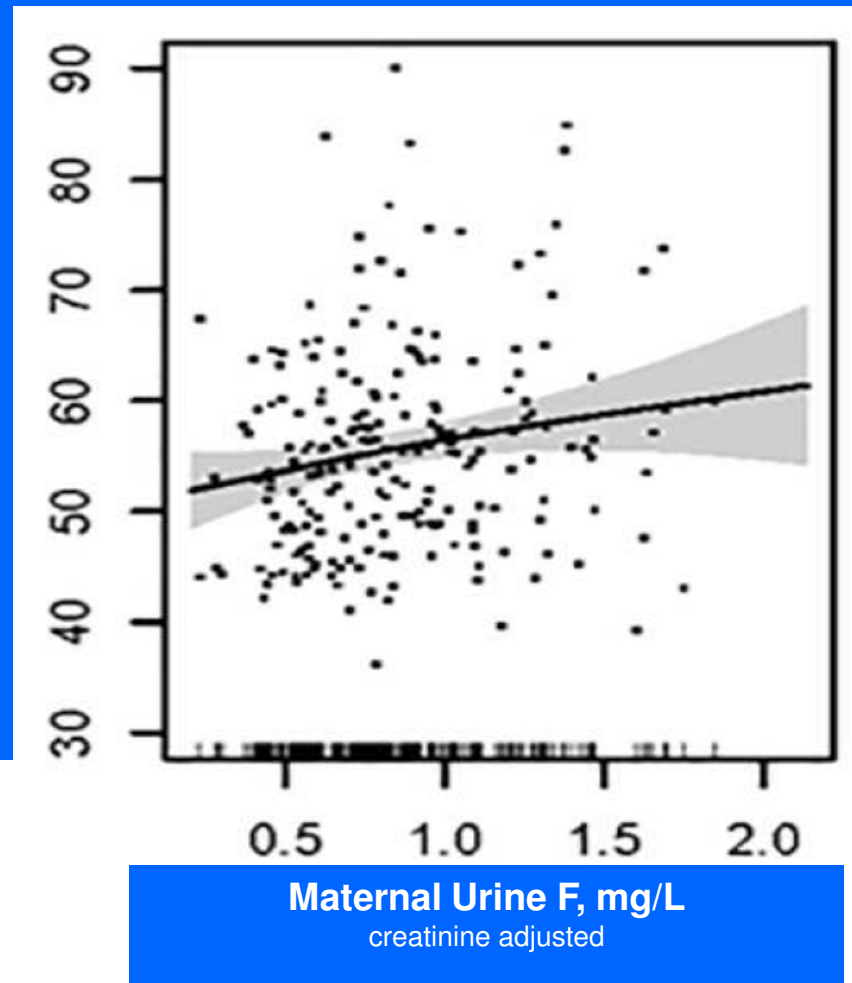
Morteza Bashash^{a,*}, Maelle Marchand^a, Howard Hu^{a,1}, Christine Till^b, E. Angeles Martinez-Mier^c, Brisa N. Sanchez^d, Niladri Basu^e, Karen E. Peterson^{d,f,g}, Rivka Green^b, Lourdes Schnaas^h, Adriana Mercado-Garcíaⁱ, Mauricio Hernández-Avilaⁱ, Martha María Téllez-Rojoⁱ

F and ADHD

Bashash 2018

Statistically significant increase in ADHD Total Score (inattentive and hyperactive-impulsive behaviors combined) with higher maternal urine F.

ADHD Total Score, DSM IV
Conners' Rating Scales-Revised (CRS-R)



Riddell 2019

Riddell 2019

High quality study of F and ADHD; Canada.

Environment International 133 (2019) 105190



Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint



Full length article

Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth

Julia K. Riddell^{a,*}, Ashley J. Malin^b, David Flora^a, Hugh McCague^c, Christine Till^a

^a Faculty of Health, York University, Ontario, Canada

^b Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States

^c Institute for Social Research, York University, Ontario, Canada



Riddell 2019

Found almost **300% higher risk of ADHD** for those living in fluoridated areas in national sample of Canadian children.

Found **600% higher risk of ADHD** for every 1 mg/L increase in tap water F.

Riddell 2019

F and ADHD

“In conclusion, we found that higher tap water fluoride levels and fluoridation of municipal water supplies were associated with a higher risk of an ADHD diagnosis as well as increased symptoms of hyperactivity and inattention, especially among adolescents.”

The NTP Review 2020
(second draft made
public Sept 28)

In 2016

- FAN requested that the US National Toxicology Program (NTP) conduct a systematic review of fluoride's neurotoxicity



National Toxicology Program (NTP) systematic review and health assessment of the neurotoxicity of fluoride (DRAFT)

**National Toxicology Program (NTP)
systematic review and health assessment
of the neurotoxicity of fluoride:**

“Conclusions: NTP concludes that fluoride is presumed to be a cognitive neurodevelopmental hazard to humans. This conclusion is based on a consistent pattern of findings in human studies across several different populations showing that higher fluoride exposure is associated with decreased IQ or other cognitive impairments in children.”

FAN's TSCA Lawsuit

In 2016

- FAN petitioned the US EPA to ban the deliberate addition of fluoridating chemicals to the drinking water under provisions in the Toxic Substances Control Act (TSCA)
- The EPA rejected the petition but FAN and other groups have now taken the EPA to Federal Court
- The case will be heard in June 2020 via video

www.FluorideALERT.org

TRENDING TOPICS

1 2 3 4 5 6 7 8 9 10

NEW RULING: TSCA CASE WILL GO TO TRIAL!

LEARN MORE

THE TSCA FLUORIDE LAWSUIT
TRIAL DATES START APRIL 20, 2020 IN SAN FRANCISCO

Conclusions

1. For any community to continue fluoridation with all these studies - **including several US-government funded studies and a draft NTP Review** - on the table is reckless.
2. The **risks** to fetal and infant brain development far outweigh any **benefit** to teeth from ingestion of fluoride during fetal and infant development.
3. Other countries have shown that these benefits can be secured by other means



90 Years of Caring for Children—1930–2020

October 5, 2020

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Fax: 847/434-8000
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Dear Protection and Policy Committee,

On behalf of the American Academy of Pediatrics (AAP), a non-profit professional organization of 67,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults, I write to support the recommendations of the Centers for Disease Control and Prevention (CDC) and the American Dental Association (ADA) in stating that community water fluoridation is safe, effective, and prevents unnecessary dental disease, a costly and painful condition.

The AAP is particularly concerned with the high rates of early childhood caries (tooth decay) in the United States and the detrimental effects this disease can have on children. Dental caries, although largely preventable, is the most common chronic childhood disease, five times more common than asthma. Dental caries can lead to severe health problems, including serious infection, debilitating pain, dietary and speech problems, and in rare cases, even death.

The AAP supports community water fluoridation to help protect children's teeth. Regular and frequent exposure to small amounts of fluoride is the best way to protect the teeth against caries. This exposure can be readily accomplished through drinking water that has been optimally fluoridated and brushing with fluoride toothpaste twice daily.¹ The delivery of fluoride includes community-based, professionally applied, and self-administered modalities. Community-based water fluoridation intervention optimizes the level of fluoride in drinking water, resulting in pre-eruptive and post-eruptive protection of the teeth.

Water fluoridation is a cost-effective means of preventing dental caries, with the lifetime cost per person equaling less than the cost of one dental restoration. In short, fluoridated water is the cheapest and most effective way to deliver anti-caries benefits to communities.² Water fluoridation is seen as effective and inexpensive, does not require daily adherence, and promotes equity, because it benefits everyone regardless of socioeconomic status.³

The AAP continues its mission to ensure the health and well-being of all children, and, to this end, supports local and state efforts for children to have access to safe, optimally fluoridated water. If you require additional information, please contact Hollis Russinof, hrussinof@aap.org.

Sincerely,

Sara H. Goza, MD, FAAP
President

SHG/hr

¹ Bright Futures Guidelines for the Health Supervision of Infants, Children, and Adolescents, 4th Edition. 2017.

² Fluoride Use in Caries Prevention in the Primary Care Setting. *Pediatrics*. 2014;134(3): 626-633.

³ Early Childhood Caries in Indigenous Communities. *Pediatrics*. 2011;127(6):1190-1198.

Don't let your community down

**Dr John F Beal MBE, PhD, BDS, MFDS,
MFPH(Hon), FRSPH**

Hon Senior Lecturer, University of Leeds

**Former Consultant in Dental Public Health,
Yorkshire Region, England**

Member of Leeds City Health & Wellbeing Board

**Former Hon Treasurer, UK Public Health
Association**

Fluoridation reduces tooth decay

The next slide shows that not only does fluoridation reduce tooth decay but it benefits poor children most and reduces inequalities

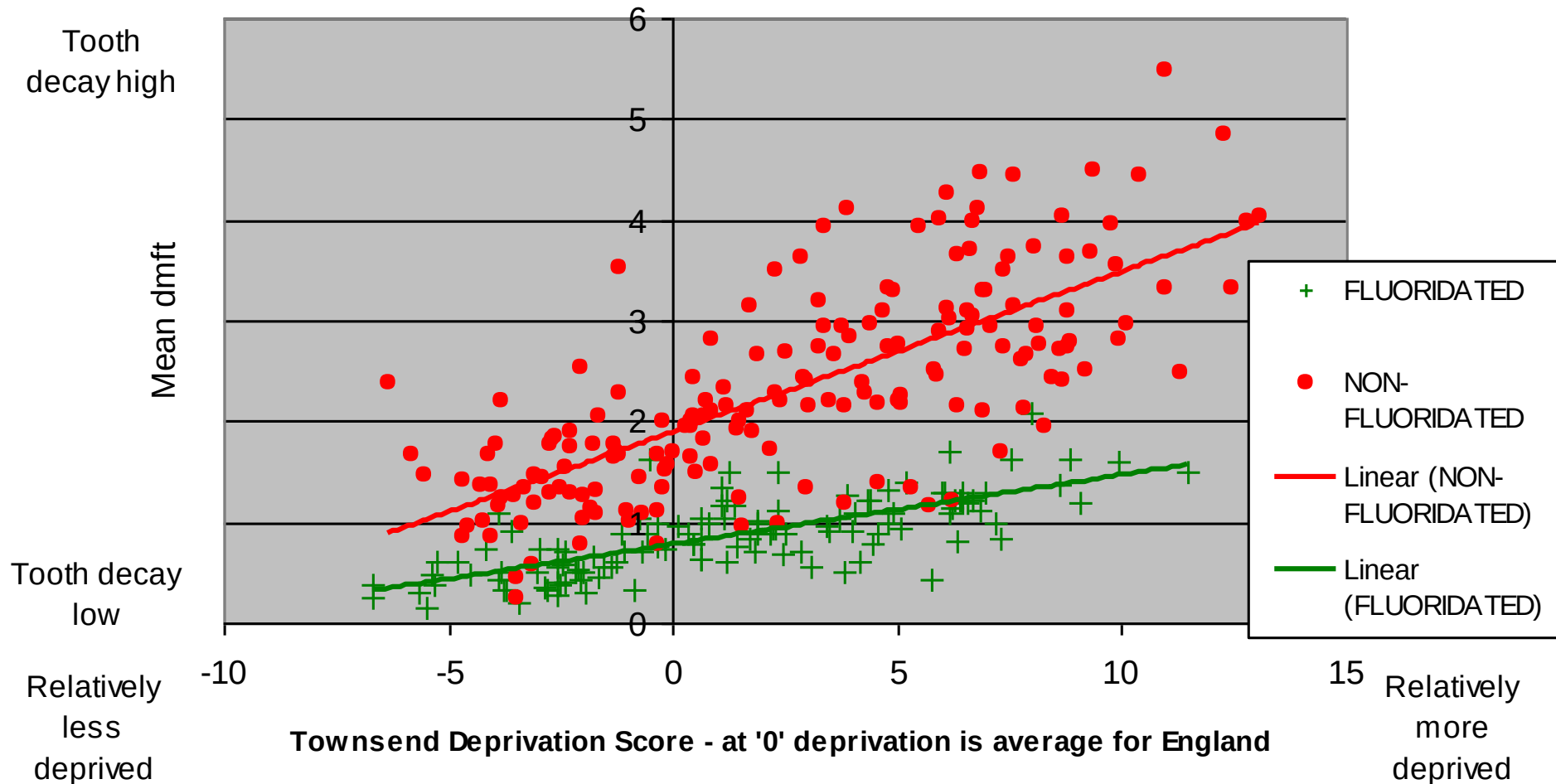
“Fluoride gives poor children rich kids teeth”

Green Bay keep doing what you can for your poorest residents

Fluoridation reduces inequalities

Red dots non-fluoridated : Green dots fluoridated

Left – affluent : right - deprived



Fluoridation at 0.7 mg per litre does not cause mottling

There are nearly 100 possible causes of tooth discolouration

The next slide shows that even at 1mg per litre there is no difference in opacities (discolouration) except for very faint white striations that can hardly be seen with the naked eye – the diagnosis in the study was made by photographs much magnified and projected onto a screen

Percentage of 9-10-year old children with opacities on their upper central incisors

	Leeds (NF)	Birm (F)
None	68%	59%
White <2mm	12%	10%
White >2mm	12%	13%
Brown <2mm	0%	0%
Brown >2mm	0%	1%
White striations	7%	16%
Pitting	1%	0%

Levine, Beal & Fleming, 1989

**Don't be scared off by
pseudo-science and let your
community down**

**Green Bay you are doing something
remarkable for your community -
reducing toothache, improving smiles,
making life better for the population for
whom you are responsible**

.

**The International Academy of
Oral Medicine and Toxicology (IAOMT)**
8297 ChampionsGate Blvd, #193
ChampionsGate, FL 33896
Phone (863) 420-6373; Website: www.iaomt.org



August 21, 2020

Dear Esteemed Protection and Policy Committee Members of the City of Green Bay,

This letter is being sent to you to establish that there is scientific evidence demonstrating the potential for harmful health effects caused by water fluoridation. Since you have been tasked with the responsibility of taking part in a decision about whether to fluoridate the water in your community, we urgently request that you take this opportunity to fairly and conscientiously evaluate the risks associated with fluoride use. We are aware that some dentists and health professionals will tout benefits of ingested fluoride; however, it is crucial that you also examine the most up-to-date body of facts relevant to hazardous impacts of fluoridation.

The International Academy of Oral Medicine and Toxicology (IAOMT) has been dedicated to its mission of protecting public health through the practice of biocompatible dentistry since it was founded in 1984. We are an organization of over 1,000 dentists, physicians, and research professionals in more than 35 countries, and the scientific activities of the IAOMT are overseen by a Scientific Advisory Board composed of leaders in Biochemistry, Toxicology, and Environmental Medicine. Our members have been expert witnesses about dental products and practices before the United Nations Environment Programme (UNEP), the U.S. Congress, the U.S. Food and Drug Administration (FDA), Health Canada, and other government bodies around the globe.

We recently reviewed hundreds of scientific studies and research articles and produced a detailed position paper against fluoridation that features over 500 citations supporting the potential for fluoride to cause adverse health outcomes. A summary of our official position is that **given the elevated number of fluoride sources and the increased rates of fluoride intake in the American population, which have risen substantially since water fluoridation began in the 1940's, it has become a necessity to reduce and work toward eliminating avoidable sources of fluoride exposure, including water fluoridation, fluoride-containing dental materials, and other fluoridated products.**

We implore you to read our full position paper, which can be found online at <https://iaomt.org/wp-content/uploads/IAOMT-Fluoride-Position-Paper.pdf>. Additional resources about fluoride from the IAOMT can be accessed at <https://iaomt.org/resources/fluoride-facts/>. You might also be interested in the Fluoride Action Network (FAN)'s [Professionals Statement to End Water Fluoridation](#), which has been signed by over 4,000 medical, dental, scientific, and environmental professionals. **It is further imperative for you to review two new research studies (2019 and 2020) linking fluoride with adverse effects on children's intellectual development.** Please feel free to contact us at info@iaomt.org or (863) 420-6373 if we can further assist you in understanding that fluoridation is an outdated, dangerous practice with the potential to harm your citizens and your community at large.

Sincerely,

A handwritten signature in black ink that reads 'David Kennedy DDS'.

David Kennedy, DDS, MIAOMT

A handwritten signature in black ink that reads 'John Kall DMD'.

John Kall, DMD, FAGD, MIAOMT

A handwritten signature in black ink that reads 'E. Griffin Cole'.

E. Griffin Cole, DDS, NMD, MIAOMT

Date: October 6, 2020

To: Green Bay, WI Mayor Genrich, Common Council; Alderpersons and Protection and Policy Committee

From: Dione Snitker – Mother, Grandmother

REGARDING: COMMUNITY WATER FLUORIDATION – REASONS I SUPPORT IT

First I want to thank you for your efforts to ensure Green Bay, WI remains a city that is safe for its residents and those who visit. I appreciate your thorough, scientific review into the safety of community water fluoridation. I also thank you for your insight to hear from those of us who have experienced life with and without community water fluoridation. It is paramount when making one of Green Bay's most important contributions to the health of its citizens and visitors.

I believe and know community water fluoridation, prevents tooth decay, protects all ages against cavities, and saves money for those who are privileged enough to have it. I can attest to these statements as my family and I have experienced life with and without community water fluoridation. As brief as I can, I'd like to share our experience.

I grew up on a farm, our water came from a deep well and there was no added fluoride. My parents took us to the dentist yearly, however my siblings and I suffered from multiple toothaches and cavities each year. I specifically remember having five fillings during one visit, and having each tooth filled without any pain medication. Our dentist didn't give shots for pain unless you wiggled too much, however he allowed you to lift your hand when you felt pain and he would stop drilling for a minute or two. Needless to say, I remember my cavities and fillings.

Once married, my family continued rural living without fluoride added to the water. We took our boys to the dentist twice a year, however they also suffered multiple cavities yearly. During one visit when our oldest son was six or seven, our dentist said he had six cavities, so we made the filling appointments. Returning for the second visit to fill his teeth, we literally had to chase our son down in the parking lot to get him in the dentist office. It was a horrible feeling knowing the pain and fear he faced yet still forcing him in the office to get his teeth filled. I do not wish that on any child or parent, especially when so much can be prevented with access to fluoridated water.

A year later we moved to Denver, Colorado, where fluoride is added to the water. I didn't know anything about community water fluoridation at the time. However, I can tell you our family saw a substantial decline in cavities. We never had another dental visit with six cavities between the four of us. We still had a few cavities now and again, but the change was significant. Even when the boys had braces, they had few cavities. Not only did we not have the pain, we saved hundreds of dollars each year in the cost of dental care. This savings was desperately needed at the time.

Community Water Fluoridation makes a huge difference. I am very thankful for and commend those who had and have the insight and power to make decisions to add fluoride to community water sources. Please continue to support your citizens' oral health by voting in favor of community water fluoridation. Thank you, for your time and consideration to continue community water fluoridation.



90 Years of Caring for Children—1930–2020

October 5, 2020

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Sara H. Goza, MD, FAAP
President

SHG/hr

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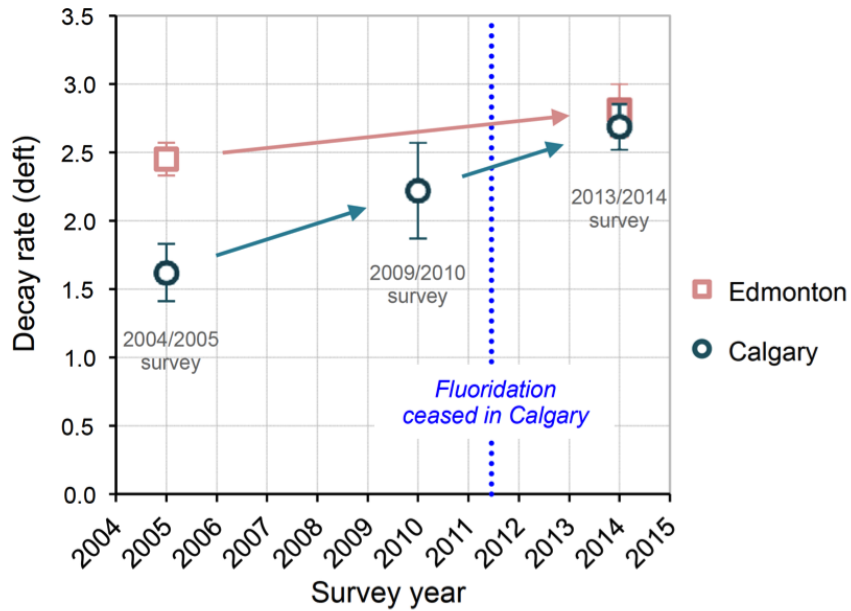
² Fluoride Use in Caries Prevention in the Primary Care Setting. *Pediatrics*. 2014;134(3): 626-633.

³ Early Childhood Caries in Indigenous Communities. *Pediatrics*. 2011;127(6):1190-1198.

From: Neurath et al, Limitations of fluoridation effectiveness studies: Lessons from Alberta, Canada, 2017

<https://onlinelibrary.wiley.com/doi/abs/10.1111/cdoe.12329>

(B) Decay rates over time in Calgary and Edmonton (deft)



For Agenda: The Importance of Community Water Fluoridation ⓘ



B

Boeckman, Julie <julie.boeckman@health.mo.gov>

22 MINUTES



To: 'Eric.Genrich@greenbaywi.gov', 'district1@greenb... Cc: 'celestineje@gr...

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I hope this email finds you well. I'm Julie Boeckman and the Program Manager of Missouri's Office of Dental Health. I've also been in public health for nearly 20 years. I've also grown up hearing about the benefits of water fluoridation. I'm also a mom to two beautiful, healthy, intelligent young adults who have consumed fluoridated water their whole lives. My son had his first cavity at the age of 19 and my daughter has yet to have one and she is nearly 18 years old.

I have grown up knowing community water fluoridation is safe and effective. My mom has touted it for years, saying how lucky I was that I was growing up in a community with water fluoridation and even toothpaste with fluoride in it.

The optimal amount of fluoride in drinking water is 0.7 ppm, this is the equivalent of 1 penny in \$14,000.

Over 100 national & international health organizations, ADA, CDC, WHO, American Academy of Pediatrics, just to name a few endorse and tout the benefits of water fluoridation.

I hope Green Bay continues to fluoridate the water. Thank you for your time. Take care.

Julie Boeckman
Program Manager, Office of Dental Health
Missouri Department of Health & Senior Services
PO Box 570
Jefferson City, MO 65102
Phone: 573-751-6249
Fax: 573-751-0702
Email: julie.boeckman@health.mo.gov

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Add a comment...

Fluoridation: Nature thought of it first

By Kurt Ferre DDS
Protection & Policy Committee
Green Bay, WI
October 8, 2020



Volunteering: 23 Years Later





Public Health

- Goal is to improve the health of a population
- It values the “collective good”
- 3 Criteria to justify public health measure:

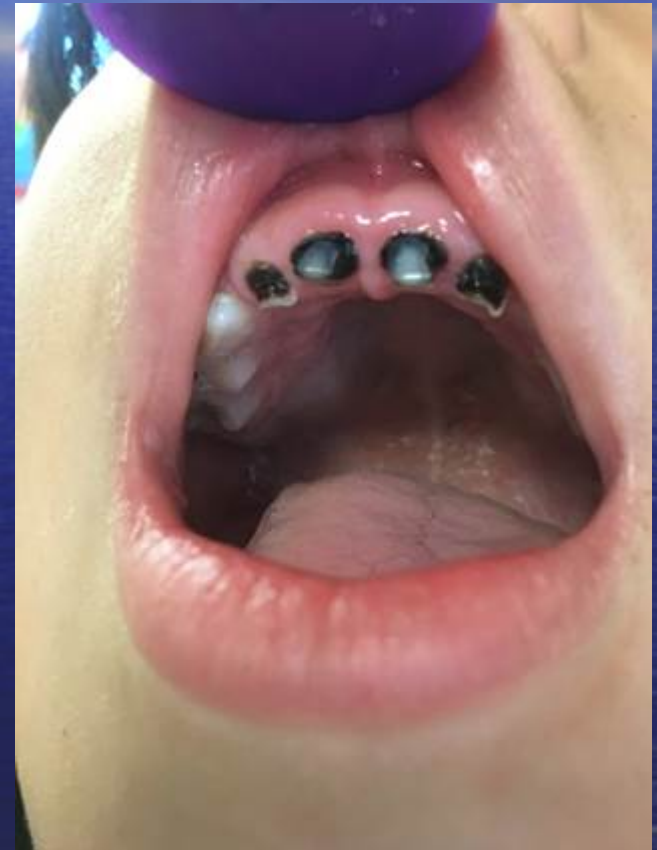


Public Health

- 3 Criteria to justify public health measure:
 1. reduction of ill health
 2. reduction of health disparities
 3. concern for children who constitute a vulnerable group

Oral Disease “Learnings”

- Cannot have good health without good oral health
- Healthy kids learn better
- Cannot drill our way out of this “mess”
- Prevention is key





Water Fluoridation: **Definition**

Fluoridation is the adjustment, either upward or downward of the existing naturally occurring fluoride levels in drinking water to an optimal level that has been determined by our public health experts in the U.S.



Water Fluoridation: **History**

Fluoridation has been practiced in the U.S. for **75 years.**

Grand Rapids, Michigan, fluoridated its public water supply on **January 25, 1945.**

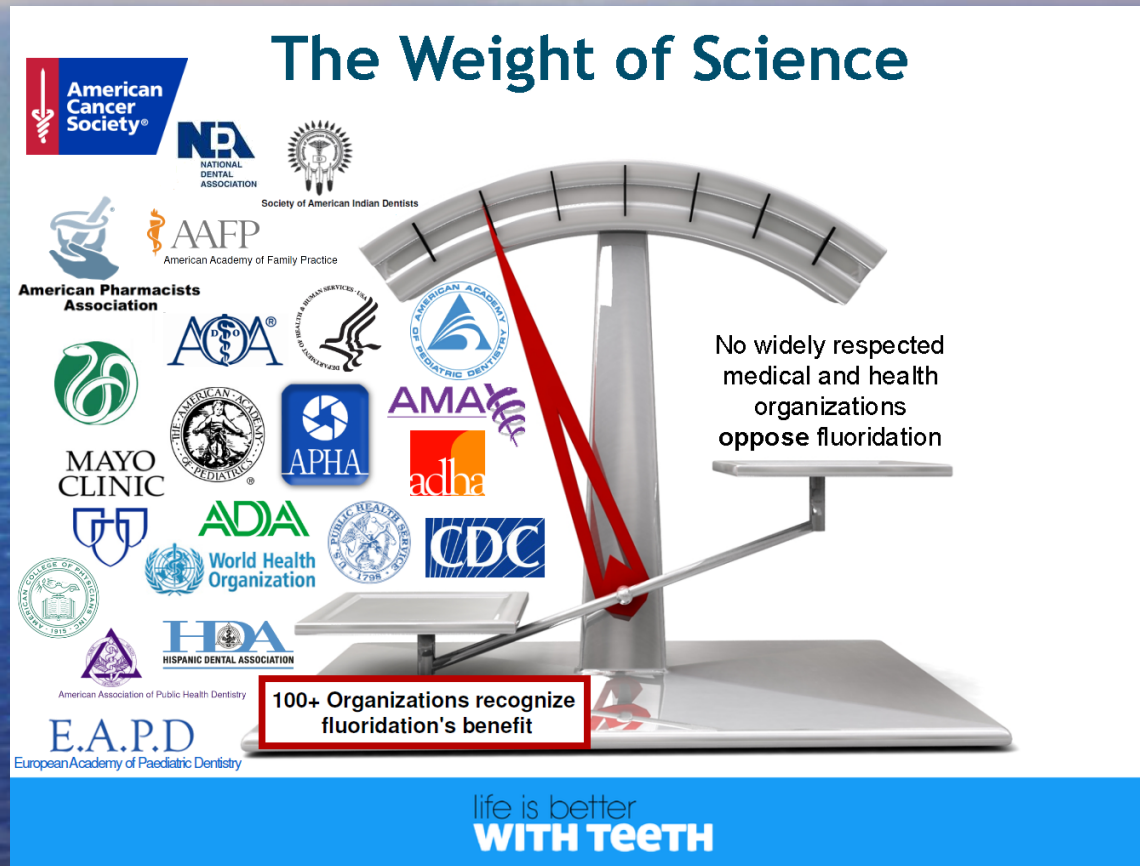
#Fluoride4health75



Scientific Consensus

- “It’s part of why scientific consensus is so remarkably valuable: it only exists when the overwhelming majority of qualified professionals all hold the same consistent professional opinion.”

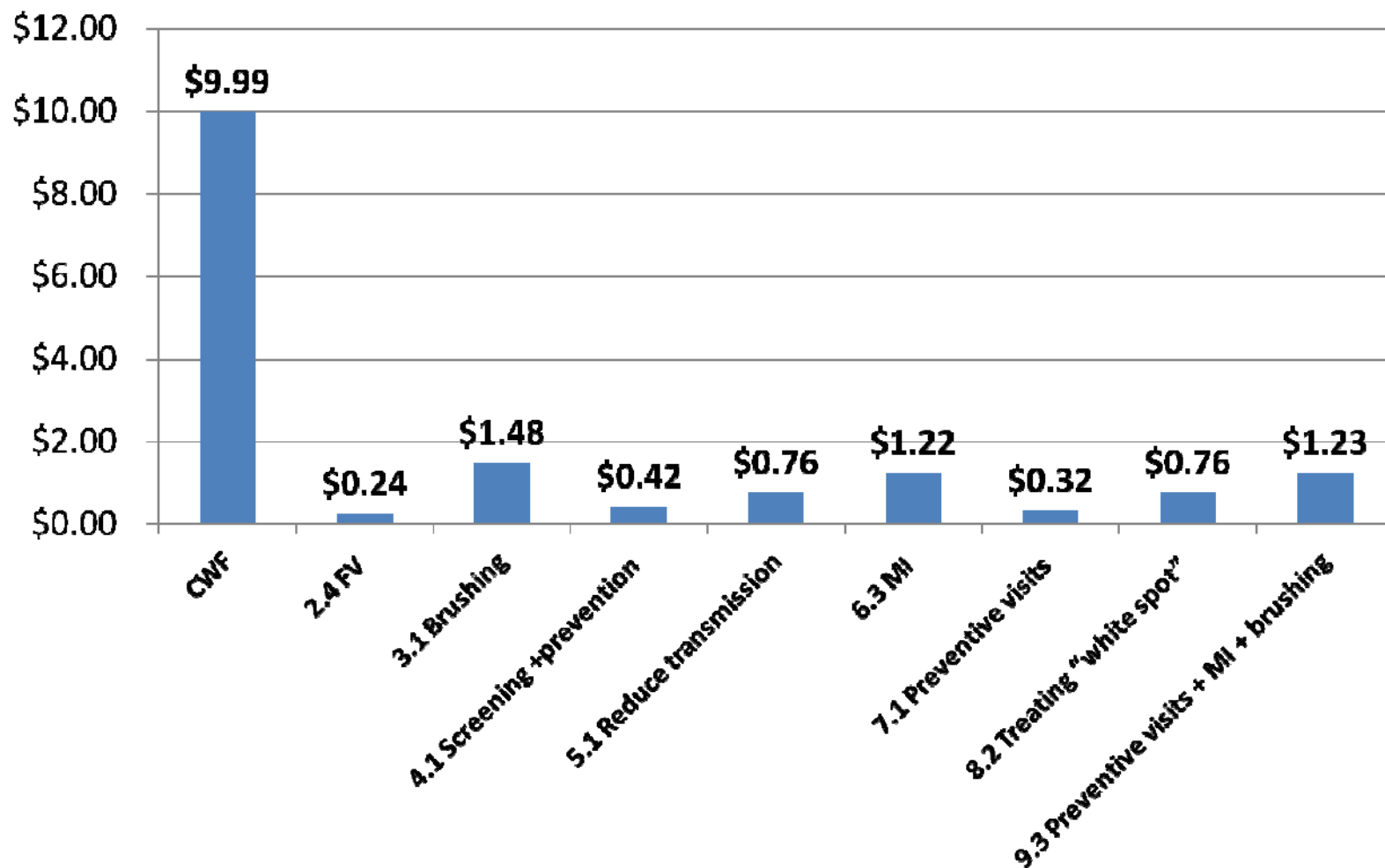
Overwhelming Scientific Consensus



Application of Systems Dynamic Modeling for Prevention of Early Childhood Caries

Jayanth Kumar, DDS, MPH
New York State Department of Health
National Oral Health Conference, 2014. Fort Worth, TX

Relative Payback for \$1 Invested





Toxicity: Dose Related

- “All Substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy.”

Water Can Be Toxic!

...died of hyponatremia, a rare condition caused by overdosing on water.

The Press Republican **Plattsburgh, New York**

05/01/03

Water intoxication rare but dangerous

By ANNA JOLLY, Staff Writer

PLATTSBURGH — Walter Dean Jennings died of hyponatremia, a rare condition caused by overdosing on water.

Jennings, an 18-year-old pledge of the unrecognized Psi Epsilon Chi organization at Plattsburgh State, was forced to drink large amounts of water that eventually caused his brain to swell.

He died March 12 after he was treated at hospitals in Plattsburgh and Burlington.

Plattsburgh City Police Chief Desmond Racicot said Wednesday that he was not sure how much water Jennings was forced to swallow during his 10-day pledge cycle, although he described it as "pitchers and pitchers" given through a funnel.

Water intoxication or overhydration occurs when a person swallows enough water to significantly lower the amount of sodium in the blood.

The sodium imbalance produces a decreased level of consciousness that ranges from lethargy to stupor to coma and even death.

Symptoms of water overdose include drowsiness, nausea, vomiting, headache and possible seizures.

According to Web MD, a person would have to chug about three quarts or more of water at one time to overdose.

Infants and small children are most vulnerable to water intoxication because of their lower blood volume and body weight.

The condition is rare among adults, but dehydrated marathon runners with depleted sodium levels have suffered from water-intoxication seizures.

Overhydration has recently been linked to a child-abuse case in Salt Lake City where a 4-year-old girl died.

Water intoxication is also becoming more common among some Greek organizations because binge-drinking water is seen as less dangerous than chugging alcohol.

Racicot said water intoxication and other forms of physical and mental hazing were used throughout the 10 days Jennings pledged.

He was in his last day of pledging March 12 when he was rushed to CVPH Medical Center in an unresponsive state.



3 Key Observations

- It's much easier to scare the public than to un-scare the public.
- The support for fluoridation is a mile wide, but the passion is an inch deep while the opposition support is an inch wide,.....
- Stopping a fluoridation program can be as difficult as starting a fluoridation program.

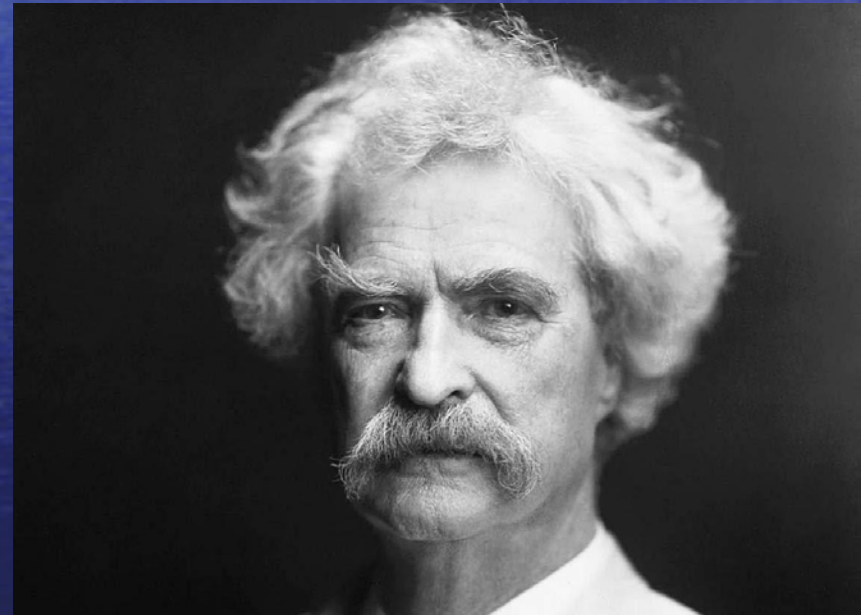


Understanding Fluoridation Politics

- “A lie can travel halfway around the world while the truth is putting on its shoes”.

Mark Twain

1835-1910



Fluoridation Fib

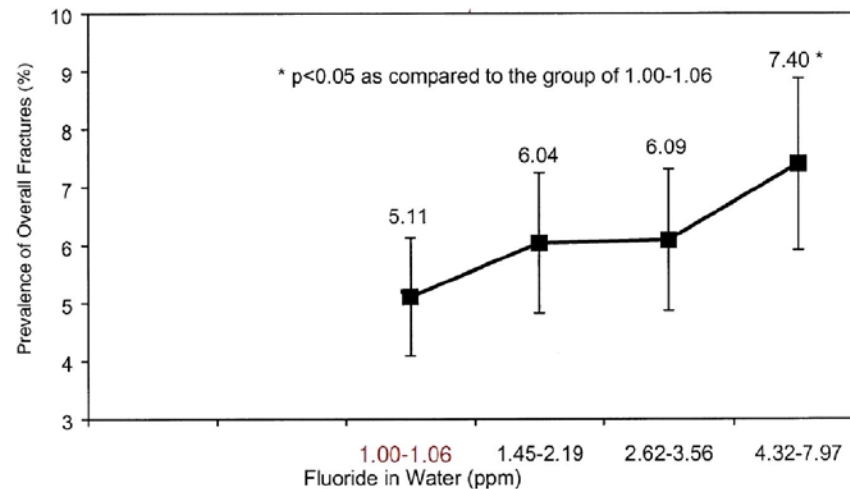
What the Fluoride Action Network Cites

Journal of Bone and Mineral Research
JBMR

J Bone Miner Res. 2001 May;16(5):932-9.

Effect of long-term exposure to fluoride in drinking water on risks of bone fractures.

Li Y, et al Center for Dental Research, Loma Linda University School of Dentistry, California 92350, USA.



Fluoridation Fib

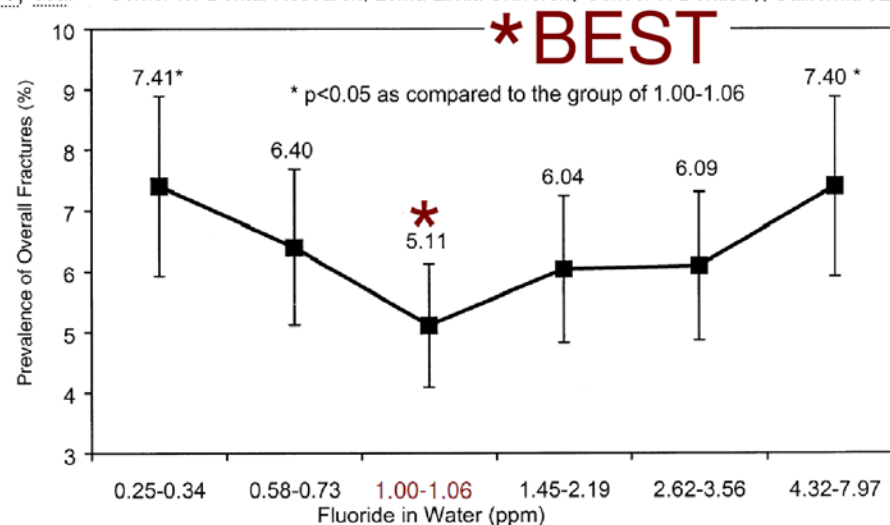
The Rest of the Story

Journal of Bone and Mineral Research
JBMR

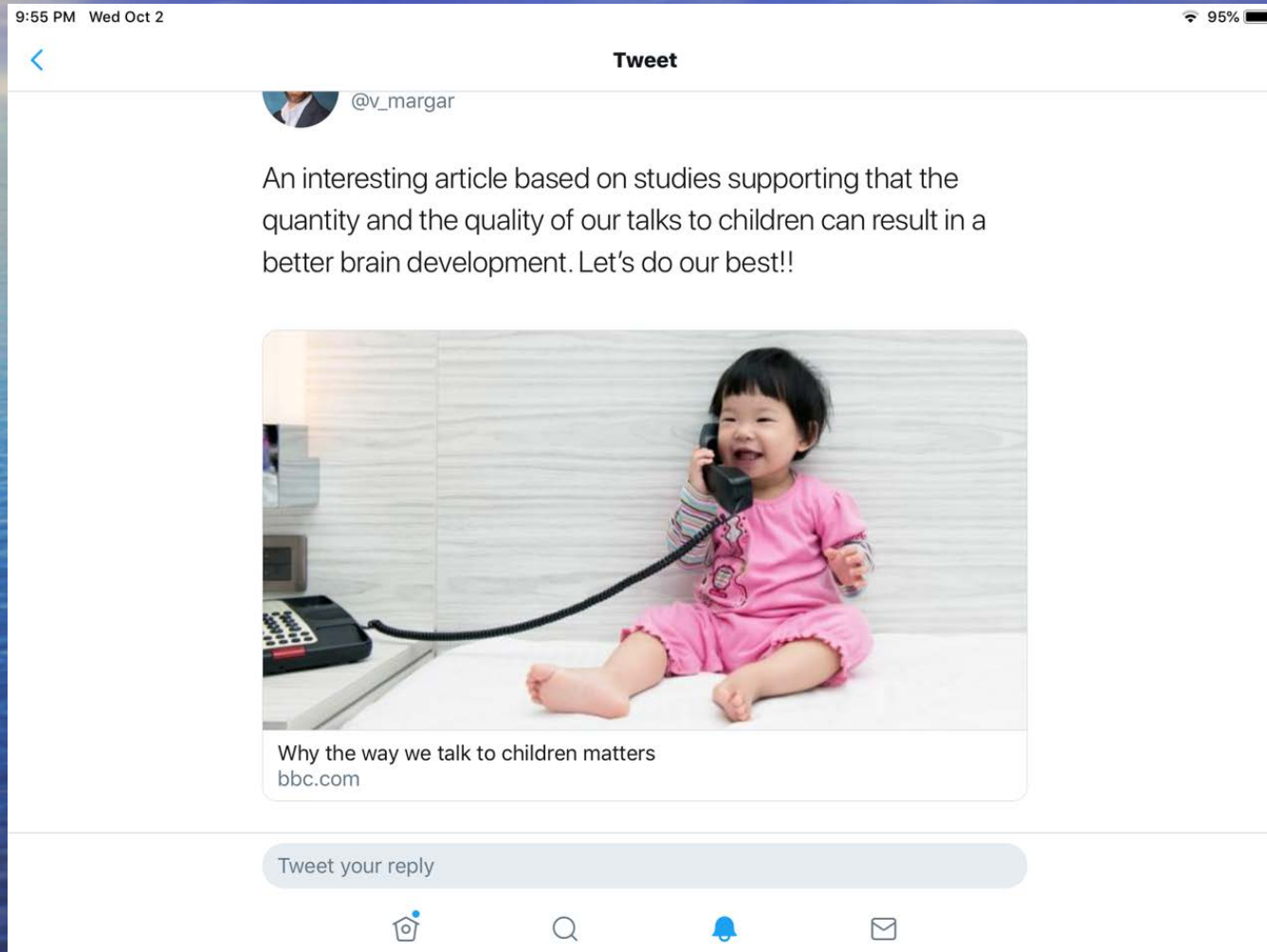
J Bone Miner Res. 2001 May;16(5):932-9.

Effect of long-term exposure to fluoride in drinking water on risks of bone fractures.

Li Y, et al. Center for Dental Research, Loma Linda University School of Dentistry, California 92350, USA.



IQ and Talking to Your Child



From K. Ferré Twitter Page

Fluoridation = Prevention for All

“In a perfect world we would not need safety net dental clinics or fluoridation. We do not live in that world.”

Charlie LaTourette, Past E.D.,
Dental Foundation of OR



Missouri Department of Health and Senior Services

P.O. Box 570, Jefferson City, MO 65102-0570 Phone: 573-751-6400 FAX: 573-751-6010
RELAY MISSOURI for Hearing and Speech Impaired and Voice dial: 711

Randall W. Williams, MD, FACOG
Director



Michael L. Parson
Governor

October 7, 2020

Members of the Common Council

Green Bay, Wisconsin

To whom it may concern:

As the State Dental Director of Missouri, I would like to take this opportunity to voice my support for Community Water Fluoridation in Green Bay. Removal of the fluoride from the water supply will have a profound negative effect on the oral health of the children and adults in your community. Even those groups that are against water fluoridation will admit that removing the fluoride will result in at least 1 additional filling per person per year. The research done in Juneau, Alaska showed higher numbers of new tooth decay among the Medicaid population in that area.

Let's look at what one filling per person per year will look like in Green Bay. The population of your city is listed at 104,000 people. We know from the American Dental Association that about 40% of the population don't receive regular dental care so for the purposes of this estimate we can remove them, so the population actively seeing dental care will be about 62,400.

Have you been to the dentist lately, a single surface tooth colored filling will set you back at least \$135! Now if you have dental insurance you will probably only have to pay 20% of that fee. Many families are unemployed and have lost their dental benefits and it would not apply to them. So annually in Green Bay there will be an increase of \$8,424,000 of new dental services, which is probably not subject to sales tax in your community. If you look at the effect on families if you have a family of 4 that is an unexpected expense of \$540. That is \$540 that the family won't have to spend on other normal expenses in the community.

The ADA has said that for every dollar spent on fluoridating the water in your community you will get at least \$20 return on investment. Please consider the effects on people in your community and keep water fluoridation for your City.

Respectfully,

John N. Dane, DDS
Dental Director
Missouri Department of Health and Senior Services.

www.health.mo.gov

Healthy Missourians for life.

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AN EQUAL OPPORTUNITY / AFFIRMATIVE ACTION EMPLOYER: Services provided on a nondiscriminatory basis.

October 6, 2020

Members of the Green Bay Protection and Policy Committee:

On behalf of the Academy of General Dentistry (AGD) and its over 40,000 members, including more than 600 that make up the Wisconsin AGD (WIAGD), I am writing to express our strong support of community water fluoridation (CWF).

The AGD was founded in 1952 and has grown to be the second largest dental association, proudly working to address the most pressing issues that face general dentistry. General dentists are the primary oral health care providers for patients of all ages, and take responsibility for the diagnosis, treatment, and coordination of services to meet patients' oral health needs. Approximately 82% of Wisconsin's licensed dentists are general dentists.

We work diligently to advocate for effective policies that will most benefit the oral health care of patients and the public. Among our top priorities is increasing access to oral health care in every community, which cannot be solved by any one silver bullet, but is a multipronged approach. Many barriers to oral health care are complex and timely in terms of identifying effective and equitable solutions. However, CWF is one of the single most effective ways proven to prevent dental caries (cavities) and accessible to every single community member regardless of other barriers to care they may face.

Through 75 years of practice and decades of research, CWF is proven to be effective and safe in reducing dental caries in both children and adults. The evidence surrounding CWF is why the Center for Disease Control and Prevention (CDC) named it one of [ten great public health achievements of the 20th century](#). Nearly all credible health organizations recognize CWF's efficacy alongside the CDC, despite the many attempts by opponents to discredit and denounce it.

Several studies have demonstrated how the removal of fluoridation from public water supplies can negatively impact members of that community. [BMC Oral Health published a peer-reviewed research article](#) that compared average caries-related procedures and treatment costs in Juneau, Alaska, before and after discontinuing their CWF. Results showed the study population in 2003, during optimal CWF, was 25.2% less likely to receive dental caries procedures than in 2012, almost six years post-CWF cessation. The difference between children seven years and younger was significantly greater than that of the entire study population.

It is most important to note that results were based off Medicaid dental claim records from Medicaid-eligible residents of Juneau. This data represents children and adolescents whose family's income is no more than 150-200% of the Federal Poverty Level: one of the most vulnerable populations in today's society. This does not even touch on adults, who States are not required to provide any oral health benefit to under their Medicaid program. This does not touch on how COVID-19 and the current state of

our nation has created additional barriers. Finally, this does not touch on the wide range of residents who may have been benefitting from CWF but simply didn't fall into this study's population.

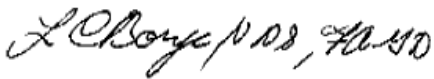
With optimal levels of water fluoridation, all members of the Green Bay community, and the four communities who purchase their water from Green Bay, have the opportunity to protect their teeth regardless of age, race, income or barriers to oral health care. We respectfully urge the Committee and City of Green Bay to continue fluoridating its public water system. We ask that you stand with us in protecting the oral health of your community.

Thank you for allowing the AGD to express our support of CWF and we appreciate your consideration in advance. If you have any questions, please contact our Government Relations staff at ninia.linero@agd.org.

Regards,



Connie White, DDS, FAGD
President
Academy of General Dentistry



Lou Boryc, DDS, FAGD
President
Wisconsin Academy of General Dentistry

Date: October 6, 2020

To: Green Bay, WI Mayor Genrich, Common Council; Alderpersons and Protection and Policy Committee

From: Dione Snitker – Mother, Grandmother

REGARDING: COMMUNITY WATER FLUORIDATION – REASONS I SUPPORT IT

First I want to thank you for your efforts to ensure Green Bay, WI remains a city that is safe for its residents and those who visit. I appreciate your thorough, scientific review into the safety of community water fluoridation. I also thank you for your insight to hear from those of us who have experienced life with and without community water fluoridation. It is paramount when making one of Green Bay's most important contributions to the health of its citizens and visitors.

I believe and know community water fluoridation, prevents tooth decay, protects all ages against cavities, and saves money for those who are privileged enough to have it. I can attest to these statements as my family and I have experienced life with and without community water fluoridation. As brief as I can, I'd like to share our experience.

I grew up on a farm, our water came from a deep well and there was no added fluoride. My parents took us to the dentist yearly, however my siblings and I suffered from multiple toothaches and cavities each year. I specifically remember having five fillings during one visit, and having each tooth filled without any pain medication. Our dentist didn't give shots for pain unless you wiggled too much, however he allowed you to lift your hand when you felt pain and he would stop drilling for a minute or two. Needless to say, I remember my cavities and fillings.

Once married, my family continued rural living without fluoride added to the water. We took our boys to the dentist twice a year, however they also suffered multiple cavities yearly. During one visit when our oldest son was six or seven, our dentist said he had six cavities, so we made the filling appointments. Returning for the second visit to fill his teeth, we literally had to chase our son down in the parking lot to get him in the dentist office. It was a horrible feeling knowing the pain and fear he faced yet still forcing him in the office to get his teeth filled. I do not wish that on any child or parent, especially when so much can be prevented with access to fluoridated water.

A year later we moved to Denver, Colorado, where fluoride is added to the water. I didn't know anything about community water fluoridation at the time. However, I can tell you our family saw a substantial decline in cavities. We never had another dental visit with six cavities between the four of us. We still had a few cavities now and again, but the change was significant. Even when the boys had braces, they had few cavities. Not only did we not have the pain, we saved hundreds of dollars each year in the cost of dental care. This savings was desperately needed at the time.

Community Water Fluoridation makes a huge difference. I am very thankful for and commend those who had and have the insight and power to make decisions to add fluoride to community water sources. Please continue to support your citizens' oral health by voting in favor of community water fluoridation. Thank you, for your time and consideration to continue community water fluoridation.

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:29 AM
To: Jaime Fuge
Subject: Fwd: Water fluoridation issue: "New Science"
Attachments: Letter to Green Bay Mayor and Common Council_7-16-2020.pdf; ATT00001.htm; Letter to Green Bay Mayor and Common Council_7-16-2020.pdf; ATT00002.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: July 16, 2020 at 3:31:28 AM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: "celestineje@greenbaywi.gov" <celestineje@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Water fluoridation issue: "New Science"

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLest,

I am writing to you regarding the fluoridation issue that is before you, the "new research". In 2017, this issue was brought before the common council and I was asked to come to help present the credible science which supported fluoridation then as effective and safe. I am pleased to report that ongoing research continues to show the same. I am a scientist, but I am also a son, father, and grandfather. I would not support a public health measure if it were not supported by solid, credible science that has been repeated, validated, and shown to be clinically relevant. 75 years of fluoridation in the U.S. has produced over 6,600 research projects and papers that are available on Pubmed. The preponderance of the evidence supports the effectiveness and safety of fluoridation. Fluoridation is the closest thing that we have to a vaccination against the dental disease of cavities. It reduces cavities by 25% above and beyond those already reduced by fluoridated toothpaste, mouth rinses, and professionally applied fluorides (dental office). All of these are needed. One does not replace the other. Just as when airbags were invented. We didn't stop wearing seatbelts. They work together to provide more prevention. The same is true for the different forms of fluoride. Water fluoridation is the only preventive dental care that some

people will ever receive in our communities.

Fluoridation Cessation:

Ceasing water fluoridation has been well documented. It is extremely sad and unfortunate. Three recent, high-quality studies have been conducted in Juneau, Alaska, Calgary, Alberta, Canada, and Windsor, Ontario, Canada.

1. Juneau's children under the age of 7 years old Medicaid (low income) data was compared before and after water fluoridation stopped. What was found was an increase of one more cavity related procedure/child/year in the group that had no fluoridated water. Consider a preschool class of 30 kids before fluoridation ended compared with a class of 30 after it stopped. In the first year, the class w/o fluoride would have 30 more cavity related procedures than the pre-cessation class. Next year it would be 60 more (30+30), and the third year 90 more (30+30+30) cavity related procedures (fillings, root canals, crowns, etc).

2. Calgary, Alberta, Canada: Just three years after fluoridation was stopped, a study was done to examine the changes in cavities in 2nd grade children. Edmonton, a fluoridated city to its north, was used as the comparison city. While cavities were going up in both cities, the cavity rates in Calgary shot up 146% (when fluoridation stopped) when compared with continuously fluoridated Edmonton. A second study is nearing completion which would capture kids born after the cessation. In the first study, the children had benefitted from fluoridation before it was stopped. From what dentists are seeing there since the cessation in 2011, cavities are out of control. Hospitalizations of children for full mouth dental care under general anesthesia has skyrocketed.

3. Windsor, Ontario, Canada: The city council had decided to stop fluoridation in 2013. However, they made a request of the health unit: Keep statistics of adults and children for five years and come back and report to us. In December 2018, the city council asked the Medical Officer of Health, Dr. Wajid Ahmed, to present the findings. During the time of cessation, cavities and emergency dental needs climbed 51%. Adults showed similar results. After hours of testimony, the city council voted 8-3 to return fluoridation.

I know the authors of the studies of the first two studies, Dr. Jennifer Meyer (Juneau) and Dr. Lindsay McLaren (Calgary). I also know Dr. Ahmed (Windsor) very well. I was asked to testify in Calgary last October and in Windsor in Dec. 2018. All of these folks would be happy to share their research with you and questions that you may have. I am very familiar with their studies. If there's something that I or my colleagues in AFS can't answer, we will get an answer to you within 24 hours. Dr. Jennifer Meyer is on our Science Advisory Committee.

I've attached an email letter that discusses the "new study" that has been presented to you, the Canadian study on fluoridation and IQ. I've limited my discussion to this study, as well as the evaluations of it by credible scientific bodies. I have not included two other studies/abstract which have shown that fluoride in water at levels of fluoridation show zero effects on IQ (2017, Aggeborn and Ohman), and another (2019, Santa-Marina et al) which showed that fluoridation resulted in increased IQ. I would be happy to discuss and supply these to you.

Please do not hesitate to contact me with any questions. Our group, the American Fluoridation Society, is listed on the CDC's website as a professional organization recognizing the benefits of community water fluoridation. We are also listed on the American Dental Association's website in the same manner. The American Fluoridation Society is an all-volunteer group of healthcare providers who disseminate credible and accurate literature on community water fluoridation. We

do not accept any money for our efforts. We do this work because we will not allow a handful of people with the internet to broadcast their messages to create fear in our country's families. Especially pregnant mothers. We live in a democratic society, one in which the greater good of all is placed first and foremost. Public policy cannot be tailored for the few who do not want it. Whether it is water fluoridation, stopping at a traffic light, stopping at a crosswalk for children at school, paying for public roads, or wearing a seatbelt, public health exists for the safety and well-being of everyone in the community.

Please do the right thing and keep Green Bay fluoridated. For your review, I've included the outstanding members of our Scientific Advisory Committee below. They are some of the top researchers on fluoridation in the world. Our Board of Directors is also listed.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

American Fluoridation Society's Board of Directors and Advisory Committees

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Pediatric Dentist

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Dental Hygienist
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Centers for Disease Control and Prevention

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University of Birmingham School of Dentistry,
former national lead for water fluoridation with
Public Health England and regional consultant for
the Midlands and East of England

Howard Pollick, BDS, MPH

Professor, Preventive & Restorative Dental Sciences
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Oral Health Services, Former Director of Brisbane
Dental Hospital

Timothy Wright, MS, DDS

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at the UNC Adams School of Dentistry, Chapel Hill,
NC

Jennifer Meyer, PhD, MPH, CPH, RN

Assistant Professor of Health Sciences, University of
Alaska Anchorage, AK



July 16, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I am writing to you regarding the water fluoridation issue that is before you. Some of you may recall that I was asked to come to Green Bay in 2017 as a subject matter expert on community water fluoridation (CWF) when it was being challenged back then. Thankfully, credible science won out over personal opinions of those attempting to stop it.

The current topic before you is about the "new science" since that meeting in 2017. As such, I will limit my discussion to that topic. However, I am available to answer any questions that you may have about this or other studies. Many of the authors and/or co-authors are good friends or good acquaintances of mine. Their input is readily available from them directly, or through information that they've shared with me.

From personal experience, I know that your inboxes are going to be filled with emails from others trying to sway you from providing this proven effective and safe public health measure to all of your residents. Trust me and the hundreds of thousands of scientists and researchers worldwide when I say that the day that the overwhelming body of credible scientific evidence shows a harm from the miniscule amount of fluoride in CWF, we will be the first ones shouting from the mountain tops to stop it. As medical and dental healthcare professionals, we provide care for you, your children, parents, grandparents, and grandchildren. We would not do anything to put their health in peril. I'm a son, father, and grandfather. My family all drinks optimally fluoridated water daily. I would not hurt my family just as I would not hurt your family.

Background:

A little about me. I practiced in Palm Harbor until I became disabled from a bicycle accident. The abrupt end of my career was difficult to wrap my head around, but as my pastor advised me, "the good Lord didn't push you off the bicycle, but he's laid opportunities out in front of you. Open your eyes."

In 2011, I was directed to take action when our Pinellas County Board of County Commissioners voted 4-3 to cease water fluoridation to over 700,000 residents. I was in disbelief. These were our elected officials that were entrusted with making decisions about health and safety issues for our residents every single day. And here, four of them chose to listen to a handful of vociferous opponents to water fluoridation over the proven effectiveness and safety of it. Leading health and medical groups around the world endorse and recognize community water fluoridation as effective and safe for everyone, regardless of age, race, ethnicity, socio-economic status, level of education, or access to dental care. Not a single credibly recognized health or medical organization in the world opposes water fluoridation. Not one.

My Masters of Science thesis and research project at the University of North Carolina, Chapel Hill, was on the content of fluoride in infant formula, water fluoridation, and fluorides. I was asked to lead the re-fluoridation effort in Pinellas County because of my background in fluoridation.

Sadly, it took two of the four county commissioners who had voted against CWF and were running for reelection to be voted out of office. The sole issue in the election for the candidates who ran to replace them was to restart CWF the first day they were in office. And that they did. Fifteen months after CWF had been halted, the fluoride faucet was turned back on.

The media that covered this issue wrote a 10-part editorial series on this cessation and the solid science behind CWF. They won a Pulitzer Prize for their editorial series.

The new science:

The new science that was brought before you on CWF was from a study conducted in Canada on urine samples that had been collected as part of a different large study. The "new science" is about CWF and IQ effects:

"Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada", *Rivka Green, MA; Bruce Lanphear, MD; Richard Hornung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Raichel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD*

Of primary importance is what the primary author, Christine Till, and a co-author, E. Angeles Martinez Mier, had to say about this study and pregnant mothers drinking CWF. The following slide communicates this appropriately and contains hyperlinks to their public statements:

What did Till and Martinez-Mier have to say?

August 19, 2019: *Christine Till, lead author*

Pregnant women should consider reducing their exposure to fluoride, Till said. That might include **avoiding public water sources that are fluoridated...**

September 7, 2019: *Angeles Martinez-Mier, co-author*

That **DOES NOT MEAN** eliminating CWF, which benefits all and is the only public health program that is viable in the US given our current healthcare system. I disagree with Christine (Till)

September 14, 2019: *Christine Till*

"I think this message could be easily misconstrued as us saying don't drink fluoridated water -- **we're not saying that**," study author Christine Till, professor of psychology at York University in Toronto, told BuzzFeed News.



fluoride is essential for strong bones and teeth. It is added to public water supplies in the United States to help prevent tooth decay. Fluoride is also found in toothpaste, mouthwash, and some foods. It is important to use fluoride products correctly to get the most benefit.

The primary author, Till, first stated pregnant mothers might avoid fluoridated water. Here is a statement made to NPR, August 19, 2019, on the magnitude of IQ loss across the world:

- *"We would feel an impact of this magnitude at a population level," Till says. "because you would have millions of more children falling in the range of intellectual disability, or an IQ of under 70, and that many fewer kids in the gifted range."*
- After that statement, a co-author, Angeles Martinez-Meir, spoke out on what was being stated and that she disagreed with Till. Martinez-Meir stated that pregnant mothers *can* drink CWF (September 7, 2019).
- One week after Martinez-Meir's statement, Till reversed her position on pregnant mothers drinking CWF. Till stated *"I think this message could be easily misconstrued as us saying don't drink fluoridated water-we're not saying that"*.

To summarize, the primary author and a co-author on this study being presented to the Green Bay Common Council as 'new research' to show that CWF causes IQ deficits is not even being stated as such by Till and Martinez-Meir. With those words from the study's authors themselves, how can those who oppose CWF present this to you, the Green Bay Common Council, as anything different than what the authors themselves had to say?

What ensued after the publication of the Green et al study:

Green et al deny access to their data:

- Academicians, researchers, and others around the world requested the raw data from the Green et al study so that they could run independent statistical analyses. They had concerns with the data and the conclusions reached from that data. Sharing of data is commonplace in research:
- *"Sharing research data:
As a researcher, you are increasingly encouraged, or even mandated, to make your research data available, accessible, discoverable and usable."*

The Green et al paper, published in JAMA Pediatrics, contained the following statement:

Author Contributions: Ms Green and Dr Till had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ms. Green and Dr. Till stated that they **had full access** to all of the data in the study. *However*, when asked for their data, they denied they had it. They would not share it. Increasingly, their denial led worldwide scientific researchers and academicians to demand that it be shared. The study was funded by the National Institute of Environmental and Health Sciences (NIEHS).

A national and international group of 30 prominent researchers, academicians, and others co-signed a letter to the NIEHS asking to have this data released. They extensively detailed their concerns that they had with the study, and asked that the NIEHS ask the authors to release this data to allow for independent analyses.

Canadian Agency for Drugs and Technologies in Health (CADTH) review Green et al study:

CADTH is an independent, not-for-profit organization responsible for providing health care decision-makers with objective evidence to help make informed decisions about the optimal use of health technologies. Created in 1989 by Canada's federal, provincial, and territorial governments, CADTH was born from the idea that Canada needs a coordinated approach to assessing health technologies. The result was an organization that harnesses Canadian expertise from every region and produces evidence-informed solutions that benefit patients in jurisdictions across the country.

CADTH conducted a review of the Green et al study. This review included many other studies and their reviews of them as well.

- "CADTH RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects", October 23, 2019, made the following statements on the Green et al study (a few of numerous statements regarding the study's limitations):
- *"The study by Green et al., 2019¹⁵ concluded that 'maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.' (p. E1) This conclusion was not supported by the data."*
- *"No attempt was made to control for potential important confounding factors including parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, child's health status, and other confounders between birth and the children's age of 3 or 4 when IQ was measured.^{18,19} Although the authors controlled for and performed sensitivity analysis to test the robustness of association estimates for a number of substances (including lead, mercury, arsenic) in the mothers' blood samples, they did not consider postnatal exposure of children to these substances. Lead, in particular has been found to have a high association with IQ in children.²³ With incomplete control for potential confounders, it remains uncertain to know if the effect is true, and if it is due to prenatal exposure or postnatal exposure."*
- *"The evidence is weak due to multiple limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors); therefore, the findings of this study should be interpreted with caution."*

Toxicology Systematic Review on fluoride toxicity and neurotoxicity:

A comprehensive, systematic review on the toxicity of fluoride and evidence for human developmental neurotoxicity was published a few months ago in a prestigious toxicological journal:

REVIEW ARTICLE

"Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses", Guth et al, Archives of Toxicology, 26 March 2020

In this Review, the researchers concluded that:

- *"based on the totality of currently available scientific evidence, the present review does not support the presumption that fluoride should be assessed as a human developmental neurotoxicant at the current exposure levels in Europe."*

The Review specifically made this statement about the Green et al study:

- *"An additional limitation of the study performed by Green et al. (2019) is that the intelligence tests have been performed only once between the age of 3 and 4 years, but the exact age of the children at the time point of the test has not been considered in the statistical analysis. This may be problematic, because the IQ of children changes strongly between 3 and 4 years."*

Additional Reviews of Green et al:

In addition to the CAITH review of Green et al, others have critically evaluated this study:

Is Fluoridated Water Affecting Our Kids' Intelligence? By F. Perry Wilson, MD, MScP, Nephrologist

https://www.medscape.com/viewarticle/916971?nid=131232_5322&src=WNL_mdplsnews_190823_mscedit_wir&uac=127293MT&spn=17&impID=2070820&ga=1

International responses:

<https://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-maternal-exposure-to-fluoride-and-iq-in-children/>

A series of articles written by an Epidemiologist from Johns Hopkins University. He critiques Green's study in a way that leaves no doubt:

<https://epidemiological.net/2019/09/19/the-hijacking-of-fluorine-18-998-part-one/>

<https://epidemiological.net/2019/09/21/the-hijacking-of-fluorine-18-998-part-two/>

<https://epidemiological.net/2019/09/23/the-hijacking-of-fluorine-18-998-part-three/>

ADA Statement

<https://www.ada.org/en/press-room/news-releases/2019-archiycs/august/ada-statement-on-study-in-jama-pediatrics>

ADA article on reactions to Green study by national and international groups:

https://www.ada.org/en/publications/ada-news/2019-archive/august/responses-to-fluoride-study-flood-in-from-all-over-the-globe?fbclid=IwAR1GM-T_4uX73L67w0kBpPYIfwDXeedQ5yK3k17HuiQMPfZmZJ1qPgwtVcg

American Association of Dental Research:

<http://ga.dentalresearchblog.org/?p=3409>

American Academy of Pediatrics:

<https://www.nappublications.org/news/2019/08/19/fluoride081919>

American Fluoridation Society:

<http://americanfluoridationsociety.org/wp-content/uploads/2019/08/AFS-on-Green-Study-2019-1.pdf>

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3. CDC
4. Mayo Clinic
5. U.S. Department of Defense
6. World Health Organization

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I hope that these documents and references will provide insights into the new study that has been brought before you. Please do not hesitate to call on me if you have any questions.

Warm regards,



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Diplomate, American Board of Pediatric Dentistry
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President, American Fluoridation Society
Web: AmericanFluoridationSociety.org
E: DrJohnnyJohnson@gmail.com
C: 727-409-1770

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Vascular Surgeon

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Adams School of Dentistry
The University of North Carolina

Mark Moss, DDS, PhD

Associate Professor, Department of Foundational
Sciences, East Carolina School of Dentistry,
Greenville, NC

Gary D. Slade, BDS, DipDPH

John W. Stamm Distinguished Professor of Dentistry
at the UNC Adams School of Dentistry, Chapel Hill,
NC

Jennifer Meyer, PhD, MPH, CPH, RN

Assistant Professor of Health Sciences, University of
Alaska Anchorage, AK



July 16, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLust,

I am writing to you regarding the water fluoridation issue that is before you. Some of you may recall that I was asked to come to Green Bay in 2017 as a subject matter expert on community water fluoridation (CWF) when it was being challenged back then. Thankfully, credible science won out over personal opinions of those attempting to stop it.

The current topic before you is about the "new science" since that meeting in 2017. As such, I will limit my discussion to that topic. However, I am available to answer any questions that you may have about this or other studies. Many of the authors and/or co-authors are good friends or good acquaintances of mine. Their input is readily available from them directly, or through information that they've shared with me.

From personal experience, I know that your inboxes are going to be filled with emails from others trying to sway you from providing this proven effective and safe public health measure to all of your residents. Trust me and the hundreds of thousands of scientists and researchers worldwide when I say that the day that the overwhelming body of credible scientific evidence shows a harm from the miniscule amount of fluoride in CWF, we will be the first ones shouting from the mountain tops to stop it. As medical and dental healthcare professionals, we provide care for you, your children, parents, grandparents, and grandchildren. We would not do anything to put their health in peril. I'm a son, father, and grandfather. My family all drinks optimally fluoridated water daily. I would not hurt my family just as I would not hurt your family.

Background:

A little about me. I practiced in Palm Harbor until I became disabled from a bicycle accident. The abrupt end of my career was difficult to wrap my head around, but as my pastor advised me, "the good Lord didn't push you off the bicycle, but he's laid opportunities out in front of you. Open your eyes."

In 2011, I was directed to take action when our Pinellas County Board of County Commissioners voted 4-3 to cease water fluoridation to over 700,000 residents. I was in disbelief. These were our elected officials that were entrusted with making decisions about health and safety issues for our residents every single day. And here, four of them chose to listen to a handful of vociferous opponents to water fluoridation over the proven effectiveness and safety of it. Leading health and medical groups around the world endorse and recognize community water fluoridation as effective and safe for everyone, regardless of age, race, ethnicity, socio-economic status, level of education, or access to dental care. Not a single credibly recognized health or medical organization in the world opposes water fluoridation. Not one.

My Masters of Science thesis and research project at the University of North Carolina, Chapel Hill, was on the content of fluoride in infant formula, water fluoridation, and fluorides. I was asked to lead the re-fluoridation effort in Pinellas County because of my background in fluoridation.

Sadly, it took two of the four county commissioners who had voted against CWF and were running for reelection to be voted out of office. The sole issue in the election for the candidates who ran to replace them was to restart CWF the first day they were in office. And that they did. Fifteen months after CWF had been halted, the fluoride faucet was turned back on.

The media that covered this issue wrote a 10-part editorial series on this cessation and the solid science behind CWF. They won a Pulitzer Prize for their editorial series.

The new science:

The new science that was brought before you on CWF was from a study conducted in Canada on urine samples that had been collected as part of a different large study. The "new science" is about CWF and IQ effects:

"Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada", Rivka Green, MA; Bruce Lanphear, MD; Richard Hornung, PhD; David Flora, PhD; E. Angeles Martinez-Mier, DDS; Rachel Neufeld, BA; Pierre Ayotte, PhD; Gina Muckle, PhD; Christine Till, PhD

Of primary importance is what the primary author, Christine Till, and a co-author, E. Angeles Martinez Mier, had to say about this study and pregnant mothers drinking CWF. The following slide communicates this appropriately and contains hyperlinks to their public statements:

What did Till and Martinez-Mier have to say?

August 19, 2019: Christine Till, lead author

Pregnant women should consider reducing their exposure to fluoride, Till said. That might include avoiding public water sources that are fluoridated...

September 7, 2019: Angeles Martinez-Mier, co-author

That **DOES NOT MEAN** eliminating CWF, which benefits all and is the only public health program that is viable in the US given our current healthcare system. I disagree with Christine (Till)

September 14, 2019: Christine Till

"I think this message could be easily misconstrued as us saying don't drink fluoridated water → we're not saying that," study author Christine Till, professor of psychology at York University in Toronto, told BuzzFeed News.



Lead photo by iStockphoto.com/Robert H. Jones. All other photos are the property of the American Fluoridation Society. All rights reserved. No part of this publication may be reproduced without the written permission of the American Fluoridation Society.

The primary author, Till, first stated pregnant mothers might avoid fluoridated water. Here is a statement made to NPR, August 19, 2019, on the magnitude of IQ loss across the world:

- *"We would feel an impact of this magnitude at a population level," Till says, "because you would have millions of more children falling in the range of intellectual disability, or an IQ of under 70, and that many fewer kids in the gifted range."*
- After that statement, a co-author, Angeles Martinez-Meir, spoke out on what was being stated and that she disagreed with Till. Martinez-Meir stated that pregnant mothers *can* drink CWF (September 7, 2019).
- One week after Martinez-Meir's statement, Till reversed her position on pregnant mothers drinking CWF. Till stated *"I think this message could be easily misconstrued as us saying don't drink fluoridated water-we're not saying that"*.

To summarize, the primary author and a co-author on this study being presented to the Green Bay Common Council as 'new research' to show that CWF causes IQ deficits is not even being stated as such by Till and Martinez-Meir. With those words from the study's authors themselves, how can those who oppose CWF present this to you, the Green Bay Common Council, as anything different than what the authors themselves had to say?

What ensued after the publication of the Green et al study:

Green et al deny access to their data:

- Academicians, researchers, and others around the world requested the raw data from the Green et al study so that they could run independent statistical analyses. They had concerns with the data and the conclusions reached from that data. Sharing of data is commonplace in research:
- *"Sharing research data:
As a researcher, you are increasingly encouraged, or even mandated, to make your research data available, accessible, discoverable and usable."*

The Green et al paper, published in JAMA Pediatrics, contained the following statement:

Author Contributions: Ms Green and Dr Till had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ms. Green and Dr. Till stated that they had full access to all of the data in the study. *However*, when asked for their data, they denied they had it. They would not share it. Increasingly, their denial led worldwide scientific researchers and academicians to demand that it be shared. The study was funded by the National Institute of Environmental and Health Sciences (NIEHS).

A national and international group of 30 prominent researchers, academicians, and others co-signed a letter to the NIEHS asking to have this data released. They extensively detailed their concerns that they had with the study, and asked that the NIEHS ask the authors to release this data to allow for independent analyses.

Canadian Agency for Drugs and Technologies in Health (CADTH) review Green et al study:

CADTH is an independent, not-for-profit organization responsible for providing health care decision-makers with objective evidence to help make informed decisions about the optimal use of health technologies. Created in 1989 by Canada's federal, provincial, and territorial governments, CADTH was born from the idea that Canada needs a coordinated approach to assessing health technologies. The result was an organization that harnesses Canadian expertise from every region and produces evidence-informed solutions that benefit patients in jurisdictions across the country.

CADTH conducted a review of the Green et al study. This review included many other studies and their reviews of them as well.

- "CADTH RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects", October 23, 2019, made the following statements on the Green et al study (a few of numerous statements regarding the study's limitations):
- *"The study by Green et al., 2019¹³ concluded that 'maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.' (p. E1) This conclusion was not supported by the data."*
- *"No attempt was made to control for potential important confounding factors including parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, child's health status, and other confounders between birth and the children's age of 3 or 4 when IQ was measured.^{18,19} Although the authors controlled for and performed sensitivity analysis to test the robustness of association estimates for a number of substances (including lead, mercury, arsenic) in the mothers' blood samples, they did not consider postnatal exposure of children to these substances. Lead, in particular has been found to have a high association with IQ in children.²² With incomplete control for potential confounders, it remains uncertain to know if the effect is true, and if it is due to prenatal exposure or postnatal exposure."*
- *"The evidence is weak due to multiple limitations (e.g., non-homogeneous distribution of data, potential errors and biases in the estimation of maternal fluoride exposure and in IQ measurement, uncontrolled potential important confounding factors); therefore, the findings of this study should be interpreted with caution."*

Toxicology Systematic Review on fluoride toxicity and neurotoxicity:

A comprehensive, systematic review on the toxicity of fluoride and evidence for human developments neurotoxicity was published a few months ago in a prestigious toxicological journal:

REVIEW ARTICLE

"Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses", Guth et al, Archives of Toxicology, 26 March 2020

In this Review, the researchers concluded that:

- ♦ *"based on the totality of currently available scientific evidence, the present review does not support the presumption that fluoride should be assessed as a human developmental neurotoxicant at the current exposure levels in Europe."*

The Review specifically made this statement about the Green et al study:

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American Association of Dental Research:

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Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: AmericanFluoridationSociety.org
E: DrJohnnyJohnson@gmail.com
C: 727-409-1770

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Assistant Professor of Health Sciences, University of
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Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:25 AM
To: Jaime Fuge
Subject: Fwd: Water fluoridation issue: "New Science"
Attachments: image.png; ATT00001.htm; image.png; ATT00002.htm; image.png; ATT00003.htm; image.png; ATT00004.htm; image.png; ATT00005.htm; Science says fluoride in water is good for kids. So why are these towns banning it_.pdf; ATT00006.htm; The AntiFluoridationist Threat to Public Health.pdf; ATT00007.htm; When public action undermines public health- a critical examination of antifluoridationist literature Jason M Armfield.pdf; ATT00008.htm; Water Fluoridation and the Environment-Current perspective in the U.S._Pollick.pdf; ATT00009.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: July 16, 2020 at 10:18:45 AM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: "celestineje@greenbaywi.gov" <celestineje@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Re: Water fluoridation issue: "New Science"

Good morning Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I am acutely aware of the email barrages that you have received over the past three days. Respectfully, my colleagues and I have refrained from responding to them as we wanted to show respect for your time and your abilities to separate the facts from the fiction. It is what you were elected to do. And I have faith that you will do that. This is why you are being hit very hard by the opponents to community water fluoridation (CWF). The science is clear and has been over the past 75 years of fluoridation in the U.S. Yet, those opposed have never given up a fight to stop trying to get their own will imposed on the general public.

The attacks against sound studies, people who promote CWF as lobbyists and conspirators, and discrediting the best scientific minds in the world over the past 75 years of CWF is just too much to tolerate. The scientific community is reacting to these attacks and plan to be on the Zoom meeting next week from around the world. They too are sick and tired of this vociferous small group of opponents cherry-picking tidbits of credible research, mixing in their own personal opinions, throwing them all into a Kitchenaid blender, then pouring it out over an unsuspecting public. The internet has given them the means to do this very easily.

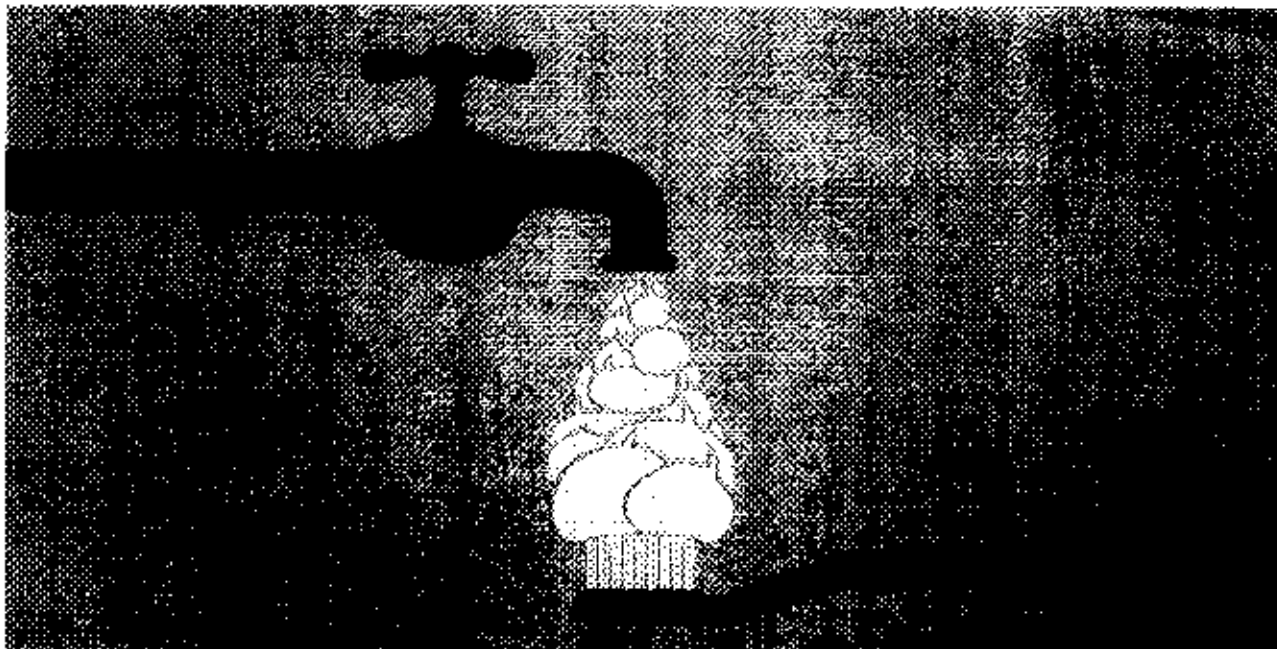
Paul Connett, a retired chemistry professor from the U.K., heads up the opposition group, the Fluoride Action Network. This group joined forces with the leading anti-vaccination group in the U.S. a few years ago under the name of Health Liberty. You can prominently see Connett's [picture](#) and his purpose for being there. The anti-vax website is headed by Joseph Mercola, D.O., who also promotes anti-CWF materials and videos.

I do not wish to enter into mudslinging with this group. However, you deserve to know who they are and how they operate. I've attached two short articles that describe who the players are and their tactics to cease CWF.

Additionally, it is important for you to know that the Royal Society of Chemistry in the U.K. moderated a meeting in the city of Hull in the north of England a couple of years ago. Hull is preparing to fluoridate their water. Both sides of the issue were represented. This is what they had to say:

Science says fluoride in water is good for kids. So why are these towns banning it?

In the past five years, 74 cities have voted to remove fluoride from their drinking water, despite thousands of studies showing it prevents cavities.



"Anti-fluoridationists" claim, without scientific evidence, that fluoride lowers IQ and causes everything from Alzheimer's to cancer.

Patricia Calkins / for ABC News

Oct. 17, 2018, 4:29 AM EDT / Updated Oct. 17, 2018, 6:57 AM EDT

By Elizabeth Chuck

It has been hailed by the Centers for Disease Control and Prevention as one of the top public health achievements of the 20th century. Numerous studies have proven its safety and efficacy. But fluoride -- the naturally occurring compound that prevents cavities and tooth decay -- is still sparking heated debates, seven decades after it was first added to America's water supply.

"Anti-fluoridationists" -- a small but vocal minority -- are disputing long-established science to say that fluoride added to tap water lowers IQ and causes everything from acne to anemia to Alzheimer's.

These anti-fluoride believers are active online but also at the polls: In the past five years, 74 cities have voted to remove fluoride from their drinking water, according to the American Dental Association. This year, there have been 13 votes around the country on fluoridation, and at least three more cities have fluoride referendums on the ballot in November: proposed bans in Brooksville, Florida, and Houston, Missouri, and a vote on bringing fluoridated water back in Springfield, Ohio.

The fears over fluoride are reminiscent of the unfounded fear that vaccines cause autism: disproved by science, yet steadfast nonetheless. The persistence of fluoride conspiracy theories -- which emerged in the 1950s with claims that fluoridation was a communist plot to dumb down Americans -- is alarming public health officials, including the American Dental Association and the American Academy of Pediatrics, who say fluoride is a safe, inexpensive way to boost children's oral health.

Dr. Johnny Johnson, a retired pediatric dentist who is president of the nonprofit American Fluoridation Society, calls the anti-fluoride efforts "cult-like."

"You cannot tailor public health to the whims of a small group of people," he said. "If you are doing that, you are harming a large group of people."

The anti-fluoridationists, though, say that it's the fluoride supporters who are harming the public's health. Some argue that the government uses fluoride as a form of mind control; others believe it's designed to boost the sugar lobby by enabling people to eat more sweets without getting cavities; and still others believe that health officials are afraid to reverse course on fluoride after promoting it for decades.



Paul Bieher, president of the New York State Coalition Opposed to Fluoridation, speaks at a 2012 press conference in New York City.
Bryan Smith / Zuma Press file

They spread the word on Facebook groups, like that of the New York State Coalition Opposed to Fluoridation, which blames fluoride for problems including thyroid damage and was slammed in 2012 for falsely claiming that the federal government "recommends avoiding fluoridated water when making infant formula." (The CDC says it's fine to use fluoridated tap water for formula, though the agency notes it may cause mild spotting on babies' teeth, so parents can use low-fluoride bottled water some of the time instead.) Reddit users claim fluoride kills gut bacteria. And on Twitter, fluoride is regularly called a cancer-causing neurotoxin.

The anti-fluoride movement has also made headway offline. In June, the Texas Republican Party opposed water fluoridation in its 2018 platform. In New Jersey, where more than 80 percent of residents do not have fluoridated water, the town of East Brunswick stopped fluoridating three years ago after Mayor David Stahl called it "mass medication of the public," a familiar refrain on anti-fluoridation forums. In Brooksville, Florida, a city of 8,000 about an hour north of Tampa, Mayor Betty Erhard has said for years that fluoride is a toxin and a waste of taxpayer money. Next month, at her urging, Brooksville will vote on removing it.



Dr. Johnny Johnson, president of the American Fluoridation Society, campaigns to keep fluoride in the water in Brooksville, Florida.
Courtesy of Dr. Johnny Johnson

"I believe that people should consent to what's in their water," Erhard said. Some townspeople agree.

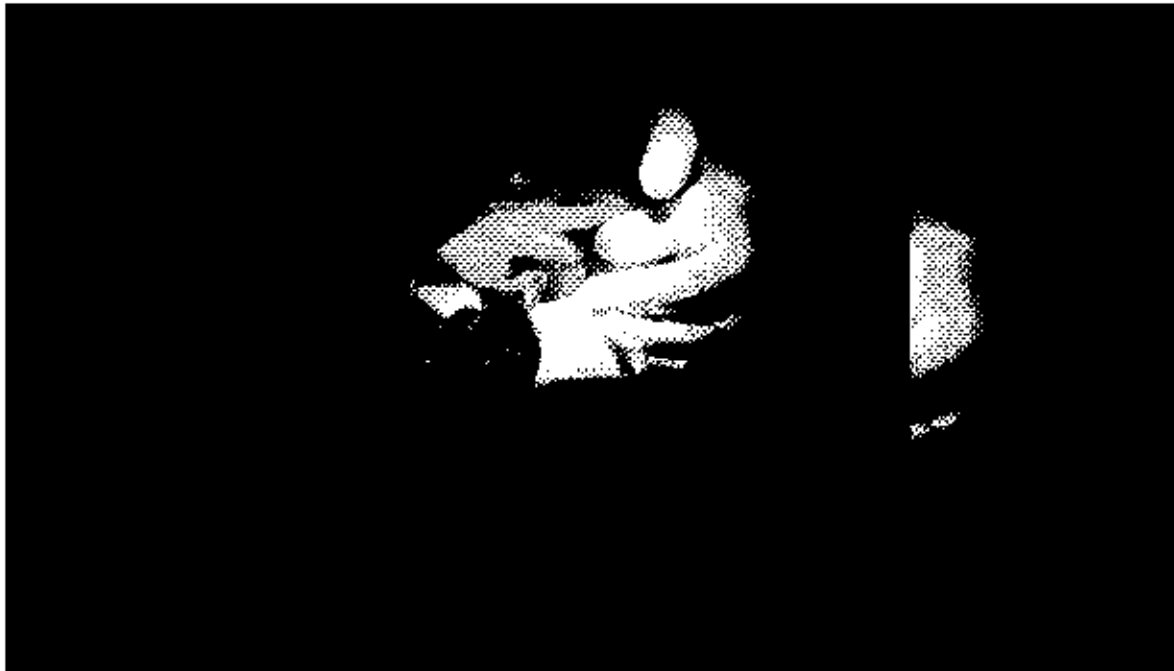
"Fluoride is a dangerous cancer-causing agent. I don't even like taking a shower in it," one wrote on Erhard's Facebook page.

CONTROVERSY FROM THE VERY START

The first place in America to receive fluoridated water was Grand Rapids, Michigan, in 1945, when residents there became guinea pigs for the theory that boosting existing natural fluoride levels in water would decrease tooth decay, particularly in children. The experiment, by the United States Public Health Service, was done without residents' consent – still a point of contention among anti-fluoridationists.

The experiment was so successful that 11 years into what was supposed to be a 15-year study, researchers announced the rate of cavities among Grand Rapids' 30,000 schoolchildren had dropped by 60 percent. But not everyone was pleased.

"I was called a murderer and a communist," Dr. Winston Prothro, director of public health in Grand Rapids during the early days of fluoridation, told The Washington Post in 1988. "I must have had letters from every city in America, and plenty from other countries, too. It fell on me to defend the physical and moral health of our entire city."



Treating dental care as an afterthought has dangerous consequences

JULY 9, 2018 02:54

Since then, the conspiracy theories have evolved from fears of a communist plot to other worries about purported dangers of fluoride – an abundant element that occurs naturally in water, even when it's not added by the government.

"Now, you have this weird backlash where people think that anything that is a chemical is bad, even though everything is a chemical," said University of Miami associate professor Joseph Uscinski, co-author of the book "American Conspiracy Theories." "There are groups of people who think that if something isn't natural, it is somehow impure or bad, and it grosses them out."

To experts, objecting to fluoride is nonsensical. The compound, consumed in water or applied topically through toothpaste or mouthwash, prevents cavities by replacing weakened structures in the teeth, said Dr. Kerry Maguire, associate clinical investigator of Forsyth, an independent research institute specializing in oral health.

It's true that too much fluoride can be dangerous – one complication is skeletal fluorosis, which causes stiffening and pain of the joints and bones or abdominal pain, nausea and vomiting – but those effects only occur with prolonged exposure to a far higher level of fluoride than is found in public water systems in the U.S., experts say. In this country, the only common side effect of fluoridation is fluorosis of the teeth – minor staining that is often only visible to a dentist.

THE ANTI-FLUORIDE MOVEMENT

Today, nearly 75 percent of the U.S. receives fluoridated water from community water systems.

That's a number that Paul Connett, a chemistry professor emeritus at St. Lawrence University in Canton, New York, hopes to get down to zero.

"There's unproven ways that fluoride can cause damage," said Connett, executive director of the nonprofit Fluoride Action Network, which aims to end fluoridation worldwide.

Connett was initially skeptical of concerns about fluoride when his wife asked him two decades ago about its health effects.

"The prevailing attitude is that people who are opposed to fluoride are crazy, so I didn't want to be stigmatized in that way," Connett said.

But the more he looked into it, the more convinced Connett became that fluoride was indeed toxic.

He now cites what he bills as a "dynamite" 2017 study that concluded that higher prenatal fluoride exposure was associated with lower cognitive outcomes in children in Mexico.

The findings, he says, are consistent with more than 50 other studies that concluded that fluoride lowers IQ.

But many dental experts dismiss such studies as bogus, particularly because many of them were done in other countries, where natural fluoride levels are far higher than in the U.S. and there may be other factors, like polluted water.

"You can't do that in science."

"It's as though you have something you want to prove, so you look at other countries that have naturally high levels of fluoride at multiples of what we have in the United States, and they see changes and then they backwards extrapolate it to water fluoridation," said Johnson of the American Fluoridation Society. "You can't do that in science."

Some anti-fluoridationists oppose all fluoride, including in toothpaste. (Sales of fluoride-free toothpastes are relatively small but projected to grow; an article in the dental journal Gerodontology in August found that such toothpastes have "no impact" on preventing cavities.) Fluoride opponents seize on the warning label on toothpaste cautioning that a poison control center should be called if a child accidentally ingests too much, saying that proves fluoride is a toxin.

The American Dental Association, which has supported water fluoridation since 1950, disputes that, pointing out that the amount of fluoride in an entire tube of toothpaste wouldn't be fatal, but other additives would likely cause a child to vomit.

As for fluoride in water, "there have been literally thousands of studies published in peer-reviewed journals that demonstrate the safety of community water fluoridation," said Dr. Brittany Seymour, the American Dental Association's consumer spokeswoman, calling it "the single most important public health measure to prevent cavities."

"Which is more important: protecting your children's brain, or protecting your children's teeth?"

The Fluoride Action Network disagrees. The group sued the Environmental Protection Agency in federal court in San Francisco last April to stop water fluoridation.

"Which is more important: protecting your children's brain, or protecting your children's teeth?" Connett said.

He expects the case to be heard next August. The EPA said it does not comment on pending litigation.

MORE THAN A TOOTHACHE

Kentucky is the only state to require fluoridation in every community water system that serves 1,500 or more people, and as a result, 99.99 percent of residents receive fluoridated water. Anti-fluoridationists have tried to reverse the law, but it's not going anywhere, said Dr. Julie

Watts McKee, the state dental director of the Kentucky Oral Health Program, a public initiative that carries out community programs to reduce oral disease. The cost to fluoridate water for a person's entire lifetime is cheaper than the price of a single filling, McKee said.

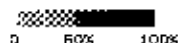
"The science -- the true science -- proves its effectiveness over and over again," she said. "It helps people of all ages. It helps the kids better because they have growing teeth and are at a cavity-prone age, but it helps us all."

Elsewhere in the country, the percentage of residents receiving water varies, with Hawaii at the low end at 11.7 percent.

Fluoride by the numbers

The percentage of people in each state who receive fluoridated water

Percentages range from states to water coverage



Note: Data as of December 31, 2014

Source: CDC

Graphics: Michael Wu / NBC News

It's not always a health fear that keeps states from raising fluoridation levels; sometimes the decision is budgetary. Either way, the low levels are troubling to fluoridation proponents, who argue that it gives everyone a shot at fighting cavities -- regardless of access to dental care.

The effects of cavities, particularly untreated ones, can be far-reaching.

"It's very, very difficult to concentrate when you have a toothache, and if we are trying to help children succeed in school ... this is an important component that is often overlooked," Maguire said. "It is a winnable war."

In Brooksville, Florida, where the vote on removing fluoride is just a couple weeks away, Mayor Erhard has high hopes that her townspeople will vote it out. The city has spent about \$19,000 on fluoridation over the past five years, and she would like to see that money go someplace else -- such as repairing the city's roads.

Erhard said she doesn't worry about how kids will fare with nonfluoridated water, so long as parents do their part to encourage good oral health.

"If you're feeding them a lot of sugar, naturally, you're going to get a lot of cavities," she said. "I can tell you firsthand from my experience that I've always brushed and I love going to the dentist, and my teeth are healthy."







Institute for Science in Medicine

WHITE PAPER

**THE ANTI-FLUORIDATIONIST THREAT
TO PUBLIC HEALTH**

PREPARED BY

JOHN E. DODES, DDS, FISM

AND

MICHAEL W. EASLEY, DDS, MPH, FISM

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Institute for Science in Medicine (ISM) is an international, educational and public-policy organization comprised of health care professionals, scientists, and researchers who agree that the best science available should be used to determine health policy and to establish a standard of care that both protects and promotes the public health. We necessarily oppose policies which erode a science-based standard of care and thereby significantly expose the public to fraudulent, worthless, or harmful medical practices and products.

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White Paper: The Anti-Fluoridationist Threat to Public Health

Declared by the Centers for Disease Control and Prevention to be one of the ten greatest public-health achievements of the Twentieth Century,¹ community water fluoridation has been under attack by a small band of critics since its inception. The scientific consensus over fluoridation's health benefits, safety, social justice, and economics has been firmly established over six decades of widespread use in the United States and elsewhere. Nevertheless, anti-science critics have never relented in their opposition — recycling previously disproven charges of harm, inventing new ones out of whole cloth, misrepresenting scientific facts and research, exaggerating risks, understating benefits, inappropriately invoking the precautionary principle, and accusing public health officials of corruption, conspiracy, and 'mass medication' of whole populations.

Background

Tooth decay is the most common disease of all mankind. Decay and loss of teeth due to decay can affect general health, especially for the elderly, and adversely impact an individual's emotional and social well-being. Fluoride is a micro-nutrient essential to the development and maintenance of teeth and bones. Fluoride-fortified teeth are significantly resistant to dental caries.

Community water fluoridation (CWF) is an adjustment to the amount of fluoride that occurs naturally in all water supplies to a safe level that is optimal for dental health and safe for overall health. Scientific studies have established that CWF lowers the rate of tooth decay by 20-40% in children, over and above the effect of toothpaste and other sources of fluoride.² Moreover, it benefits all residents of a community, regardless of age and socio-economic status.³ CWF is remarkably economical for community water systems serving 1,000 people or more. For such communities, every dollar spent on CWF on average saves \$38 to \$80 per year in dental treatment.^{4,5} To look at it another way, for the cost of a single small tooth restoration, an individual can be protected for life.

Thousands of reliable scientific studies have established the safety of CWF at the levels of optimal fluoridation. After decades of observation and examination, reviews by major scientific organizations have found there is no epidemiological evidence for any other threat to public or individual health associated with CWF.

In the United States, 62.2% of the population has access to public water supplies that are optimally fluoridated. Over 360 million people worldwide, in approximately 60 countries enjoy the benefits of fluoridated drinking water. Dr C. Everett Koop, a former US Surgeon General, has stated, "Fluoridation is the single most important commitment that a community can make to the oral health of its citizens."

Yet in spite of overwhelming scientific evidence and greatly improved dental health, opposition to CWF persists. This opposition has had success in delaying the adoption of CWF in some

White Paper: The Anti-Fluoridationist Threat to Public Health

communities, and even causing others to abandon it, depriving tens of thousands of citizens of optimal dental health and putting a heavy financial burden on the community's health care resources. Because of this threat to public health, the tactics of the anti-fluoridationists warrant examination and exposure.

Tactics of the Anti-fluoridation Movement

Misrepresenting the Conclusions of Valid Research

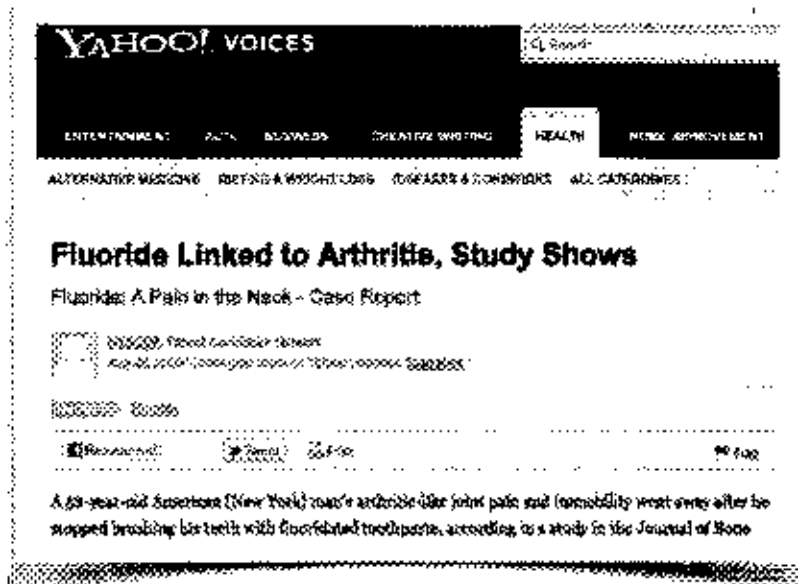
The National Research Council (NRC) is a group of distinguished experts that issues independent reports to improve government, decision making and public policy. In 2006, the NRC issued a report on fluoride.⁶ Anti-fluoride groups often cite the NRC's report when they try to raise fears about community water fluoridation, but these groups' statements misrepresent the NRC's findings.⁷ Although the report's title cites "drinking water," the NRC produced a summary of its report, reiterating the focus of its concern, i.e. people living in areas of the United States with *natural* levels of fluoride in water that are at least double or triple the level used to fluoridate a public water system. As the NRC itself stated, "it is important to note that the safety and effectiveness of the practice of water fluoridation was outside the scope of this report and is not evaluated." ⁸

Citing Strange, Far-Fetched Case Studies to Attack Fluoridation

The New York State Coalition Opposed to Fluoridation (NYSCOF) has cited bizarre case studies of people that are in no way representative of normal behavior or normal conditions. These case studies are not scientifically relevant to whether Americans drink fluoridated water. Here are some examples of the case studies that are presented with fearful headlines by NYSCOF.

White Paper: The Anti-Fluoridationist Threat to Public Health

- In 2009, NYSCOF posted a press statement that quoted its president saying that “even water fluoridation will cause arthritic-like symptoms in susceptible individuals...”⁹ However, NYSCOF provided no evidence connecting fluoridated water to arthritis. One of the articles that the group cited to back up its claim was from a French medical journal.



That article described a

bizarre case study that had nothing to do with whether Americans drink fluoridated water. It was about a woman who brushed her teeth 18 times a day and swallowed the toothpaste, *consuming a tube of toothpaste every two days*.¹⁰ It is irresponsible to attack water fluoridation with a case study that (a) does not involve fluoridated water, and (b) is not representative of normal behavior. It is also instructive to note that while fluoride levels in water fluoridation do not exceed 1.0 parts per million, the fluoride levels in toothpastes range from 1100 to 1500 parts per million depending on the brand.

- In 2010, NYSCOF cited the case of a 53-year-old British woman in a *Facebook* post headlined, “Fluoride Damages Bones, Studies Show.” Unless people read the full article, they never learn what a bizarre lifestyle this woman had, drinking six cups of high-fluoride “brick tea” and brushing her teeth 8-10 times each day.¹¹ Ordinary Americans do not drink that type of tea, and they do not brush their teeth every two hours they’re awake. Presenting this woman’s case as a reason to fear water fluoridation in the United States is misleading.¹²

Engaging in Misleading Spin about Europe and Fluoride

Fluoridation.com, an anti-fluoride website managed by Canadian activist Elke Bahiuk, contends that “99% of western continental Europe has rejected, banned, or stopped fluoridation due to environmental, health, legal, or ethical concerns.”¹³ There is no citation for this statement, and this assertion is a classic example of spin. Based on this language, one would conclude that virtually nobody in Western Europe regularly receives systemic forms of fluoride. The reality is very different.

White Paper: The Anti-Fluoridationist Threat to Public Health

First, the insertion of the word “continental” is a way of ignoring that millions of Irish and British people drink water that is optimally fluoridated. In fact, fluoridated water is provided to 12 million Europeans, mostly reaching residents of Great Britain, Ireland, Spain and other countries.¹⁴

Second, this statement by Fluoridation.com obscures the fact that fluoride is widely used in Europe. In fact, at least 70 million Europeans consume fluoridated salt, and this method of fluoridation reaches most of the population in Germany and Switzerland. These two countries have among the lowest rates of tooth decay in all of Europe.¹⁵ Fluoridated milk programs reach millions of additional Europeans.¹⁶

Italy has not tried to create a national system of water fluoridation, but there are logical reasons for this. Firstly, many Italians regularly drink bottled water. Secondly, a number of areas in Italy have water supplies with natural fluoride levels that already reach the optimal level that prevents decay.¹⁷

Misrepresenting the Positions of Governmental or Health Organizations

In 2012, a group called the New York State Coalition Opposed to Fluoridation (NYSCOF) claimed in an Internet article that the U.S. Department of Health and Human Services (HHS) “recommends avoiding fluoridated water when making infant formula.”¹⁸ The hyperlink contained within this statement takes readers to yet another article by NYSCOF that makes the same inaccurate claim.¹⁹ NYSCOF asserted that its source for this assertion is a video commentary recorded by Dr Howard Koh, HHS’s Assistant Secretary for Health in 2011. But in the video, Dr Koh did not warn parents against using fluoridated water for infant formula.²⁰ This is what he actually said:

Parents and caregivers can use fluoridated water for preparing infant formula. However, if the child is exclusively consuming infant formula reconstituted with fluoridated water, there is an increased potential for mild dental fluorosis. The majority of fluoride comes from the water used to mix the formula. Some parents may choose to use low-fluoride bottled water some of the time to mix infant formula.

This HHS message suggests another option for parents who may be concerned about fluorosis, but it is a far cry from telling parents to avoid fluoridated water. Incidentally, nearly all fluorosis in the United States is a mild, cosmetic condition that doesn’t affect the health or function of the teeth. In most cases, only a dentist will detect the condition because the faint white streaks on teeth are so subtle.

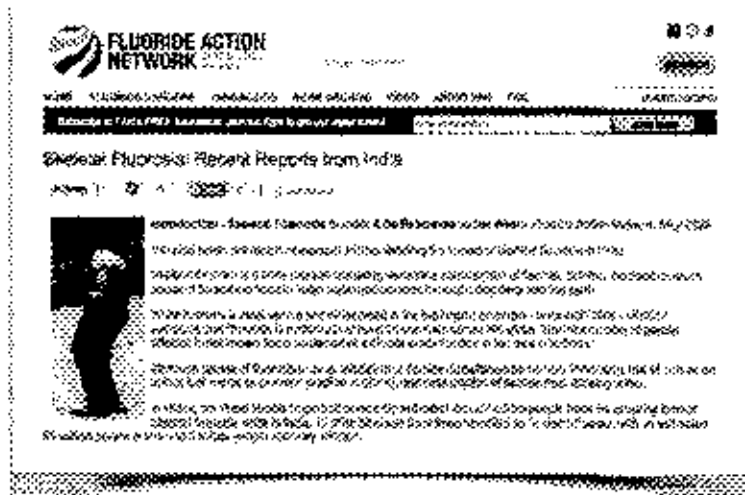
Painting an Inaccurate Picture of Dental Fluorosis

One typical way that anti-fluoride activists raise fears about safety is by talking about a condition called dental fluorosis. They don’t mention that nearly all fluorosis in the United States is a mild, cosmetic condition that is so subtle that only a dentist is usually able to detect it and only

White Paper: The Anti-Fluoridationist Threat to Public Health

when the teeth are completely dry. Mild fluorosis does not cause pain, and it does not affect the health or function of the teeth. Here are two examples of how opponents misrepresent what fluorosis is:

- The Fluoride Action Network (FAN), a web-based anti-fluoridation organization, has cited the incidence of fluorosis in India and other nations to raise concern about water fluoridation. Yet FAN neglects to inform readers that the cause of this condition is *not* fluoridated water.²¹ In fact, the process of adjusting fluoride in public water systems is extremely rare in India.²² The problem is that several regions of India have



geological conditions that make the *natural* fluoride levels between four and 15 times higher than the level used to fluoridate water in the United States.²³ Moreover, some excessive levels of fluoride in India's ground water is the result of widespread unabated industrial pollution. India's leading health officials do not blame the practice of what is called "fluoridation." In fact, the director of India's Institute of Public Health publicly endorsed water fluoridation.²⁴ Skeletal fluorosis is a condition that is virtually unheard of in the United States.

- The leader of NYSCOF posted a statement on the web about fluoridation in which he declared that a study links dental fluorosis to bone fractures.²⁵ The Chinese study he cited was about fluorosis "from drinking traditional brick-tea."²⁶ Although brick tea is consumed in many areas of China, it is virtually unheard of in the United States. Brick tea has a concentration of fluoride that is between three and 10 times higher than the level recommended to fluoridate drinking water in the United States.²⁷ This study was described in an anti-fluoride publication called *Fluoride*, which does not have the same rigorous standards for peer review and integrity that are required of full-fledged scientific journals. For example, the World Health Organization's guidelines recommend that a study's methodology be "clearly defined" and the procedures used in a study "should be described in detail."²⁸ The article in *Fluoride* is only three and a half pages long, and most of one page consists of photographs. Few details are provided of the methodology or procedures used by the Chinese researchers. The article states that the children had "a known regular consumption" of brick tea, but there is no way

White Paper: The Anti-Fluoridationist Threat to Public Health

to determine how much brick tea was consumed by the children who were studied — or for how many years they consumed such tea.

Leaving Out Critical Facts

- An anti-CWF group cited a study about a city in Cuba that ceased fluoridation, presenting it as proof that fluoridation offers no benefits.²⁹ It's true that decay rates fell for children in this city after CWF ended in 1990, but the anti-fluoride group ignored a crucial point that could well have influenced these rates — that very same year, this city started a weekly, fluoride mouth-rinsing program in its schools.³⁰ Effective mouth-rinsing programs generally cost significantly more per person than CWF.
- Citizens for Safe Drinking Water (www.nofluoride.com) has posted anti-fluoridation quotes on its website, claiming that these statements “are made by the top medical authorities...based on the latest medical research.” But several of these quotes are more than 40 years old and, therefore, are not based on the latest research. The group even cites a quote from an American Medical Association leader, without revealing that he was AMA's president in the 1930s — many years before fluoridation was first tried in the United States.³¹ The American Medical Association has since endorsed CWF as an effective public health strategy.

Using a “Rhetorical Question” to Create Fear

One example of anti-fluoride propaganda seeks to raise a major health concern, claiming a link between fluoride and fibromyalgia, without offering any credible evidence to back it up. Instead, this article engages in guesswork:

Is it possible that some cases of fibromyalgia are actually cases of fluoride poisoning? Again, it is a possibility. ... The problem is, there is no actual research to determine a solid connection between fluoride and fibromyalgia...³²

Saying something is “possible” is a poor reason for raising a concern that is not backed by scientific evidence. People who suffer from

Fluoridation As a Potential Cause of Fibromyalgia Symptoms



Fibromyalgia is a debilitating disease that is difficult to diagnose because Fibromyalgia symptoms can mimic other health issues.

Diagnosis seems to be a process of elimination of other chronic diseases. Even then, many doctors aren't willing to make the diagnosis.

Just as frustrating, the cause of fibromyalgia is not known. Scientists believe it is caused by a genetic predisposition that is often triggered by an illness or other trauma.

Environmental factors contributing to fibromyalgia cannot be overlooked, however. Along with an increase in the number of cases and chemicals in the environment, there is also an increase in illnesses that are sometimes referred to as “mystery illnesses”, or diseases that are difficult to diagnose and of which the cause may be unknown.

Is Fluoride Leading to “Mystery Illnesses”?

Our environment, home that may be responsible for a number of health issues as fluoride.

White Paper: The Anti-Fluoridationist Threat to Public Health

fibromyalgia deserve our compassion, not our wild speculations about their illness. The article was written by a woman who is described as a writer “with a special interest in health-related topics.” Yet there is no indication that she holds a medical degree or has any expertise in this particular field.

Holding Extreme Views About Health and Medicine

Several of the leading voices in the anti-fluoride movement have expressed radical views that place them at odds with the scientific and medical community.

- **Mike Adams**, editor of NaturalNews.com, is a vocal opponent of water fluoridation. In 2009, he launched an online petition endorsing a health reform plan for the United States that including a provision preventing state medical boards from being able to license “who can or cannot practice medicine.”³³ Adams also attacks vaccines. In 2011, he wrote, “Vaccines make you stupid. The chemical adjuvants added to vaccines actually cause neurological damage and interfere with healthy cognitive function.”³⁴
- **Dr. Joseph Mercola** is a leading opponent of fluoridation who claims it “causes teeth to rot and crumble.”³⁵ In 2010, Dr Mercola posted a series of lengthy interviews with Paul Connett, leader of the FAN, and kicked off these interviews by declaring his intent “to remove fluoride from the water supply of the United States.”³⁶ In 2011, the website Quackwatch reported, “Many of Mercola’s articles make unsubstantiated claims and clash with those of leading medical and public health organizations.” Quackwatch also reports these claims include articles opposing immunization and promoting dietary supplements.³⁷ For instance, Mercola’s website has warned women against getting mammograms to screen for breast cancer. Instead, Mercola encourages women to use thermograms – digital images of skin temperatures – as a tool for detecting cancer and other health conditions. Since 2005, Mercola has received at least three letters from the Food and Drug Administration, ordering him to stop making certain claims about thermograms or other products promoted on his website. The FDA has concluded that the broad claims made by the Illinois physician do not accurately reflect the medical evidence about thermograms. *The Chicago Tribune* reported that “science has yet to back his claims” about the Med2000, a thermographic camera that Mercola promotes.³⁸ According to the American Cancer Society, “no study has ever shown that [a thermogram] is an effective screening tool for finding breast cancer early. It should not be used as a substitute for mammograms.”³⁹
- **John Yiamouyiannis**, a PhD chemist whose anti-fluoride articles are still cited by FAN, co-wrote a book making the false claim that the virus HIV does not cause AIDS.⁴⁰ Yiamouyiannis also predicted that people who received childhood vaccinations would have a higher rate of AIDS—another assertion that is at odds with the evidence.⁴¹ Yiamouyiannis died at age 58 of cancer. He had neglected symptoms of rectal cancer, and then, rejecting standard treatment, he opted for IV vitamin C and laetrile at a Mexican clinic. Many years ago, *Consumer*

White Paper: The Anti-Fluoridationist Threat to Public Health

Reports criticized the junk science behind Yiamouyiannis's attacks on fluoridation,⁴² but FAN continues to praise him as an expert on the subject.⁴³

- **Stanley Monteith, MD**, is a retired orthopedic surgeon. He has a syndicated program called *Radio Liberty* that airs on over 50 stations. A long-time member of the John Birch Society, Monteith's favorite issues include a "secret cabal" that controls the United States, the "New World Order," promoting belief in the supernatural, and a conspiracy to reduce the world's population to 500 million using fluoridation which he claims lowers sperm production.⁴⁴ In 2004, he published the book *Hidden Agenda: The Fluoride Deception (Training Manual for Parents, Physicians, and Dentists)*.
- **Mehmet Oz, MD**, reaches a TV audience of millions with the *Dr. Oz Show*. Oz recommends individuals purchase reverse osmosis filters, as his family has done, for the purpose of removing fluoride from drinking water. Oz also promotes Joseph Mercola (see above) and many discredited health care practices, such as Reiki and acupuncture; he even claims that homeopathy is "worth considering."⁴⁵ As a practicing cardiothoracic surgeon, Oz brought a "radical energy healer" into his operating room to reduce patients' anxiety stemming from their repressed "birth trauma."⁴⁶
- **Paul H. Connett**, a retired professor of chemistry at St. Lawrence University, authored *The Case Against Fluoride: How Hazardous Waste Ended Up in Our Drinking Water and the Bad Science and Powerful Politics That Keep It There* (2010). Connett is the head of the family-operated FAN. At the end of 2011, fewer than 200 of America's 150,000 dentists had signed Connett's "Professionals' Statement to End Fluoridation."⁴⁷ Connett considers fluoridation to be forced medication and repeats many of the usual anti-fluoridation arguments. He often frames his opposition to fluoride in the form of questions, such as "What parent in their right mind would put the interest of their children's teeth...above the interest of their brains?" He also claims that with fluoridation, "There's no adequate margin of safety."⁴⁸ In an unguarded moment with an interviewer, Connett recently stated, "All these liberal commentators around the world immediately jump in and use the fact that the Tea Party is involved to slam us as being crazy conspiracy theorists. We might be wrong, but we're not looney."⁴⁹
- **Christopher Bryson** is a reporter whose book, *The Fluoride Deception*, purports to link water fluoridation to the Manhattan Project at Los Alamos. In an interview aired on *Democracy Now*, Bryson stated, "The post-war campaign to fluoridate drinking water was less a public health innovation than a public relations ploy sponsored by industrial users of fluoride—including the government's nuclear weapons program."⁵⁰ The studies Bryson refers to are of poor quality and don't hold up to scientific scrutiny. He refers to fluoride as "rat poison."
- **Hardy Limeback** is a Canadian dentist who teaches at the University of Toronto and who has opposed fluoridation since 1998. He seems to have changed his support for fluoridation after losing a bid for the presidency of the Canadian Dental Association. He repeatedly makes the scientifically unfounded claim that, "In Canada, we are now spending more money treating dental fluorosis than we do treating cavities."⁵¹ He often asserts that fluoride has cumulative

White Paper: The Anti-Fluoridationist Threat to Public Health

toxic effects that can be 'catastrophic,' although he cites scientific evidence that actually does not support his assertions.

- **Carol Kopf** appears to be principal voice behind the New York Coalition Opposed to Fluoridation (NYSCOF). A Long Island housewife without any health-related training, Kopf peppers the internet with unscientific articles under her actual name and the *nom de plume* "Sally Stride." She bombards newspapers with letters to the editor in response to almost any mention of fluoridation. It also appears that she is the ghost writer for attorney Paul Beeber, titular head of NYSCOF.

Conclusions

For decades, a small, but vocal, movement of anti-fluoridation activists has spread unfounded fears among the public about community water fluoridation, with the result that some communities have opted to stop this beneficial and cost-effective public health measure. While the value of fluoride is gaining gradual acceptance, overcoming the misinformation promoted by those opposed to fluoridation is a long and difficult process.

The anti-fluoridationists' fake scientific controversy has resulted in reduced dental health, needless pain, suffering, and lost productivity, with substantially increased financial burdens on individuals and our health care system.

The anti-fluoridation movement employs classic propaganda methods, such as misrepresentation, fear mongering, false analogies and outright lies to further their political goals. As William Jarvis, past executive director of the National Council Against Health Fraud, has said:

These charges seem to grow out of a mentality of distrust. Anti-fluoridation groups are led by many of the same people who oppose immunization, pasteurization, sex education, mental health programs, and other public health advances. Most are closely connected with sellers of alternatives to medically accepted products and services.

Fluoridation is safe, effective, efficient, socially equitable, and environmentally sound public health policy for the prevention of the most common disease afflicting children and adults. It is imperative that the optimal fluoridation of community water systems continue throughout the United States and, indeed, the world.

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Debate

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When public action undermines public health: a critical examination of antifluoridationist literature

Jason M Armfield

Address: Australian Research Centre for Population Oral Health, School of Dentistry, University of Adelaide, South Australia, Australia

Email: Jason M Armfield - jason.armfield@adelaide.edu.au

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Abstract

Background: The addition of the chemical fluorine to the water supply, called water fluoridation, reduces dental caries by making teeth more resistant to demineralisation and more likely to remineralise when initially decayed. This process has been implemented in more than 30 countries around the world, is cost-effective and has been shown to be efficacious in preventing decay across a person's lifespan. However, attempts to expand this major public health achievement in line with Australia's National Oral Health Plan 2004–2013 are almost universally met with considerable resistance from opponents of water fluoridation, who engage in coordinated campaigns to portray water fluoridation as ineffective and highly dangerous.

Discussion: Water fluoridation opponents employ multiple techniques to try and undermine the scientifically established effectiveness of water fluoridation. The materials they use are often based on Internet resources or published books that present a highly misleading picture of water fluoridation. These materials are used to sway public and political opinion to the detriment of public health. Despite an extensive body of literature, both studies and results within studies are often selectively reported, giving a biased portrayal of water fluoridation effectiveness. Positive findings are downplayed or trivialised and the population implications of these findings misinterpreted. Ecological comparisons are sometimes used to support spurious conclusions. Opponents of water fluoridation frequently repeat that water fluoridation is associated with adverse health effects and studies are selectively picked from the extensive literature to convey only claimed adverse findings related to water fluoridation. Techniques such as "the big lie" and innuendo are used to associate water fluoridation with health and environmental disasters, without factual support. Half-truths are presented, fallacious statements reiterated, and attempts are made to bamboozle the public with a large list of claims and quotes often with little scientific basis. Ultimately, attempts are made to discredit and slander scientists and various health organisations that support water fluoridation.

Summary: Water fluoridation is an important public health initiative that has been found to be safe and effective. Nonetheless, the implementation of water fluoridation is still regularly interrupted by a relatively small group of individuals who use misinformation and rhetoric to induce doubts in the minds of the public and government officials. It is important that public health officials are aware of these tactics so that they can better counter their negative effect.

Background

The addition of fluorine to the water supply, termed water fluoridation, is carried out as a public health measure to improve oral health. One of the ways fluorine confers its benefit is by changing the crystalline structure of teeth. Fluorine ions replace hydroxide ions in calcium hydroxyapatite, $\text{Ca}_5\{(\text{PO}_4)_3\text{OH}\}$, in teeth, forming calcium fluoroapatite, $\text{Ca}_5\{(\text{PO}_4)_3\text{F}\}$, which is more chemically stable and more resistant to acid attack than calcium hydroxyapatite [1]. However, as well as making the enamel more resistant to acid attack by altering the chemical structure of the enamel, fluoride helps to protect teeth by promoting the remineralisation of early decayed lesions and by reducing the ability of the bacteria on the teeth to produce acid.

Water fluoridation was first carried out in the USA after studies by Dean [2,3] found that higher levels of fluoride (fluorine when part of a chemical compound) in the water supply appeared to confer a caries preventive effect. Since then, water fluoridation has been adopted in over 30 countries, reaching an estimated 350 million people worldwide [4]. Indeed, the fluoridation of drinking water to control dental disease has been referred to by the US Centers for Disease Control as one of the Top 10 public health achievements of the 20th century [5]. Fluoridated water reaches people from all socio-economic strata of society [6-8] helping to erode the socio-economic gradient in oral disease experience. It is efficient, cost-effective and considered the single most effective means of preventing tooth decay over a person's lifetime [9]. In addition, water fluoridation alters the dynamics of decay initiation. Rather than just affecting an individual at a point in time, water fluoridation reduces the incidence of decay. This is a phenomenon played out over a person's lifetime. The effect of water fluoridation is not a static 'one-off' benefit.

Oral health is fundamental to overall health, yet many adult Australians and a significant percentage of children still suffer persistent high levels of oral disease and disability. As a response to a report released in 2001 on the 'Oral Health of Australians' [10], the National Advisory Committee on Oral Health, established by the Australian Health Minister's Conference, signed off on 'Australia's National Oral Health Plan 2004-2013' [11]. One of the four broad themes underpinning the plan was the need to adopt a population health approach, with a strong focus on oral health promotion and the early identification and treatment of oral disease. Although most dental services are provided within the private sector, both the Commonwealth and the States and Territory governments can and do provide financial support for dental services to certain sections of the population. State and Territory governments are also responsible for the implementation of

water fluoridation under a raft of different legislative arrangements, although in practice, and for various reasons, those responsibilities are often devolved to local councils. One of the short term goals of population oral health promotion under the National Oral Health Plan was the extension of the fluoridation of public water supplies to all communities across Australia with populations of 1000 people or more. The suggested population cut-off was based on research from New Zealand which showed that this was the practical lower bound at which water fluoridation remained cost-effective [12].

Discussion

Partially in response to the objective of extending water fluoridation announced in the National Oral Health Plan, there has been renewed advocacy at the State and Territory level for fluoride to be added to public waters to improve oral health. Nonetheless, this major public health initiative continues to meet considerable opposition where ever it is mooted. Such a response is not confined to Australia. Attempts worldwide to introduce water fluoridation are often thwarted [13,14]. In the US and Canada, for example, one anti-fluoridation organisation claims that more than 150 communities have rejected water fluoridation in referenda since 1990 [15] while between 1989 and 1994 just over 40% of referenda were defeated in the US [13].

Efforts to introduce water fluoridation are almost universally met with a coordinated campaign involving newspaper articles, calls to talkback radio, letterbox leaflet drops, public forums and community agitation. Proponents of water fluoridation are invited to public forums to debate against fluoridation opponents and these are often given prominent media coverage. If advocates of water fluoridation attend these debates they may be bombarded with one claim after another of which they have no hope of adequately addressing in the limited opportunities afforded in a public debating match [16]. If, however, water fluoridation proponents decline to attend public fluoride debates they are labelled as being arrogant, condescending and contemptuous [17] and their desire to not attend lambasted as "an insult to both science and democracy" [18]. Opponents of water fluoridation make the inaccurate claim that public debates are a forum for 'open, rational, scientific argument and evidence' and that by refusing to attend debates proponents of water fluoridation are maintaining the process by using political power and influence [19].

Statements regarding the scientific controversy surrounding water fluoridation are generally regarded as artefacts of anti-fluoridationist activity, with actual scientific debate over water fluoridation being resolved decades ago. Almost all major dental and health organisations either

support water fluoridation or have found no association between it and adverse health effects [20]. Nonetheless, propagating the idea of an ongoing scientific debate gives the illusion of scientific uncertainty and is a favoured tactic of water fluoridation opponents. In 1978, *Consumer Reports* published a two-part series on fluoridation that concluded:

The simple truth is that there's no 'scientific controversy' over the safety of fluoridation. The practice is safe, economical, and beneficial. The survival of this fake controversy represents, in Consumers Union's opinion, one of the major triumphs of quackery over science in our generation." [21]

And yet, more than a quarter of a century after these words were printed the manufactured 'controversy' shows no signs of diminishing.

In the US, those opposed to water fluoridation have been described as a heterogeneous group and range from well-intentioned and concerned citizens to professional activists to extremists [22]. In the 1980s, Hastreiter argued that the leaders of the movement in the US were 'individuals who are marginal to the social, psychological, political, and professional mainstream' [23]. Also involved in water fluoridation opposition in most countries are companies selling bottled water and water filters, purveyors of alternative medicines and therapies, and some environmental scientists. Opponents of water fluoridation share the characteristic of being highly mobilised and organised and rely heavily on propagating their opinion via the popular media, which is often willing, if not keen, to publish their sensationalist claims. While provocative and emotive arguments are commonly aired in the media, the ability of water fluoridation opponents to delay or halt the introduction of water fluoridation through their public lobbying campaigns represents a serious and detrimental public health outcome. Campaigns are often based on information available on anti-fluoride websites and are often spearheaded by one of a small number of ardent fluoridation opponents.

Scientific journals provide an essential role in both information sharing and as a forum for scientific debate. The process of peer review in these journals helps ensure that poor quality research is rejected, unsupported conclusions are censured, and ascientific speculation is appropriately identified. With the advent of the World Wide Web, however, opinion can be propagated from any web site, by anyone, to reach a potential audience of millions.

Because Internet resources are increasingly being used by the public as a source for dental and general health information [24-26], the uncontrolled spread of information on the Internet has led to concern over its appropriateness and quality. Water fluoridation information on the World Wide Web is presented to the public indiscriminately and has been found to range from factual, to unsubstantiated opinion, to outright fraud [27]. Although the overwhelming majority of scientific enquiry supports the benefits of water fluoridation, members of the public who type the term 'water fluoridation' into any of the major search engines would immediately be presented with a disproportionate percentage of anti-fluoridation websites (Table 1). If a concerned member of the public were to type in the search term 'water fluoridation dangers' almost the only information presented to them would reflect an anti-fluoride perspective.

Adding to the one-sided presentation of information on water fluoridation on the Internet is a bias in media reporting. Although the media have a social responsibility to inform the public of possible impending dangers [28], they are often poorly equipped to adequately explain the underlying complexities of risk issues in science [29]. There is a payoff for generating controversy in an increased audience. In 2001, the Dental Health Foundation in Ireland analysed 240 recent print, radio and television articles relating to water fluoridation over a one-year period, finding the media coverage to be predominantly negative (52%) with only 14% of articles judged as being positive [30]. A similar bias was found with press cuttings in the UK [31]. Easley explains this bias as demonstrating subversion of the media; that is, winning over the media

Table 1: Classification of first 20 results based on Internet searches for "water fluoridation" and "water fluoridation dangers" using five major search engines

Search engine	"water fluoridation"				"water fluoridation dangers"			
	For	Against	Reviews	Other	For	Against	Reviews	Other
Google	7	9	3	1	0	20	0	0
Yahoo	5	11	1	3	0	19	0	1
MSN	8	10	1	1	1	18	0	1
AOL	6	9	3	2	0	20	0	0
Ask	3	16	1	0	0	20	0	0

Note: Search conducted on 10 April 2006, from Australia. Listed search engines account for 90.3% of all US Internet searches (AC Nielson, 2005)

by presenting controversy, 'sensationalist' claims and a David vs Goliath concept which appeals to people's proclivity to support the 'underdog' in conflicts [16]. Radio talk shows, an increasingly powerful force in US politics, have been found to present a barrage of negativity about water fluoridation and have been known to screen out supportive viewpoints so that only a one-sided view reaches the public [13].

Researchers in Ireland argue that the high percentage of negative coverage most likely stems from its increased dramatic and sensationalist appeal, providing a payoff in an increased readership or audience [30]. Of course, concerns regarding the content of media coverage effect not just water fluoridation but other public health strategies. For example, an analysis of the print media's coverage of heroin prescription trials [32], compulsory vaccinations [33] and many other public health and health related issues reveals similar bias. Of concern is that consumers may more readily recall this negative media coverage than the positive coverage.

The major public health implications of the spread of misinformation regarding water fluoridation on the Internet is that this information finds its way into local anti-fluoride campaign materials which are used to influence councils who ultimately are required to make decisions on water fluoridation implementation. The standard procedure for making council decisions on matters outside of the expertise of council members is to invite comment from representatives of different sides of the issue. Councillors are presented with conflicting information of which they are not qualified to judge, and under public pressure by a small number of committed activists, may decide to maintain the status quo which means to not introduce water fluoridation. Other councillors may decide to carry out their own research and may turn to the Internet which is the primary source of misinformation regarding the fluoridation of water. One councillor from Northern NSW has quipped that "It took five minutes of research to confirm my opinion about fluoride" [34].

Public plebiscites are also frequently adopted by councillors as a solution to not having to make what is sometimes viewed as an unpopular decision, and anti-fluoride misinformation is used to sway the public opinion in this scenario as well. For example, a leaflet distributed by a rural council area in NSW prior to a public plebiscite on the addition of fluoride to the town water supply claimed that water fluoridation was unethical, unsafe and ineffective [35]. That the anti-fluoride rhetoric was given the same space as for the 'Yes campaign' puts these viewpoints on a par and gives the impression that both viewpoints have equal weight, despite the fact that no credible public health, dental or medical organisations anywhere in the

world are opposed to water fluoridation. Opponents of water fluoridation in Australia make extensive use of the steady stream of ready-made misinformation available from overseas sources.

In modern democracies it is vital that choices be informed, and scientific evidence is critical for this to occur. Scientific evidence forms the fundamental bedrock for decision making for public health practitioners, but the process for much of the population is more complex with any decision based on a range of opinions, beliefs, emotions, risk assessments, and experiences. Indeed, it has been argued that appealing to facts, and to accredited experts for their interpretation, has been increasingly compromised by an awareness of the limitations of experts and expert knowledge in resolving issues of public controversy [36]. Further, it is believed that there is a growing public perception that experts can and do disagree and that purportedly 'disinterested' advice may be influenced by economic, professional, or political considerations [36]. Such perceptions are attributed partly for the increased resistance of the general public to health promotion messages and interventions [37]. At the same time, levels of cynicism regarding politicians are at an historic high [38]. Unfortunately, decisions to do with the implementation of water fluoridation are often subverted to political purposes. Politicians as well as opposition groups are quick to pick up on rhetoric which may resonate with the public, with resistance to public health measures often having at their heart an appeal to an individualistic ideology that valorises the fight against the erosion of civil liberties and promotes suspicion of 'faceless' authority figures [39].

In population public health there is frequently a tension between public good and individual freedoms. Kass, for instance, has described the dilemma faced by the population-based focus of public health concerning the infringement on individual liberties in ethically troublesome ways [40,41]. The introduction of bans on public smoking, the requirements to wear seatbelts in cars or helmets on motorcycles, and compulsory childhood immunisations all infringe to some extent on personal choice, yet all are supported by public health advocates and backed by government legislation. The ethics behind this process is now well established, and generally accepted by the community. This perhaps explains why a significant majority of the Australian population continue to support the practice of water fluoridation [42,43].

It should be noted that antagonism towards and opposition to the views of public health practitioners by minority groups is not restricted to the fight over water fluoridation. Parallels can be drawn with some other public health controversies such as compulsory child immu-

nisations or the use of genetically modified (GM) foods. There is now, for example, an extensive body of research analysing the debate over the safety of the MMR (measles, mumps, and rubella) vaccine [44-48]. Concerns over the MMR vaccine first surfaced following a study by Wakefield et al. published in the *Lancet* linking the vaccine to autism [49]. The study prompted widespread concern and the resultant controversy has been blamed on a significant decrease in vaccination rates in the UK [48,50] and to a lesser extent in Australia and the US [45]. Fitzpatrick has argued that the perceptions of risk, choice and chance are central to the public's response to the controversy [46] and as a result of these concerns a number of groups have formed to oppose the compulsory MMR immunisation of children. However, while a number of anti-vaccination websites do exist [51,52], concerns over vaccinations are believed to have been led more by the media in response to the Wakefield et al. study than by organised or influential opposition groups as with water fluoridation [48,53].

While the moral, ethical and social concerns over water fluoridation are both legitimate and fully deserving of further investigation, they lie outside of the intent of this current paper. Instead, this paper will restrict its analysis to a critique of anti-fluoridationist literature. Rather than attempt a rebuttal to every claim and research finding put forward by water fluoridation opponents, a task attempted elsewhere [20,54,55], an analysis of the anti-fluoride lobby's techniques and tactics will be pursued. It is hoped that this may achieve two purposes: (1) to aid health and public health officials in countering the anti-fluoridationist strategies; and (2) to provide information to help both the general public and public health advocates sort the truth from the fiction and learn to identify the use of rhetoric, misinformation and misrepresentation relating to water fluoridation. Indeed, the irony of water fluoridation opponents claim that "fluoridation is an issue where the scientific method and principles are being set aside by public health authorities" [56] is that nowhere is the scientific approach more blatantly flouted than within anti-fluoridation literature.

Denying the benefits of water fluoridation

One of the fundamental tactics of water fluoridation opponents is to either deny or to besmirch the benefits of water fluoridation. It is argued that water fluoridation is either not effective or, at best, only minimally effective [57,58]. It has even been argued that water fluoridation actually harms teeth, making them more susceptible to caries [59]. These claims have been adequately addressed elsewhere with numerous systematic reviews finding that water fluoridation is associated with improved oral health [60-62]. Nonetheless, opponents of water fluoridation use several techniques to try and mislead the public in terms of the effectiveness of water fluoridation.

Selective reporting of studies

Each year hundreds of studies are published in the scientific literature regarding the effects of fluoride on animals and humans. In order to examine a relationship between variables across an extensive body of literature scientists often make use of literature reviews or meta-analyses. Water fluoridation opponents, however, take a contrary approach. Rather than trying to discern a given outcome for fluoride exposure across all available studies, they handpick studies to cite. Findings not supporting their viewpoint are entirely disregarded while other findings may be prominently utilised. As an example, the York report, a large and comprehensive systematic review of the water fluoridation literature published in 2000, found that of the 29 studies included that examined the relationship between incidence of bone fracture and water fluoridation, four indicated a significant increased risk of fracture, five indicated a significant decrease in risk of fracture, while the other studies found no significant associations [60]. An article by Kauffman, however, stated that one of the harmful effects of water fluoridation is bone fracture [63] with this contention based on a single published study from the systematic review [64]. While the cited study does represent one of the four studies identified in the York Report as indicating increased risk, no mention is made of the studies finding lower incidence of fractures with water fluoridation nor is any mention made of the 20 studies that failed to find a significant result in any direction.

Selective reporting of results

To make the selective reporting of studies even more misleading, often specific results within specific studies are reported while any disconfirming results are ignored. For example, in a study examining the relationship between children's caries experience and consumption of non-fluoridated bottle and tank water [65] the lack of a statistically significant effect on the permanent tooth decay experience of 12-year-olds was the source of numerous articles, paid for press releases, and world-wide presentations. Water fluoridation opponents cite the study as evidence that water fluoridation is ineffective [66,67]. However, the finding of a strong beneficial effect of water fluoridation on the caries experience of younger children's teeth has been entirely ignored. Interestingly, while Pollick [68] in his article 'Scientific evidence continues to support fluoridation of public water supplies' cites this study as supporting water fluoridation, Connert [69] uses the same study to support a diametrically opposed view in his paper 'Scientific evidence fails to support fluoridation of public water supplies'.

Downplaying or ignoring the evidence

Water fluoridation opponents claim that there is either no 'significant' or no 'substantial' reduction in tooth decay

resulting from exposure to fluoridated water [57]. Numerous studies are cited showing no difference, many of which simply compare one community with another without any control for other possible variations between those communities. Systematic reviews, such as the York report [60], which include no studies classified by its criteria as Level A, are cited as supposed proof of the total absence of high quality evidence [59], confusing the concept of quality with the York report's evidence classification. Reductions of 'a fraction of one decayed tooth per child' are dismissed as not substantial. Finally, findings of reductions in decay experience in non-fluoridated areas are used as evidence that fluoridation provides no added benefit to changes occurring in the absence of water fluoridation [59,70]. All of these arguments, however, are flawed and misrepresent study results.

Water fluoridation is a population-level caries preventive strategy. Therefore, the appropriate method of measuring effectiveness is to look at the population level effect rather than look at the effect on any given individual. The York report's systematic review [60] found reductions of between 0.5 and 4.4 decayed, missing and filled teeth per child on average. Reductions of between 20% and 40% have elsewhere been commonly reported. Differences of between 32% and 55% in the deciduous teeth and 20% and 65% in the permanent teeth have been reported in Australia [71]. Contrary to claims made by opponents of water fluoridation, these differences have been found to be statistically significant in published scientific research. In addition, although the generally low caries levels in Australia and some other countries might make such percentage differences work out to only a fraction of a tooth per child, at a population level this equates to a tremendous reduction in the amount of disease present. For instance, a recent Australian study found that across socio-economic groups water fluoridation was associated with caries reductions of between 48% and 75% [72]. However, in a paid-for press release by the New York State Coalition Opposed to Fluoridation (NYSCOF), Paul Beeber, President of the NYSCOF, argued that this indicates a waste of taxpayers money "for such a slim, if any, benefit" [73]. While a difference in decay experience between fluoridated and non-fluoridated areas of 0.7 teeth on average might be dismissed by anti-fluoridation lobby groups as "meagre" [73], if this finding could be extended across the Australian child population of 1.8 million children, it would translate into over a million teeth saved from decay, affecting hundreds of thousands of children. Such a result would be significant in terms of the extra disease prevented, the associated reduction in suffering, and savings in treatment costs.

Another example of downplaying the evidence of the effectiveness of water fluoridation is the argument that

fluoridated water is not required to be ingested to be effective. Opponents of water fluoridation often present quotes by researchers saying that the primary effect of fluoride is topical (that is acting on the tooth surface) rather than systemic [59]. However, recent research in Australia by Singh and colleagues [74-76] has found that the pre-emptive or systemic effect of fluoride in water supplies is at least as important in accounting for the caries preventive effect of consumption of fluoridated water as the post-eruptive or topical effect. It is common for opponents of water fluoridation to cling to old or out-of-date research while ignoring newer research that might cast doubt on their theories. Sometimes statistics and results from many decades ago are quoted to support their beliefs and statements.

Using ecological comparisons

Another ploy of water fluoridation opponents is to use ecological comparisons in an effort to demonstrate that water fluoridation is ineffective. With this tactic, the decay experience of children in a specific fluoridated area is compared unfavourably to that of children in a specific non-fluoridated area [59,77]. Despite such ecological comparisons providing a poor level of evidence due to their inability to take into account other variations between the areas which are also related to dental health (such as differences in diet, socio-economic status, exposure to discretionary fluorides, and oral health behaviours) this type of 'evidence' has been frequently used to shore up the arguments of water fluoridation opponents [72]. Although selected associations such as these provide no evidence of causality, many people may be inclined to accept ecological comparisons as a valid test of the effectiveness of water fluoridation and opponents of water fluoridation continue to use this approach to mislead the public and government officials.

Fear mongering

One of the easiest ways to preserve the status quo is by raising potentially dangerous or fearful consequences associated with possible change. This technique is common in politics where allusion to personal impropriety or dire economic consequences may be enough to taint a political candidate or party. Water fluoridation opponents, like politicians, make extensive use of fear mongering. Fluoride exposure has been linked in the antifluoridationist literature to poisonings and various accidents, allergies, brain dysfunctions such as Alzheimer's disease, hyperactivity, low intelligence, arthritis, bone diseases including hip fractures and osteosarcomas, cancers, dental fluorosis, gastrointestinal problems, diseases of the kidney, pineal gland and thyroid gland, reproductive issues, AIDS, and even with increased tooth decay [20]. Links have been made between fluoride consumption and birth defects, perinatal deaths and increased

crime. Claims that governments are using water fluoridation to 'dumb down' the population [78-80], help the spread of communism [81], or prepare the way for the New World Order [81,82] are used occasionally in anti-fluoridationist writings. A consistent thread is that those scientists and government officials who are pro-fluoride are under the sway of multi-national corporations or funded to support water fluoridation.

Despite the extensive claims of water fluoridation opponents, the only substantiated link between fluoride exposure and any health side effect is for dental fluorosis [60,61]. This condition involves a hypomineralisation of the tooth surface in contrast to the demineralisation of the tooth surface associated with decay. In addition, there is no evidence that there is any financial remuneration from the sugar or aluminium industry for scientists publishing materials that show the benefits of water fluoridation.

Misrepresentation of the truth

In many cases information is misrepresented in order to support the anti-fluoride argument. Misrepresentation involves taking information out of the context in which it is presented in order to make it support a viewpoint which the author or authors did not intend. Statements are taken out of context, and results are selectively reported. In Australia, for example, opponents of water fluoridation make the false claim that the National Health and Medical Research Council (NHMRC) recommends "that NO additional fluoride be given to children under three years" [59]. It is argued that there is a contradiction between this claimed recommendation and support by the NHMRC for water fluoridation. However, the NHMRC actually recommends that no fluoride supplements be given to children under three years of age [62]. Fluoride supplements are tablets or drops, often available from a chemist, used to increase intake of fluoride in non-fluoridated areas. There is, therefore, no contradiction with the NHMRC supporting water fluoridation. Yet, such misrepresentations continue to be made.

Misrepresentation often takes place by omission. Connett [83,84], for example, has regularly cited a study from China [85] as finding a doubling of hip fractures when people consume water with 1.5 ppm fluoride and a tripling of fractures when consuming water of greater than 4.3 ppm fluoride. This is cited as evidence of the deleterious effect of water fluoridation on the bones. What Connett does not state is that the doubling of hip fractures at 1.5 ppm is not statistically significant and that the authors' find a 'U' shaped relationship between the amount of fluoride in the water and fractures, with optimally fluoridated water actually conferring a protective effect on bone fractures. Yet, handpicked and misrepresentative information may find its way from the Internet to prominent

pieces in national newspapers [86] with little regard for the truth.

The big lie

Bernhardt and Sprague have argued that the basic technique of anti-fluoridationists is to make the claim that water fluoridation causes a number of serious ailments that people fear [87]. This technique involves telling a lie so large that it defies anyone to believe that someone would distort the truth to such an extreme extent, and is aided in its effectiveness by constant repetition. Research findings indicate that if something is said often enough people will tend to think there is some truth in it, a process now called the illusory-truth effect [88]. Further to this technique is what is called the 'laundry list' approach, listing so many 'evils' that even if water fluoridation proponents can adequately respond to some they can not address all [89]. Such a technique is particularly effective in debates, letters to the editor or in the popular media where the time and opportunity to reply is limited or non-existent. The American Dental Association catalogues about 30 adverse health effects linked in anti-fluoridation literature to water fluoridation [20].

Half-truths

A half-truth is a statement that is only partly true and is generally intended to deceive. If an uninformed member of the public were to read and believe the following text, taken from an anti-fluoride website, they might have good grounds for being concerned about water fluoridation:

'Did you know that sodium fluoride is ... one of the basic ingredients in both PROZAC (Fluoxetine Hydrochloride) and Sarin Nerve Gas (Isopropyl-Methyl-Phosphoryl FLUORIDE) - (Yes, folks the same Sarin Nerve Gas that terrorists released on a crowded Japanese subway train!). Let me repeat: the truth the American public needs to understand is the fact that Sodium Fluoride is nothing more (or less) than a hazardous waste by-product of the nuclear and aluminium industries. In addition to being the primary ingredient in rat and cockroach poisons, it is also a main ingredient in anesthetic, hypnotic, and psychiatric drugs as well as military NERVE GAS! Why, oh why then is it allowed to be added to the toothpastes and drinking water of the American people?' [78]

People may not normally consider that many substances can be harmful or poisonous depending upon the dose. Excessive intake of vitamin D, salt or even water may result in poisoning. The issue of dosage and its relationship to toxicity is rarely mentioned in anti-fluoridationist rhetoric because it undermines the intended link between water fluoridation and harm. The inclusion of a substance in a poison or toxin does not mean that at smaller doses

in humans the substance is still toxic. For example, Warfarin, an anti-coagulant which is the active ingredient in the common rat poison, RatSAK, is also used as a medicine for people in danger of stroke [90,91] and in cases of deep-vein thrombosis [92,93]. The toxic Sarin gas ($C_4H_{10}FO_2P$), contains not just fluoride but oxygen, hydrogen and carbon. The fact that a given substance is toxic does not mean that every element contributing to it is also toxic.

Innuendo

Innuendo involves an indirect or subtle, usually derogatory, implication in expression. Water fluoridation opponents often link water fluoridation to other medical and government sanctioned practices that have led to aversive and unexpected consequences. An example is thalidomide, a drug that was prescribed to pregnant women during the late 1950s and 1960s to aid sleeping, morning sickness and other pregnancy symptoms and was later found to be teratogenic in foetal development, causing physical deformities [94,95]. Statements such as "When the truth about fluoridation is finally exposed, it may well dwarf the thalidomide tragedy", attributed to Albert Schatz and published by the New Zealand Fluoride Action Network [96], is an example of the use of innuendo. Similarly, Bryson writes "It was an era of thalidomide and plutonium; school segregation and human experimentation; ... atmospheric Hbomb testing and DDT... Fluoridated water was idealized as the ultimate form of 1950's failsafe social engineering" [97]. Again, water fluoridation is linked to a number of dangerous and now controversial practices in an attempt to discredit it by association. The question: "Can we not learn from past assurances of the safety of DDT, thalidomide, and the hundreds of other 'safe' chemicals?" [98], uses innuendo to imply that water fluoridation is also an environmental disaster waiting to happen. It should be realised that this rhetorical practice is intended to sway the opinion of an audience and presents no evidence indicating that water fluoridation causes harm. Thousands of drugs, medicines and chemicals have proven safe and effective and have led to a longer and better quality life. Only a small number of medical substances have proven harmful in the long run and there is no validity in using these as evidence for the danger of any other substance.

Follow the leader

Opponents of water fluoridation, despite arguing that water fluoridation should not be introduced just because other areas have implemented it, argue that it should be rejected in Australia in the same way that it has been allegedly rejected by 98% of Western Europe [99]. They state that Austria, Belgium, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Sweden and large sectors of the United Kingdom do not have water fluoridation

in place and directly or by insinuation make the argument that there must be something wrong with water fluoridation for these countries to have not implemented the practice. This argument is flawed for two reasons. First, it is equally applicable to argue that because the United States, Australia, New Zealand, Ireland, Brazil, some sectors of the United Kingdom, and various other countries have introduced water fluoridation then other nonfluoridated countries should also introduce the process. The second is that countries that do not have water fluoridation have mostly not rejected the benefits or science of water fluoridation but have not introduced water fluoridation for a range of other reasons [4]. These have to do with cost, the use of other population preventive practices such as salt fluoridation or the belief that water fluoridation is unnecessary because universal and extensive dental care programs are already in place.

Enforced medication

Antifluoridationist literature is replete with scare words, such as "pollutant", "chemical" and "toxic waste" that reinforce the idea of harm. The idea of 'enforced medication' is another expression that comes up repeatedly when efforts are made to extend water fluoridation to non-fluoridated areas. According to this argument, fluoride is a medicine, taking medicine should only be a function of individual choice, and therefore water fluoridation is an impingement on our freedom of choice. Use of the term medicine implies something which should only be administered by a doctor acting for the good of an individual. Terminology such as "mass medication" or "forced medication" is often picked up on and used by local government officials who are responsible for decision making [100,101].

The rejoinder to this line of argument is that fluoride added to the water supply is not a medicine. In Australia, for example, fluoride only appears in the Standard for the Uniform Scheduling of Drugs and Poisons as a schedulable substance when used in amounts of more than 1000ppm. In any event, such a population preventive strategy is certainly not without precedent. Iodine is added to salt to help prevent goiter and low intelligence. Folate is added to bread and rice products because of its importance in the development of babies. Vitamins, minerals and other additives are now commonplace in many foods because they are believed to confer health benefits. While fluoride may differ from iodine, folate and other substances in terms of its pharmacological effect, it shares the feature of being one of a number of successful population preventive public health strategies.

Bamboozling with science

Anti-fluoridation literature attempts to overwhelm readers with claims about scientific research, with figures and

statistics, and with scientific terms and buzzwords. Unpacking such a dense presentation of facts, quotes and figures is beyond most people, who have neither the time nor capacity to access most of the publications required to check on the plethora of claims. A classic example of bamboozling with science is the 8-page Lifesavers Guide to Fluoridation, produced by Viamouyiannis [102], which contains 250 references from a variety of journals, court cases, books, newsletters, symposia and newspapers, as well as several personal communications. Many of these references were subsequently used in the book 'Fluoride: the aging factor' [103], a major reference source for water fluoridation opponents. A two-year search for the cited literature by a team of people revealed less than half of the cited references to be in peer reviewed journals [54]. Almost all references were found to be incompletely cited and Viamouyiannis was found to make superficial observations, leap to unwarranted conclusions and present a pervasive bias in his evaluation of data. However, more than two decades later the same studies continue to be cited in anti-fluoridation literature.

Opponents of water fluoridation may also attempt to bamboozle the public with language, often verging on nonsensical, yet purveying a sense of drama and foreboding. An example is shown in this quote taken from a prominent Australian fluoridation opponent:

"A maze is a model of fluoridation dental thinking, its paths (claims) leading to nowhere but neonlighted with imaginary posters of great rewards at the end of the rainbow trail which never ends, and importantly has no qualified scientific exit...The fluoridation maze hides the secrets of so-called dental science where it can be worshipped unseen with its faceless hierarchy of long on words but short of substance." [104].

Such bombastic language, combined with a litany of unsubstantiated claims, is designed to overwhelm the reader who may well find it easier to simply believe what they are being told than to try and trace the facts for themselves.

Moving the goalposts

Ultimately, whatever research is released showing that water fluoridation is not associated with aversive outcomes will be judged as unacceptable by fluoridation opponents. The goalposts have now been moved to such an extent that satisfying calls for supporting studies is practically impossible. Chairman of the Anti-fluoridation Association of Victoria, Glen Walker, expresses this sentiment with his statement that "there is no evidence of a scientific study proving fluoridation is perfectly safe for humans in all public circumstances" [105].

Paranoia, conspiracy theories and extremism

Although many opponents of water fluoridation distance themselves from extremist views, any Internet search will reveal numerous instances of these still being propounded. There is an audience for such views. Extremist arguments find fertile ground among disenfranchised, psychologically disturbed, and alienated individuals [23]. A subculture has now developed around and for such people who are believed to find psychological gratification in imagining themselves heroically in the possession of such secret and 'subversive' information [106].

Conspiracy theories relating to water fluoridation are common. Some claim that the basis of the science for water fluoridation is rooted in protecting the U.S. atomic bomb program from litigation [107]. Others argue that adding fluoride to water was pioneered by a German chemical giant to "reduce an individual's power to resist domination, by slowly poisoning and narcotizing a certain area of the brain, thus making him submissive to the will of those who wish to govern him" [108]. Still others claim that water fluoridation is part of a plot by the New World Order, a group of Illuminati, intent on taking over the world [109]. An example of paranoia is demonstrated by the following excerpt from a Christian organisation based on the preachings of William Branham:

"Fluoride is a hypnotic drug that accumulates in the body, producing schizophrenia. It was used in Russian prison camps and is harmful to dental health. The real purpose behind water fluoridation is to reduce the resistance of the masses to domination and control, and loss of liberty." [110]

The belief that water fluoridation was a communist plot to alter society was famously parodied in the movie *Dr Strangelove*. However, such claims were common in the 1950s at the height of the cold war between the USSR and USA. Indeed, Newbrun has described a chronology of anti-fluoridation propaganda in the US since the 1950s with the main themes found to reflect the social and political environment in the US at the different points in time [22].

Even some of the more prominent water fluoridation opponents often engage in what Newbrun calls the conspiracy gambit [22]. Researchers and bureaucrats are believed to be in the pay of and therefore beholden to the sugar and aluminium industries. In a pamphlet distributed by local council to residents of the rural Australian town of Deniliquin prior to a plebiscite on water fluoridation in 2004, it was claimed that: "Behind the dental and medical associations, who promote fluoridation with religious fervour, are powerful corporate and political interests" [35]. The sugary food industry, the phosphate

fertiliser industry, the aluminium industry, and some governments are listed as the ominous forces behind the proponents of water fluoridation [19]. Others see water fluoridation as a cover used by generations of decision makers for the alleged failure to provide dental care to poor people. Again, no evidence is or can be offered for any of these claims.

Summary

The list of techniques and methods described and analysed above are by no means the full extent of techniques used by water fluoridation opponents, although they are perhaps most pertinent to their promulgated literature. Common additional ploys involve neutralising politicians by massive letter writing campaigns to give the illusion of controversy, requesting public plebiscites which often have low turnouts and are dominated by people opposing change, the use of so-called experts to lend credence to anti-fluoridation claims, urging that fluoridation be delayed until better research is conducted or until the fabricated doubts can be resolved, inventing organisations with official sounding names in order to create credibility, and using public debates which give the illusion of scientific controversy and move dialogue away from scientific discussion by allowing rhetorical practices [16,111,112].

The evidence for the effectiveness of water fluoridation is incontrovertible. More than a dozen large-scale literature reviews have found water fluoridation, even against a backdrop of high discretionary fluoride use, to confer a caries preventive benefit in children. Further to this, water fluoridation and its effect on the tooth structure provides a benefit to adults across their lifespan. The situation whereby a small group of determined individuals can manage to deny half a century of science pays testimony to the power of emotional arguments and the potential of misleading propaganda. It is here that scientists must continue their stand, reinforcing the arguments for water fluoridation while using their knowledge of the literature and their understanding of anti-fluoridation tactics to assist health departments. Table 2 presents both a number of the arguments put forward by water fluoridation opponents and a possible response by water fluoridation proponents. While it is not the intention here to provide a response to every possible argument, Table 2 provides brief useful responses for the most common claims and arguments made by water fluoridation opponents. Other lists, such as those put out by the Department of Human Services Victoria, offer more complete and extensive coverage [113].

Despite more than half a century of implementation, the addition of fluoride to the water for the prevention of dental decay is still considered a controversial and debated

public health measure by some segments of the population. In and of itself this state of affairs is nothing new. Campaigns have been waged over the addition of chlorine to water supplies, compulsory child immunisations, the compulsory wearing of seatbelts in cars and many other public health initiatives. However, water fluoridation suffers the inglorious distinction of being one of only a few public health initiatives to still be regularly thwarted as a result of public action based on emotional and often misleading appeals.

If Australia's National Oral Health Plan is to be implemented and water fluoridation extended to all those non-fluoridated Australian communities with populations in excess of 1000 people, a considerable effort of political will is going to be required. With decision making in most States devolved to local councils, extension of water fluoridation will occur only in a piece-meal fashion typified by a succession of emotionally charged battles between public health official and organised anti-fluoridation groups both attempting to engage the support of the public. It is therefore hoped that by better understanding the techniques and tactics of water fluoridation opponents, public health advocates, government officials, and ultimately the public, will come to dismiss many of the anti-fluoridation arguments as little more than fallacious non-science, paving the way for the extension of water fluoridation to those areas yet to benefit from its implementation.

Competing interests

The author(s) declare that they have no competing interests.

Table 2: Suggested responses to anti-fluoridationist arguments

Anti-fluoride argument	Suggested response
Water fluoridation confers no oral health benefit	Numerous systematic literature reviews from a number of countries have found water fluoridation to provide a significant caries preventive effect.
Water fluoridation causes hip fractures, cancers, Alzheimer's, reduced intelligence in children, etc.	Research finding associations between water fluoridation and various diseases offer no proof, as causality cannot be established in these studies. Water fluoridation opponents handpick studies and may misrepresent the results so as to support their views. Large-scale systematic reviews have not confirmed any associations between water fluoridation and the large list of diseases linked to it by opponents of water fluoridation.
Fluoride is a toxic poison.	Fluorine is a naturally occurring element that, like many other natural substances, can be toxic if consumed in excess. Water fluoridation ensures ingestion of fluoride well below any toxic level, both for adults and children.
Fluoride is used in rat poison and other dangerous substances.	It is dose that determines the level of toxicity. Many essential and commonly occurring elements form poisonous or toxic substances.
Numerous other countries have rejected water fluoridation.	Some other countries have elected not to introduce water fluoridation because they prefer, or already have, other approaches to improving dental health. Nonetheless, many countries do have water fluoridation and benefits are conferred to all people, including those at high risk who may not effectively use individual fluoride exposures.
Water fluoridation is supported only by 'shoddy' science.	Decades of research and hundreds of scientific articles published in peer-reviewed journals support water fluoridation. This research is so convincing that almost all major dental and health authorities support it.
There should be a public plebiscite. It is undemocratic to have water fluoridation forced upon us.	In almost all democratic systems representatives of a population are elected to make decisions on behalf of the population. Plebiscites or public referendums are not required to pass legislation that is compatible with the constitution or charter under which the country operates. Water fluoridation fits within a government's duty of care to the country's citizens.
Tooth decay has declined in countries with and those without water fluoridation. Water fluoridation makes no difference.	Declines in tooth decay have occurred as a result of changing exposures to fluoride and dietary changes. Regardless, water fluoridation reduces tooth decay above and beyond these other effects. Ecological comparisons of some countries with others offer no support for or against water fluoridation as many other factors may account for differences in disease experience from one country to the next. Water fluoridation does make a difference.
Most people do not want water fluoridation.	Independent research in most places where water fluoridation is being considered shows that people support water fluoridation. Generally, the more knowledge people have the more likely they are to support it.
Water fluoridation is costly and not economically viable.	Research has previously found water fluoridation to be cost-effective. Newer technologies have made water fluoridation cost-effective for increasingly smaller populations. In addition to being cost-effective, it is also necessary to keep in mind the reduction in dental disease and therefore the pain and suffering reduced as a result of water fluoridation.
Water fluoridation infringes freedom of choice and individual rights and is unconstitutional.	Adding fluoride to water is just one of many instances where a chemical or nutrient is added to a food or beverage for public health benefits. It already occurs in water with the addition of chlorine, which aids greatly in eliminating water borne disease, as well as in several foodstuffs. Water fluoridation sets no precedent.
Water fluoridation is being pushed on us as a result of 'big business' interests.	The scientists researching the effectiveness of water fluoridation as well as health officials and dentists do not receive money from sugar, aluminium or any other companies for their research or opinions.
There is more caries in fluoridated X than in non-fluoridated Y. This proves water fluoridation does not work.	Ecological comparisons involving the arbitrary selection of fluoridated and non-fluoridated communities or areas do not provide credible evidence of the effectiveness or otherwise of water fluoridation as any differences may be the result of other factors which are linked to tooth decay but differ across the areas. Scientific research has found water fluoridation to be effective.
We should wait until water fluoridation is proved to be safe.	Water fluoridation has been implemented in some places for more than half a century – long enough that any dangers would be apparent if they existed. The weight of evidence strongly indicates that water fluoridation is safe.

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Water Fluoridation and the Environment:

Current Perspective in the United States

HOWARD F. POLLICK, BDS, MPH

Evidence of water fluoridation's effects on plants, animals, and humans is considered based on reviews by scientific groups and individual communities, including Fort Collins, CO, Port Angeles, WA, and Tacoma-Pierce County, WA. The potential for corrosion of pipes and the use of fluoridation chemicals, particularly fluorosilicic acid, are considered, as is the debate about whether fluoridation increases lead in water, with the conclusion that there is no such increase. The arguments of anti-fluoridationists and fluoridation proponents are examined with respect to the politics of the issue. **Key words:** fluoridation; environment; toxicology.

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Prior to 1945, epidemiologic and laboratory studies confirmed the association between the environment (naturally-occurring fluoride in water supplies) and the health and cosmetic appearance of teeth.¹ Where fluoride levels were low, prevalences and severity of dental caries were high among lifetime residents, yet where fluoride levels were high, the prevalences and severity of dental caries were low, but dental fluorosis occurred with high prevalence and severity. This led to the concept of creating an ideal environment for optimal dental health through adjusting the naturally occurring fluoride level to about 1 mg/L (1 part per million). In 1986, the U.S. Environmental Protection Agency (EPA) set the maximum contaminant level (MCL) for naturally-occurring fluoride in public drinking water at 4 mg/L, with a secondary standard at 2 mg/L.²

Water fluoridation, then, is the controlled adjustment of fluoride concentrations of community water systems to optimal levels to minimize the incidence of dental caries (tooth decay) and dental fluorosis (enamel mottling). From initial efforts begun as community trials in 1945, water is now fluoridated in thousands of public water systems and reaches two thirds of the U.S. population served by such systems.³ Community water fluoridation and other uses of fluorides, such

as in toothpaste, have significantly reduced the prevalence of dental caries in the United States.¹

Early investigations into the physiologic effects of fluoride in drinking water predated the first community field trials.⁴⁻⁷ Since 1950, opponents of fluoridation have claimed it increases the risks for cancer, Down's syndrome, heart disease, osteoporosis and bone fracture, acquired immunodeficiency syndrome, low intelligence, Alzheimer disease, allergic reactions, and other health conditions.⁸ The safety and effectiveness of water fluoridation have been re-evaluated frequently, and no credible evidence supports an association between fluoridation and any of these conditions.^{9,10}

The Environment

Environmental concerns have been investigated in literature reviews for the Tacoma-Pierce County Health Department, Washington (August 2002),¹¹ and the City of Port Angeles, Washington (October 2003),¹² and no negative impact of water fluoridation on the environment has been established. Issues related to discharge to water; emissions to air; production, storage, or release of toxic or hazardous substances; or production of noise have been found to be nonsignificant. Emissions of fluoride into the air are not released outside the well houses. Fluoride concentrations in rivers downstream of the discharges increase by less than 0.01 mg/L due to adding fluoride to the water supply system.

Fluoridated water losses during use, dilution of sewage by rain and groundwater infiltrate, fluoride removal during secondary sewage treatment, and diffusion dynamics at effluent outfall combine to eliminate fluoridation related environmental effects. In a literature review, Osterman found no instance of municipal water fluoridation causing recommended environmental concentrations to be exceeded, although excesses occurred in several cases of severe industrial water pollution not related to water fluoridation.¹³ Osterman found that overall river fluoride concentrations theoretically would be raised by 0.001-0.002 mg/L, a value not measurable by current analytic techniques. All resulting concentrations would be well below those recommended for environmental safety.

A study conducted in Phoenix, Arizona, to test the efficacy of soil aquifer treatment systems indicated that fluoride concentrations decline as water travels under-

Received from the Department of Preventive and Restorative Dental Sciences, School of Dentistry, University of California San Francisco, San Francisco, California.

Address correspondence and reprint requests to Howard Pollick, Department of Preventive and Restorative Dental Sciences, 707 Parnassus Avenue, San Francisco CA 94143-0758.

ground. This study suggests that 40-50% of the fluoride discharged to groundwater is removed as the water travels through the soil and aquifer. Thus, fluoride does not concentrate in groundwater.¹⁴

PLANTS AND ANIMALS

The concentration of fluoride in the treated water does not reach levels that could harm any plant or animal species.^{11,12} A report of the effect of industrial pollution, from an aluminum plant on salmon indicated that the usual fluoride concentration of the river was 0.1 mg/L, and when the concentration was raised experimentally to 0.5 mg/L, there was an effect on the salmon.¹³ Since rivers and streams are not fluoridated and the increase in the fluoride concentration of a river as a result of runoff from fluoridated water would be insufficient to raise the level to even 0.2 mg/L, fluoridation of water can have no effect on salmon.

There is no evidence that fluoridated water has any effect on gardens, lawns, or plants. Although silver fluoride is not used in water fluoridation, silver fluoride at 1 mg/L used as a disinfectant had no effect on growth of wheat.¹⁶ There is evidence that very high concentrations of fluoride have no toxic effect on plants in ponds:

The fate of fluoride in a simulated accidental release into an experimental pond was observed for 30 days in Grenoble, France. The components investigated were water, sediments, plants, algae, molluscs, and fish. Twenty-four hours after the release, most (99.8%) of the fluoride was distributed in the physical components (water and sediments), and the biological agents contained only 0.2% of the fluoride released. Despite an exposure to hot spots of 5,000 ppm at the beginning of the accidental release, no visible toxic effects were observed on the biological components such as plants, algae, molluscs, and fish.¹⁷

There is evidence that ladyfinger (okra) can withstand up to 120 mg/L fluoride. The consumption by people of this plant grown with fluoridated water at 1 mg/L would be 0.2 mg per kg:

Because of suggestions that food is a rich source of fluoride to humans and the absence of permissible and upper limits of fluoride for irrigation water, plant uptake studies were conducted using fluoride-rich irrigation water. Ladyfinger was grown in sand and soil cultures for 18 wk and the accumulation of fluoride in various plant parts was studied. The potential for ingestion of fluoride by humans through this route was also considered. The percentage uptake was greater in sand-cultured plants than in soil-cultured plants. The root accumulates most of the fluoride supplied through irrigation water and the fruit accumulates the least. Up to 120 mg/L fluoride of irrigation water did not harm the plants. The ingestion of fluoride by humans from plants irrigated with water containing 10 mg/L fluoride would be 0.20 mg per 100 g ladyfinger.¹⁶

HUMANS

The Institute of Medicine, Food and Nutrition Board has estimated that the tolerable upper limit for human daily intake of fluoride is 10 mg per day for adults and children over 8 years of age.¹³ Ten independent U.S. and Canadian studies published from 1958 to 1987 showed that dietary fluoride intakes by adults ranged from 1.4 to 3.4 mg/day in areas where the water fluoride concentration was 1.0 mg/L. Where the water concentration was less than 0.3 mg/L, daily intakes ranged from 0.3 to 1.0 mg/day.¹⁹

Several municipal or territorial reviews of the water fluoride issue have concluded that available information indicates that there is no significant adverse health impact associated with water fluoridation. The Fort Collins review²⁰ included reviews from other communities, including Brisbane, Australia (1997),²¹ Natick, Massachusetts (1997),²² Calgary, Alberta, Canada (1998),²³ Ontario, Canada (1999),²⁴ and Escambia County Utilities Authority, Florida (2000).²⁵ Additionally, the Fort Collins review considered several "Tier One" reviews, including reviews by or for the Centers for Disease Control and Prevention,¹ the Institute of Medicine (1999),¹⁸ the World Health Organization (1994),²⁶ the National Research Council (1993),⁹ the U.S. Public Health Service (1991),²⁷ the International Programme on Chemical Safety (1984),²⁸ the Medical Research Council, UK (2002),²⁹ the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service (2001 draft and 1993),³⁰ and York, U.K. (2000).³¹

The Fort Collins report found that:

- The weight of the evidence suggests that there is caries (cavities) reduction in populations exposed to water fluoridation at or near an optimal level
- Likely total exposure values for children older than six months living in communities with water fluoridated at up to 1.2 mg/L (ppm) do not exceed the upper limit set to be protective of moderate dental fluorosis by the Institute of Medicine. Total dietary exposures of fluoride can exceed this threshold amount (0.7mg/day) in infants fed formula reconstituted with optimally fluoridated water.
- There is no consistent evidence from human or animal studies that exposure to optimally fluoridated drinking water and other sources causes any form of cancer in humans, including bone and joint cancer
- The FTSG agrees with the conclusion of the Medical Research Council of Great Britain that states, "The possibility of an effect on the risk of hip fracture is the most important in public health terms. The available evidence on this suggests no effect, but cannot rule out the possibility of a small percentage change (either an increase or a decrease) in hip fractures." [Medical Research Council 2002, page 3]

- At the concentrations of fluoride provided in Fort Collins water including exposures from all sources over a lifetime, skeletal fluorosis caused by drinking water exposure is not likely to be a health issue.
- At the concentrations of fluoride provided in Fort Collins water, in combination with other sources of fluoride, as many as one in four children under age 8 may develop very mild to mild dental fluorosis. This degree of fluorosis may or may not be detectable by the layperson. With oral health as the goal, this degree of dental fluorosis is considered an acceptable adverse effect given the benefits of caries prevention.
- In the literature reviewed, doses appropriate for caries reduction were not shown to negatively impact thyroid function. Studies in which humans received doses significantly higher than the optimum fluoride intake for long periods of time showed no negative impact on thyroid function.
- Overall, evidence is lacking that exposure to fluoride through drinking water causes any problems to the human immune system.²⁰

In general, there is no credible evidence indicating a cause-and-effect relationship between water fluoridation and increased health risks.

CORROSION

According to the U.S. Environmental Protection Agency and the National Association of Corrosion Engineers, corrosion is not related to fluoride.³² Corrosion by potable water is primarily caused by dissolved oxygen, pH, water temperature, alkalinity, hardness, salt, hydrogen sulfide, and certain bacteria. Fluoride, at concentrations found in potable water, does not cause corrosion. A small increase in the corrosivity of potable water that is already corrosive may occur after treatment with alum, chlorine, fluorosilicic acid, or sodium silicofluoride, which decreases pH. This may occur in some potable water sources with little buffering capacity; it can easily be resolved by adjusting the pH upward.^{11,12,33}

CHEMICALS USED FOR FLUORIDATION

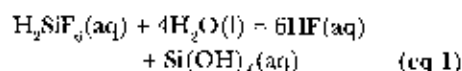
Fluorosilicates

Urbansky reviewed available information on fluorosilicates, with three objectives:

- (1) to enumerate unresolved chemical issues germane to understanding fluoridation and ascertaining the fate of fluoride and fluorospecies, (2) to critically review what is known or reported, and (3) to assemble a knowledge base to provide a starting point for future study.³⁴

Urbansky states:

Since [1962], toxicity and adverse health impacts have tested fluoride rather than fluorosilicates. As a recent example, in 2001, the FDA reported that Americans' exposure to fluoride had increased from dentifrices, and it demonstrated that any increases did not produce observable health effects in rats. Fluoride salts were continually tested instead of fluorosilicates because the complete and fast dissociation-hydrolysis (eq 1) of fluorosilicates to fluoride and (hydr)oxosilicates was generally accepted as a chemical fact. Accordingly, no reason was apparent to test fluorosilicates separately.



all the rate data suggest that equilibrium should have been achieved by the time the water reaches the consumer's tap if not by the time it leaves the waterworks plant. . . . The most common fluoridating agents used by American waterworks are sodium fluoride (NaF), fluorosilicic acid (H_2SiF_6), and sodium fluorosilicate (Na_2SiF_6) (see table below).

TABLE³⁴

	Sodium Fluoride	Sodium Fluorosilicate	Fluorosilicic Acid
(a) Number of Utilities	2491	1635	5876
(b) People served	11,700,000	36,100,000	80,000,000

*Data for the United States from the CDC's 1992 *Fluoridation Census*³⁵: (a) Number of utilities using specific additives as reported by those that fluoridate their water; (b) Populations served by specific additives (millions of people) of those drinking supplementally fluoridated water (does not include waters with naturally occurring fluoride).

Although 25% of the utilities reported using NaF, this corresponds to only 9.2% of the U.S. population drinking fluoride-supplemented tap water. The ease in handling NaF rather than fluorosilicates accounts for the disproportionate use of NaF by utilities serving smaller populations. On the other hand, the cost savings in using fluorosilicates result in large systems using those additives instead. The reduced cost of large volume offsets the costs associated with handling concentrated stocks of the fluorosilicates, which require accommodations similar to hydrochloric acid, which is sometimes used to adjust pH. In acidic solution, the dissociation and hydrolysis of fluorosilicic acid, which occurs upon dilution, is given by eq 1. In drinking water, pH is adjusted with the addition of base (e.g., NaOH, NaHCO_3). $\text{H}_2\text{SiF}_6(\text{aq}) + 4\text{H}_2\text{O}(\text{l}) \rightarrow 6\text{HF}(\text{aq}) + \text{Si}(\text{OH})_4(\text{aq})$ (eq1).³²

While there may be evidence of toxicity of these substances when workers involved in their production are not protected, there is no credible evidence of toxicity when they are diluted for use in fluoridated water. Fluorosilicic acid is diluted with water from an initial aqueous concentration of about 23–24% by about 1:250,000–1:300,000 when used for fluoridating

water.³⁵ This produces the final concentration of between 0.7–1.2 mg/L, the specific level set according to CDC guidelines.³⁷

Concerns have been raised about arsenic and lead in fluorosilicic-acid-treated water.^{38,39} However, there is no credible evidence that this is of concern.⁴⁰ Urbansky and Schock add:

The vast preponderance of the lead(II) in nearly all tap waters originates from the plumbing materials located between the water distribution mains and the end of the faucet used by the consumer.

Arsenic and lead may be present at minute undetectable concentrations, well below all current (50 ppb) and proposed (10 ppb) EPA standards. Following dilution with water, the calculated range of arsenic concentrations in the finished water contributed by fluorosilicic acid feed is 0.10 to 0.24 µg/L (parts per billion, ppb).³⁶ The analytic detection limit for arsenic is 2 µg/L, so the amount added by the fluorosilicic acid would not be detected.³⁶ In Fort Collins, the concentration of lead in the source waters was below the detection limit for lead in the department's laboratory of 1.0 µg/liter (ppb). Because lead levels are below the detection limits both before and after the addition of fluorosilicic acid, the actual changes in lead concentrations were not measurable.³⁶

Masters and Coplan have alarmed the public with their reports linking fluoridation, increased lead levels and crime.^{39,41} Urbansky and Schock criticize the conclusion reached by Masters and Coplan by stating:

Interestingly, the bibliographies of the Masters and Coplan study most strongly asserting the adverse effects of silicofluoride shows only a single reference related to sampling of drinking water or the control of lead or other metals by water treatment, so the level of awareness in the design of the studies and interpretation of the data is highly questionable. By not measuring or statistically testing numerous other water and plumbing characteristics that could correlate with lead(II) levels with equal to or greater statistical significance than those relationships that were put forth, the studies of [Reference 2] are intentionally biased towards what appears to be a preconceived conclusion. Even simple analytes that are known to affect lead mobility, such as pH or alkalinity, or analytes known to play important dietary roles in health, such as calcium, sodium or magnesium, were not reported to be measured in their study, so possible confounding variables are conspicuously excluded from evaluation.

... Recent reports [41, 39] that purport to link certain water fluoridating agents, such as fluorosilicic acid and sodium fluorosilicate, to human lead uptake are inconsistent with accepted scientific knowledge. The authors of those reports fail to identify or account for these inconsistencies, and mainly argue

on the basis of speculation stated without proof as fact. The sampling scheme employed in the studies is entirely unrelated to any credible statistically-based study design to identify drinking water lead and fluoride exposure as a significant source of blood lead in the individuals. The authors use aggregated data unrelated in space and time and then attempt to selectively apply gross statistical techniques that do not include any of thousands of other possible water quality or exposure variables which could show similar levels of correlation utterly by accident. Many of the chemical assumptions are scientifically unjustified, are contradicted by known chemistry data and principles, and alternate explanations (such as multiple routes of PbII exposure) have not been satisfactorily addressed. The choice in water fluoridation approach is often made for economic, commercial or engineering reasons that may have a regional component that could also be related to various community socio-economic measures, and so should not be considered to be a purely independent variable without investigation. At present, the highly-promoted studies asserting enhanced lead uptake from drinking water and increased neurotoxicity still provide no credible evidence to suggest that the common practice of fluoridating drinking water has any untoward health impacts via effects on lead(II) when done properly under established guidelines so as to maintain total water quality. Our conclusion supports current EPA and PHS/CDC policies on water fluoridation.⁴⁶

Nevertheless, concerns have been raised about the acidity of drinking water that may be created by fluoridation. According to Urbansky and Schock, "one cannot demonstrate that an increase in blood lead(II) ion levels can be linked to acidity from SiF_6^{2-} hydrolysis any more than one can demonstrate it results from consuming soft drinks." Additionally they state: "Note that the species PbSiF_6^0 is present at such low concentrations that we would expect to find *only one molecule of this complex in more than 1,000 liters of tap water at pH 6*, which of course, far exceeds the volume possible for water consumption and the human stomach."

A critique of this review was included in "Comments on The April 17, 2002 ICCEC Approach to Silicofluorides Study" by Coplan.⁴² The ICCEC is the U.S. Public Health Service National Toxicology Program (NTP) Interagency Committee for Chemical Evaluation and Coordination. Coplan states his concerns about the way in which Urbansky and the EPA and CDC have investigated silicofluorides. For example, he provides the following headings in his review: "EPA's acknowledged ignorance about a position they have adamantly held"; "EPA's continued effort at misdirection"; "Why Urbansky and Schock cannot be trusted"; "Why the CDC cannot be trusted"; "A substantial body of evidence has been submitted to the NTP clearly supporting the need for a comprehensive program of animal testing for health effects from chronic ingestion of SiF treated water. This

is true now and would remain true no matter what the EPA may learn about dissociation chemistry from a contractor selected by EPA employees whose objectivity and scientific integrity are less than impeccable."

Coplan's comments are in keeping with his stance as an anti-fluoridationist (one who is strongly opposed to the fluoridation of public water supplies).⁴³ It should be pointed out that Urbansky and Schock have been highly critical of the work of Masters and Coplan. It appears that the main thrust of contemporary anti-fluoridation tactics is to assert that the chemicals used in fluoridation are causing problems of one sort or another. Such tactics have emanated from the work of Masters and Coplan.

The toxicology of sodium fluorosilicate and fluorosilicic acid has been reviewed for the EPA.⁴⁴ The authors of that review state:

In water, the compound (sodium fluorosilicate) readily dissociates to sodium ions and fluosilicate ions and then to hydrogen gas, fluoride ions, and hydrated silica. At the pH of drinking water (6.5-8.5) and at the concentration usually used for fluoridation (1 mg fluoride/L), the degree of hydrolysis is essentially 100%. ... Like its salt, its (fluorosilicic acid) degree of hydrolysis is essentially 100% in drinking water. At equilibrium, the fluorosilicate remaining in drinking water is estimated to be <<1 part per trillion.⁴⁵ In addition, exposure to impurities in the fluoridating agent is judged to be of low health risk when properly treated water is ingested. For example, in fluorosilicic acid, iron and iodine are usually below the levels considered useful as a dietary supplement; the phosphorus level is reported to be insignificant; and silver is usually <4 parts per septillion in the fluoridated water.⁴⁵

The Colorado City of Fort Collins has been fluoridating with fluorosilicic acid and has responded to concerns raised about that chemical.⁴⁶ The Report of the Fort Collins 2003 Fluoride Technical Study Group, April 2003, provides a comprehensive review that includes "The Potential for Increased Contaminant Levels Due to the Use of Hydrofluorosilicic Acid."

The FTSG's review identified three potential concerns associated with hydrofluorosilicic acid (HFS). 1) co-contamination (i.e., arsenic and lead), 2) decreased pH leading to increased lead solubility or exposure, and 3) potential toxicological effects from incomplete dissociation products of HFS. The FTSG used the raw and finished water quality data for the City of Fort Collins to determine whether the addition of HFS was responsible for the potential addition of contaminants such as heavy metals to the city's drinking water. There was no evidence that the addition of HFS increased the concentrations of copper, manganese, zinc, cadmium, nickel, or molybdenum. The concentrations of arsenic and lead were below the detection limit for the Fort Collins Water Quality Control Laboratory in both the source water and the

finished water and below the maximum contaminant level (MCL) for these naturally occurring elements. There was no evidence that the introduction of HFS changed the pH of the water appreciably. Concern that HFS incompletely dissociates may be unfounded when the fundamental chemical facts are considered. Therefore, it is unlikely that community water fluoridation poses a health risk from the exposure to any of these chemicals present in the water as it leaves the plant. Further studies related to the health effects of HFS are in progress.⁴⁶

Reeves (fluoridation engineer at the CDC) outlined the process by which the safety of fluoridation chemicals is assured:

Concern has been raised about the impurities in the fluoride chemicals. The American Water Works Association (AWWA), a well-respected water supply industry association, sets standards for all chemicals used in the water treatment plant, including fluoride chemicals. The AWWA standards are ANSI/AWWA B701-99 (sodium fluoride), ANSI/AWWA B702-99 (sodium fluorosilicate) and ANSI/AWWA B703-00 (fluorosilicic acid). The National Sanitation Foundation (NSF) also sets standards and does product certification for products used in the water industry, including fluoride chemicals. ANSI/NSF Standard 60 sets standards for purity and provides testing and certification for the fluoride chemicals. Standard 60 was developed by NSF and a consortium of associations, including the AWWA and the American National Standards Institute (ANSI). This standard provides for product quality and safety assurance to prevent the addition of harmful levels of contaminants from water treatment chemicals. More than 40 states have laws or regulations requiring product compliance with Standard 60. NSF tests the fluoride chemicals for the 11 regulated metal compounds that have an EPA MCL. In order for a product [for example, fluorosilicic acid] to meet certification standards, regulated metal contaminants must be present at the tap [in the home] at a concentration of less than ten percent of the MCL when added to drinking water at the recommended maximum use level. The EPA has not set any MCL for the silicates as there is no known health concerns, but Standard 60 has a Maximum Allowable Level (MAL) of 16 mg/L for sodium silicates as corrosion control agents primarily for turbidity reasons. NSF tests have shown the silicates in the water samples from public water systems to be well below these levels.⁴⁷

Sources of Fluoride Pollution Unrelated to Water Fluoridation

The principal sources of fluoride pollution are industries, particularly phosphate ore production and use as well as aluminum manufacture, mining, and coal burning.^{23,47,48} In the absence of adequate emission control in such settings environmental pollution can be a problem. Such pollution has been a problem in the past in

industrialized countries, and the WHO warns that unless proper environmental safeguards are adhered to, there is a danger of its occurring in developing countries with increasing industrialization. Fluoride pollution is therefore recognized as an industrial hazard; however water fluoridation is not considered a potential source of fluoride pollution.⁴⁶

Arguments of Opponents and Proponents

Whereas anti-fluoridationists try to prevent the unnecessary exposure of living things to fluoride, often in the misguided belief that any amount of fluoride is toxic, pro-fluoridationists try to reduce tooth decay through the judicious use of fluoride, with the understanding that there is an optimum amount, appropriately delivered, that is both beneficial and safe. This distinction leads to a difference in interpretation of the scientific and popular literature on this topic, whether related to the effects of water fluoridation on teeth or other organs of the body, or the effects on the environment. Similarly, there are those who may judge water fluoridation on political or philosophical grounds, such as being supportive or opposed to what government agencies may advocate. Some may have personal or anecdotal experience that is counter to what opponents or proponents recommend. Newbrun has characterized the fluoridation debate as a religious argument.⁴⁹

While opponents of fluoridation are not without their supporters and supporting groups,⁵⁰ almost every reputable, recognized, competent scientific and/or public health organization or government unit endorses fluoridation of drinking water as safe and effective.^{51,52} Furthermore, community water fluoridation has been heralded as one of the ten great public health measures of the 20th century.⁵³

Proponents of fluoridation assert that the dose of fluoride determines whether it is beneficial or toxic, and that there are threshold levels that must be exceeded before there are toxic effects. This is a basic principle of toxicology and is true of every chemical approved for use in treating drinking water. "All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy." Paracelsus (1493-1541).⁵⁴

While there has been considerable scientific study of the effects of fluorides on health and the environment, there will *always* be the need for more research.⁵⁵ However, proponents argue that it is not rational that the gains made from water fluoridation should be undone because not all the research has been completed. Further, it is strongly recommended that those communities that have not yet fluoridated their water supplies should do so to protect the dental health of their current and future residents.⁵⁶

Both sides use arguments related to freedom of choice. Those supporting fluoridation argue that the

public water supply is designed to protect public health and it is more important to protect people's health than to protect some people's concern for their freedom to use unfluoridated water.^{56,57} Additionally, pro-fluoridationists invoke the ethical principle of social justice arguing that the safe public health measure is socioeconomically equitable, providing greater benefit to the disadvantaged.¹

Current anti-fluoridation tactics have focused on chemicals used to fluoridate water supplies. As has been shown above, there is no credible evidence to support the notion that the chemicals are unsafe. In the past, tactics have focused on studies that purported to show that fluoridation was linked to cancer and myriad other health problems.⁴⁸ However, such assertions were based on improper science, and numerous subsequent studies found no association between fluoridation and cancer.⁵⁸

CONCLUSION

Scientific evidence supports the fluoridation of public water supplies as safe for the environment and beneficial to people. Reports at the local, national, and international levels have continued to support this most important public health measure. There appears to be no concern about the environmental aspects of water fluoridation among those experts who have investigated the matter. Furthermore, since the chemicals used for water fluoridation are co-products of the manufacture of phosphate fertilizers, and the raw material used is a natural resource (rocks excavated for their mineral content), water fluoridation could accurately be described as environmentally friendly, as it maximizes the use made of these natural resources, and reduces waste.⁵⁹

Note: In the text, the term "fluorosilicic" has been substituted for fluosilicic, hydrofluorosilicic, and hexafluorosilicic (all being synonymous); similarly, "fluorosilicate" for fluosilicate, hexafluorosilicate, and silicofluoride. However, the original terms in all references have not been substituted.

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Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:24 AM
To: Jaime Fuge
Subject: Fwd: Response to Connett's email
Attachments: AFS - NASEM Review of Monograph.pdf; ATT00001.htm; connett.green-bay.statement.7-15-20_JJ response 7-16-20.pdf; ATT00002.htm

Follow Up Flag: Follow up
Flag Status: Flagged

Johnny Johnson, Jr., DMD, MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: July 16, 2020 at 1:46:24 PM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: celestincje@greenbaywi.gov, Nancy Quirk <NancyQu@greenbaywi.gov>, clerkinquiries@greenbaywi.gov, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Response to Connett's email

July 16, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and Vanderlost,

I received a copy of the email that was sent to you by Dr. Paul Connett. I have taken the liberty to answer as many points as I could before your meeting today.

I've attached Connett's with my remarks shown in yellow highlights. I would be happy to discuss any of these points with you. Please know that some of this material has been used by Connett for a long, long time. Hence, some of my answers are cut and pasted from previous encounters with him.

I have attached the AFS Release on the NASEM Review that is referenced in my highlighted material in Connett's email

Please do not hesitate to call on me if I may be of assistance.

Warm regards.

Johnny

Johnny Johnson, Jr., DMD, MS

Pediatric Dentist

Diplomate, American Board of Pediatric Dentistry

Life Fellow, American Academy of Pediatric Dentistry

President, American Fluoridation Society

www.AmericanFluoridationSociety.org

@AFS_Fluoride

c: 727.409.1770



**AMERICAN
FLUORIDATION
SOCIETY**

FOR IMMEDIATE RELEASE
Tuesday, March 10, 2020

Contact: Dr. Johnny Johnson at 352-658-0441
or johnny@americanfluoridationsociety.com

National Academies: NTP's Conclusion about Fluoride Is Not Backed by Science

National Academies Report Cites Numerous Concerns with NTP's 2019 monograph

Last September, the National Toxicology Program (NTP) released a draft monograph concluding that "fluoride is presumed to be a cognitive neurodevelopmental hazard to humans." Before finalizing its monograph, NTP asked a committee of the National Academies of Sciences, Engineering and Medicine to review its conclusion and decide whether it is supported by the scientific evidence. In a new report, the Committee finds that NTP's monograph failed to provide adequate support for its conclusion.

The National Academies committee voiced "substantive concerns" with how NTP evaluated the human evidence in the draft of its *Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*. The Committee wrote that NTP "needs to state clearly that the monograph is not designed to be informative regarding decisions about fluoride concentrations for water fluoridation."

The NTP draft monograph stated that its conclusion was based primarily on fluoride exposure levels that are roughly double the concentration used for community water fluoridation. Nonetheless, the NTP document raised concern among many public health leaders and dental professionals who worried that NTP's conclusion might create needless fear or confusion among the public.

"This report by the National Academies makes it clear that NTP's conclusion was not backed up by solid science. Tooth decay is the most common chronic disease among children, and agencies like this need to be careful and cautious before they arrive at weak conclusions that could potentially scare children and adults away from fluoride in water, toothpaste or other products," said Dr. Johnny Johnson, a pediatric dentist who is president of the American Fluoridation Society, a nonprofit 501(c)4 organization.

The National Academies committee was not asked to adopt a position as to whether fluoride is safe or not. Instead, the Committee was given one task — evaluate NTP's draft monograph by assessing whether its conclusion accurately reflects the scientific literature. The Committee's report stated that NTP would need to conduct and present more analysis before it could reach and support a conclusion about fluoride's effect on neurodevelopment.

Throughout its report, the National Academies committee raises concerns with numerous areas of the NTP monograph. The Committee's concerns include the following:

- The studies included in NTP's systematic review "did not undergo rigorous statistical review" and called this "problematic" because some of these studies had issues or errors that "compromised their internal validity."
- NTP appeared to have applied its "risk of bias" criteria inconsistently.

- NTP failed to address the misclassification of fluoride exposure “thoroughly and consistently,” raising the question of whether NTP’s evaluations “were sufficient and supported its conclusion.”
- Researchers should consider potential confounding as they design and analyze a study to ensure that an association is not attributed by error to the wrong variable. With this in mind, the National Academies report identified “many cases in which NTP’s evaluation of confounding was insufficient, difficult to understand, or applied inconsistently across studies.”
- NTP classified some studies as having a low risk of bias even though “the measure of the neurodevelopmental and cognitive outcome was seriously flawed.”
- NTP’s protocol did not disclose the inclusion and exclusion criteria it used for selecting the studies it considered in drafting its monograph. Clarity in this area is “critical for transparency of the process and reproducibility of the findings.”

One of the more disturbing concerns raised by the National Academies committee was NTP’s decision to use a group called the Fluoride Action Network (FAN) as a source to identify relevant literature. “The process by which FAN identified and selected studies is unclear,” the Committee writes, “and that uncertainty raises the question of whether the process could have led to a biased selection of studies. Such a concern raises the need for a formal evaluation of any potential bias that might have been introduced into the literature-search process.”

The NTP decision to establish this relationship with FAN is astonishing considering the following facts:

- FAN is not a “research” organization. It uses the web and social media to disseminate messages encouraging local communities to oppose community water fluoridation. Additionally, FAN is one of the leading plaintiffs in a federal lawsuit seeking to ban a leading type of fluoride additive that is used for CWF.
- FAN has demonstrated a lack of scientific rigor through its interactions with federal health agencies. In 2003, Environmental Protection Agency (EPA) officials evaluated a set of research articles that FAN had submitted to support its objections to the Sulfuryl Fluoride Pesticide Tolerance Rule. In its evaluation, EPA found that most of the FAN articles “did not require a detailed review” because they suffered from one or more weaknesses, including articles with no toxicity data, articles lacking a clear explanation of methodologies, and papers “that did not contain any data on fluoride.”
- FAN has a history of making false or inaccurate statements related to fluoride or fluoridation. In fact, the Pew Center on the States identified multiple occasions in which FAN’s content included deceptive language.

The weeks that followed the release of the NTP draft monograph demonstrated how poorly NTP misjudged FAN’s integrity and intentions. Within days of the monograph’s release, FAN and other fluoridation opponents used social media and web-based messages in an effort to scare the public about fluoride. This inflammatory headline on FAN’s website home page is only one example. Even worse, the photo that accompanied the FAN home-page story wrongly implied

that the NTP monograph was a finished document that had been commercially printed for distribution.

No one can credibly argue that FAN's actions were innocent. NTP's monograph included a statement on its page headers that cautioned readers from interpreting the document as an approved policy or final document (see Attachment). This disclaimer advised readers that the "DRAFT Monograph" -- using all caps for the word 'draft' --- was being distributed "solely for the purpose of pre-dissemination peer review and does not represent and should not be construed to represent any NTP determination or policy." FAN ignored this disclaimer.

For more information about the American Fluoridation Society and community water fluoridation, visit <https://americanfluoridationsociety.org/>.

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Fluoride Action Network

<https://fluoridealert.org/>

Email: pconnett@gmail.com

DATE: July 15, 2020

TO: Members of the Green Bay Policy Protection and Policy Committee (with copies to the full council).

FROM: Paul Connett, PhD, Director of the Fluoride Action Network

Thank you again for the opportunity to speak at your meeting Monday. It was a pleasure to make your acquaintance via Zoom and speak to the serious health risks of water fluoridation.

Representing the Fluoride Action Network (FAN), I wish to correct the misinformation that was given out by the fluoridation proponents at Monday's meeting.

First, I want to acknowledge one error from someone opposing fluoridation (I don't recall who it was), who was citing cities that have rejected it. It's accurate that Portland, Honolulu and Wichita have all defeated fluoridation. However, San Diego is fluoridated.

False claims made by Dr. Johnny Johnson, President of the American Fluoridation Society

Now let me turn to the statements made by Johnny Johnson, a retired dentist, representing the American Fluoridation Society. Partly, because of his friendly and grandfatherly demeanor, over the last few years Dr. Johnson has been able to persuade a number of councils in Canada and the USA to continue – and even in some cases restart – fluoridation. Johnson is certainly entitled to his own opinions but not to his own "facts." It is fairly easy for those of us who have followed this issue closely for 20 years or so, to see through many of his unfounded but confidently articulated claims, but for those less steeped in the subject it is more difficult. If this was just an academic debate, I wouldn't necessarily be writing this. But it's clear that we're talking about a practice that threatens the mental development of our children. Decision-makers like yourselves need the truth.

Johnson's claim: "The legal case (against the EPA) was about the Toxic Substances Control Act (TSCA), not about actual fluoridation."

Fact check: This legal case is precisely about water fluoridation. TSCA authorizes EPA to prohibit the "particular use" of a chemical that presents an unreasonable risk to the general public or susceptible subpopulations. The Fluoride Action Network, together with other non-profits and individuals, petitioned the U.S. Environmental Protection Agency (EPA) under Section 21 of TSCA to prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies on the grounds that a large body of animal, cellular, and human research showed that fluoride was neurotoxic at doses within the range now seen in fluoridated communities. (see more at <https://fluoridealert.org/issues/tsca-fluoride-trial/fact-sheet/>)

Addressed in a previous email: Opponents to community water fluoridation (CWF) have attempted a myriad of ways to get CWF ceased in the U.S. These cases are listed on FLUJDLaw.org. Using TSCA is one more attempt, albeit novel, to cease CWF.

A failed petition by opponents to the EPA in 2013 to cease the use of Fluorosilicic acid (the fluoridating agent used in Green Bay and most of the country) was filed under TSCA as well. The EPA's response after careful evaluation of the petition was:

From the EPA evaluation:

After careful consideration, EPA denied the TSCA section 21 petition primarily because EPA concluded that petitioners have not set forth sufficient facts to establish that HFSA presents or will present an unreasonable risk and that it is necessary to initiate a TSCA section 6(a) rulemaking to protect adequately against such risk.

1. Arsenic: EPA evaluated the cost-benefit analysis submitted by the petitioners and determined that the petitioners miscalculated net benefits for pharmaceutical grade NaF compared to HFSA. Specifically, it appears that the petitioners failed to convert their estimates of lifetime cancer risk to estimates of annual cancer risk for the purpose of calculating annual net benefits. This error alone results in a 70-fold overestimation of the number of annual cancer cases due to arsenic. (U Bolding)

Johnson's claim: "The National Research Council has been mentioned a lot. That 2006 committee – that is a totally different subject than water fluoridation."

Fact check: The NRC wasn't asked to specifically endorse or oppose fluoridation. But the title of the NRC review itself, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* (2006) should make it obvious that this review was also all about it. It states at the bottom of page xiii to xiv: "The committee was charged to review toxicologic, epidemiologic and clinical data on fluoride . . . and exposure data on orally ingested fluoride from drinking water and other sources."

Addressed in previous email: The comment by Connett "should make it obvious" is exactly how this NRC Review is being misrepresented and backwards-extrapolated from naturally occurring levels of fluoride in drinking water from 2 mg/L (ppm) to 4 mg/L (ppm) and attempting to apply that Review to CWF. You can't do that in science.

As was stated on pp 20-21 of that Report:

"The committee is aware that some readers expect this report to make a determination about whether public drinking water supplies should be fluoridated. That expectation goes beyond the committee's charge. As noted above, the MCLG and SMCL are guidelines for areas where fluoride concentrations are naturally high. They are designed with the intent to protect the public from adverse health effects related to fluoride exposure and not as guidelines to provide health benefits." (U Bolding and italics)

Johnson's claim: "The science - nobody (a city) has ever been stopped over the science. It has never been stopped in any community over the science of fluoridation. That is crystal clear."

Fact check: FAN has documented that since 2010, over 250 communities have stopped fluoridation. In any community where there has been a discussion and vote by either a city council or a city-wide campaign, we aren't aware of any city stopping fluoridation where science and health risks haven't been emphasized by fluoridation opponents.

Answered in previous email: CWF has continued to increase every year since it began in 1945 in the U.S. Nowhere has it been stopped over the credible science. I did not say "where science and health risks haven't been emphasized by fluoridation opponents," as you stated above.

Connett states that "250 communities have stopped since 2010." Thanks for the link, Paul. Your data is outdated and incorrect in many areas in the U.S. **ADDITIONALLY**, you include communities in Ireland, Australia, Canada, U.K., and the country of Israel.

FACTS:

Israel did stop, but has their Knesset voted to restart CWF.

Albuquerque, NM voted to restart CWF.

Bucks County, PA never fluoridated their own water. They purchased it from Philadelphia which is fluoridated.

Bucks County decided to build their own water plant(s) and did not implement CWF.

Jonesborough, TN voted to restart CWF
 Windsor, LaSalle, and Tecumseh Ontario Canada voted to restart CWF
 Clarksburg, WV, never stopped CWF

Other cities listed as "stopped" had never started: Hernando County, FL; Portland, OR; Buda, TX, and Wichita, KS

For instance, this is from a Sept. 11, 2012 article in the Wichita Eagle: "Opponents of adding fluoride to Wichita's drinking water have frequently cited the Harvard research (Choi et al study) finding higher fluoride levels in water linked to lower IQ's in children in their efforts to persuade Wichitans to reject a ballot initiative that would require the water department to introduce the cavity-fighting chemical into the water supply."

"Harvard University scientists say that Wichita voters shouldn't depend on a research study they compiled to decide whether to put fluoride in the city's drinking water to fight tooth decay. (J. Bolding)

While the studies the Harvard team reviewed did indicate that very high levels of fluoride could be linked to lower IQs among schoolchildren, the data is not particularly applicable here because it came from foreign sources where fluoride levels are multiple times higher than they are in American tap water. (J. Bolding)

Opponents of adding fluoride to Wichita's drinking water have frequently cited the Harvard research in their efforts to persuade Wichitans to reject a ballot initiative that would require the water department to introduce the cavity-fighting chemical into the water supply.

The e-mail was jointly signed by the study's primary authors, research scientist Anna Choi and Associate Professor Philippe Grandjean, of the Department of Environmental Health at the Harvard School of Public Health. (J. Bolding)

This is from a flyer from the 2013 Portland, OR, campaign: "Health risks: Recent science from the National Academy of Sciences and other top researchers supports that **even low concentrations of fluoride pose real risks to human health** including the brain, thyroid, and bones."

Johnson's claim: "They (scientists) did not measure what happens between birth and three years old."

Fact check: Yes, they did. Please refer to FAN's one-pager, *Fluoridation's Neurotoxicity*. A 2020 Canadian study, funded by the U.S. National Institutes of Health (Till et al.) found that babies fed formula mixed with fluoridated water averaged 4 IQ points less than those mixed with non-fluoridated water. Losses of non-verbal IQ were even more serious, an average of 9 points.

Green et al's study on fluoride in urine and IQ: Answered and validated in a previous email with evaluations by the Canadian Agency for Health and Technologies in Health (CADTH). The articles that followed used the same cohort as the Green et al study used.

It is important to point out that Green et al used the journal *Fluoride* for three of its references. The journal *Fluoride* is not found on Pubmed. It is a publication where fluoridation opponents can publish articles that other journals will not.

Additionally, Green et al used a reference article that has been proven to be incorrect in its content. Authors should be held to high standards when they choose their references. This is expected in the scientific community.

Johnson's claim: "The overwhelming body of literature is what we base our information on, not one or two new studies."

Fact check: Actually, we agree with Dr. Johnson's approach on this. We just wish he'd walk the walk in his presentations. Again, referring to *Fluoridation's Neurotoxicity*:

- The 2012 Harvard meta-analysis (Choi et al.) found that children ingesting higher fluoride levels tested an average 7 IQ points lower in 26 out of 27 studies. Most had higher fluoride concentrations than in U.S. water, but many had total exposures to fluoride no more than what millions of Americans receive.

The Meta-analysis above had a control group and the test group. The control group had naturally fluoride levels in the water that were approximately equal to CWF. The test group had naturally occurring fluoride in the water at multiples, up to 10-15 times that of CWF.

The control group did not have any IQ deficits.
Only the test group with high fluoride in the water had 7 IQ point loss.

- The original 2016 Citizens' Petition to the EPA to end fluoridation documented 57 out of 61 human studies showing higher fluoride levels linked to lower IQ's in children. It also cited 112 out of 115 animal studies showing fluoride's neurotoxic harm to animals.

Connett fails to mention the 2018 NTP study of fluoride on rats that they pushed for. It showed NO neurologic harms from fluoride in water at levels from CWF and higher. See graphic later below.

- A 2019 systematic review of 149 human studies and 339 animal studies by the U.S. National Toxicology Program concluded that "fluoride is presumed to be a cognitive neurodevelopmental hazard to humans." The report is still in draft form, but NTP also said there is little chance they will change their finding.

Johnson made a charge against Christine Till, the lead researcher of two of the important IQ studies (Green 2019, and Till 2020). This charge is being addressed separately.

Finally, Johnson referred to the study performed in Calgary, which he claimed showed an exponential increase in tooth decay when that city stopped fluoridation. Chris Neurath, the science director for Fluoride Action Network, will be sending you the documentation refuting that false claim.

I will address this separately. FAN has made its own interpretations of the data, which are incorrect.

Other false or misleading claims made by fluoridation promoters and defenders at the Monday meeting (FAN's response is indented throughout).

Matt Crespín – Milwaukee Children's Alliance.

-Fluoride is naturally occurring and is naturally in every source of drinking water.

*Naturally occurring doesn't equal safe. Arsenic is also a naturally occurring element but no one would say that it is safe to drink.

*The Fluoridation chemicals used are not "naturally occurring" but a highly toxic byproduct of the fertilizer industry called fluorosilicic acid which is contaminated with heavy metals, radionuclides and arsenic.

As a PhD chemist, Connett knows that there is no difference between fluoride ions. There is only ONE fluoride ion. Thanks for finally stating this Paul. You've never stated this before. Every chemistry student knows that a fluoride ion is a fluoride ion.

Per the CDC:

Fluoride Additives Are Not Different From Natural Fluoride

Some consumers have questioned whether fluoride from natural groundwater sources, such as calcium fluoride, is better than fluorides added "artificially," such as FSA or sodium fluoride. Two recent scientific studies, listed below, demonstrate that the same fluoride ion is present in naturally occurring fluoride or in fluoride drinking water additives and that no intermediates or other products were observed at pH levels as low as 3.5. In addition, the metabolism of fluoride does not differ depending on the chemical compound used or whether the fluoride is present naturally or added to the water supply.

<https://www.cdc.gov/fluoridation/engineering/wladditives.html#NaturalFluoride>

*Over 90% of groundwater and surface water, where public water supplies come from, has only trace amounts of fluoride (under 0.2 ppm), whereas fluoridation artificially increases the natural level by up to 7 times.

-The committee should have received a letter listing all of the Wisconsin organizations that endorse fluoridation (Delta Dental, various hospitals).

*Endorsements are not science-based; they're often based on political influence and grant funding.

The first and most important endorsement of water fluoridation came in 1950, when the US Public Health Service endorsed fluoridation in 1950 (half way through the fluoridation trials) with virtually no health data on the table. Within two years nearly every major dental, public health and medical organization had also endorsed water fluoridation but still with little science on the table. These organizations have continued to endorse fluoridation for over 70 years with little or any formal review of the literature.

None of the Wisconsin organizations listed have conducted a systematic review—or even an objective review—of the neurotoxicity literature on fluoride, or polled their membership for support of fluoridation.

-New research has debunked the myth that fluoride causes osteosarcoma.

Unfortunately, this is not correct. Bassin et al. (2006) found a 5-7 fold increase in osteosarcoma in young boys when exposed to fluoride between the ages of 6 and 8 years (corresponding to a period of rapid growth in the bone). This window of vulnerability has never been refuted. See a comparison of two studies.

Dr. Connett decides to use partial study results of a 15 year research project to investigate any potential correlation between optimally fluoridated water and Osteosarcoma, and to promote this as a final, undisputed fact of the entire study. Dr. Connett is quite obviously not an astute medical researcher.

In the words of Dr. Elyse Bassin, her Conclusion:

"Conclusions: Our exploratory analysis found an association between fluoride exposure in drinking water during childhood and the incidence of osteosarcoma among males but not consistently among females. Further research is required to confirm or refute this observation."
<http://www.ncbi.nlm.nih.gov/pubmed/16596294>

Dr. Connett takes the liberty of interpreting the results of a 15 year study conducted at Harvard University by some of the top researchers in the world, and coming to a conclusion that he, a

PhD Chemist, has more knowledge than the investigators of this landmark study. This just isn't so.

The conclusions that were drawn upon at the completion of the 15-year research project were published in 2011. The conclusions of the completed study, which included the data from Dr. Bassin's partial study PhD dissertation, are:

"The major advantage of this study is the use of bone fluoride concentrations as the measure of fluoride exposure, rather than estimating fluoride exposure in drinking water (Bassin et al., 2006). Since 99% of the body burden of fluoride is located in calcified tissues, and fluoride concentration is dependent upon the amount and duration of exposure as well as the rate of bone turnover (Turner et al., 1993), if chronic fluoride intake was a risk factor for osteosarcoma, then it would be reasonable to expect that cases would have significantly higher bone fluoride concentrations than tumor controls. This study did not demonstrate an association between fluoride levels in bone and osteosarcoma."

J Dent Res. 2011 Oct;90(10):1171-6. doi: 10.1177/0022034511418828. Epub 2011 Jul 28.

-There was also a study conducted by the *Archives of Toxicology* that addressed the IQ issue. (Reads quote: based on the totality of neurotoxicity evidence, it does not support that fluoride is a developmental neurotoxin at the current exposure levels in Europe)

- 1.) None of the authors of the so-called review has ever published a single paper on fluoride, let alone on fluoride neurotoxicity.
- 2.) None of the authors appears to have any expertise in epidemiology, so they are not qualified to judge the human studies. The authors appear to only have expertise in animal studies. Authoritative bodies who have reviewed all the evidence, including the EPA, agree there is now so much human epidemiological evidence that it is not necessary to rely on animal studies.
- 3.) The review reaches almost the opposite conclusion of the NTP's review. The NTP is part of NIH which is part of HHS. The NTP is specifically charged with evaluating the toxicity of chemicals and is the highest authority on such questions in the USA. The NTP is much more credible than this so-called review from Germany, which appears to have been intended as a way to muddy the science, not honestly review the science.

The NTP GAET Monograph was reviewed, per their request, by the National Academies of Science, Engineering, and Medicine (NASEM):

NASEM had multiple concerns with how NTP arrived at their statement that fluoride in water above 1.5ppm is a presumed neurotoxin. One of the greatest concerns was the use by the NTP of documents provided by FAN and interpreted by FAN. Several other inconsistencies that failed to show transparency in how the NTP arrived at their conclusion led to the statement by NASEM:

"The committee was tasked with assessing whether NTP satisfactorily supports its conclusion. In light of the issues raised by the committee regarding the analysis of various aspects of some studies and the analysis, summary, and presentation of the data in the monograph, the committee finds that NTP has not adequately supported its conclusion."

Connett fails to even hint of the assessment by NASEM:

4.) The conclusion that the "levels found in EUROPE did not pose a neurotoxic risk" is misleading, because most of Europe does not fluoridate its water, so such a conclusion is not relevant to artificial fluoridation in the USA.

5) The *Archives of Toxicology* is a journal that has a reputation for publishing industry-friendly reviews of toxic chemicals that always end up finding "no harm". In fact, it is part of a family of journals whose editor was implicated in a recent lawsuit against Monsanto as allowing Monsanto to "ghost-write" a review of a Monsanto chemical that concluded the chemical caused no harm (glyphosate). Monsanto was never declared as having a role in helping write and review the article, as was required by standard conflict-of-interest rules in scientific publishing. The lawsuit where this was revealed ended up with a verdict against Monsanto of hundreds of millions of dollars, with much of that amount as a penalty for Monsanto having improperly manipulated the science by such methods as ghost-writing ostensibly objective reviews. So, anything published in the *Archives of Toxicology*, where the same editor remains in charge, is suspect. This review of fluoride appears to be a similar situation where authors have found a receptive journal to peddle what was described by an independent scientist in the Monsanto court case as "agenda driven".

Nancy Quirk – General Manager of Water Utilities

-Nancy started out by saying she invited pro-fluoridation lobbyists Johnny Johnson to join the call.

*Local and state employees ought to be objective, not advocates for anything other than safe drinking water. Unfortunately, Nancy Quirk called the primary lobbyists for fluoridation to lobby the council.

-No studies have been published showing harm from fluoridation. If that did happen, I would have brought it to the attention of the council to protect our citizens. This claim is incorrect and indicates that Nancy Quirk has not done any independent research on the matter.

* These three Mother-Offspring fluoride studies reported reduced IQ in the offspring of women exposed to fluoride levels that mothers living in fluoridate communities would experience (Bashash et al., 2017; Green et al. 2019; Till et al, 2020.) The latter study by Till et al. also reported significantly lower IQ in formula-fed babies living in fluoridated communities compared to formula-fed babies living in non-fluoridated communities. These three studies were funded by the U.S. National Institute of Environmental Health Sciences.

Also, during Quirk's tenure, the CDC reported that 41% of adolescents now have some form of dental fluorosis (CDC, 2010).

Quirk's statements would suggest that

1. that the government bodies advising water directors are failing to inform their members of fluoridation studies indicating harm, and
2. She is not up to date on the science.

-In regard to chemical costs...(Note Quirk never answered the question of the cost of the fluoridation chemical).

*Cities of similar size (approx. 100,000 people) using the same fluoridation chemical as Green Bay pay around \$70,000 – \$100,000 annually for their fluoridation additives depending on the distributor and quality (number of contaminants present in the additive). Water directors from around the country have stated that fluoridation additives are generally the most expensive additive they use, and certainly the most dangerous for water operators to work with.

-I have not seen any studies credible enough to cause me to stop protecting our citizens.

Clearly, Quirk is unaware of these published fluoride studies:

- 65 Human studies reporting lower IQ due to fluoride exposure;
- 7 Mother-Offspring studies reporting IQ and Cognitive effects;
- 158 Human studies reporting damage to the brain;
- 288 Animal studies reporting damage to the brain;

These were addressed by the 2018 NTP study on rats

Research confirms fluoridation's safety

Opponents: "The NTP should conduct a study."

Source: Dr. Russ Dunkel, DDS, State Dental Director for Wisconsin. He has been quoted in numerous news outlets, including the Wisconsin State Journal, the Milwaukee Journal Sentinel, and the Green Bay Press-Banner. He is a member of the American Dental Association and the American Fluoridation Society.

- The National Toxicology Program (NTP) conducted a study
- The NTP "observed no exposure-related differences in motor, sensory, or learning and memory performance" for any of the 9 tests they conducted
- Thyroid hormone levels were not affected — even at levels of 0, 10 or 20 parts per million of fluoride



FLUORIDE ALERT.ORG
FLUORIDE SAFETY

NEW FLUORIDE/BRAIN STUDY COULD END FLUORIDATION

By Dr. Russ Dunkel, DDS, State Dental Director for Wisconsin

The National Toxicology Program (NTP) has completed a study on the effects of fluoride on rats. The study found that fluoride at levels of 0, 10, or 20 parts per million (ppm) did not affect motor, sensory, or learning and memory performance in any of the 9 tests conducted. This is a significant finding, as it suggests that fluoride is safe for consumption at these levels.

The study also found that thyroid hormone levels were not affected by fluoride at these levels. This is important because thyroid hormone is essential for normal growth and development, and fluoride is known to interfere with thyroid function.

The NTP study is a landmark study, as it is the first to evaluate the effects of fluoride on rats at these levels. It provides strong evidence that fluoride is safe for consumption at these levels, and it could lead to the end of fluoridation.

Dr. Russ Dunkel, DDS – State Dental Director for Wisconsin

-Windsor put fluoridation back in the water after conducting a 5-year study and witnessing severe consequences of having no fluoride. They estimated that the cost of emergency room visits due to dental infections caused by lack of fluoridation to be \$500,000 annually.

This was not a formal study

-Regarding the Green and Till studies, the IQ change in males was only from 108.7 vs. 108.2. That was the only change.

Completely false or reveals lack of understanding of the study. The study controlled for numerous potentially confounding factors, and it is important that it did so. The values of 108.7 and 108.2 are before any control for confounding factors and just go to show that it was necessary to control for confounders to get the true relationship between F and IQ, taking into account the other factors that affect IQ.

In the study, fluoridated water in Canada (0.6 mg/L) was predicted to be associated with a 2 to 3 IQ average drop compared to unfluoridated water. That is 4 to 6 times larger effect than is misrepresented by the people who claim the difference was 108.7 vs 108.2. It is also a very large

effect, comparable to that from Pb.

-It (the Green study) was also gender specific. Girls in the fluoridated group had a higher IQ than girls in the non-fluoridated group.

For the one measure of fluoride exposure, there was no statistically significant association between F and IQ for girls. It is not correct to say the girls had a higher IQ in the fluoridated group because their result may be due to random error. In contrast, the boys had a statistically significant reduced IQ. Furthermore, the study used two other ways of measuring F exposure, and in both of those the girls and boys both had reduced IQ with higher F exposure.

-It was done on a spot urine analysis, and to be accurate you must do a 24-hour sample, not a spot urine sample due to short half-life of fluoride.

This has been a frequently repeated falsehood of fluoridation defenders. Spot urine samples have been shown to be sufficiently accurate in the studies that have used them. Furthermore, if they had used 24-hour urine samples, it is almost certain that the observed loss of IQ would be even larger and closer to the true loss of IQ. So, whatever inaccuracies might exist by using spot urine samples rather than 24-hour urine samples would only result in underestimates of the true effect, not overestimates.

-There were a lot of flaws in these studies that couldn't be justified or confirmed. We need to look at the "true" science.

These studies were vetted thoroughly at multiple levels. They were awarded millions of dollars in funding from the NIH. That required very rigorous review of the study design, the reputations of the researchers, etc. Then, before they were published in highly respected scientific journals, they all underwent some of the most rigorous peer-review ever experienced by these journals. That comes directly from the JAMA Pediatrics editors who oversaw the peer-review. All of these studies, due to the controversial nature of subject, underwent some of the most careful reviews of any studies on any environmental health topic. In contrast, the criticisms of the papers have all come from a handful of people who have absolutely no background in fluoride or even in neurotoxicity. The critics seem to have been organized by a group in England called the Science Media Centre. The Science Media Centre has been identified as funded in part by industries including Monsanto and pharma industries, and instead of producing genuinely independent commentary on science topics, have been a way for these industries to hide behind an ostensibly independent front.

~~Answered in a previous email~~

Robbyn Kuester – Fluoridation Program Coordinator with Wisconsin Association of Public Health

-Studies confirm that those living in fluoridated communities have a 25% reduction in dental decay as opposed to those living in non-fluoridated communities.

It is important to put this claim into perspective. It is a *relative* difference not an *absolute* difference in tooth decay and expressed as percentage it is far more "impressive" than the actual amount of tooth decay saved. The number comes from a paper by Brunelle and Carlos (1991) and was based upon a survey conducted by the National Institute of Dental Research in 1986 (the largest survey of tooth decay ever undertaken in the USA). For children who lived all their lives in

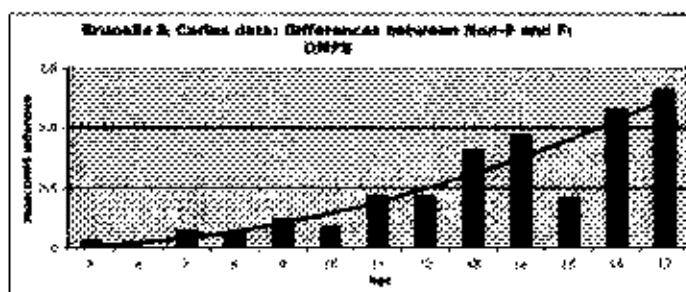
-0.7ppm, a very tiny amount, does not pose harm to human health.

The study can be summed up in the following slide, courtesy of Dr. Howard Pollack.

ADA 2016

Incremental benefit of water fluoridation: depends how old you are

- NIDR 1986-87 US school-based oral examination survey (Brunelle and Carlos).
- Increasing preventive benefit of tooth surfaces saved from decay by age.
- While 5-6 years olds have few if any permanent teeth, all but the wisdom teeth are present by age 12 years or so.
- The overall benefit for 5-17 year-olds is a mean of 0.6 of a tooth surface, but that benefit increases to 1.5 tooth surfaces by age 17.


$$\frac{d}{dt} \left(\frac{1}{2} m v^2 + \frac{1}{2} I \omega^2 \right) = \sum_i \vec{r}_i \cdot \frac{d\vec{F}_i}{dt}$$

As can be seen, cavity reductions from CWF begin to rise as all of the permanent teeth have erupted, approximately age 12. The slope of the rise is where CWF is showing its benefits to these teeth.

Connecti uses an average over the entire range from 5-17 years old. This is an extremely misleading statement.

Actually, compared to the natural levels of fluoride in mothers' breast milk, 0.7 ppm is very large. It is almost 200 times the level in mothers milk (0.004 ppm, NRC, 2006, p.40).

Updated information from a forum in Australia showed that Upper Limits for fluoride intakes by infants should be doubled based on the latest research. Article is available.

-Wisconsin Health Services does not conduct research on fluoridation studies. We rely on federal partners for that. They have the expertise and the panel of experts to look at that. We really rely on our federal partners to guide us on in that way to help us make public health policy to protect all residents. They certainly look at that research and take into consideration the most vulnerable populations, including babies and the fetus.

-I have seen the NIH studies, and I can tell you that the federal organizations have reviewed them and haven't changed their fluoridation recommendations. If any research did come out showing harm from fluoridation we would certainly look at that and change our policies as well.

In FAN's TSCA lawsuit these NIH studies were subjected to close examination by attorneys for both the plaintiffs and Department of Justice (appearing for the US EPA). The authors of the key papers (Howard Hu and Bruce Lanphear) gave testimony. The overall conclusion, shared by both plaintiffs, the EPA and the Judge was that these NIH studies have been the most rigorous studies on this subject conducted to date.

We can understand the reluctance of health bureaucrats to admit that a practice that they have enthusiastically endorsed for many decades may be posing an unreasonable risk to the developing brains of our children but that is what the best current science is showing. To their credit the NIH funded these studies, but it is not to their credit that they have been very slow to warn health bodies at the state level of the studies' findings.

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:23 AM
To: Jaime Fuge
Subject: Fwd: Your letter to the GB Protection and Policy Committee dated July 16, 2020
Attachments: Response to Till's GB Letter 7-17-20.pdf; ATT00001.htm; Till letter_Green Bay Policy Protection and Policy Committee 07.16.2020.pdf; ATT00002.htm

Johnny Johnson, Jr., DMD, MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: July 17, 2020 at 2:57:13 PM EDT
To: ctill@yorku.ca
Cc: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>, celestineje@greenbaywi.gov, clerkinquiries@greenbaywi.gov, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Your letter to the GB Protection and Policy Committee dated July 16, 2020

Dear Dr. Till,

I received a copy of your letter to the Green Bay Protection and Policy Committee. I have attached a letter that I respectfully request that you read and respond to the full Common Council, Mayor, and me.

I have also attached a copy of your letter in case the Mayor and Common Council did not receive it.

Thanking you in advance,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry

Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770



July 17, 2020

Dear Dr. Till,

I received copies of the documents that you sent to the members of the Protection and Policy Committee yesterday regarding my testimony. There are three key omissions in your letter that I believe could confuse or mislead the Green Bay Common Council:

1. In your letter you stated that I made **“inaccurate comments in his testimony about the conclusions of our study”** ... (your bolding). However, your letter did not specifically cite what I said that you claim is inaccurate. If I have misstated anything, certainly I would want to **make that right** for the council members of the Protection and Policy Committee and the Common Council and Mayor and you.

2. Now, here is the second omission. Your letter neglected to disclose the point of view that you expressed to a health journalist one month after your study was published. This is what you said to a journalist at BuzzFeed News:

“I think this message could be easily misconstrued as us saying don’t drink fluoridated water - we’re not saying that.”

Why did you decide not to disclose this earlier statement to the Common Council? Your letter to the Green Bay Common Council seems to encourage them to cease water fluoridation. Your letter and your BuzzFeed News statement seem to contradict each other.

3. Perhaps the biggest omission was what you failed to disclose to the Common Council about the National Toxicology Program’s (NTP) draft monograph (*Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*). You stated that “the NTP concluded that ‘fluoride is presumed to be a cognitive neurodevelopmental hazard to humans’.” Yet you failed to inform the Common Council that the NTP asked the National Academies of Science, Engineering, and Medicine (NASEM) to review their monograph. In March, NASEM announced in a news release that it “does not find that NTP has adequately supported its conclusion that ‘fluoride is presumed to be a cognitive neurodevelopmental hazard to humans’.”

Omitting the NASEM review from your letter may lead the members of the Protection and Policy Committee, as well as the Common Council and Mayor with the impression that the 2019 NTP’s conclusion was definitive. It is not.

I look forward to hearing from you.

Sincerely



Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: <https://americanfluoridationsociety.org/>
Cell: 727-409-1770
Email: drjohnnyjohnson@gmail.com



July 16, 2020

FACULTY OF HEALTH

Department of
Psychology

4700 Keele St.
Toronto, ON
M3J 1P3
T 416 736 2100
F 416 736 5514
www.psych.yorku.ca

RE: Clarification for the members of the Protection and Policy Committee of the City of Green Bay regarding the meeting on community fluoridation

Dear Chair Mark Steuer and Committee Members,

Dr. Johnny Johnson made **inaccurate comments in his testimony about the conclusions of our study** titled, *Association between Maternal Fluoride Exposure during Pregnancy and IQ Scores in Offspring in Canada*. This study, published in JAMA Pediatrics, was based on a prospective pregnancy and birth cohort from Canada.

We found that higher levels of fluoride in pregnant women and their drinking water were associated with a 3- to 5-point lower IQ score in their preschool aged children.

I am writing to clarify that my co-authors and I have recommended reducing fluoride intake during pregnancy. Some of my coauthors have recommended this reduction includes fluoridated water because water is the main source of fluoride for people who live in communities with fluoridation; one pointed out the need for more research before making specific recommendations for community water fluoridation.

Dr. Johnson said we should not change policy because of one or two new studies. Our recommendation to reduce fluoride intake during pregnancy is based on our findings, as well as those reported by others, showing similar findings. A 2019 systematic review on fluoride neurotoxicity by the National Toxicology Program concluded that "fluoride is presumed to be a cognitive neurodevelopmental hazard to humans". This report, which is still in draft form, underscores the consistency across the large number of human and animal studies.

We discuss the challenges of conducting fluoride research and some of the biases we have encountered in the attached commentary entitled: *The evolving science of fluoride: When new evidence doesn't conform with existing beliefs*.

Sincerely,

A handwritten signature in cursive script that reads 'Christine Till'.

Christine Till, PhD
Associate Professor
ctill@yorku.ca
York University, Toronto



Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:22 AM
To: Jaime Fuge
Subject: Fwd: COVID-19 Prevention: THANK YOU!!!

Johnny Johnson, Jr., DMD, MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: July 26, 2020 at 11:29:46 AM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>,
"district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov"
<district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>,
"district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov"
<district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>,
"district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov"
<district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>,
"district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov"
<district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: celestineje@greenbaywi.gov, nancy.quirk@gmail.com, clerkinquiries@greenbaywi.gov,
Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: COVID-19 Prevention: THANK YOU!!!

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I wanted to thank you for your difficult vote to require mandatory facemask wear. Being from one of the hotbeds in the country for COVID-19, Florida, and as one who had it back in February, your decision was based in solid science.

I heard that you all have received death threats because of your decision. That is truly horrible and is criminal acts of terror. Dr. Fauci revealed this morning that he too has received these threats to himself and his family. He called the threats as coming from fringe people who oppose his public health measures intended to protect everyone in our country from this awful virus. At 64, I can share that it is extremely rough on us, and I'm in pretty good shape.

People who oppose vaccinations and fluoridation receive threats as you have. Live rattlesnakes in mailboxes, wanted posters of health advocates with bullet holes in their foreheads, and even death threats. These folks are on the fringes in a cult-like following, much as Dr. Fauci alluded to. We know the risk of standing up for what is

the right thing to do. While we don't want harm to come to us or our families, we have learned to wear it as a badge of courage and honor. As a YMCA Director said at a meeting a couple of years ago that I attended, "When you stand for something, you stand against something". That absolutely hit the nail on the head.

Our lives and careers are threatened for standing up for the right things, as are yours. Re-election for you, gag-orders for us, and legal action are common from those opposing you and us. Healthcare professionals do not lose their licenses for opposing something that they don't agree with within their professions. If that were the case, why were actively practicing dentists from other states on the call at your first meeting? They still have their licenses. Freedom of speech is a basic right assured to us in our great country. However, if you are practicing outside of accepted standards of care for your profession, action can be taken against professionals for the health and safety of the community. Speaking against fluoridation does not fit into that category whatsoever.

I just wanted to write to you and thank you for what you did. Please know that the majority of your residents are behind you. You have to make the tough decisions, even though they may not be the popular ones with a vocal minority. Keep up the great work!!

Have a Blessed Sunday.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:22 AM
To: Jaime Fuge
Subject: Fwd: Questions and concerns raised at the first Zoom meeting of the Protection and Policy Committee
Attachments: Letter to Chairman Steuer on meeting one and issues raised.pdf; ATT00001.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: August 5, 2020 at 2:08:37 PM EDT
To: Mark Steuer <district10@greenbaywi.gov>, "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>,, district1@greenbaywi.gov <district1@greenbaywi.gov>,, district2@greenbaywi.gov <district2@greenbaywi.gov>,, district3@greenbaywi.gov <district3@greenbaywi.gov>,, district4@greenbaywi.gov <district4@greenbaywi.gov>,, district5@greenbaywi.gov <district5@greenbaywi.gov>,, district6@greenbaywi.gov <district6@greenbaywi.gov>,, district7@greenbaywi.gov <district7@greenbaywi.gov>,, district8@greenbaywi.gov <district8@greenbaywi.gov>,, district9@greenbaywi.gov <district9@greenbaywi.gov>,, district10@greenbaywi.gov <district10@greenbaywi.gov>,, district11@greenbaywi.gov <district11@greenbaywi.gov>,, district12@greenbaywi.gov" <district12@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>
Cc: celestinejc@greenbaywi.gov, clerkinquiries@greenbaywi.gov, "Zokaie, Tooka" <zokaie@ada.org>, Erika Valadez <evaladez@wda.org>, Steve Slott <steveslott@gmail.com>, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Questions and concerns raised at the first Zoom meeting of the Protection and Policy Committee

Dear Chair Steuer, members of the Protection and Policy Committee, Mayor Genrich, and Alders of the Common Council,

I am writing to you regarding the information that you have been receiving from community water fluoridation opponents. To that end, it is vitally important that you receive accurate, science-based information that

represents the preponderance of scientific consensus that has been credibly conducted, and published in credibly recognized, peer-reviewed scientific journals. The scientific consensus continues to show that water fluoridation is effective at reducing cavities and safe for everyone. I have attached a letter that discusses a few of the questions and concerns that you and other members of the Protection and Policy Committee had.

My colleagues and I will never allow misinformation to guide policy decisions. The group of opponents that were on the first call of the Protection and Policy Committee exhibited exactly what typifies the anti-vaccination/anti-fluoridation movement in this country. The anti-fluoridation movement began 75 years ago when fluoridation first began. They do not care one bit about people who live in communities in the U.S. who have naturally high levels of fluoride in their drinking water ***up to and exceeding 15 milligrams of fluoride in one liter of water*** (aka ppm). They make no attempt to have those folks fluoride levels reduced. Their **sole** purpose is to stop the addition of fluoride ions that are already present in your water to the recommended level of 0.7 ppm. At that level, it stops 25-50% of cavities for adults and children by simply drinking the water. Opponents know that stopping fluoridation has severe outcomes for the families, especially those that are the poorest of the poor, with more cavities, more severe cavities, abscessed teeth which do lead to systemic illnesses like sepsis and death and harms a community's economy. They want what they want, period.

The attached letter outlines a few points from that first meeting that were made along with questions that you had. I have also asked Dr. Steve Slott, Communications Officer of the American Fluoridation Society, to address the misinformation that was sent to you in emails following that meeting. He will do that immediately. Dr. Slott provides succinct refutations of the false claims and provides credible science that backs these positions. I think that you will find it very helpful in understanding the misinformation that keeps coming in. The Calgary, Alberta Canada City Council thoroughly understood his materials and chose to continue moving forward with restarting their water fluoridation for over 1.3 million residents. Many of the same group of people who spoke against fluoridation on that first call were present in Calgary for that nine-hour meeting. Their misinformation and cherry-picking of tidbits of information didn't work there. And it shouldn't work in Green Bay.

Please follow the science, just as you did in implementing mandatory facemasks. And do not hesitate to contact me with any questions or concerns that you may have.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS

Pediatric Dentist

Diplomate, American Board of Pediatric Dentistry

Life Fellow, American Academy of Pediatric Dentistry

President, American Fluoridation Society

www.AmericanFluoridationSociety.org

@AFS_Fluoride

c: 727.409.1770



August 5, 2020

TO: Mark Steuer, Chair Protection and Policy Committee
RE: 1. First meeting of PPC – points discussed
2. Complaints lodged against dental and dental hygiene licenses
3. Introduction of Dr. Steve Slott
4. Credentials of groups who are sending you information

Dear Chair Steuer,

Several conversations, issues, and questions were raised by you and the alders on the Protection and Policy Committee's (PPC) meeting on July 13, 2020. I would like to highlight these and to clarify a few points that were made during the meeting.

1. At the first meeting of the PPC, several issues were raised that led to concerns on the part of the PPC.

In the following days after the meeting, you were inundated with emails from those in opposition to community water fluoridation. This, along with the Zoom meeting on the 13th, was a well-orchestrated effort to overwhelm you all with misinformation and half-baked truths. Especially disturbing was the participant who sat with his background of weapons on the wall behind him. After the Common Council's decision on mandatory face masks and the serious threats that you all have received, I believe that this type of display was by no means an accident.

2. Over the past week, official complaints have been lodged against the licenses of Dr. Russel Dunkel, the Wisconsin Dental Director in the Department of Health. Complaints have also been lodged against the licenses of Matt Crespin, RDH, and Robbyn Kuester, RDH (with the Department of Health, Fluoride Operations).

These complaints are a direct threat to the licenses of these two public servants (Dr. Dunkel and Robbyn Kuester) and the head of the Children's Health Alliance of Wisconsin, CHAW (Matt Crespin). They are intended to intimidate them into silence. These complaints have resulted in these representatives of public health to have to hire attorneys to help protect them from losing their state licenses. This is an outrage beyond words.

Further, there were opponents to community water fluoridation (CWF) on the call who stated that if dentists speak out against CWF, they could lose their licenses.

Well, let's think about that for a second. Had any of them lost their licenses to practice? That would be an emphatic no. Nor would speaking out against recommended preventive dental care like dental sealants to prevent cavities. I know dentists who are not fans of them for a variety of their own personal opinions. However, they would *never* lose their licenses for their own positions.

To lose your professional license, you would have to be practicing outside of the scope of accepted practice for your area in medicine or dentistry. Like dentists who state that silver fillings cause health issues and falsely use this incorrect information to advise their patients to take them all out and replace them with white fillings. One dentist that I recall lost his license several years ago from doing this when he was advised multiple times to stop following this pathway. He chose to blatantly ignore this recommendation.

Summary:

To summarize, dentists *are not* afraid to speak out against fluoridation or any other practice that they don't agree with. That is a statement that is made over and over in every community where these opponents to CWF are working to cease CWF. The American Dental Association and the Wisconsin Dental Board will readily verify this. I have included Tooka Zokaie of the American Dental Association and Erika Valdez of the Wisconsin Dental Association on this email so that you can verify this information directly with them.

3. I would like to introduce you to Dr. Steve Slott, Communications Officer of the American Fluoridation Society. Dr. Slott responds to emails like you all received from Brenda Staudenmaier, Chris Neurath, and British-American chemist Paul Connett.

Dr. Slott has prepared a point by point discussion of each of these claims and assertions made in the emails. He has dissected them, addressed them with credible scientific studies/information, and provided links to that information for you. I will ask Dr. Slott, also copied here, to begin sending his refutations to you immediately so that you have the opportunity to review them.

4. Lastly, I ask that you compare the credentials of people that the opponents have in their organization, the Fluoride Action Network, to the credentials of the people that the American Fluoridation Society (AFS) has in our Board of Directors and Advisory Committees. AFS's Advisory Committees are replete with experts in water fluoridation research on its effectiveness and safety around the world. Additionally, the immediate past CDC National Fluoridation Engineer is part of our group. Naysayers readily discount the CDC on water fluoridation as if it is some conspiracy to keep it. Let me ask you, do you think that these same people, the opponents to CWF, kept eating tainted romaine lettuce when the CDC advised not to? I'm going to bet that they stopped it, just as the grocery stores listened and responsibly pulled it from the shelves. So, why would they not listen to the CDC on CWF? Because they have one goal....stop the adjustment of fluoride that's already

in your water to a level that prevents cavities for everyone.

Chair Steuer, we live in a democratic society, not one that is a free-for-all chaotic society. Like your decision on mandatory facemask wear, you all did it for the protection of the entire community. Public health and well-being cannot be tailored to the wishes of the few who don't want it. As you sadly experienced, you all started to receive death threats after that decision. I have received them too, as well as threats of lawsuits. When we stand for something, we stand against something. Please follow the credible science on CWF just as you did with your decision on facemasks. It's the right thing to do.

Warm personal regards,



Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: <https://americanfluoridationsociety.org/>
Cell: 727-409-1770
Email: drjohnnyjohnson@gmail.com

American Fluoridation Society's Board of Directors and Advisory Committees

Board of Directors

President:

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist

Vice President:

Myron A. Allukian, Jr., DDS, MPH
Public Health Dentist, Educator

Communications Officer:

Steven Slott, DDS
Dentist

Treasurer:

Kurt Ferré, DDS
Dentist

Emeritus:

Charles Haynie, MD, FACS

Secretary:

Jennifer Martinson, BS, RDH
Dental Hygienist

Vascular Surgeon

Bruce Austin, DMD
Immediate past Oregon State Dental Director

Kimberlie Yineman-Payne, BA, RDH
Dental Hygienist
Immediate past North Dakota State Dental Director

Science Advisory Committee

William Maas, DDS, MPH, MS

Former Director, Division of Oral Health, U.S.
Centers for Disease Control and Prevention

John Morris, DDS (UK)

University of Birmingham School of Dentistry,
former national lead for water fluoridation with
Public Health England and regional consultant for
the Midlands and East of England

Howard Pollick, BDS, MPH

Professor, Preventive & Restorative Dental Sciences
University of California San Francisco, School of
Dentistry

Michael Foley, BSc, MPH, MEd (Aus)

Director of Research and Advocacy for Metro North
Oral Health Services, Former Director of Brisbane
Dental Hospital

Timothy Wright, MS, DDS

Bawden Distinguished Professor
Pediatric and Public Health
Adams School of Dentistry
The University of North Carolina

Mark Moss, DDS, PhD

Associate Professor, Department of Foundational
Sciences, East Carolina School of Dentistry,
Greenville, NC

Gary D. Slade, BSc, DipDPH

John W. Stamm Distinguished Professor of Dentistry
at the UNC Adams School of Dentistry, Chapel Hill,
NC

Jennifer Meyer, PhD, MPH, CPH, RN

Assistant Professor of Health Sciences, University of
Alaska Anchorage, AK

Water Advisory Committee

Kip Duchon, P.E.

Immediate past CDC National Fluoridation Engineer

Communications Committee

Steve Slott

Randy Johnson

AFS Communications Officer

Biology

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:21 AM
To: Jaime Fuge
Subject: Fwd: Email received from Green Bay resident today-RN
Attachments: Email letter response to email from RN.pdf; ATT00001.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: August 10, 2020 at 2:03:30 PM EDT
To: Mark Steuer <district10@greenbaywi.gov>, District One <District.1@greenbaywi.gov>, District Two <District.2@greenbaywi.gov>, District Three <District.3@greenbaywi.gov>, District Four <District.4@greenbaywi.gov>, District Five <District.5@greenbaywi.gov>, District Six <District.6@greenbaywi.gov>, District Seven <District.7@greenbaywi.gov>, District Eight <District.8@greenbaywi.gov>, District Nine <District.9@greenbaywi.gov>, District Eleven <District.11@greenbaywi.gov>, District Twelve <District.12@greenbaywi.gov>, "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>
Cc: celestineje@greenbaywi.gov, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, Steve Slott <steveslott@gmail.com>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Email received from Green Bay resident today-RN

Hi Chair Steuer, members of the Protection and Policy Committee, Mayor Genrich, and members of the Common Council,

I have attached a letter addressing the points raised by Green Bay resident Lacey Kuehl RN, BSN. I am sympathetic to the health issues that she and her daughter have, as well as her concerns. While she believes that the causes of those, plus others that she listed exist, the overwhelming body of scientific evidence does not support these claims.

Please take a look at the attachment. I want to thank you all for doing your due diligence in evaluating the information being sent to you.

Please rely on the scientific and health organizations that endorse fluoridation as effective and safe for everyone. This includes:

1. American Academy of Pediatrics
2. American Dental Association
3. CDC
4. Mayo Clinic
5. Department of Defense
6. World Health Organization

Not a single, credibly recognized scientific or health organization in the world opposes fluoridation. Not one.

Please do the right thing for all of your residents and keep fluoridation for your families. Listen to the hundreds of thousands of experts that are in the organizations that back fluoridation as effective and safe.

Please do not hesitate to contact me with any questions or concerns that you may have.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770



August 10, 2020

Dear Chair Steuer, members of the Protection and Policy Committee, Mayor Genrich, and Alders of the Common Council,

Good afternoon,

I received a copy of an email that was sent to you by Lacey Kuehl RN, BSN this morning.

While my heart goes out to her for her medical and dental ills, her concerns voiced are not founded in science-based information. The preponderance of scientific research conducted over the past 75 years has continued to show that fluoride levels in water fluoridation do not cause any adverse health effects.

Cavities are due to multiple factors: diet, oral health practices, frequency of sugar or fermentable carbohydrate intake (bread, pasta, and other foods), timing of that intake, and access to dental care.

Prevention of cavities involves multiple modalities to prevent them. These include topical fluorides like toothpaste, mouth rinses, fluoride at the dental office, regular dental visits, dental sealant placement, a well-balanced diet, good oral hygiene practices, and community water fluoridation (CWF).

CWF prevents at least 25% of cavities above and beyond those already prevented by the topical fluorides listed above. If CWF prevents 25% and up to 50% or more as studies have shown, that still means that we will get 50-75% of cavities if we do not employ the other preventive measures as listed above. Almost all cavities are preventable. As a pediatric dentist of 35 years now, and having seen tens of thousands of children and young adults both poor and of means, I can attest to the fact that some behaviors we cannot change: oral hygiene practices, diet, and changes in sticky sugary candies. I take pride in what I do, and I am not pleased with the manner in which we cannot affect change in our country or elsewhere in this respect.

What I will tell you is that through the use of topical fluorides, CWF, and dental sealants, we can stop approximately 90% of cavities that people will ever get. CWF does not take a cognizant change in anyone's daily behavior to benefit from its cavity-fighting measures. Drink the water and get at least 25% less cavities.

Lead in Pipes:

Green Bay has led the nation in addressing the potential for lead in the water of homes, schools, and businesses. Kudos to you all for this great public health measure.

Lead is a known neurotoxin that can affect IQ and learning issues. As Ms. Kuehl has stated, she was concerned by the lead in the water when she was growing up and its effects on her and her daughter. Whether the lead in her pipes were in excess of the EPA's maximum allowable limit of the current 10 ppb (parts per billion), without testing her water we can't know for sure how much was in it. The EPA sets the level of 10 ppb as the enforceable limit that is considered technically feasible and protective of public health. While the maximum goal is zero, this is not feasibly attainable at this time.

From the EPA on Lead:

Children

Even low levels of lead in the blood of children can result in:

- Behavior and learning problems
- Lower IQ and hyperactivity
- Slowed growth
- Hearing problems
- Anemia

From the CDC:

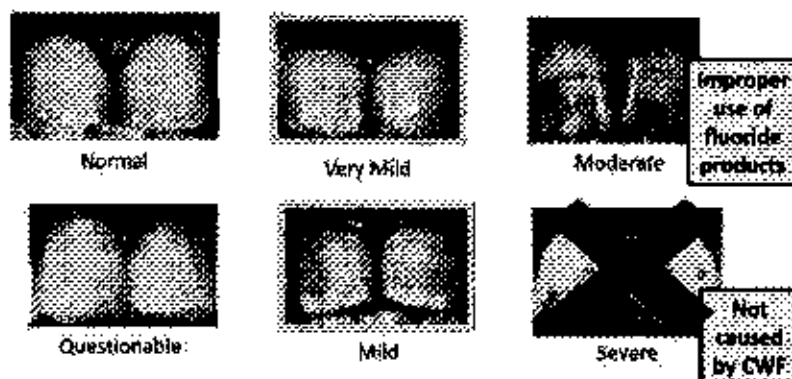
Community Water Fluoridation: Effective and Safe:

"Scientists in the United States and around the world have studied the safety and benefits of fluoridated water for a century and have not found consistent and convincing evidence to link water fluoridation with any potential unwanted health effect (JJ color emphasis) other than dental fluorosis.

Dental fluorosis is a change in the appearance of tooth enamel and can occur when young children (less than 8 years of age) regularly ingest too much fluoride while their permanent teeth are still developing. Most dental fluorosis in the United States—more than 90 percent—occurs in its mildest form, as barely noticeable white spots on the tooth surface."

Critics distort the facts about dental fluorosis

Variations in tooth enamel (fluorosis)



(The American Fluoridation Society is a non-profit organization dedicated to the promotion of water fluoridation as a public health measure. It is not affiliated with the CDC or any other government agency.)

Photos courtesy of CDC

Effective and Safe:

"Fluoridated water works by keeping a low level of fluoride in the mouth throughout the day. Fluoride and water mix with saliva and are absorbed by dental plaque, and the fluoride bonds with any weakened tooth enamel it encounters. **Even when common fluoride products such as toothpaste and mouth rinses are used, fluoridated water reduces tooth decay another 25% among children and adults** (JJ bolding and color change). School children in communities with water fluoridation have, on average, 2 fewer decayed teeth than children in communities that do not fluoridate.

That's important because oral health affects every aspect of our lives—diet, sleep, mental health, social connections, school, and work. Untreated tooth decay can cause pain, school or work absences, and difficulty concentrating, as well as affect the appearance of your mouth and teeth—all of which impact one's quality of life and ability to succeed.

Fluoridation has been identified as the most practical and cost-effective method of delivering fluoride to all members of a community, regardless of age, education, or income. These advantages, combined with fluoridation's contribution to dramatic declines in both the prevalence and severity of tooth decay, led the Centers for Disease Control and Prevention (CDC) to name water fluoridation one of ten great public health achievements of the 20th century."

Infant Formula:

"Can I use fluoridated tap water to mix infant formula?"

Yes, you can use fluoridated water for preparing infant formula. However, if your child is only consuming infant formula mixed with fluoridated water, there may be an increased chance for mild dental fluorosis. To lessen this chance, parents can use low-fluoride bottled water some of the time to mix infant formula; these bottled waters are labeled as de-ionized, purified, demineralized, or distilled, and without any fluoride added after purification treatment. The U.S. Food and Drug Administration (FDA) requires the label to indicate when fluoride is added."

Hypothyroidism:

Studies do not validate that CWF causes any endocrine disorders, including hypothyroidism. Even at the EPA maximum allowable fluoride level of 4 ppm, *six times* the level of fluoride in CWF, the 2006 National Research Council did not definitively find any adverse health effects at 4 ppm of fluoride naturally occurring in water except severe dental fluorosis. This went away at 2 ppm, *three times* the level in CWF.

Research confirms fluoridation's safety

Opponents: "NRC's 2006 report shows CWF is harmful."

Was there
definitive
evidence at 4.0
ppm showing
that fluoride
had an effect
on...?

- | | |
|-----------------------------|---------------------------------------|
| • Tooth enamel ✓ | • Cancer ✗ |
| • Liver ✗ | • Musculoskeletal system ✗ |
| • Kidneys ✗ | • Reproduction and development ✗ |
| • Endocrine system ✗ | • Neurotoxicity and neurobehavioral ✗ |
| • Gastrointestinal system ✗ | • Genetic damage ✗ |
| • Immune system ✗ | |



In a community in Florida, Brooksville, the Executive Director of the Fluoride Action Network, Paul Connett (who has written you and was on the first call), was stating that CWF was causing thyroid disorders.

The past president of the Thyroid Society in the U.S. (president multiple times and leading expert) was so appalled at Connett's claim that she came out strong to strike down the claim:

Opponents claim harm to endocrine system-Thyroid



August 27, 2019

To Whom It May Concern:

As a practicing endocrinologist, I was appalled at the claim that fluoridated drinking water caused clinically significant harm to the endocrine system.

Obviously, in more than 30 years of seeing patients, I have never seen any fractures or thyroid problems associated with fluoridated water. Early puberty is more associated with obesity than anything else, though there are many endocrine disruptors that have estrogenic effect. Fluoride has not been implicated, though bisphenol, tea tree oil and BPA, substances found commonly in hair products, have been.

Endocrinology and Metabolic Diseases
University of Florida
Gainesville, FL



Pharmaceutical-grade Fluoride additives:

The comments about pharmaceutical-grade fluoride being used instead of the fluoride additive that you all use has been addressed by Nancy Quirk and Dr. Steve Slott. Pharmaceutical-grade fluoride is not an approved additive by the American Water Works Association, nor is it appropriate to use. You can read about the issues and lack of restrictions on pharmaceutical-grade fluoride as an additive [here](#) on the CDC's website.

IQ:

This subject has been discussed and will be discussed in more detail in another email. New studies and systematic reviews over the past few years have shown no impact of CWF on IQ whatsoever. Opponents do not like these studies as they do not support their positions.

As a scientist, pediatric dentist, son, father, and grandfather, I would **never** allow my family or patients to drink CWF if there was overwhelming consensus in the scientific community that it causes health harms. As a business person, yes, we would make more money doing more fillings, crowns, root canals, implants, and other procedures. **HOWEVER**, dental cavities are an infectious and transmissible disease. It is the #1 chronic disease of children and teens. We want to eradicate this disease. Just as we want to eradicate COVID and did Smallpox. Do you really think that physicians were disappointed that they couldn't earn more money treating these diseases instead of preventing them? Absolutely not.

Thank you for your time in reading this email today. I promise to keep our emails to a minimum, only to reply to the claims that are counter to the credible scientific evidence.

Warm regards,



Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: <https://americanfluoridationsociety.org/>
Cell: 727-409-1770
Email: drjohnnyjohnson@gmail.com

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Immediate past CDC National Fluoridation Engineer

Communications Committee

Steve Stott

AFS Communications Officer

Randy Johnson

Biology

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:20 AM
To: Jaime Fuge
Subject: Fwd: Email received from Green Bay resident today-RN

Johnny Johnson, Jr., DMD, MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: August 10, 2020 at 2:43:36 PM EDT
To: Mark Steuer <district10@greenbaywi.gov>, District One <District.1@greenbaywi.gov>, District Two <District.2@greenbaywi.gov>, District Three <District.3@greenbaywi.gov>, District Four <District.4@greenbaywi.gov>, District Five <District.5@greenbaywi.gov>, District Six <District.6@greenbaywi.gov>, District Seven <District.7@greenbaywi.gov>, District Eight <District.8@greenbaywi.gov>, District Nine <District.9@greenbaywi.gov>, District Eleven <District.11@greenbaywi.gov>, District Twelve <District.12@greenbaywi.gov>, "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>
Cc: celestinejc@greenbaywi.gov, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, Steve Slott <steveslott@gmail.com>
Subject: **Rc: Email received from Green Bay resident today-RN**

I need to make one correction in my email/letter. I was referring to arsenic, not lead as far as levels that is considered an "Action Level".

My apologies for this error. The Action Level for lead is 15 ppb. The hyperlink to the EPA was to lead, not arsenic. Nurse Kuehl had mentioned arsenic in her comments on fluoride additives. That level is set by the EPA at 10 ppb. All of the impurities in additives come from the rock from which they're mined. They are not added. Each fluoride additive is strictly controlled by the EPA. NSF International sets even more strict standards for fluoridation additives. They cannot contain more than 10% of the EPA level of 10 ppb, or they cannot be used as a fluoride additive. In other words, fluoride additives cannot have more than 1 ppb of arsenic or they are rejected for use in the U.S.

The section on pharmaceutical-grade fluoride in the letter had a link to the CDC's website. I feel that it deserves inclusion here:
(Note: anything other than H2O molecules in water is considered a contaminant - this includes odor)

United States Pharmacopeia (USP) Grade Fluoride Products

Some have suggested that pharmaceutical grade fluoride additives should be used for water fluoridation. Pharmaceutical grading standards used in formulating prescription drugs are not appropriate for water fluoridation additives. If applied, those standards could actually exceed the amount of impurities allowed by AWWA and NSF/ANSI in drinking water.

The U.S. Pharmacopeia-National Formulary (USP-NF) publishes monographs on tests and acceptance criteria for substances and ingredients by manufacturers for pharmaceuticals. The USP 29 NF-24 monograph on sodium fluoride provides no independent monitoring or quality assurance testing. The USP does not include acceptance criteria for fluorosilicic acid or sodium fluorosilicate. As a result, the manufacturer is responsible for quality assurance and reporting. The USP does not provide specific protection levels for individual contaminants, but establishes a relative maximum exposure level for a group of related contaminants. **Some potential impurities have no restrictions by the USP, including arsenic, some heavy metals regulated by the U.S. EPA, and radionuclides** (JJ bolding). Given the volumes of chemicals used in water fluoridation, a pharmaceutical grade of sodium fluoride for fluoridation could potentially contain much higher levels of arsenic, radionuclides, and regulated heavy metals than an NSF/ANSI Standard 60-certified product.

In addition, AWWA-grade sodium fluoride is preferred over USP-grade sodium fluoride for use in water treatment facilities because the granular AWWA product is less likely to result in exposure to fluoride dust by water plant operators than the more powder-like USP-grade sodium fluoride.

<https://www.cdc.gov/fluoridation/engineering/wfadditives.htm#USP>

Again, my apologies for the error.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

On Mon, Aug 10, 2020 at 2:03 PM Johnny Johnson <drjohnnyjohnson@gmail.com> wrote:

Hi Chair Steuer, members of the Protection and Policy Committee, Mayor Genrich, and members of the Common Council,

I have attached a letter addressing the points raised by Green Bay resident Lacey Kuehl RN, BSN. I am sympathetic to the health issues that she and her daughter have, as well as her concerns. While she believes that the causes of those, plus others that she listed exist, the overwhelming body of scientific evidence does not support these claims.

Please take a look at the attachment. I want to thank you all for doing your due diligence in evaluating the information being sent to you.

Please rely on the scientific and health organizations that endorse fluoridation as effective and safe for everyone. This includes:

1. American Academy of Pediatrics
2. American Dental Association
3. CDC
4. Mayo Clinic
5. Department of Defense
6. World Health Organization

Not a single, credibly recognized scientific or health organization in the world opposes fluoridation. Not one.

Please do the right thing for all of your residents and keep fluoridation for your families. Listen to the hundreds of thousands of experts that are in the organizations that back fluoridation as effective and safe.

Please do not hesitate to contact me with any questions or concerns that you may have.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:19 AM
To: Jaime Fuge
Subject: Fwd: Community Water Fluoridation in Green Bay WI
Attachments: image001.jpg; ATT00001.htm; image002.png; ATT00002.htm; AADR CWF Policy w letter to Mayor Green Bay WI.pdf; ATT00003.htm

Johnny Johnson, Jr., DMD, MS
c: 727.409.1770

Begin forwarded message:

From: Makyba Charles-Ayinde <mcaayinde@iadr.org>
Date: August 18, 2020 at 12:25:06 AM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: "celestineje@greenbaywi.gov" <celestineje@greenbaywi.gov>, "clerkinquiries@greenbaywi.gov" <clerkinquiries@greenbaywi.gov>, "Nancy.Quirk@greenbaywi.gov" <Nancy.Quirk@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>, "Christopher H. Fox" <cfox@iadr.org>
Subject: Community Water Fluoridation in Green Bay WI

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I hope this email meets you all well. On behalf of the American Association for Dental Research (AADR) I would like to share the attached letter which details our Associations' Community Water Fluoridation policy and expresses our support for the fluoridation of the community water supply for Green Bay, WI.

We would like to encourage you to read our CWF policy in detail and stand ready to work with Green Bay officials to advance the understanding of the benefits of community water fluoridation and its impact on dental health. Thank you for consideration and if you have any further questions, please do not hesitate to contact me via email or by phone at (703) 299-8099.

Warm regards,

Makyba

Makyba Charles-Ayinde, M.S., Ph.D.

Director of Science Policy

International & American Associations for Dental Research

1619 Duke Street, Alexandria, VA 22314-3406, USA

T: +1.703.299.8099 | F: +1.703.548.1883 | E: mcayinde@iadr.org

www.iadr.org www.aadr.org

Publishers of *Journal of Dental Research* and *JDR Clinical & Translational Research*



American Association
for Dental Research

August 17, 2020

Eric Genrich,
100 N Jefferson Street,
Green Bay City Hall,
Green Bay, WI, 54301

Re: Community Water Fluoridation within Green Bay Wisconsin

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

The American Association for Dental Research (AADR), represents 3,400 and 107 institutional members working throughout dental, oral and craniofacial research. On behalf of our members we would like to take the opportunity to share our Community Water Fluoridation (CWF) policy with you and Common Council members. Our CWF policy was developed in consultation with our Science Information Committee and other cutting-edge scientists who are deeply engrossed in the research and study of the impact of fluoridation on dental health.

AADR appreciates the complexities associated with application of widespread community water fluoridation policies. However, AADR supports community water fluoridation as a safe and effective, evidence-based intervention for the prevention of dental caries. Residents of communities who drank from naturally fluoridated water supplies experienced less tooth decay than those living in communities without naturally fluoridated water. Therefore, we would like to express our support for the fluoridation of the community water supply for Green Bay, WI as the benefits for this practice can result in improved dental health within your community.

AADR would also like to encourage you to read our CWF policy in further detail (included below). We stand ready to work with Green Bay officials to advance the understanding of the benefits of community water fluoridation and the etiologic relationship between fluoridation and dental health. Thank you for consideration and if you have any further questions, please contact Dr. Makyba Charles-Ayinde, Director of Science Policy, at mcaayinde@iadr.org.

Sincerely,

Christopher H. Fox, DMD, DMSc
Chief Executive Officer
American Association for Dental Research

☎ +1 703.548.0066
☎ +1 703 548.1893
1617 Duke Street
Alexandria, VA 22314-3406, USA
www.aadr.org

COMMUNITY WATER FLUORIDATION

AADR supports community water fluoridation as a safe and effective, evidence-based intervention for the prevention of dental caries. While fluoride occurs naturally in water, fluoridation is the controlled addition of fluoride to community water systems to the level recommended for caries prevention. The practice of adding fluoride to community water supplies began after Dr. H. Trendley Dean – the first director of what later became the National Institute of Dental and Craniofacial Research – observed that residents of communities who drank from naturally fluoridated water supplies experienced less tooth decay than those living in communities without naturally fluoridated water. What began as a small trial of the controlled addition of fluoride to water in Grand Rapids, Michigan has now reached 75% of the United States population who drink from a community water system and has resulted in a significant decrease in dental caries.^{1, 2}

Dental caries – the destruction of dental hard tissues – can result in pain, infection and tooth loss. Caries is caused by acidic byproducts produced from bacterial fermentation of sugar. Dental caries is a very common disease that affects both adults and children. Over one-third of children ages 2-8 experience caries in their primary teeth. One in 5 children ages 6-11 and over half of adolescents ages 12-19 experience caries in their permanent teeth. On average older adults can expect at least one new decayed tooth surface per year. Children with poor oral health are more likely to miss school and suffer academically. Parents may also accrue absences from school or work to seek treatment for their children. Both children and adults with caries may experience embarrassment, exhibit withdrawal, have difficulty eating and sleeping, and limit facial expressions and behaviors that facilitate social interaction.³⁻⁹

Many studies point to the effectiveness of community water fluoridation in decreasing dental caries. A systematic review of 20 studies by Cochrane, an independent group that reviews medical research to inform evidence-based policies and health guidelines, showed that water fluoridation decreased tooth decay in both the primary and permanent teeth of children and increased the number of children free of decay in primary and permanent teeth.^{10, 11} Another review by the Community Preventive Services Task Force (CPSTF), an independent panel of public health experts appointed by the Director of the Centers for Disease Control and Prevention (CDC), found that starting water fluoridation decreased caries in children ages 4-17 by 30-50% and that stopping water fluoridation increased caries by 18%.¹² Furthermore, reducing childhood caries experience and severity may have benefits into adulthood by halting disease progression that can result in adult tooth loss. Lifelong exposure to fluoridated water has been associated with reduced tooth decay in adults.^{13, 14}

Community water fluoridation is a cost-effective method of delivering caries prevention to a large population. A systematic review by the CPSTF compared the cost of fluoridation to the money saved on dental restorations in communities that drink from fluoridated water sources. CPSTF found that water fluoridation is cost saving. In other words, the savings from fewer dental restorations are greater than the cost of fluoridation for communities of greater than 1,000 people, and the larger the community, the greater the cost saving.¹⁵ A 2016 analysis confirmed this finding.¹⁶

Community water fluoridation may also reduce oral health disparities. Children and adults from socioeconomically disadvantaged backgrounds are more likely to suffer from dental caries and are less likely to be treated for the disease.^{6, 17} When added to drinking water, fluoride can be delivered to community residents regardless of socioeconomic status or ability to access dental services. Some studies have shown decreased inequalities in caries in communities that drink from a fluoridated community water source, revealing that children of a lower socioeconomic status who have access to a fluoridated water source have less severe tooth decay and require less expensive care than children of

lower socioeconomic status who do not drink fluoridated water. More research is needed to determine the circumstances in which water fluoridation reduces disparities, as not all fluoridated communities show reduced disparities.^{10, 18}

Community water fluoridation is a safe method of delivering fluoride on a population level. There have been numerous systematic reviews on claims of the potential adverse health effects of water fluoridation. None has concluded that there is a significant or consistent association between water fluoridation and the outcomes examined, including neurologic conditions, cancer or osteoporosis.¹⁹⁻²³ Dental fluorosis resulting in tooth discoloration is the only known adverse health effect of water fluoridation. Teeth are only at risk of fluorosis until about age 8 during enamel formation. The United States Public Health Service recommends a concentration of 0.7 milligrams of fluoride per liter of water to achieve caries prevention while minimizing the risk of dental fluorosis.²⁴ While people who drink from fluoridated water sources are at greater risk of dental fluorosis, most people who drink fluoridated water do not develop dental fluorosis. The cases of dental fluorosis that do develop are very mild, such that discoloration is not usually visible to the naked eye and does not affect the function of the teeth. Severe cases of dental fluorosis are rare. Some studies have shown that Black/African-American and Mexican-American children are at greater risk of developing dental fluorosis. However, this has not been clearly linked to fluoridated water and may be due to cumulative fluoride intake from various sources, such as toothpaste, supplements and food and beverages prepared with fluoridated water.^{10, 17, 25}

Community water fluoridation is supported by various groups, including the American Association of Public Health Dentistry, the American Public Health Association, the American Dental Association and the American Academy of Pediatrics, among others. Additionally, in 1999, the CDC identified community water fluoridation as one of 10 great public health achievements of the 20th century because of its effectiveness and ability to distribute fluoride equitably and cost-effectively.²⁶ Information about the fluoride concentration of communities participating in water fluoridation can be found on the CDC website "My Water's Fluoride".²⁷

While AADR always welcomes research on water fluoridation safety and effectiveness in the current context of fluoride availability, the balance of evidence currently shows that community water fluoridation is safe, effective and cost-saving and in some communities, reduces oral health disparities. Therefore, AADR supports community water fluoridation and recommends the fluoridation of community water sources to a level of 0.7 milligrams of fluoride per liter of water.

*The authors of the Cochrane systematic review determined that the evidence for community water fluoridation for the prevention of dental caries was low quality and that many studies were conducted before 1975. The Cochrane review method considers randomized clinical trials as the gold standard of evidence and automatically rates common methods for evaluating public health interventions as low. However, randomized trials are usually not feasible for interventions at the population level. The authors noted this gap in their evidence grading system and that the evidence pointed in the same direction of fluoridation reducing tooth decay.

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(adopted 2018)

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:19 AM
To: Jaime Fuge
Subject: Fwd: A State Official's Guide to Science-Based Decision-Making
Attachments: A State Official's Guide to Science-Based Decision-Making.pdf; ATT00001.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: August 19, 2020 at 1:29:43 PM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, Mark Steuer <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>
Cc: Celestine Jeffreys <Celestine.Jeffreys@greenbaywi.gov>, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>, "Dunkel, Russell D - DHS" <russell.dunkel@dhs.wisconsin.gov>, "Kuester, Robbyn L - DHS" <Robbyn.Kuester@dhs.wisconsin.gov>, "Crespin, Matthew" <MCrespin@chw.org>
Subject: A State Official's Guide to Science-Based Decision-Making

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

As you weave through the maze of information that you are receiving on the subject of water fluoridation, there is a document produced by the Council of State Governments that is intended to assist decision-makers in evaluating the information that they receive. It is a short document, but one that was extremely well written to aid you and others in deciphering the good from the not so good information that is received.

The document, "A State Official's Guide to Science-Based Decision-Making", methodically goes through how to look at science, the source of the information, and how to evaluate parameters that separate science from advocacy.

Please take a few minutes of your time to look over this document. I've attached it as well. A lot of time and effort is being put into this public health policy by all of you. You have many other pressing needs to get to for Green Bay. Please depend on credible sources for your information.

Do not hesitate to contact me with any questions or comments that you may have.

Warm regards,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770



A State Official's Guide to
**SCIENCE-BASED
DECISION-MAKING**



Center for Science and Technology Policy

*** ACKNOWLEDGMENTS ***

The Council of State Governments would like to express appreciation to the Sound Science Advisory Board for lending its expertise to this project and reviewing drafts of the report. Advisory board members include:

- Sarah Brozena, Senior Director Regulatory and Technical Affairs, American Chemistry Council
- Dr. Steve Cohen, Executive Director, The Earth Institute, Columbia University
- Representative Mike Fortner, Illinois
- Dr. Scott Heid, Associate Director-Scientific Communications, The Procter & Gamble Company
- Representative Phyllis Kahn, Minnesota
- Al Kaufman, Senior Vice President Technical Affairs, Toy Industry Association
- John Lyons, Assistant Secretary for Climate Policy, Kentucky Energy and Environment Department
- Teresa Marks, Director, Arkansas Department of Environmental Quality
- Dr. Matt McKinney, Director, University of Montana Center for Natural Resources and Environmental Policy

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- Mary Branham, Managing Editor
- Jennifer Ginn, Associate Editor

GRAPHIC DESIGNERS

- Jessica Hughes, Senior Graphic Designer
- Rebecca Jackson, Senior Graphic Designer
- Chris Pryor, Design Coordinator

This report refers to several examples of state and federal policies that are based on scientific information. These examples were chosen solely for their relevance to the concepts explained in the text. Neither CSG nor the Sound Science Advisory Board advocate these policies.

TABLE OF CONTENTS

Executive Summary	5
Introduction	7
Science-based Decision-making—Its Intent	7
Contested Science	7
Scientific Method	9
The Scientific Method Applied	11
Common Research Techniques	11
Integrating the Knowledge	16
Peer Review	16
Risk	16
Adaptive Management	19
Conclusion	20
Glossary	21







*** EXECUTIVE SUMMARY ***

A STATE OFFICIAL'S GUIDE TO SCIENCE-BASED DECISION-MAKING

Policymakers are bombarded by information in today's ever-connected, fast-paced world. Advances in communication platforms, like social media, and information technology have brought a sea change in the public's ability to access data at unimaginable depths and speeds. This interconnectedness can also pose challenges for state officials trying to solve already difficult issues by adding another layer of complexity to the public policymaking process. As information becomes more available and immediate, policymakers often must make decisions without the technical background necessary to fully vet all the considerations involved.

The Council of State Governments developed *A State Official's Guide to Science-based Decision-making* to provide strategic guidance that can cut through the jargon and spin that can accompany technical issues. The guide includes recommendations and helpful tools for policymakers, regardless of background, to confidently assess the assumptions, conclusions and results found in state public hearing witness testimony and scientific studies.

"The aim of the guide is not to suggest what to think; rather, the impetus is to provide a roadmap of how to approach an issue so state thought leaders can make the most informed decision possible."

Assessing the Expert

Nearly all public meetings or hearings on technical issues will feature expert witness testimony or studies of some kind. State officials must be able to distinguish advocacy from expertise and recognize when witness statements or testimony ventures into areas of personal opinion, anecdote or conjecture. Advocacy has an important place in the public policymaking process, but its primary goal is to influence or promote a cause rather than provide unbiased information.

Questions to Ask and Warning Signs:

- What educational background or training does the expert have?
- What types of work has the expert done in the field?
- Does the source of the research have anything to gain by the study's outcome? Are there conflicts of interest either financially or professionally?
- Is the expert or the expert's employer concerned about implications of a policy/decision?
- Be on guard for an observer's bias or potential vested interest.

Assessing the Methods

Data can be derived from many sources, including case studies, observational studies, controlled studies and risk assessments. This process analyzes how the data collection was performed or how information was gathered, which underpins a study or set of results. Many studies make calculated assumptions and can involve intricate variables. How those variables are controlled can have a tremendous impact on the final results, which can form the basis of an economic impact analysis, policy decision or regulatory action, etc.

Questions to Ask and Warning Signs:

- Who gathered this information?
- What specific data or studies form the basis of the researcher's scientific conclusions?
- Have the data or studies been evaluated by other scientists? How extensive was the review?
- Have important variables been overlooked or ignored?
- Is the sample size used in the study truly representative?
- What specific hypotheses or questions did the researchers set out to test? Were steps taken to control other effects?
- Watch for studies that lack accepted standards or credible references.

Assessing the Results

Once data are produced, a policymaker must then be able to make sense of its outcome and relevancy. One common mistake is a confusion of correlation, which is an apparent connection between variables when they frequently occur together, with causation, in essence, a statement of cause begetting an effect. Further, a general understanding of the statistical significance of the results in a study is paramount. Statistical significance is a technique that calculates the probability that an effect observed in a research study is occurring because of chance.

Questions to Ask and Warning Signs:

- What are the underlying systematic uncertainties? What degree of uncertainty surrounds the results?
- Were conclusions based on personal stories/anecdotal evidence?
- Do the results demonstrate causality, rather than correlation?
- Are the results statistically significant?
- Are statistics adequately explained? If not, ask for a practical explanation.
- To whom or for what do the results apply? Can they be extrapolated to the general population?
- Do the conclusions logically follow from the scientific results?
- Be on guard for conclusions making statements of absolute certainty.

Integrating the Knowledge

This segment focuses on critically assessing and formulating the disparate data points and facts learned or gleaned from testimony, study methodologies and results to help inform the actual decision-making process. This segment will address the role of risk assessments in integrating knowledge and helping policymakers in their decision-making.

Questions to Ask:

- Have the study results been published? If yes, was it in a journal that requires peer review prior to publication? Have any scientific peer review panels considered the study results?
- Is there a consensus about the key findings of the studies? What are the areas of agreement/disagreement?
- Do other scientists share the researcher's views? Who doesn't and why?
- Have the results been repeated, confirmed or supported by other studies?
- What are your views on the practical applications of this scientific knowledge/decision?
- Is the timeliness of study relevant to today's issues?
- What are the consequences/implications of action or inaction, including risks? Is there a balanced approach? Why or why not?

Conclusion

Science informs just one part, albeit a critically important one, of the policymaking process; it is not a policy itself. Sometimes there simply is no clear-cut answer science can provide to determine consensus. Policymakers must be able to distinguish advocacy from expertise, understand how scientific data were gathered, be willing to assess the process to gather the data and recognize the relevancy of the data to present-day topics. After policymakers learn and assess data and facts, they must then utilize risk assessment to make decisions. Ultimately, the choices made in resolving complex technical issues reside in a leader's ability to ask straightforward questions about the data and distinguish facts from advocacy—no easy task in today's hypercharged political environment. This guide strives to help make that process less daunting and facilitate better outcomes that could be applied across a host of policy discussions.

*** INTRODUCTION ***

State officials face tremendous challenges and opportunities when making policy decisions in the Internet age. Officials and their constituents have instant access to huge amounts of information and scientific knowledge. This nearly inexhaustible wealth of information can provide state officials with valuable resources for making informed decisions. On any given issue, they can review reams of data, read numerous studies and consult an endless parade of experts. A greater understanding of health, environmental, economic and social issues empowers state officials to enhance their constituents' quality of life as never before. Consider this: according to Peter Diamandis and Steven Kotler's book *Abundance*, a Masai warrior in sub-Saharan Africa has access to more computing power through a smartphone than was available to the president of the United States in 1997.

This flood of information, however, further complicates addressing policy issues. Inundated with scientific studies, expert opinions and attention-grabbing headlines, policymakers may have more information than they possibly can assimilate. But that quantity of information is compounded by uncertain utility—just because the information exists does not mean it is accurate or relevant. Policymakers also should keep in mind that science does not always have the answers to policy questions.

Distinguishing quality information from the bad and useful information from the irrelevant has never been more challenging than with the rise of Internet publishing and its effects on the policy process. After all, state officials cannot dismiss the immense contributions of science to public policy. At the same time, they must be wary of misallocating public resources based on misleading scientific claims. Officials need to know how to recognize credible and pertinent scientific studies, which questions to ask of scientific experts and how to integrate scientific information into their policy decisions. Therefore, The Council of State Governments has developed *A State Official's Guide to Science-based Decision-making* as a high-level reference tool to assist in separating the wheat from the chaff.

Science-based Decision-making—Its Intent

Uncertainty is an inherent part of science-based decision-making, and state officials should be prepared to look past the attention-grabbing headline and dig deeper to question claims or studies that do not document potential variables. The goal of this document is to help improve that decision-making process by removing clutter and offering a path toward clarity.

State officials do not have the capability to sort scientific research presented to them into two bins labeled "Useful in Decision-making" and "Junk: Discard." Instead, science comes in varying levels of quality and usefulness.

"The scientific community views research as more credible when it clearly states the problem being tested, follows established procedures for collecting and analyzing data, and is reviewed by other scientists."

The scientific community views research as more credible when it clearly states the problem being tested, follows established procedures for collecting and analyzing data, and is reviewed by other scientists. Studies that deviate from one or more of these criteria, however, may provide state officials with useful information, such as identifying potential risks to public or environmental health that should be monitored as they develop. Before dismissing such claims or studies, state officials should review them with closer scrutiny.

Science cannot explain our world with 100 percent certainty. Basic mathematic principles uphold fundamental pillars of quantitative natural sciences like chemistry and physics. But no scientific study can guarantee that it accounted for all factors at work, nor can its results, based on a limited sample, be generalized to an entire population in all cases. Accepted beliefs are discarded when new evidence is collected through additional studies and with improved research tools. Persistence is as necessary and valuable today as it was when Copernicus startled the medieval world by theorizing the Earth was not the center of the universe. Credible scientists and organizations are careful to explain sources of uncertainty in their findings, studies and testimony.

Contested Science

Everyone agrees public policy should be based on the best available scientific and technical information. But it is not uncommon for experts and others to have different interpretations of facts. These differences seem to emerge for one or more of the following reasons.

Lack of Information

Although the amount of data and information has grown in recent decades, along with access to such information, it is rare to face a policy problem where the information lights the way to an obvious solution. Often parties do not have the information they need because there is not enough data; there's too much data to absorb; the data that do exist are outdated; access to certain data may be restricted; the data are inconclusive or isn't relevant to the decision at hand; existing studies have different objectives, assumptions, or methods of data collection and analysis; and data exist but has not been analyzed sufficiently to provide useful information.

Lack of Agreement

Decision-makers, experts and advocates also may disagree on what information is needed to inform a particular decision. Participants in the policy process may define the problem and objectives differently, which thereby leads them to different conclusions about what information is needed. They also may disagree on procedures for assessing data and how to interpret data.

Lack of Incentives

The process of formulating and implementing public policy is characterized by an adversarial environment that often pits science against politics and one interest group against another. Advocates seek to prevail rather than to resolve their differences effectively. Each side seeks to gain an advantage by exploiting existing scientific and technical uncertainty. Incomplete understanding is used to delay decisions opposed by one group or individual. Scientists with different interpretations of the same data are pitted against each other, thereby canceling out what they have to say. The use of science in an adversarial way undermines trust in science, experts and the decision-making process.

Lack of Capacity

In some situations, some stakeholders have access to the data and others do not, either because the information is confidential or because parties have unequal scientific and technical resources. It is also not uncommon for some stakeholders to have more expertise and a better understanding of the data than others. Finally, different participants are likely to have different tolerances for risk and uncertainty.

Lack of Communication

Disputes over scientific and technical information also may emerge because of a lack of communication and understanding among experts, decision-makers and advocates. This lack of communication is fostered when issues of interest to scientists are not those of most interest to decision-makers and stakeholders; the decision-making process is on a shorter timetable than is the science; scientists' values influence the questions they are asking; or the participants have unrealistic expectations of the experts, science and ability to predict the future.

Media Hyperbole or Oversimplification

Bad news sells, and some members of the media may highlight minimal disagreements or cite antagonists that make the issue look out of proportion. In addition, many writers do not have a technical background and may lose important details or nuance when summarizing a story or gathering information on a debate. State policymakers must look beyond the headline of a news story before drawing conclusions.



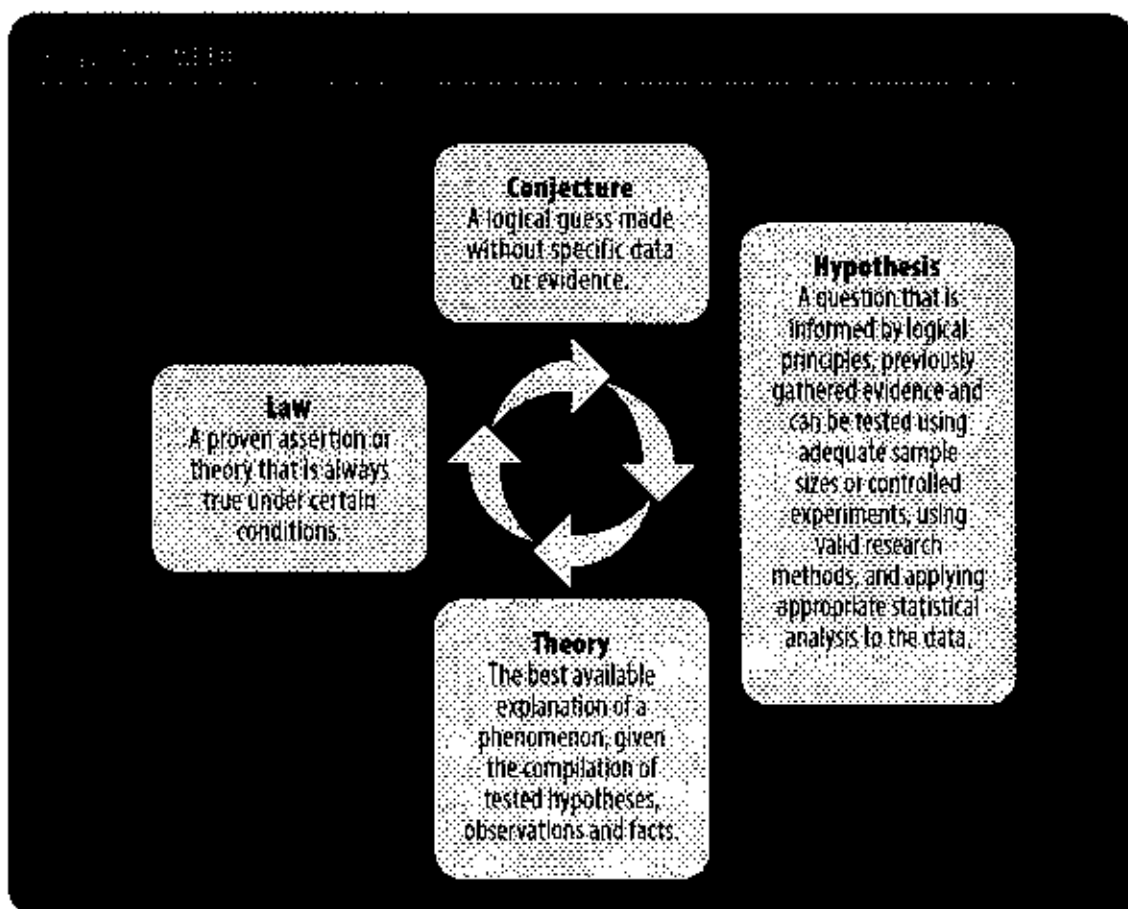
*** THE SCIENTIFIC METHOD ***

Quality science can be described as research conducted by trained individuals using documented methodologies that lead to verifiable results and conclusions. The scientific method, as illustrated on Page 9, is the conventional model of a research process that meets these criteria. Though not all scientific studies follow each step in this model, the scientific method is a convenient benchmark for state officials to use when evaluating scientific studies. The principles of the scientific method can essentially be broken into four aspects:

- * **Conjecture** – a logical guess made without specific data or evidence;
- * **Hypothesis** – a question that is informed by logical principles, previously gathered evidence and can be tested using adequate sample sizes or controlled experiments, using valid research methods, and applying appropriate statistical analysis to the data;
- * **Theory** – the best available explanation of a phenomenon, given the compilation of tested hypotheses, observations and facts; and
- * **Law** – a proven assertion or theory that is always true under certain conditions.

The scientific community develops theories from the accumulation of research findings. Commonly accepted theories can change as scientific knowledge evolves, demonstrating the inherent uncertainty of science. Because other variables could be tested and more subjects or research trials could be studied, no experiment can produce results that are 100 percent certain. Science is inherently dynamic. Scientific theories can on occasion become scientific laws, but the process for doing so is quite difficult and can take decades. Scientific laws are most often found in the natural sciences like chemistry and physics which involve mathematic equations. However, it's important to remember that scientific questioning led a technical assistant in the Swiss Patent Office named Albert Einstein to question Newton's laws of mechanics when he developed his General Theory of Relativity.

"Quality science can be described as research conducted by trained individuals using documented methodologies that lead to verifiable results and conclusions."



Methods	Disadvantages	Advantages	Disadvantages	Advantages
Case studies	An in-depth analysis, often through observation, of one or several individual examples in hopes of generalizing the results to a larger population.	Provides extensive knowledge of particular cases; can help in problem recognition and hypothesis formulation.	Cannot be certain the example is representative of the entire population.	Background information; hypothesis formulation; identification of emerging problems.
Clinical trials	A carefully designed investigation of the effects of a drug, medical treatment or device on a group of human subjects as cases and controls.	Allows researchers to ensure the safety of medical treatments before they are made accessible to the general public.	Treatment may have unexpected side effects on test patients; control subjects may be denied a beneficial treatment.	Medical studies of pharmaceutical or surgical efficacy (often associated with the Food and Drug Administration)
Epidemiological studies	An attempt to measure the frequency and severity of disease in populations, identify harmful environmental effects, and establish the safety and effectiveness of drugs, surgery and other forms of medical treatment.	Suggests a relationship between two factors or events; best at identifying powerful associations but may produce contradictory results with weaker relationships.	Cannot establish cause and effect.	Health reports; establishing possible risks or factors to target for prevention programs.
Field or observational study	An experiment conducted in a natural setting, often when investigating cause and effect relationships that cannot be brought into a controlled setting. Sometimes used in combination with scientific computer modeling.*	Relies on observation of real-life situations, rather than a laboratory construct.	May be difficult to replicate; does not permit the level of control or confidence of a laboratory-based experiment; difficult to establish causation.	Environmental impact research; behavioral studies.
Laboratory experimentation	The study of a proposed cause-and-effect relationship in a highly controlled setting. Often involves the use of a treatment group and control group.*	Controlled experimental setting maximizes accuracy of cause-and-effect findings.	Laboratory setting may be too artificial to produce realistic results, making generalizations from the findings difficult.	Elaboration on observations that have been made in people; test for possible hazards or benefits of substances or circumstances.
Meta-analysis	A statistical analysis of multiple studies of recent research on a particular topic or phenomenon. Provides a means to increase the statistical power of small numbers of observations by pooling data from two or more studies.	May be more efficient than setting up and conducting an experiment; provides thorough assessment of prior research.	Does not provide original research on an issue; pooling data from multiple studies conducted by different researchers with different subjects may not be valid.	Evaluating the statistical strength of the conclusions from a collection of scientific studies.
Surveys	A method of collecting information directly from people, usually in the form of a questionnaire or interview, analyzing the responses, and inferring how the findings relate to a larger group of individuals.	Allows for direct response from human subjects.	Sampling may not be representative of the population under study; responses rely on recall and truthfulness, either of which factors may lessen the accuracy of survey responses.	Social scientific research, such as cultural issues and marketing studies; health studies.
Scientific (computer) modeling	A simulated representation of a real-world process based on an assembly of knowledge gained from a wide array of observations. Models are tested under varied conditions in order to assess their reliability.	Used to understand what has caused various changes; to test different control strategies; and to develop predictions; enables researchers to answer the question "What if...?" or to examine the possible consequences of certain actions before harm is caused.	A model cannot prove a theory, only demonstrate the implications of what is already known about a process; limited by what is currently known about causal variables; unknowns must be fixed by assumptions or left out of model.	Climate and weather; environmental impacts; animal behavior.

*Source: *Interpreting Communication Research*. Carl H. Botan, Lawrence R. Frey, Paul G. Friedman and Gary L. Kreps. Englewood Cliffs, 1992.

As a general guide, the scientific method outlines recognizable characteristics of quality studies: a credible source, sound methodology, careful statements of association or causality, clear measures of confidence, some degree of peer review or evaluation by fellow practitioners, and the publication in a scientific journal where findings can be evaluated by outside sources to determine veracity. State officials can refer to these characteristics when looking for warning signs that a study may be faulty, which should lead them to question the study more critically.

The Scientific Method Applied

Note to reader: Starting below and throughout the Guide to Science-based Decision-making, a fictional character named Mr. Greenthumb will be used as an illustrative example of the technical concepts discussed.

An example of the scientific method at work might begin with a plant shop owner noticing that his plants are less healthy than those of a nearby store owner who talks to her plants each day. To figure out why the other nursery's plants are larger than his own, Mr. Greenthumb proposes the hypothesis: "Talking to your plants for 15 minutes a day will cause them to grow faster."

Mr. Greenthumb then develops a methodology to test this hypothesis. He gathers an experimental group of 30 plants of the same type and same height. He plans to treat 15 plants in Room A—the treatment group—to daily conversation and to avoid any speech while tending to the 15 plants in Room B—the control group. The control group will test whether a single variable—daily conversation—is responsible for an observed effect—increased plant growth. To conclude that any variation in height between the groups of plants is the result of conversation, Mr. Greenthumb must keep all other variables—such as sunlight, temperature and watering amounts—the same in both rooms.

Mr. Greenthumb then performs the experiment and collects data. For one month, he talks animatedly to each of the plants in Room A for 15 minutes each day, and he remains silent while in Room B. Before, during and after this experiment, he measures and records the height of all 30 plants.

Once the experiment is complete, Mr. Greenthumb's data analysis and interpretation of the plant measurements show what happened during the month of disparate treatments. Suppose the data analysis shows the plants in Room A grew faster than those in Room B. He uses statistical analysis to determine if the variation in growth between the two groups falls within the normal range for these plants. Because the growth rate is greater than would be expected in the typical plant population, Mr. Greenthumb concludes the results support his original hypothesis—talking to the plants did increase their growth rate.

In light of these findings, Mr. Greenthumb sends a report of the study to a scientific journal. Before publishing the report, the journal editors send it to several botanists to conduct a peer review of the study's methodology and conclusions. They scrutinize the study for consistent, logical arguments and for reasonable findings based on the data presented. Based on the peer review, the editors may recommend Mr. Greenthumb collect more data or revise the report. Once the editors are convinced Mr. Greenthumb's study is sound, the journal publishes the report to be reviewed by the scientific community. This may lead to replication or extension of Mr. Greenthumb's research as other scientists try to confirm his results or to expand them in new testable hypotheses.

Common Research Techniques

Scientists can use several common research techniques during the experimentation phase. Researchers tend to rely on the methods that best suit their subject area. For instance, medical researchers favor clinical trials to determine the effectiveness and possible side effects of new medications. While these studies are not the best for evaluating causation, environmental scientists frequently use field or observational studies to evaluate subjects or events in

Warning Signs of Pseudoscience

Dr. Robert L. Park is a professor of physics at the University of Maryland at College Park and the former director of public information for the American Physical Society. He developed seven warning signs the public should consider as indicators of scientific claims that are out of bounds of rational scientific discourse.

1. The discoverer pitches the claim directly to the media.
2. The discoverer says a powerful establishment is trying to suppress his or her work.
3. The scientific effect involved is always at the very limit of detection.
4. Evidence for a discovery is anecdotal.
5. The discoverer says a belief is credible because it has endured for centuries.
6. The discoverer has worked in isolation.
7. The discoverer must propose new laws of nature to explain an observation.

Source: The Observer, "Hobbes's Dilemma," 27, 2003. The author is quoted in The Science of Conspiracy, 2003.



research to identify potential policy problems—such as global climate change—and to applied research for possible solutions to problems.

Assessing the Expert

Nullius in verba, the motto of one of the world's oldest scientific associations—the Royal Society—means literally, “take no one's word for it.” Policymakers constantly hear from experts and organizations who advocate a position on a bill, regulation or study. It is important to understand the abilities and perspective of the individual(s) performing or presenting research or testimony in a hearing. To be considered a credible source, the researcher should be qualified, either through formal training or work experience, to design and conduct the study and to draw reasonable conclusions from it. The researcher should be well acquainted with the subject area and the body of technical information pertaining to it; a substantial and relevant publication record usually indicates that expertise. Although academic or professional credentials are not necessary or adequate to ensure thorough scientific conduct, the majority of qualified researchers in highly specialized fields today have earned postgraduate degrees.

If a wildlife expert is speaking on the economic ramifications or implications of a decision, that person has expertise, but only in his or her field of study. The individual may have opinions and strongly held beliefs backed up with some pertinent facts, but that person has now strayed out of a scientific realm and into the advocacy realm. Advocacy is integrally important to the democratic process and is a key externality that influences public policy. Advocacy, however, is not science and science is not advocacy. The data resulting from a study or hypothesis do not change with the party in power, nor should it be tailored—omitting key facts or advancing weak causal relationships—in order to fit a specific agenda.

Vested interest is another factor state officials should consider when gauging the credibility of a source of scientific information. Individuals who stand to benefit—either financially, politically or socially—from a particular outcome may express a bias in interpreting scientific findings. Because scientists also have an interest in maintaining their reputation in the scientific and policy communities, they have an incentive to provide reasonable conclusions that can stand up to the scrutiny of other scientists and parties affected by the policy decision. To understand the perspective of the source, state officials can question the researcher's personal or professional reasons for asking a specific scientific question.

“An important distinction must be made: Not all studies by industry and advocacy organizations should be dismissed simply because they come from a certain source.”

The issues of qualifications and perspective often arise during expert testimony to legislative committees. The objective of this critical thinking strategy is to encourage policymakers to consider and understand the perspective of witnesses and the potential variables at play. This is why the ability to evaluate the quality of the data and whether the study design was appropriate for your questions and decisions is so important. State officials may determine a researcher's credentials and interests in the policy decision at hand by watching for warnings signs and asking pertinent questions of expert witnesses as outlined below.

WARNING SIGN:

Observer Bias and Vested Interest

The source's record of objectivity is important in determining a study's soundness. Even unconsciously, predispositions can shape interpretation of study results. In addition to questioning experts about their biases, state officials can be more confident of a study's objectivity if the scientific community has reviewed it.

Example: Suppose Mr. Greenthumb (from the earlier example) is promoting plants from his shop for being of a superior quality because he talks to them on a daily basis. The conclusions he drew from his experiment may have been biased as a result of his efforts to prove his claim and sell more plants.

WARNING SIGN:

The Presenter Released Findings Directly to the Media

Typically, the common practice among scientists is to delay release of a study's findings to the public until it has gone through the peer review process (more is available in the “Integrating the Knowledge” section of this guide). For example, the New England Journal of Medicine's editorial policy abides by the so-called “Inglefinger Rule,” which delays a media release in order to conduct peer review and provide more time to review studies that may have minor mistakes that could be misinterpreted by the media due to their complex nature. There is, however, a robust debate over public access and media embargos by those seeking a right to know.

Example: Mr. Greenthumb decides, for either economic or personal reasons, to promote his findings that his

experiment of talking to plants really does increase their growth rates through a press release picked up by the local newspaper, rather than submitting his study to a journal where trained botanists could analyze his methods and conclusions.

Questions to Ask about the Expert:

- What educational background or training does the expert have?
- What types of work has the expert done in the field?
- Does the source of the research have anything to gain by the study's outcome? Are there conflicts of interest either financially or professionally?
- Is the expert or the expert's employer concerned about implications of a policy/decision?

Assessing the Methods

Credible scientific conclusions are based on well-established research practices. The principles of the scientific method provide key indicators of a sound process. For example, the study should describe the methodology used in the experiment in a manner that enables others to repeat the test—and verify the results.

All studies and modeling work contain some type of built-in assumptions. Those assumptions are not always causes for concern. Assumptions are justifiable by performing tests of the hypothesis in conjunction with experimental tests that can be verified separately. State officials should ask about underlying assumptions made in a study to ascertain the need for its inclusion and whether scenarios or variables considered can withstand scrutiny in real world applications. For example, a study warning about the dangers of the very rare cases of caffeine overdoses should include information about the ingestion levels that would warrant public action and concern. To reach fatal levels of caffeine toxicity in the blood, which is 5 to 10 grams depending on weight and health factors, a person would have to consume roughly 42, eight-ounce cups of coffee at one sitting.

Standards of reference also are important when deciphering the conclusions of a scientific study. When a researcher reports the population of an endangered species has tripled during the past five years, knowing the original population contained five individuals rather than 500 changes the context of these findings. If a survey shows 80 percent of its respondents favored the return of gallows to public courtyards, it would be helpful to know the pollsters only surveyed corrections employees.

WARNING SIGN:

Important Variables That are Overlooked or Ignored

A variable is something that changes, or a factor that may influence the outcome of an experiment. When trying to prove one thing is related to another, researchers may overlook certain variables that may shape the outcome. For instance, a generalization that "hungry dogs are more dangerous" ignores such important factors as the breed of the dog or the way it has been trained. Officials should question whether the study was controlled for other likely variables.

Example: It's possible that Rooms A and B in Mr. Greenthumb's plant experiment did not provide identical environments for the plants. Perhaps the shop owner ignored the fact that a humidifier was located in Room A, providing more moisture for those plants, which led to their faster growth rates.

WARNING SIGN:

Inadequate Sample Size and Biased Sample Collection

Studies based on an inadequate or biased sample may produce misleading conclusions. If a scientific study examines too few subjects, its results cannot be generalized to an entire population. The size of test samples varies according to such factors as the size of the overall population of interest. For example, a study of a relatively rare form of cancer (e.g., pancreatic cancer) can be based on a much smaller sample size than a common cancer (e.g., lung cancer). To increase the likelihood the sample accurately represents diversity in the entire population, researchers should select their samples randomly. State officials should ask how the sample was selected and if it compares in size to those of similar studies. They may need to request further explanation if the sample composition seems biased or the sample size seems small. They also should question studies that do not state the number of subjects studied or experiments repeated.

Example: Mr. Greenthumb only tested his hypothesis on 30 plants of his total inventory of 2,000 plants. He may not be able to conclude reasonably that his results apply to all 2,000 of his plants based on the relatively small sample size.

WARNING SIGN:

Lack of Helpful Standards of Reference

Percentages that are reported without good standards of reference or baseline data can be misleading. Officials should ask what the outcomes would be for the normal or expected case if such guidelines were not included. A clear understanding of how different the study's outcomes were from those normally expected can help officials interpret the findings accurately.

Example: Mr. Greenthumb's plants measured 4 inches at the beginning of the experiment. But if the type of plant grows faster at a more mature phase, say 8 inches tall, he must take that into account. If he doesn't, he should conclude there is little confidence his experiment produced significant findings because the fact that the plant's growth rate changes as it matures was not documented within the experiment.

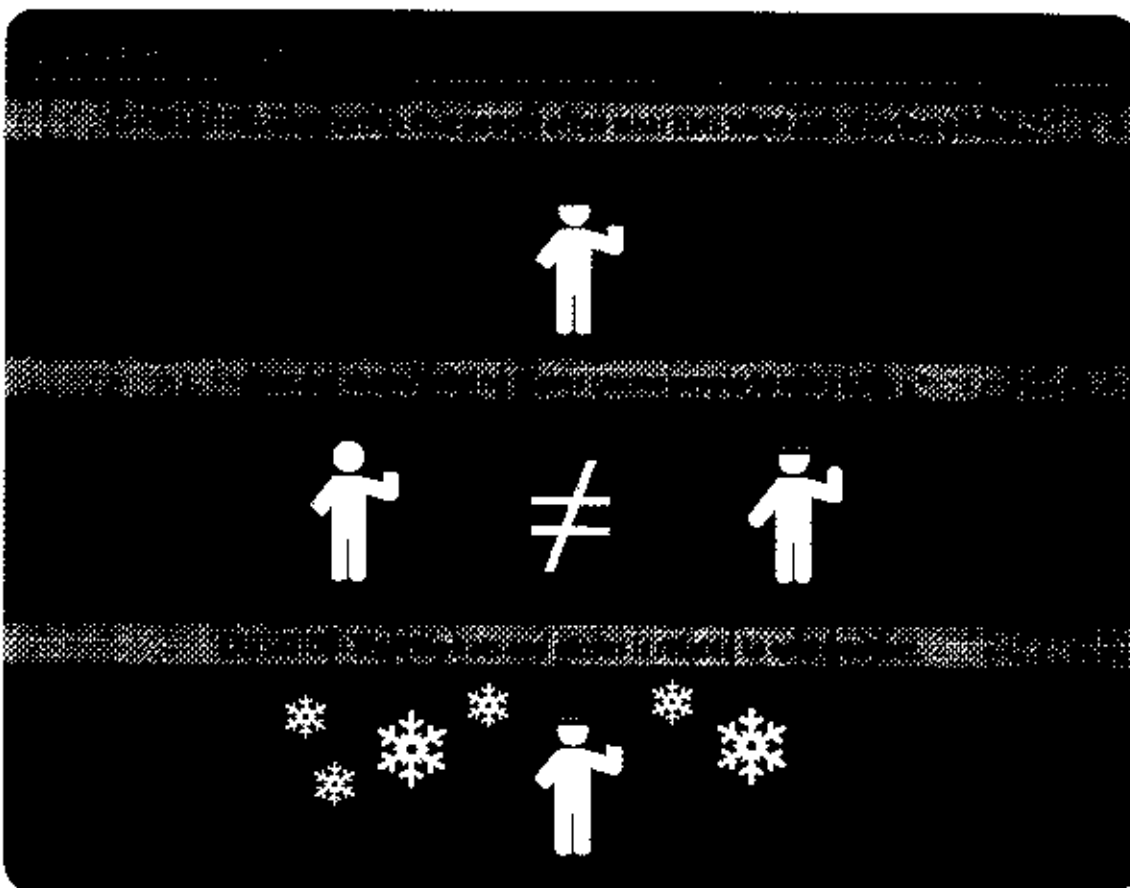
Questions to Ask about the Methods:

- Who gathered this information?
- What specific data or studies form the basis of the researcher's scientific conclusions?
- Have the data or studies been evaluated by other scientists? How extensive was the review?
- Have important variables been overlooked or ignored?
- Is the sample size used in the study truly representative?
- What specific hypotheses or questions did the researchers set out to test? Were steps taken to control other effects?

Assessing the Results

Clear data analysis should explain the relationship between the results and the original hypothesis. If a study does not include such analysis, state officials should ask questions to determine why particular steps were omitted.

A scientific study should indicate the type of relationship between variables it demonstrates either correlation or causation. Correlation, also known as association, is an apparent connection between two variables, assumed when they frequently occur together. For example, the observation that people often wear hats when they also are wearing gloves does not mean that wearing gloves causes people to wear hats. The wearing of both hats and gloves are related to another factor—cold weather. Causation is a statement of cause and effect, which means changes in one variable directly cause a particular change in another variable. Statements of causality often take the form of "if, then" statements. For instance, if you touch a hot stove, then you will burn your hand.



“Although scientists disagree on the procedure for proving causation, most agree the ability to show ‘A causes B’ is one of the most powerful statements scientists can make.”

Studies that use true experiments, which control the presence of the independent variable (the hot burner) to determine its impact on the dependent variable (the hand) seek to establish causal relationships. Other studies only try to identify a correlation between variables. For example, epidemiological research, which studies the incidence of disease in humans to control health problems, often identifies situations in which variables such as poor eating habits and disease tend to occur together. State officials should make sure the study's conclusions agree with the degree of association the research was designed to identify.

To determine if the observed results of a study are likely to be true, scientists employ a technique called statistical significance that measures the relationship between two variables to determine if the results are likely to occur or did so by happenstance. This mathematical measure determines if an observed difference is occurring by chance through an expressed value. The smaller the value, the less likely the results are occurring by chance and more likely the results are accurate.

Although it is tempting to skip over such technical details, policymakers should pay attention to the statistical terms that illustrate the degree of certainty associated with scientific findings. These statements indicate the degree of confidence with which scientists can present their conclusions. Statistical measures of confidence—standard deviation, standard error or confidence intervals—indicate the degree of certainty in the study's results. For instance, confidence intervals define the range within which results must fall in order to support the hypothesis. In some cases, state officials may be comfortable basing policy decisions on less stringent confidence measures than those required by the scientific community. Further, a careful consideration of abbreviations, acronyms and terms is critical when considering the proportionality of a study's findings. For example, the difference in a common measure of toxicity in the environment—parts per million vs. parts per billion—is enormous. One part per million of a substance in water would be equal to one teaspoon per 1,000 gallons, while one part per billion of a substance in water would be the equivalent of one teaspoon per 1 million gallons.

What Is the Significance of Parts Per Million (ppm), Parts Per Billion (ppb), and Parts Per Trillion (ppt)?

The effects of harmful and toxic substances to the environment and public health are related to the amount of exposure or dose. Some chemicals can cause toxicity even at very small doses, but it is critically important to understand how those doses are described and relate to one another compared to the substances we are exposed to every day. Most interactions we have with chemicals are not in a pure form; usually, it's through the air we breathe, the food we eat and the water we use.

The overall amount of a toxin in a given substance is referred to as its concentration. To determine a chemical's concentration, for a lake, for example, a scientist takes a small water sample that can be compared in a relative term with the lake's total volume. These are usually expressed as parts per million, or ppm, parts per billion, or ppb, and parts per trillion, or ppt. Below is an analogous chart showing what these amounts would demonstrate in time, money, distance and weight.

1 ppm	1 ppb	1 ppt
1 teaspoon per 1,000 gallons of water	1 teaspoon per 1 million gallons of water	1 teaspoon per 1 billion gallons of water
1 second in 11.6 days	1 second in 31.7 years	1 second in 317.1 centuries
1 penny out of \$10,000	1 penny of \$10 million	1 penny of \$10 billion
1 inch in 1.6 miles	1 inch in 15,780 miles	1 inch in 656,160 trips around the equator
1 minute in 1.9 years	1 minute in 19 centuries	1 minute in 1,900 millenniums
1 ounce in 62,500 pounds	1 ounce in 62,500 tons	1 ounce in 62,500,000 tons

Source: “What Is the Significance of Parts Per Million (ppm), Parts Per Billion (ppb), and Parts Per Trillion (ppt)?” by Mark M. Foster and Mark M. Foster, Secretary of Food and Nutrition Assistance, 2012. <http://www.fda.gov/oc/ohrt/>

WARNING SIGN:

Correlation Confused with Cause and Effect

Even if two events occur together, one may not be the actual cause of the other. Both may be related to another factor that is the true cause. If a study or expert does not clearly establish an intended cause-and-effect relationship, officials should ask questions to determine if the evidence has confused correlation with causation.

Example: A study finds the number of drowning deaths in the U.S. increases with amount of domestic ice cream sales. The author suggests the consumption of ice cream causes drowning and recommends consumption be curtailed. In this case, the author did not account for seasonal and temperature changes where consumers buy more ice cream in warmer weather, which also happens to correspond with vacation season and more trips to the beach or pool. Another useful example illustrating the confusion of correlation with causation would be a report issued by a group tracking the rates of autism diagnoses and increased sales of organic food. Both have increased substantially from the late 1990s through 2011, almost on the same exact linear curve, yet the information is completely coincidental and insignificant.

WARNING SIGN:

Conclusions Based on Personal Stories or Anecdotal Evidence

People often draw incorrect conclusions from personal stories, especially when they are presented in a familiar or appealing way. Although many public speaking courses emphasize the importance of personalizing a speech or debate to make it more convincing, personal stories or testimonials cannot be applied universally. Officials should be sure they draw conclusions from well-designed scientific studies, rather than from anecdotal information.

Example: Suppose Mr. Greenthumb was particularly fond of a large plant he enjoyed talking to, and he strongly believed the plant responded to his voice by growing. His marketing claim then would be based on anecdotal evidence, with no scientific proof to support his assertions.

WARNING SIGN:

Statements of Certainty

Though based on the best evidence available at the time, scientific statements cannot be 100 percent certain. Thus, conscientious scientific communicators rarely use absolute terms such as always, only or never. Instead, they explain the study's limitations—such as which unmeasured variables may have influenced the results—and communicate the degree of certainty in their findings—statistical measures of confidence. When considering whether results are meaningful, state officials can examine and seek clarification on such measures to discern the level of statistical significance.

Example: Suppose a sign outside Mr. Greenthumb's store proclaims, "The Fastest-Growing Plants in the Business—They Thrive on Conversation!" The absolute term, fastest, should serve as a signal for the need to question and examine his evidence.

Questions to Ask about the Results:

- Has the research been reviewed by other scientists and interested parties? How extensively?
- What are the underlying systematic uncertainties?
- Were conclusions based on personal stories/anecdotal evidence?
- Do the results demonstrate causality rather than correlation? Are the results statistically significant?
- Are statistics adequately explained? If not, ask for a practical explanation.
- What degree of uncertainty surrounds the results?
- To whom or for what do the results apply? Can they be extrapolated to the general population?
- Do the conclusions logically follow from the scientific results?



*** INTEGRATING THE KNOWLEDGE ***

Once a policymaker has gathered technical information and questioned experts, the final step in the decision-making process is integrating individual pieces of knowledge into a coherent plan of action. Helpful ways to refine that process include a robust peer review process, the utilization of risk assessments and the concept of adaptive management.

Peer Review

According to the Environmental Protection Agency's Peer Review Handbook, "Peer review is a documented critical review of a specific Agency's scientific and/or technical work product. Peer review is conducted by qualified individuals (or organizations) who are independent of those who performed the work, and who are collectively equivalent in technical expertise (i.e., peers) to those who performed the original work. Peer review is conducted to ensure that activities are technically supportable, competently performed, properly documented, and consistent with established quality criteria."

During this process, other scientists assess such qualities as the relevance, accuracy and reliability of the study. Peer review typically is required for accepting publishable articles, awarding grants and approving tenure. Although it is not always perfect and cannot guarantee fraud or error will be uncovered, peer review is traditionally the best mechanism many scientific journals and funding agencies have to avoid publishing or financing poor quality research.

Publication of scientific findings often follows peer review and is an integral component of research, as it further distributes the findings to those in the scientific community, enabling them to assess, correct and develop the research results. Once a study is published, further response is likely, and state officials can use this as additional evidence.

Traditional review periods for publication in scientific journals may be up to two years or longer, depending on the prestige of the journal and competition levels within the discipline. Online publishing has greatly accelerated these timelines to allow for greater access by the scientific community, which then can analyze findings. When studies are released without peer review to a news-hungry press, researchers may have to retract their findings if other scientists find fault with their study. The consequences of scientifically unsupported decisions creates lasting misperceptions—as the earlier case study of the autism/vaccine illustrated—that may be difficult to reverse.

Several practical limitations on peer review and publication may explain why some sound studies do not meet these standards. For instance, proprietary research data, such as studies conducted by and for federal regulatory agencies or by private companies, are unavailable to the general public for peer review. Such studies are usually undertaken by industry, in some cases for the government, and held as confidential business information. Additionally, Internet publishing presents a relatively new dilemma for adequate peer review. Some scientific journals are beginning to publish articles almost instantaneously, with continual review following publication.

Risk

Risk is an inherent part of everyday life; it can be defined as the potential for harm for humans or the things they value. Scientists have developed a process for dealing with uncertainties to quantify the risk and potential damage or harm to public health, the environment, consumer products, infectious diseases, and on and on. This process is conducted through a risk assessment that characterizes and measures the magnitude and nature of potential threats.

Publications and Other Media

Professional journals, usually peer-reviewed, nine to three years to publication; contain technical jargon.

Conference proceedings; usually no peer review; six to eight months to publication; contain technical jargon.

Textbooks, peer reviewed; usually average one year to publication; may contain defined technical jargon.

Newspapers and popular magazines; typically no peer review by scientific community; days to weeks for publication; seldom contain technical jargon.

Consensus conference or scientific review panels, convened to address specific topics and reach conclusions about the state of the science; one to two years with various outputs for publication.

Source: U.S. Environmental Protection Agency, Peer Review Handbook, EPA-823-R-99-001, August 1999.



The concept of risk assessments has been around for many years and is used in a variety of applications with distinct fields of specialization by professionals. The first formal attempt to characterize risk assessments was undertaken by the National Academy of Sciences and the National Research Council in 1983 with the publication of its first Redbook. In 1994, the National Academy of Sciences further refined its original intent of characterizing risk assessments by defining it as:

“... The integration of information from the first three steps of the risk assessment process, as defined in the 1983 NAS ‘Redbook,’ to develop a qualitative estimate of the likelihood that any of the hazards associated with the agent of concern will be realized in exposed people. This is the step in which risk assessment results are expressed. Risk characterization should also include a full discussion of the uncertainties associated with the estimates of risk.”

Risk assessment conducted by the Environmental Protection Agency for both environmental and public health concerns are conducted in basically the same five-step process.

- Step 1—Planning and scoping. Who/what/where is at risk? What are the hazards of concern? Where do they come from? How does exposure occur? What populations are impacted? What are the health effects? What duration of exposure will cause a harmful effect? What are the lifetime effects from exposure?
- Step 2—Hazard identification examines whether a stressor has the potential to cause harm to humans and/or ecological systems, and if so, under what circumstances.
- Step 3—Dose response assessment examines the numerical relationship between exposure and effects.
- Step 4—Exposure assessment examines what is known about the frequency, timing and levels of contact with a stressor.
- Step 5—Risk characterization examines how well the data support conclusions about the nature and extent of the risk from exposure to environmental stressors.

State officials must understand the distinction between a risk assessment, which calculates the hazard and its consequences, and risk management, which is a process that decides if and how a hazard should be addressed. The risk management process inherently involves policy decisions and external forces, such as public input, to ultimately determine acceptable risk levels. Part of that challenge for policymakers is articulating the potential risks to the environment and public health. Scientists and technical professionals often perceive risk differently than the average person who likely is unfamiliar with conflicting interpretations of data, jargon-laced language, and the absence of absolute answers that often accompany risk assessments and studies. State officials can help in this process by focusing their communication efforts in three main areas: what is known, what is not known and what can be done to address concerns.

One potential direction that could tie the disparate areas of risk assessment, risk management and risk communication together is a set of guiding principles first developed in 1995 by a federal interagency working group

Guiding Principles for Risk Management

1. Issue identification: identify the health, environmental, social, economic, cultural, legal, political and other issues that will be considered in developing the management strategy.
2. Goal setting: establish health or ecological goals that broadly incorporate issues and concerns raised during the issue identification process.
3. Management options development: devise a range of possible risk management strategies that consider the issues and concerns identified in the first step.
4. Data compilation and analysis: identify, collect and analyze relevant data on the scientific, technical, economic, social, cultural, legal and political aspects of the options.
5. Option selection: decide on a preferred management strategy, scaled to the risk under consideration and based on analytical review of the data and input from those involved.
6. Decision implementation: initiate hazard control, immediate and/or exposure reduction activities designed to implement the preferred management strategy.
7. Tracking and evaluation: collect and analyze monitoring and assessment information and compare against baseline data and target outcomes developed during previous steps.

Source: U.S. Environmental Protection Agency, 1995. Adapted from: U.S. Environmental Protection Agency, 1995. <http://www.epa.gov/redbook/redbook.htm>. Copyright 1995.

led by the Office of Management and Budget and the Office of Science and Technology Policy. The agencies reaffirmed those basic principles in 2007 to guide policymakers in assessing, managing and communicating policies to address environmental, health and safety risks. Risk analysis was just one very important tool that needed to “retain sufficient flexibility to incorporate scientific advances.” The principles are as follows:

Risk Assessments

- Agencies should employ the best reasonably obtainable scientific information to assess risks to health, safety and the environment.
- Characterizations of risks and of changes in the nature or magnitude of risks should be both qualitative and quantitative, as well as consistent with available data. The characterizations should be broad enough to inform the range of policies to reduce risks.
- Judgments used in developing a risk assessment—such as assumptions, defaults and uncertainties—should be stated explicitly. The rationale for these judgments and their influence on the risk assessment should be articulated.
- Risk assessments should encompass all appropriate hazards. In addition to considering the full population at risk, the assessment should direct attention to subpopulations that may be particularly susceptible to such risks and/or may be more highly exposed.
- Peer review of risk assessments can ensure the highest professional standards are maintained. Therefore, agencies should develop policies to maximize its use.
- Agencies should strive to adopt consistent approaches to evaluating the risks posed by hazardous agents or events.

Case Study: Bay Delta Ecosystem

The Bay Delta sits at the juncture of the Sacramento and San Joaquin rivers at the mouth of San Francisco Bay. It represents the largest estuary on the west coast of North and South America. The delta supports a variety of plants, migratory birds, endangered fish species and many other animals. It also supplies water for agriculture, the high-tech industry and 22 million California residents.

The CALFED Bay Delta Program, a unique collaboration among 25 state and federal agencies, was created in 1985 via a negotiation agreement among state and federal governments and various stakeholders. It was charged with identifying options to improve agricultural water use efficiency while restoring the ecosystem, particularly in the face of chronic droughts. Initial attempts to address this complex set of issues were unsuccessful, in large part because of disagreement over scientific and technical information. Facing a critical deadline in 1995, CALFED hired an impartial public policy mediator to help design and facilitate a more effective process.

The mediator convened the Independent Review Panel on Agricultural Water Conservation. It included five nationally recognized scientists with expertise in conservation, hydrology, hydraulics and aquatic ecology. The panel also included technical advisers aligned with various stakeholder groups. Before assembling the panel, the mediator worked closely with stakeholders, decision makers and experts through one-on-one conversations, meetings with interested parties and a one-day public scoping meeting to identify what was known, what was not known and what information was needed to make an informed decision.

The expert panel convened for two and a half days at the end of 1998. The deliberations succeeded in identifying and narrowing the areas of scientific uncertainty and disagreement and producing new information that explained causal relationships relevant to managing the resource. The panel generated a revised approach to water conservation that relied on incentives and objectives rather than best management practices. The panel also identified areas in need of further data collection and analysis.

The mediator drafted a single-text document summarizing the panel's findings with input from all panelists. The report became a source for ongoing deliberations and was critical in formulating CALFED's Water Use Efficiency Program, which was accepted by a wide range of stakeholders and policymakers.

This case demonstrates several key components of joint fact-finding. Facilitated by an impartial mediator, the process resulted in the coproduction of policy-relevant technical information accepted by a range of stakeholders—an outcome many believed would be impossible after the failure of initial attempts to address agricultural water use. Stakeholder involvement during the scoping and selection process, transparency of the panel's deliberations and production of a single text of recommendations all contributed to the salience and credibility of the panel's findings.

Source: “Sustainable Water and Environmental Management in the California Bay Delta,” *National Research Council: The National Academies Press*, 2012.

Risk Management

- » In making significant risk management decisions, agencies should analyze the distribution of the risks and the benefits and costs—direct and indirect, quantifiable and nonquantifiable—associated with the selection or implementation of risk management strategies.
- » In choosing among alternative approaches to reducing risk, agencies should seek to offer the greatest net improvement in total societal welfare, accounting for a broad range of relevant social and economic considerations, such as equity, quality of life, individual preferences, and the magnitude and distribution of benefits and costs—direct and indirect, quantifiable and nonquantifiable.

Risk Communication

- » Risk communication should involve the open, two-way exchange of information between professionals, including policymakers, experts in relevant disciplines and the public.
- » Risk management goals should be stated clearly, and risk assessments and risk management decisions should be communicated accurately and objectively in a meaningful manner.
- » To maximize public understanding, explain the basis for significant assumptions, data, models and inferences used or relied upon in the assessment or decision; describe the sources, extent and magnitude of significant uncertainties associated with the assessment or decision; make appropriate risk comparisons, taking into account public attitudes with respect to voluntary versus involuntary risk; and provide timely, public access to relevant supporting documents and a reasonable opportunity for public comment.

Adaptive Management

Adaptive management is another important strategy to make informed choices and resolve disputes over scientific and technical information. According to Kai Lee, one of the founders of this strategy, adaptive management is a process of making public decisions using the best information, monitoring the results, learning from experience and adapting future policy prescriptions appropriately. It is based on the premise that uncertainty is a given—social, economic and environmental values change, landscapes evolve and unanticipated consequences occur. This does not mean decisions should be postponed until more complete information is available. It means policymakers should learn by doing and should create an expectation of learning from experience as the decision-making process unfolds.

How to Use Scientific Information in Policy Making

How to Use Scientific Information in Policy Making: A Guide for Federal Agencies, EPA, 2007. <http://www.epa.gov/scitech/pubs/using-science.pdf>

The following four principles have proved to improve public decisions characterized by contested science:

Clarify the questions jointly before gathering more data.—Too often, we find ourselves in disputes where data exists but people still feel their questions aren't being answered. One problem may be that people are not yet clear about what questions they care about. The key is to gather experts, decision-makers and stakeholders and have them determine jointly which questions are part of the scope of the discussion. Because different people may see the questions differently, this often means seeking answers to questions of importance to each individual or the group.

Focus on decision-relevant information.—The problems that confront policymakers clamor for *more* information. But in some cases, different advocates may be shouting so loudly about their own data that they can't hear each other. Once the participants have agreed on the questions, they also need to discuss and agree on what information is needed to answer those questions. With that as a foundation, people often are better able to review existing information, determine what they agree on, and focus any further data collection or analysis on filling agreed-upon gaps.

Let science be science, and don't confuse it with policy.—Science is needed to inform policy, but the choice of what information to collect and why is almost always shaped to some degree by someone's values and priorities. In each case, it is crucial to clarify who set the underlying assumptions and whether policymakers and stakeholders helped shape the questions being researched. Too often, leaders look to scientific information that was gathered for other reasons. For often, also, we look to science for answers it doesn't have; science cannot tell policy makers what tradeoffs to make or how much risk to accept. Though there's no requirement for scientific certainty, policymakers should be wary of setting policy before the science is clear enough to inform sound policy decisions.

Learn together.—Decision-makers and advocates should view the policymaking process as one of inquiry—clarify questions, ask what information is needed, identify what information exists and what is needed, create a process for data collection and analysis, decide who will conduct the studies, and learn from the results. This process of collaborative inquiry does not need to be burdensome, but it does need to be intentional. It may require as little as a few meetings or workshops or it could require the investment in a joint technical working group.

Source:

EPA. *Using Scientific Information to Inform Policy Through a Fact-Finding Process*. Research Report, EPA-600/R-07/001, p. 21.

EPA. *Implementing Science-Based Policy: A Guide for Federal Agencies*. EPA-600/R-07/001, p. 21. <http://www.epa.gov/scitech/pubs/using-science.pdf>

WARNING SIGN:

Peer review and publication are helpful tools for verifying scientific findings. Once a study has survived the scrutiny of peers in the scientific field, nonscientists can be more confident of its soundness. Since publication leads to further peer review, it is often more difficult to assess the technical quality of findings that are so recent they have not been published. State officials should ask for documentation of peer review or for the published study. If neither is available, officials can question the expert to determine if there are satisfactory reasons, such as protecting proprietary information, the scientific community has not reviewed the study.

Example: Mr. Greenthumb's findings have not been reviewed or tested by any other botanists for accuracy of his methods or conclusions. If the warning signs outlined indeed applied to his study, the scientific community should have questioned Mr. Greenthumb's study, perhaps opposing its publication. Without peer review and publication, a nonscientist must judge Mr. Greenthumb's claims without the expertise of the scientific community.

Questions to Ask about Integrating the Knowledge:

- Have the study results been published? If yes, was it in a journal that requires peer review prior to publication? Have any scientific peer review panels considered the study results?
- Is there a consensus about the key findings of the studies? What are the areas of agreement/disagreement?
- Do other scientists share the researcher's views? Who doesn't and why?
- Have the results been repeated, confirmed or supported by other studies?
- What are your views on the practical applications of this scientific knowledge/decision?
- Is the timeliness of the study relevant to today's issues?
- What are the consequences/implications of action or inaction, including risks? Is there a balanced approach? Why or why not?

Adaptive Management

Although its roots extend into many disciplines, adaptive management's broad features are based on research conducted by ecological scientists in the early and mid-1970s. The concept gained greater currency in U.S. federal water and science agencies during the 1990s. Current federal law mandates the Florida Everglades restoration project be managed under an adaptive management model. The federal science and management program for the Colorado River below Glen Canyon Dam is framed by adaptive management principles and the U.S. Army Corps of Engineers is promoting the concept as a guiding principle in managing the Missouri River dam and reservoir system.

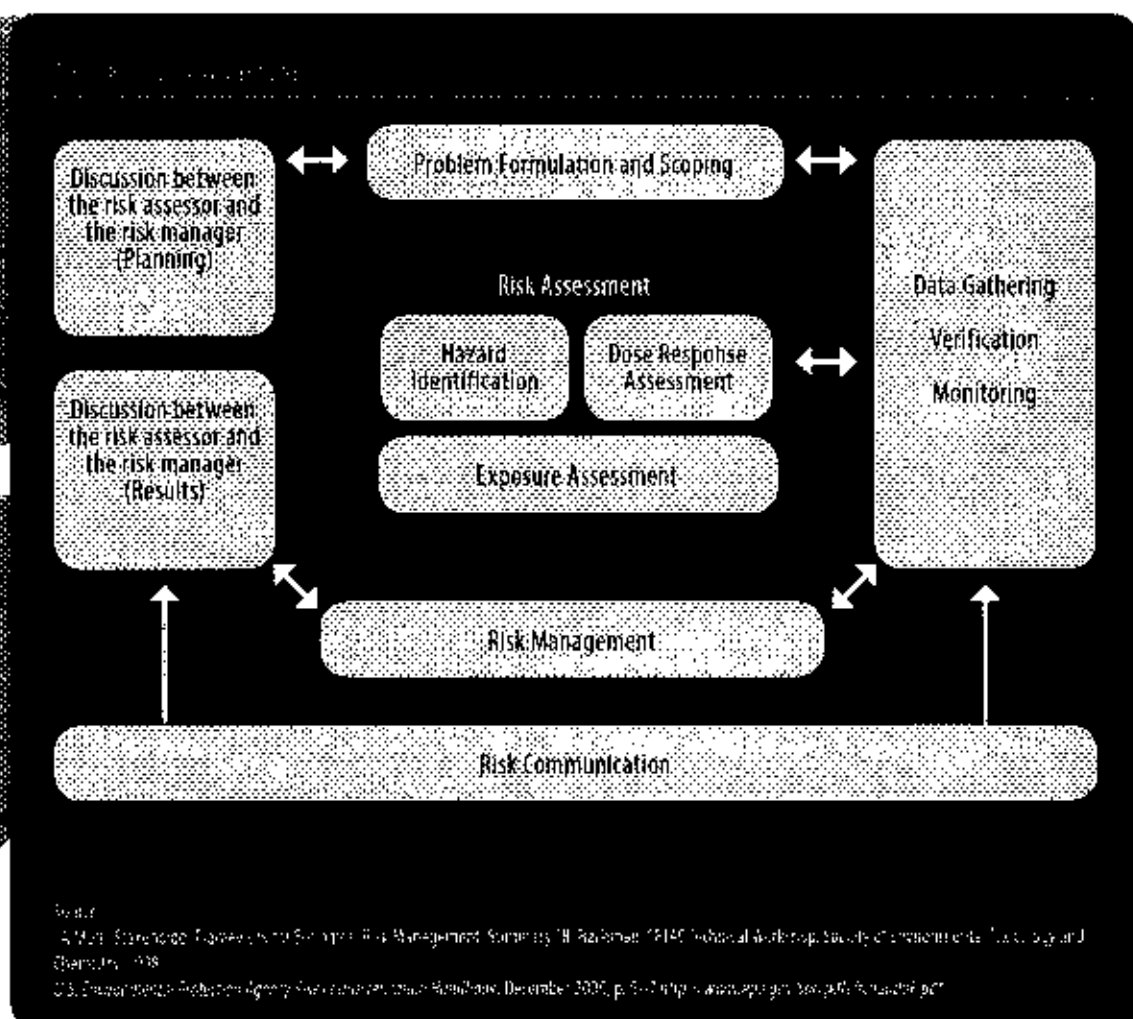
Adaptive management is interdisciplinary, has a strong theoretical component, and represents a departure from traditional management approaches in many ways. The adaptive management paradigm views management actions as flexible and amenable to adjustments. It emphasizes careful monitoring of economic and environmental outcomes of management actions. It also seeks to engage stakeholders in a collaborative learning while doing process. Other differences are:

Traditional Management	Adaptive Management
Seek precise prediction	Discover range of possibilities
Build prediction from detailed understanding	Predict from experience with aggregate responses
Promote scientific consensus	Embrace alternatives
Minimize conflict among actors	Highlight difficult tradeoffs
Emphasize short-term objectives	Promote long-term objectives
Presume certainty in seeking best action	Evaluate future feedback and learning
Seek productive equilibrium	Experiment and profit from change
Public provides input in pre-project dispute events	Public input is changing and frequent
Public interest is perceived as aggregate	Public interest perceived as pluralistic

Source: Carpenter and Barbour, *Science of the Everglades Restoration* (Fort Lauderdale, FL: St. Johns River Water Management District, 1999), pp. 24.

Conclusion

Science informs just one part, albeit a critically important one, of the policymaking process; it is not a policy itself. Sometimes there simply is no clear-cut answer science can provide to determine consensus. One tool utilized by practitioners in the energy and natural resource policy arena is joint fact finding, where an agency or group of agencies will act as a convener and final decision-maker. Its mission, however, is to engage stakeholders and nongovernmental participants in a formal discourse meant to resolve issues using quality and verifiable science. Ultimately, the choices made in resolving complex technical issues reside in a leader's ability to collaborate, dialogue and engage—no easy task in today's hypercharged political environment. This guide is intended to help make that process less daunting and facilitate better outcomes that could be applied across a host of policy discussions.



*** GLOSSARY ***

Alpha Level A level set to determine significance in research experiments. The set alpha level represents the probability (in 100) that the results could be due to chance. Most alpha levels range between 0.05 and 0.10 (5 percent to 10 percent). When a significant result is achieved at the 0.05 alpha level, there is a 5 percent chance that results were due to a chance occurrence and were not due to the experimental effect. See also statistical significance.

Baseline A preliminary measurement of behavior, health or mechanisms before experimental manipulation.

Bias An inclination that inappropriately influences a researcher's judgment. Also, a systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over others.

Carcinogen A substance or agent that produces or incites cancer.

Cohort A group of individuals having a common statistical factor in a demographic study.

Confidence Interval An estimated range of values that is likely to include an unknown population parameter, with the estimated range being calculated from a given set of sample data. For example, if a survey has a margin of error of plus or minus 4 percent at the 95 percent level of confidence, then in 95 out of 100 samples like the one used in the survey, the results obtained should be no more than 4 percentage points above or below the figure that would be obtained by interviewing the entire population being sampled. The width of the confidence interval gives some idea about how uncertain the researcher is about the unknown parameter. Confidence intervals are typically set at 95 percent (a 10 percent range), but they could be set at wider or smaller widths, such as 90 percent or 99.9 percent. See also margin of error, parameter.

Conjecture Inference from defective or presumptive evidence.

Cost-benefit Analysis A formal quantitative procedure comparing costs and benefits of a proposed project or act under a set of pre-established rules. To maximize absolute return given limited resources, benefits-costs is the appropriate form.

Data Numbers or measurements that are collected as a result of observations or experiments.

Deduction Formulation of particular conclusions from general or universal premises.

Dose-response A correlation between a quantified exposure (dose) and the proportion of a population that demonstrates a specific effect (response).

Ecological Impact The total effect of an environmental change, natural or man-made, on the community of living things.

Ecological Significance When a change that is detected or projected in the ecological system or its individual components of concern is a change of importance to the structure, function or health of the system and the change exceeds the context of natural variability.

Extrapolation In risk assessment, this process entails assuming a biologic fact based on observable responses and developing a mathematical model to describe the fact. The model may then be used to extrapolate to response levels that cannot be directly observed.

Falsification In research terms, refers to changing or misrepresenting data or experiments or credentials.

Geographic Information System (GIS) A computer based system for the capture, storage, retrieval, manipulation, analysis and display of geographic information. The number and type of applications and analyses that can be performed by a GIS are as large and diverse as the available geographic data sets.

Induction Reasoning from specific observations and experiments to more general hypotheses and theories.

In Vitro Laboratory experiments on cells or tissue samples.

In Vivo Laboratory experiments on small living animal subjects.

Latency Period The period of time from exposure to an agent to the onset of a health effect.

Longitudinal Studies A long-term study that repeatedly samples the same study group over an extensive period of time, with some lasting several generations. Most often conducted to measure long-term effects or to detect changes those researchers believe take time to manifest.

Lowest Observable Effect Level (LOEL) The smallest dose that causes any detectable effect; one of the threshold levels of exposure when measuring the effects of non-carcinogens.

Margin of Error A measurement of the accuracy of the results of a survey. For example, a margin of error of plus or minus 3.5 percent (+/- 3%) means that there is a 95 percent chance that the responses of the target population as a whole would fall somewhere between 3.5 percent more or 3.5 percent less than the responses of the sample (a 7 percent spread).

Mean The sum of scores or values of a variable divided by their number.

No-Observed-Adverse-Effect Level (NOAEL) The dose at or below which no harmful effects are detected; one of the threshold levels of exposure when measuring the effects of non-carcinogens.

No-Observed-Effect Level (NOEL) The dose at or below which no biological effects of any type are detected; one of the threshold levels of exposure when measuring the effects of non-carcinogens.

Normal Distribution Maps the range of results or scores along a "normal" or average continuum; most often associated with IQ scores in conjunction with the standard deviation. See also standard deviation.

Null Hypothesis The expectation in every study that is tested against. The null hypothesis typically states that the independent variable will have no discernible effect on the dependent variable when compared to chance.

Parameter A value summarizing a measurable characteristic of a population. The population's mean is a commonly used parameter. See also mean.

Population A complete set of individuals, objects or measurements having some common observable characteristic (e.g., all babies born in a given year). A population may include a theoretical set of potential observations (e.g., all babies regardless of when they were born or will be born).

Population at Risk A limited population that may be unique for a specific dose-response relationship.

Random Sample A subset of a population selected in such a way that each member of the population has an equal opportunity to be selected. The goal is that the sample accurately reflect all the characteristics of the population from which it was drawn so that inferences about that population can be made from the sample.

Replication Practice by which studies are substantiated by being repeated in other laboratories. A fail-safe method that adds credibility to a study if supporting data are found or refutes the study if its results are not supported.

Social Science The study of human affairs at the level of the intact organism. Fields of social science include psychology, sociology and political science.

Standard Deviation The average deviation from a given mean, indicating how closely various samples come to the mean. See also mean.

Standard Error An estimate of the standard deviation of sample means, based on the data from one or more random samples. The smaller the standard error for a particular data set, the more precise the estimates will become, which means that increasing the sample size is one way to increase the precision of statistical decisions.

Statistical Significance A finding (e.g., the observed difference between the means of two random samples) is described as statistically significant when it can be demonstrated that the probability of obtaining such a difference by chance alone is relatively low. Common significance levels are 0.05 and 0.01. See also alpha level.

True Experiment A study in which the independent variable is under the control of the experimenter.

Valid Measurement of whether a scientific study is well grounded and justifiable. Valid studies measure and reach conclusions on the variables studied.

Variable A characteristic or phenomenon that may take on different values.

❖❖❖ SOURCES ❖❖❖

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CSG HEADQUARTERS

1760 Kennedy Blvd., 10th Floor
Lexington, MA 02421
ph 800-243-8006
fax 815-244-8007
www.csg.org

CSG D.C.

444 Constitution Ave., N.W.
Suite 400
Washington, D.C. 20001
ph 202-638-4040
fax 202-638-4040
www.csgcd.org

CSG EAST

100 West Street
20th Floor
New York, NY 10005
ph 212-481-2220
fax 212-481-2574
www.csgeast.org

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P.O. Box 96129
Atlanta, GA 30399
ph 404-243-1800
fax 404-633-4800
www.southatlanta.org

CSG MIDWEST

701 E. 22nd Street
Suite 1100, Lombard, IL
60148-5063
ph 630-976-1900
fax 630-976-1611
www.csgrmidwest.org

CSG WEST

1107 Broadway
Suite 700
San Francisco, CA 94104
ph 415-774-4473
fax 415-444-0701
www.csgwest.org

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:18 AM
To: Jaime Fuge
Subject: Fwd: Keep Community Water Fluoridation
Attachments: image003.jpg; ATT00001.htm; image005.png; ATT00002.htm; image001.png; ATT00003.htm; Keep Community Water Fluoridation Green Bay 2020.pdf; ATT00004.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Georges Benjamin <georges.benjamin@apha.org>
Date: August 31, 2020 at 7:02:37 PM EDT
To: "Eric.Genrich@greenbaywi.gov" <Eric.Genrich@greenbaywi.gov>, "district1@greenbaywi.gov" <district1@greenbaywi.gov>, "district2@greenbaywi.gov" <district2@greenbaywi.gov>, "district3@greenbaywi.gov" <district3@greenbaywi.gov>, "district4@greenbaywi.gov" <district4@greenbaywi.gov>, "district5@greenbaywi.gov" <district5@greenbaywi.gov>, "district6@greenbaywi.gov" <district6@greenbaywi.gov>, "district7@greenbaywi.gov" <district7@greenbaywi.gov>, "district8@greenbaywi.gov" <district8@greenbaywi.gov>, "district9@greenbaywi.gov" <district9@greenbaywi.gov>, "district10@greenbaywi.gov" <district10@greenbaywi.gov>, "district11@greenbaywi.gov" <district11@greenbaywi.gov>, "district12@greenbaywi.gov" <district12@greenbaywi.gov>
Cc: "celestineje@greenbaywi.gov" <celestineje@greenbaywi.gov>, "clerkinquiries@greenbaywi.gov" <clerkinquiries@greenbaywi.gov>, "Nancy.Quirk@greenbaywi.gov" <Nancy.Quirk@greenbaywi.gov>, "drjohnnyjohnson@gmail.com" <drjohnnyjohnson@gmail.com>
Subject: Keep Community Water Fluoridation

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steur, and VanderLeest,

On behalf of the American Public Health Association, a diverse community of public health professionals who have championed the health of all people and communities around the world for more than 145 years, I write to urge you to maintain the fluoridation of community water supplies in Green Bay. APIA has supported community water fluoridation as a safe and effective means of preventing tooth decay for more than 60 years. APIA most recently reiterated its support for community water fluoridation by adopting the policy statement Community Water Fluoridation in the United States in 2008.

The overwhelming preponderance of scientific evidence supports community water fluoridation as a safe, effective and cost-saving public health measure for the prevention of dental caries that benefits all segments of the community. The Centers for Disease Control and Prevention recognized water fluoridation as one of ten great public health achievements of the twentieth century. The U.S. government's Healthy People initiative has included the expansion of

community water fluoridation as a national health objective in each iteration since it began in 1990, including the new Healthy People 2030 health objectives for the nation.

Consistent with the recommendation of virtually every major public health, medical and dental organization in the United States, APHA urges you continue the important public health strategy of community water fluoridation.

Sincerely,



AMERICAN PUBLIC HEALTH ASSOCIATION
For science. For action. For health.

August 31, 2020

City of Green Bay
100 N Jefferson Street, Room 106
Green Bay, WI 54301

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

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Consistent with the recommendation of virtually every major public health, medical and dental organization in the United States, APHA urges you continue the important public health strategy of community water fluoridation.

Sincerely,

Georges C. Benjamin, MD
Executive Director
American Public Health Association

Joseline Ortiz Wolfe, PhD, RDH
Chair, Oral Health Section
American Public Health Association

Cc: Mayor's Chief of Staff, Celestine Jeffreys
City Clerk, Kris Teske
Nancy Quirk (General Manager, Green Bay Water Utility)
Johnny Johnson, American Fluoridation Society

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:18 AM
To: Jaime Fuge
Subject: Fwd: IAOMT email to you
Attachments: image.png; ATT00001.htm; Email to Green Bay IAOMT 9-7-20.pdf; ATT00002.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: September 7, 2020 at 2:30:59 PM EDT
To: Barbara Dorff <district1@greenbaywi.gov>, Thomas De Wane <district2@greenbaywi.gov>, Andy Nicholson <district3@greenbaywi.gov>, Bill Galvin <district4@greenbaywi.gov>, David Nennig <district5@greenbaywi.gov>, Joe Moore <district6@greenbaywi.gov>, Randy Scannell <district7@greenbaywi.gov>, Christopher Wery <district8@greenbaywi.gov>, Guy Zima <district9@greenbaywi.gov>, Mark Steuer <district10@greenbaywi.gov>, "John S. Vander Leest" <district11@greenbaywi.gov>, Thomas Sladek <district12@greenbaywi.gov>, Eric Genrich@greenbaywi.gov
Cc: celestinejc@greenbaywi.gov, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, Johnny Johnson <drjohnnyjohnson@gmail.com>, "Kuester, Robbyn L. - DHS" <Robbyn.Kuester@dhs.wisconsin.gov>, "Dunkel, Russell D - DHS" <russell.dunkel@dhs.wisconsin.gov>, "Crespin, Matthew" <MCrespin@chw.org>, Erika Valadez <evaladez@wda.org>
Subject: IAOMT email to you

(Celestine, could you please get this email and attachment to the Board of Health before tomorrow's meeting?)

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dux, Gerlach, Galvin, Stevens, Lefebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

Today I am writing to you about some information that you have received from a group called the International Academy of Oral Medicine and Toxicology (IAOMT). This is a credible sounding organization, like many others that exist in different fields. However, they are not. References here will succinctly illustrate that this group is not a credible organization, nor is it unbiased in its published literature. They are a group that formed initially in opposition to silver fillings (amalgam) and now oppose water fluoridation.

In the words of Rationalwiki:

The International Academy of Oral Medicine and Toxicology (IAOMT) is a quack organization based in Canada that promotes dental woo.^[1] They were responsible for the "smoking tooth" video that frequently gets passed around in altie circles. Their name sounds official to lure people into their belief system. Their main issue is mercury amalgam fillings, which they claim can cause all sorts of neurological conditions such as Parkinson's and autism. They sell filling removal kits for "dentists" along with various other nature woo, mostly vitamin supplements. The organization also opposes water fluoridation, claims to put out peer-reviewed "research," and supports "health freedom."

(Note: IAOMT is now based in Orlando, FL. The yellow highlights above are mine)

I have attached a full document that discusses this in more detail, along with the true science which supports fluoridation. Please do not hesitate to contact me with any questions that you may have. The health, safety, and well-being of your residents is paramount to me. This is a replay of the 2017 Common Council Meeting on fluoridation. If I could locate it on your Youtube channel, I would send it to you to watch. Brenda Staudenmaier testified for the opponents and I testified for the proponents of CWF. Several of you were there. Retaining CWF passed by a margin of 10-1. Credible science prevailed then. I pray for the same outcome this time.

Warmest personal regards,



September 7, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I hope that you all are enjoying the Labor Day weekend with your families, safe and sound.

Labor Day has historically been a day for me to reflect on those around me and celebrate for those who are recognized by this holiday. We are all recognized on this day as people who do our respective jobs with the hard work and due diligence that goes into doing it correctly.

IAOMT:

Today I am writing to you about some information that you have received from a group called the International Academy of Oral Medicine and Toxicology (IAOMT). This is a credible sounding organization, like many others that exist in different fields. However, they are not. References here will succinctly illustrate that this group is not a credible organization, nor is it unbiased in its published literature. They are a group that formed initially in opposition to silver fillings (amalgam) and now oppose water fluoridation.

In the words of RationalWiki:

The **International Academy of Oral Medicine and Toxicology (IAOMT)** is a quack organization based in Canada that promotes dental woo.^[1] They were responsible for the "smoking tooth" video that frequently gets passed around in altie circles. Their name sounds official to lure people into their belief system. Their main issue is mercury amalgam fillings, which they claim can cause all sorts of neurological conditions such as Parkinson's and autism. They sell filling removal kits for "dentists" along with various other nature woo, mostly vitamin supplements. The organization also opposes water fluoridation, claims to put out peer-reviewed "research," and supports "health freedom."

(Note: IAOMT is now based in Orlando, FL. The yellow highlights above are mine)

Dentist Griffin Cole: Past President IAOMT

Dr. Griffin Cole, the dentist who spoke against water fluoridation at the first meeting of the Protection and Policy Committee (PPC), is a member of IAOMT and past president of this group. His testimony before the PPC was biased and unfounded in sound, scientific literature. He adheres to both of the IAOMT's opposition positions in his practice.

Community Water Fluoridation (CWF):

Dental cavities (decay, caries) are an infectious and transmissible disease. It is the number one chronic disease of children and teens. Surprising? It's even more common than asthma, obesity, and diabetes.

Cavities are multifactorial. Fermentable carbohydrates (sugary foods, bread, pasta...), bacterial plaque, oral hygiene practices, lack of optimally fluoridated water, and access to dental care all contribute to the process of cavities.

CWF is the closest thing that we have to an immunization against this disease. The miniscule adjustment of the naturally occurring level of fluoride in your water up to the optimal level of 0.7ppm (parts per million; milligrams per liter) reduces cavities by 25% in adults and children, in addition to those already reduced by fluoride toothpaste, mouth rinses, and professionally applied fluoride. It is the most cost-effective method of delivering fluoride to all. There is no substitute for CWF.

The CDC named water fluoridation as one of 10 great public health achievements of the 20th century, alongside vaccinations, seat belts, declines in deaths from coronary heart disease, and others.

Leading health and scientific organizations around the world support and endorse CWF as effective in reducing cavities for entire populations and safe for everyone to drink. A partial list of these and their active members include:

1. American Academy of Pediatrics (~67,000)
2. American Dental Association (>163,000)
3. Centers for Disease Control and Prevention (CDC)
4. American Medical Association (217,490)
5. American Academy of Pediatric Dentistry (6,761)
6. American Academy of Family Physicians (134,600)
7. American Public Health Association (>25,000)
8. U.S. Public Health Service
9. Canadian Dental Association (>18,0000)
10. Canadian Paediatric Society (>3,400)
11. Health Canada
12. Canadian Medical Association (>75,000)
13. U.S. Department of Defense
14. World Health Organization

Not a single, credibly recognized health or scientific organization in the world *opposes* community water fluoridation. Not one.

I respectfully request that you consider the sources of information that you are receiving information from. Please depend on your trusted healthcare professionals and credibly

recognized scientific and health organizations to rely on in continuing CWF. Madison, WI and other communities across the U.S. Canada, and around the world are undergoing the onslaught of misinformation and Zoom meeting hijacking to promote fear and scare tactics about CWF. Do not fall prey to these people. They are not trusted sources.

Please do not hesitate to contact me with any questions that you may have.

Warmest personal regards,



Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: <https://americanfluoridationsociety.org/>
Cell: 727-409-1770
Email: drjohnnyjohnson@gmail.com

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Alaska Anchorage, AK

Water Advisory Committee

Kip Duchon, P.E.

Immediate past CDC National Fluoridation Engineer

Communications Committee

Steve Stott
AFS Communications Officer

Randy Johnson
Biology

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Friday, October 2, 2020 8:17 AM
To: Jaime Fuge
Subject: Fwd: American Dental Association - The World's Authoritative Expert on Water Fluoridation
Attachments: image.png; ATT00001.htm; ADA FF TOC.pdf; ATT00002.htm; Fluoridation_Facts 2018.pdf; ATT00003.htm; Common claims-American Dental Association Fluoridation Facts.pdf; ATT00004.htm

Johnny Johnson, Jr., DMD. MS
c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: September 30, 2020 at 5:34:30 PM EDT
To: Eric.Genrich@greenbaywi.gov, Barbara Dorff <district1@greenbaywi.gov>, Thomas De Wane <district2@greenbaywi.gov>, Andy Nicholson <district3@greenbaywi.gov>, Bill Galvin <district4@greenbaywi.gov>, David Nennig <district5@greenbaywi.gov>, Joe Moore <district6@greenbaywi.gov>, Randy Scannell <district7@greenbaywi.gov>, Christopher Wery <district8@greenbaywi.gov>, Guy Zima <district9@greenbaywi.gov>, Mark Steuer <district10@greenbaywi.gov>, "John S. Vander Leest" <district11@greenbaywi.gov>, Thomas Sladek <district12@greenbaywi.gov>
Cc: Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, "Dunkel, Russell D - DHS" <russell.dunkel@dhs.wisconsin.gov>, "Kuester, Robbyn L - DHS" <Robbyn.Kuester@dhs.wisconsin.gov>, Erika Valadez <evaladez@wda.org>, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, "Crespin, Matthew" <MCrespin@chw.org>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: American Dental Association - The World's Authoritative Expert on Water Fluoridation

September 30, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

As you continue to receive volumes of emails and phone calls from opponents of community water fluoridation (CWF), the American Fluoridation Society (AFS) has chosen to send you information sparingly. We feel that inundating you with correspondence is not how to help you understand water fluoridation and the credible research that supports its 75 years of use in the U.S. The preponderance of scientific evidence continues to support CWF as effective in reducing cavities for all by at least 25%, and is safe for everyone to drink.

American Dental Association:

The American Dental Association has produced a booklet of common claims made by those that oppose CWF. The claims are constantly repeated in communities like Green Bay, Madison, and Spokane, WA most recently. Spokane's City Council, a city of almost 220,000, voted recently to start the process of CWF.

This booklet addresses each of those claims with the most current science and supplies voluminous references for their clarification of the opponent's claims. The booklet is updated periodically and was last released in 2018. It was first published in 1956.

If you read anything that AFS sends you, please do me this favor of looking at the ADA Fluoridation Facts Table of Contents that I've attached. It is three pages. On those pages you will see nearly every single claim that you are hearing listed. The section in the booklet that covers those claims is given. Here is just a sample of what is covered:

<i>Topic:</i>	<i>Page #</i>
22. Total intake?	43
23. Daily intake?	44
24. Prenatal dietary fluoride supplements?	46
25. Body uptake?	47
26. Bone health?	47
27. Dental fluorosis?	49
28. Fluoridated water for infant formula?	52
29. Prevent fluorosis?	52
30. Warning Label?	54
31. Acute and chronic toxicity?	55
32. Cancer?	56
33. Osteosarcoma?	57
34. Enzyme effects?	58
35. Thyroid?	59
36. Pineal gland?	60
37. Allergies?	60
38. Genetic risk?	61
39. Fertility?	61
40. Down Syndrome?	62
41. Neurological impairment/IQ?	62
42. Lead poisoning?	64
43. Alzheimer's disease?	65
44. Heart disease?	66
45. Kidney disease?	67

AFS exists to help fill in the gaps between printings of this document with the current literature on CWF. The current literature includes studies which support CWF, call into doubt CWF, or are not able to show a correlation between CWF and any health claim. In other words, we, like every major health organization in the world, read all the research that is published in credibly recognized, peer reviewed scientific journals.

I appreciate your time in browsing the ADA Fluoridation Facts booklet's Table of Contents. I have also attached the full booklet as well to read any or all parts of it that you may have concerns with. It is also available online.

Please do not hesitate to contact me personally with any questions or concerns that you may have.

Warm regards,

PRACTICAL
GUIDE
SERIES

Fluoridation Facts



ADA American Dental Association®
America's leading advocate for oral health

Table of Contents

Executive Summary.....	1	Safety.....	37
Introduction.....	5	17. Harmful to humans?.....	37
Benefits.....	13	18. More studies needed?.....	38
1. What is fluoride?.....	13	19. Recommended level?.....	39
2. Fluoride prevents tooth decay?.....	13	20. EPA maximum?.....	40
3. Water fluoridation?.....	14	21. EPA secondary level?.....	41
4. Fluoride is in your water?.....	15	22. Total intake?.....	43
5. Fluoride additives?.....	16	23. Daily intake?.....	44
6. Natural vs. adjusted?.....	16	24. Prenatal dietary fluoride supplements?.....	46
7. Effectiveness?.....	17	25. Body uptake?.....	47
8. Still effective?.....	20	26. Bone health?.....	47
9. Discontinued?.....	21	27. Dental fluorosis?.....	49
10. Tooth decay problem?.....	22	28. Fluoridated water for infant formula?.....	52
11. Adult benefits?.....	24	29. Prevent fluorosis?.....	52
12. Fluoride supplements?.....	25	30. Warning Label?.....	54
13. Fluoride for children?.....	27	31. Acute and chronic toxicity?.....	55
14. Alternatives?.....	28	32. Cancer?.....	56
15. Bottled water?.....	31	33. Osteosarcoma?.....	57
16. Home treatment systems?.....	32	34. Enzyme effects?.....	58
		35. Thyroid?.....	59
		36. Pineal gland?.....	60
		37. Allergies?.....	60
		38. Genetic risk?.....	61
		39. Fertility?.....	61
		40. Down Syndrome?.....	62
		41. Neurological impairment/IQ?.....	62
		42. Lead poisoning?.....	64
		43. Alzheimer's disease?.....	65
		44. Heart disease?.....	66
		45. Kidney disease?.....	67
		46. Erroneous health claims?.....	68

Fluoridation Practice.....75

47. Who regulates?.....	75
48. Standards for additives?.....	76
49. Lead, arsenic and other contamination?.....	77
50. Additives safety?.....	78
51. Source of additives?.....	78
52. System safety concerns?.....	79
53. Engineering?.....	80
54. Corrosion of water pipes?.....	81
55. Damage to water facilities?.....	81
56. Environment?.....	82

Public Policy.....85

57. What is public health?.....	85
58. Valuable measure?.....	86
59. Reduce disparities?.....	88
60. Support for fluoridation?.....	89
61. Courts of law?.....	91
62. Opposition?.....	92
63. Opposition tactics?.....	93
64. Internet?.....	96
65. Public votes?.....	97
66. International fluoridation?.....	101
67. Banned in Europe?.....	102

Cost.....106

68. Cost-effective and cost-saving?.....	106
69. Practical?.....	109

Figures

1. Reviewing Research.....	6
2. Tooth Decay and Dental Fluorosis Graph.....	17
3. EPA and USPHS Numbers.....	42
4. Examples of Toothpaste for Children.....	46
5. Opposition Tactics.....	95
6. ADA.org Fluoride and Fluoridation.....	97
7. Largest Fluoridated Cities.....	98
8. States Meeting National Goals.....	99
9. State Fluoridation Status.....	100

Tables

1. Dietary Fluoride Supplements.....	26
2. Dietary Reference Uptakes.....	45
3. Categories of Dental Fluorosis.....	51

PRACTICAL
GUIDE
SERIES

Fluoridation Facts



ADA American Dental Association
America's leading advocate for oral health

Dedication

This 2018 edition of Fluoridation Facts is dedicated to Dr. Ernest Newbrun, respected researcher, esteemed educator, inspiring mentor and tireless advocate for community water fluoridation.

About Fluoridation Facts

Fluoridation Facts contains answers to frequently asked questions regarding community water fluoridation. A number of these questions are responses to myths and misconceptions advanced by a small faction opposed to water fluoridation. The answers to the questions that appear in *Fluoridation Facts* are based on generally accepted, peer-reviewed, scientific evidence. They are offered to assist policy makers and the general public in making informed decisions. The answers are supported by over 400 credible scientific articles, as referenced within the document. It is hoped that decision makers will make sound choices based on this body of generally accepted, peer-reviewed science.

Acknowledgments

This publication was developed by the National Fluoridation Advisory Committee (NFAC) of the American Dental Association (ADA) Council on Advocacy for Access and Prevention (CAAP). NFAC members participating in the development of the publication included Valerie Peckosh, DMD, chair; Robert Crawford, DDS; Jay Kumar, DDS, MPH; Steven Levy, DDS, MPH; E. Angeles Martinez Mier, DDS, MSD, PhD; Howard Pollick, BDS, MPH; Brittany Seymour, DDS, MPH and Leon Stanislav, DDS.

Principal CAAP staff contributions to this edition of Fluoridation Facts were made by: Jane S. McGinley, RDH, MBA, Manager, Fluoridation and Preventive Health Activities; Sharon (Sharee) R. Clough, RDH, MS Ed Manager, Preventive Health Activities and Carlos Jones, Coordinator, Action for Dental Health. Other significant staff contributors included Paul O'Connor, Senior Legislative Liaison, Department of State Government Affairs. In addition to her legal review, Wendy J. Wils, Esq., Deputy General Counsel, Division of Legal Affairs provided greatly to the vision of this publication.

Disclaimer

This publication is designed to answer frequently asked questions about community water fluoridation, based on a summary of relevant published articles. It is not intended to be a comprehensive review of the extensive literature on fluoridation and fluorides or to promote professional advice. Readers must also rely on their own review of the literature, including the sources cited herein and any subsequently published, for a complete understanding of these issues.

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Executive Summary

- Fluoridation of community water supplies is the single most effective public health measure to prevent tooth decay.
- Throughout more than 70 years of research and practical experience, the overwhelming weight of credible scientific evidence has consistently indicated that fluoridation of community water supplies is safe.
- Studies prove water fluoridation continues to be effective in reducing tooth decay by more than 25% in children and adults, even in an era with widespread availability of fluoride from other sources, such as fluoride toothpaste.
- Because of the important role it has played in the reduction of tooth decay, the Centers for Disease Control and Prevention has proclaimed community water fluoridation (along with vaccinations and infectious disease control) one of ten great public health achievements of the 20th century.
- Community water fluoridation is the controlled adjustment of fluoride that occurs naturally in all water to optimal levels to prevent tooth decay.
- Community water fluoridation benefits everyone, especially those without access to regular dental care. Fluoridation is a powerful tool in the fight for social justice and health equity.
- Simply by drinking water, people can benefit from fluoridation's cavity protection whether they are at home, work or school.
- Water that has been fortified with fluoride is similar to fortifying salt with iodine, milk with vitamin D and orange juice with vitamin C — none of which are medications.
- When compared to the cost of other prevention programs, water fluoridation is the most cost-effective means of preventing tooth decay for both children and adults in the United States. The cost of a lifetime of water fluoridation for one person is less than the cost of one filling.
- For community water systems that serve more than 1,000 people, the economic benefit of fluoridation exceeds the cost. And the benefit-cost ratio increases as the size of the population served increases (largely due to economies of scale). Fluoridation is a cost-saving method to prevent tooth decay.
- According to data from 2014, nearly 75% of the population (3 out of 4 people) in the United States are served by public water systems that are optimally fluoridated.
- Fluoridation has been thoroughly tested in the United States' court system, and found to be a proper means of furthering public health and welfare. No court of last resort has ever determined fluoridation to be unlawful.
- The ADA supports community water fluoridation as a safe, effective, cost-saving and socially equitable way to prevent tooth decay.
- One of the most widely respected sources for information regarding fluoridation and fluorides is the American Dental Association. The ADA maintains Fluoride and Fluoridation web pages at <http://www.ADA.org/fluoride>.

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Table of Contents

Executive Summary.....	1	Safety.....	37
Introduction.....	5	17. Harmful to humans?.....	37
Benefits.....	13	18. More studies needed?.....	38
1. What is fluoride?.....	13	19. Recommended level?.....	39
2. Fluoride prevents tooth decay?.....	13	20. EPA maximum?.....	40
3. Water fluoridation?.....	14	21. EPA secondary level?.....	41
4. Fluoride is in your water?.....	15	22. Total intake?.....	43
5. Fluoride additives?.....	16	23. Daily intake?.....	44
6. Natural vs. adjusted?.....	16	24. Prenatal dietary fluoride supplements?.....	46
7. Effectiveness?.....	17	25. Body uptake?.....	47
8. Still effective?.....	20	26. Bone health?.....	47
9. Discontinued?.....	21	27. Dental fluorosis?.....	49
10. Tooth decay problem?.....	22	28. Fluoridated water for infant formula?.....	52
11. Adult benefits?.....	24	29. Prevent fluorosis?.....	52
12. Fluoride supplements?.....	25	30. Warning Label?.....	54
13. Fluoride for children?.....	27	31. Acute and chronic toxicity?.....	55
14. Alternatives?.....	28	32. Cancer?.....	56
15. Bottled water?.....	31	33. Osteosarcoma?.....	57
16. Home treatment systems?.....	32	34. Enzyme effects?.....	58
		35. Thyroid?.....	59
		36. Pineal gland?.....	60
		37. Allergies?.....	60
		38. Genetic risk?.....	61
		39. Fertility?.....	61
		40. Down Syndrome?.....	62
		41. Neurological impairment/IQ?.....	62
		42. Lead poisoning?.....	64
		43. Alzheimer's disease?.....	65
		44. Heart disease?.....	66
		45. Kidney disease?.....	67
		46. Erroneous health claims?.....	68

Fluoridation Practice.....75

47. Who regulates?.....	75
48. Standards for additives?	76
49. Lead, arsenic and other contamination?	77
50. Additives safety?	78
51. Source of additives?.....	78
52. System safety concerns?	79
53. Engineering?	80
54. Corrosion of water pipes?.....	81
55. Damage to water facilities?	81
56. Environment?	82

Public Policy.....85

57. What is public health?	85
58. Valuable measure?	86
59. Reduce disparities?	88
60. Support for fluoridation?	89
61. Courts of law?.....	91
62. Opposition?	92
63. Opposition tactics?	93
64. Internet?	96
65. Public votes?.....	97
66. International fluoridation?	101
67. Banned in Europe?	102

Cost.....106

68. Cost-effective and cost-saving?.....	106
69. Practical?.....	109

Figures

1. Reviewing Research.....	6
2. Tooth Decay and Dental Fluorosis Graph.....	17
3. EPA and USPHS Numbers	42
4. Examples of Toothpaste for Children.....	46
5. Opposition Tactics	95
6. ADA.org Fluoride and Fluoridation	97
7. Largest Fluoridated Cities.....	98
8. States Meeting National Goals	99
9. State Fluoridation Status.....	100

Tables

1. Dietary Fluoride Supplements.....	26
2. Dietary Reference Uptakes	45
3. Categories of Dental Fluorosis.....	51

Introduction

Fluoridation Facts has been published by the American Dental Association (ADA) since 1956. Revised periodically, *Fluoridation Facts* answers frequently asked questions about community water fluoridation. In this 2018 edition, the ADA Council on Advocacy for Access and Prevention provides updated information for individuals and groups interested in the facts about fluoridation. The United States now has more than 70 years of extensive experience with community water fluoridation. Its remarkable longevity and success is testimony to fluoridation's significance as a public health measure. In recognition of the impact that water fluoridation has had on the oral and general health of the public, in 1999, the Centers for Disease Control and Prevention (CDC) named fluoridation of drinking water as one of ten great public health achievements of the 20th century.^{1,2}

Many organizations in the United States and around the world recognize the benefits of community water fluoridation.

Support for Water Fluoridation

Since 1950, the American Dental Association (ADA) has continuously and unreservedly endorsed the optimal fluoridation of community water supplies as a safe and effective public health measure for the prevention of tooth decay. The ADA's policy is based on the best available scientific evidence on the safety and effectiveness of fluoridation. Since the ADA first adopted policy recommending community water fluoridation in 1950, the ADA has continued to reaffirm its position of support for water fluoridation and has strongly urged that its benefits be extended to communities served by public water systems.³

Over the years, additional support has come from numerous U.S. Surgeons General who are the leading spokespersons on matters of public health in the federal government. In 2016, Surgeon General Dr. Vivek H. Murthy in his "Statement on Community Water Fluoridation,"⁴ noted:

Water fluoridation is the best method for delivering fluoride to all members of the community, regardless of age, education, income level or access to routine dental care. Fluoride's effectiveness in preventing tooth decay extends throughout one's life, resulting in fewer — and less severe — cavities. In fact, each generation born over the past 70 years has enjoyed better dental health than the one before it. That's the very essence of the American promise.⁴

In addition to the American Dental Association, the American Medical Association,⁵ the American Academy of Pediatrics⁶ and the World Health Organization⁷ also support community water fluoridation.

Many organizations in the United States and around the world recognize the benefits of community water fluoridation. The ADA has developed a list of "National and International Organizations that Recognize the Public Health Benefits of Community Water Fluoridation for Preventing Dental Decay." Please see the ADA website at www.ADA.org/fluoride for the most current listing as well as information on reproduction and distribution of the list.

Scientific Information on Fluoridation

The ADA's policies regarding community water fluoridation are based on the best available scientific knowledge. This body of knowledge results from the efforts of nationally recognized scientists who have conducted research using the scientific method, have drawn appropriate balanced conclusions based on their research findings and published their results in refereed (peer-reviewed) professional journals that are widely held or circulated. Studies showing the safety and effectiveness of water fluoridation have been confirmed by independent scientific studies conducted by a number of nationally and internationally recognized scientific investigators. While opponents of fluoridation have questioned its safety and effectiveness, none of their charges has ever been substantiated by scientific evidence.

With the advent of the Information Age, a new type of "pseudo-scientific literature" has developed. The public often sees scientific and technical information quoted in the press, printed in a letter to the editor or distributed via an internet web page. Often the public accepts such information as true simply because it is in print. Yet the information is not always based on research conducted according to the scientific method and the conclusions drawn from research are not always scientifically justifiable. In the case of water fluoridation, an abundance of misinformation has been circulated. Therefore, scientific information from all print and electronic sources must be critically reviewed before conclusions can be drawn. (See Figure 1.) Everyone is entitled to his or her own opinion but not his or her own facts. Pseudo-scientific literature can pique a reader's interest but when read as science, it can be misleading. The scientific validity and relevance of claims made by opponents of fluoridation might be

Figure 1. A Guide to Identifying and Using Trustworthy Information

Question The Author Actively search for study authors' intellectual and financial conflicts of interest that may have affected the conduct of the study or results interpretation.	Correlation Does Not Imply Causation The fact that two things happen together does not mean that one necessarily causes the other.
Mice vs. Humans Wait for studies with human subjects to confirm animal studies' results before considering applying the research findings in practice.	Consider The Big Picture Identify systematic reviews that comprehensively summarize the evidence instead of using single studies that present only a small part of the big picture.
High Impact Journals Impact factor and reputation of a journal do not necessarily relate to the quality of the published study in question, so always remain skeptical.	The Right Study Design Some clinical questions cannot be studied using the classic randomized control (RCT) study design and non-RCT designs may be a suitable alternative.

best viewed when measured against criteria set forth by the U.S. Supreme Court.⁸

💧 *Additional information about this topic can be found in the Public Policy Section, Question 61.*

History of Water Fluoridation

Research into the effects of fluoride began in the early 1900s. Dr. Frederick McKay, a young dentist, opened a dental practice in Colorado Springs, Colorado, and was surprised to discover that many local residents exhibited brown stains on their permanent teeth. Dr. McKay could find no documentation of the condition in the dental literature and eventually convinced Dr. G.V. Black, dean of the Northwestern University Dental School in Chicago, to join him in studying the condition. Through their research, Drs. Black and McKay determined that mottled enamel, as Dr. Black termed the condition, resulted from developmental imperfections in teeth. Drs. Black and McKay wrote detailed descriptions of mottled enamel.^{9,10} (Mottled enamel is a historical term. Today, this condition is called dental or enamel fluorosis.)

In the 1920s, Dr. McKay, along with others, suspected that something either in or missing from the drinking water was causing the mottled enamel. Dr. McKay wrote to the Surgeon General in 1926 indicating that he had identified a number of regions in Colorado, New Mexico, Arizona, California, Idaho, South Dakota, Texas and Virginia where mottled enamel existed. Also in the late 1920s, Dr. McKay made another significant discovery — these stained teeth were surprisingly resistant to decay.¹⁰

Following additional studies completed in the early 1930s in St. David, Arizona¹¹ and Bauxite, Arkansas,¹² it was determined that high levels of naturally occurring fluoride in the drinking water were causing the mottled enamel. In Arizona, researchers studied in great detail 250 residents in 39 local families and were able to rule out hereditary factors and environmental factors, except for one — fluoride in the water which occurred naturally at levels of 3.8 mg/L to 7.15 mg/L.¹¹ In Bauxite, H. V. Churchill, chief chemist with the Aluminum Company of America (later changed to ALCOA), was using a new method of spectrographic analysis in his laboratory to look at the possibility that the water from an abandoned deep well in the area might have high levels of aluminum-containing bauxite that was causing mottled teeth. What he found was that the water contained a high level of

naturally occurring fluoride (13.7 mg/L). When McKay learned of this new form of analysis and Churchill's findings, he forwarded samples of water from areas where mottled enamel was commonplace to Churchill. All of the samples were found to have high levels of fluoride when compared to waters tested from areas with no mottled enamel.¹⁰

During the 1930s, Dr. H. Trendley Dean, a dental officer of the U.S. Public Health Service, and his associates conducted classic epidemiological studies on the geographic distribution and severity of fluorosis in the United States.¹³ These early studies quantified the severity of tooth decay and dental fluorosis, called mottled enamel at that time, according to fluoride levels in the water. In so doing, it was observed that "at Aurora, IL where the domestic water contained 1.2 ppm of fluoride (F) and where a relatively low tooth decay prevalence was recorded, mottled enamel as an esthetic problem was not encountered."¹⁴ Dean and his staff had made a critical discovery. Namely, fluoride levels of up to 1.0 ppm in drinking water did not cause enamel fluorosis in most people and only mild dental fluorosis in a small percentage of people.¹⁴⁻¹⁶

In 1939, Dr. Gerald J. Cox and his associates at the Mellon Institute evaluated the epidemiological evidence and conducted independent laboratory studies. While the issue was being discussed in the dental research community at the time, they were the first to publish a paper that proposed adding fluoride to drinking water to prevent tooth decay.¹⁷ In the 1940s, four classic, community-wide studies were carried out to evaluate the controlled addition of sodium fluoride to fluoride-deficient water supplies. The first community water fluoridation program, under the direction of Dr. Dean, began in Grand Rapids, Michigan, in January 1945 with Muskegon, Michigan as the nonfluoridated control community. The other three studies were conducted in the following three pairs of cities with the fluoridated city listed first: Newburgh and Kingston, New York (May 1945); Brantford and Sarnia, Ontario, Canada (June 1945) and Evanston and Oak Park, Illinois (February 1947).¹⁸⁻²⁰

In the 1940s, four classic, community-wide studies were carried out to evaluate the controlled addition of sodium fluoride to fluoride-deficient water supplies.

The astounding success of these comparison studies firmly established the practice of water fluoridation as a practical, safe and effective public health measure to prevent tooth decay that would quickly be embraced by other communities.

The history of water fluoridation is a classic example of a curious professional making exacting clinical observations which led to epidemiologic investigation and eventually to a safe and effective community-based public health intervention which even today remains the cornerstone of communities' efforts to prevent tooth decay.

In addition to the studies noted above, a number of reviews on fluoride in drinking water have been issued over the years. For example, in 1951 the National Research Council (NRC), of the National Academies, issued its first report stating fluoridation was safe and effective. The NRC has continued to issue reports on fluoride in drinking water (1977²¹ and 1993²²) with the most recent review published in 2006.²³ Additional reviews completed over the ten year period from 2007–2017 include:

- 2017 Australian Government. National Health and Medical Research Council (NHMRC). *Information Paper — Water Fluoridation: Dental and Other Human Health Outcomes*.²⁴
- 2016 O'Mullane DM, Baez RJ, Jones S, Lennon MA, Petersen PE, Rugg-Gunn AJ, Whelton H, Whitford GM. *Fluoride and Oral Health*.²⁵
- 2016 American Water Works Association. *Water Fluoridation Principles and Practices*. AWWA Manual M4. Sixth edition.²⁶
- 2015 Water Research Foundation. *State of the Science: Community Water Fluoridation*.²⁷
- 2015 The Network for Public Health Law. *Issue Brief: Community Water Fluoridation*.²⁸
- 2015 Ireland Health Research Board. *Health Effects of Water Fluoridation: An Evidence Review*.²⁹
- 2015 U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. *U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries*.³⁰

- 2014 Public Health England. *Water Fluoridation: Health Monitoring Report for England*.³¹
- 2014 Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor. *Health Effects of Water Fluoridation: a Review of the Scientific Evidence*.³²
- 2013 U.S. Community Preventive Services Task Force. The Guide to Community Preventive Services. *Preventing Dental Caries: Community Water Fluoridation*.³³
- 2011 European Commission of the European Union Scientific Committee on Health and Environmental Risks (SCHER). *Fluoridation*.³⁴
- 2008 Health Canada. *Findings and Recommendations of the Fluoride Expert Panel*.³⁵
- 2007 Australian Government. National Health and Medical Research Council A *Systematic Review of the Efficacy and Safety of Fluoridation; Part A: Review Methodology and Results*.³⁶

Water Fluoridation as a Public Health Measure

Throughout decades of research and more than 70 years of practical experience, fluoridation of public water supplies has been responsible for dramatically improving the public's oral health. In 1994, the U.S. Department of Health and Human Services (HHS) issued a report which reviewed public health achievements.³⁷ Along with other successful public health measures such as the virtual eradication of polio and reductions in childhood blood lead levels, fluoridation was lauded as one of the most economical preventive interventions in the nation.³⁷

Because of the important role fluoridation has played in the reduction of tooth decay, the Centers for Disease Control and Prevention proclaimed community water fluoridation one of ten great public health achievements of the 20th century.^{1, 2} Other public health achievements included in the 1999 announcement were vaccinations (which have been responsible for the elimination of polio in the Americas), recognition of tobacco use as a health hazard and the decline in deaths from coronary heart disease and stroke. In 2000, U.S. Surgeon General Dr. David Satcher issued the first ever Surgeon General

report on oral health, *Oral Health in America: a Report of the Surgeon General*.³⁸ In the report, Dr. Satcher stated that community water fluoridation continues to be the most cost-effective, practical and safe means for reducing and controlling the occurrence of tooth decay in a community. Additionally, Dr. Satcher noted that water fluoridation is a powerful strategy in efforts to eliminate health disparities among populations. Studies have shown that fluoridation is the most significant strategy employed to reduce disparities in tooth decay.^{38–42}

◆ Additional information about this topic can be found in the Public Policy Section, Question 59.

Because of the important role fluoridation has played in the reduction of tooth decay, the Centers for Disease Control and Prevention proclaimed community water fluoridation one of ten great public health achievements of the 20th century.^{1, 2}

In the 2003 *National Call to Action to Promote Oral Health*,⁴³ U.S. Surgeon General Dr. Richard Carmona called on policymakers, community leaders, private industry, health professionals, the media and the public to affirm that oral health is essential to general health and well-being. Additionally, Dr. Carmona urged these groups to apply strategies to enhance the adoption and maintenance of proven community-based interventions such as community water fluoridation.

Writing in *Public Health Reports* in 2010, Surgeon General Dr. Rebecca Benjamin noted that, “Community water fluoridation continues to be a vital, cost-effective method of preventing dental caries.”⁴⁴

In a 2015 Surgeon’s General Perspective⁴⁵ issued to coincide with the release of the updated USPHS recommendation on fluoride levels in drinking water to prevent tooth decay, Surgeon General Dr. Vivek H. Murthy stated, “As Surgeon General, I encourage all Americans to make choices that enable them to prevent illness and promote well-being. Community water fluoridation is one of the most practical, cost-effective, equitable, and safe measures communities can take to prevent tooth decay and improve oral health.”⁴⁵

Established by the U.S. Department of Health and Human Services (DHHS), Healthy People 2020⁴⁶ provides a science-based, comprehensive set of ambitious, yet achievable, ten-year national objectives for improving the health of the public. Included under oral health is an objective to expand the fluoridation of public water supplies. Objective 13 states that at least 79.6% of the U.S. population served by community water systems should be receiving the benefits of optimally fluoridated water by the year 2020.⁴⁷ In 2014, the CDC indicated that 74.4% of the U.S. population on public water systems, or a total of 211.4 million people, had access to fluoridated water.⁴⁸

After more than four years of additional research and review following the initial notice of intent, in 2015 the DHHS announced that the U.S. Public Health Service had made a final recommendation on the fluoride level in drinking water³⁰ that updated and replaced the 1962 Drinking Water Standards related to community water fluoridation. In this guidance, the optimal concentration of fluoride in drinking water of 0.7 mg/L (milligrams per liter) was defined as “the concentration that provides the best balance of protection from dental caries while limiting the risk of dental fluorosis.”²⁰

◆ Additional information about this topic can be found in the Safety Section, Question 19.

Water Fluoridation’s Role in Reducing Tooth Decay

Water fluoridation has played a significant role in improving oral health. Numerous studies and reviews have been published making fluoridation one of the most widely studied public health measures in history. Fluoridation of community water supplies is the single most effective public health measure to prevent tooth decay. Studies show that community water fluoridation prevents at least 25 percent of tooth decay in children⁴⁹ and adults,⁵⁰ even in an era with widespread availability of fluoride from other sources, such as fluoride toothpaste. Fluoridation helps to prevent, and in some cases, reverse tooth decay across the life span. Increasing numbers of adults are retaining their teeth throughout their lifetimes due in part to the benefits they receive from water fluoridation. Dental costs for these individuals are likely to have been reduced and many

hours of needless pain and suffering due to untreated tooth decay have been avoided. By preventing tooth decay, community water fluoridation has been shown to save money, both for families and the health care system. The return on investment for community water fluoridation varies with size of the community, and in general, increases as the community size increases. Community water fluoridation is cost-saving, even for small communities.

⚡ *Additional information about this topic can be found in the Cost Section, Question 68.*

Fluoridation of community water supplies is the single most effective public health measure to prevent tooth decay. Studies show that community water fluoridation prevents at least 25 percent of tooth decay in children and adults, even in an era with widespread availability of fluoride from other sources, such as fluoride toothpaste.

Community water fluoridation is a most valuable public health measure because:

- Optimally fluoridated water is accessible to the entire community regardless of socioeconomic status, educational attainment or other social variables.⁵¹
- Individuals do not need to change their behavior to obtain the benefits of fluoridation.
- Frequent exposure to small amounts of fluoride over time makes fluoridation effective through the life span in helping to prevent tooth decay.⁵²
- Community water fluoridation is more cost-effective and cost-saving than other forms of fluoride treatments or applications.^{53,54}

Tooth decay is caused by sugars in snacks, food and beverages being converted into acid by the bacteria in dental plaque, a thin, sticky, colorless deposit on teeth. The acid attacks the tooth enamel (the hard surface of the tooth) or root surface. After repeated attacks, the enamel or root surface loses minerals (demineralization) and the acids and bacteria penetrate the dentin and finally the pulp. The soft

tissue of the pulp contains nerves and blood vessels. Once the decay enters the pulp, it becomes infected and without treatment, the infection progresses and travels into the surrounding tissues. It can enter the bloodstream and potentially spread the infection to other parts of the body which can be life-threatening.

⚡ *Additional information about this topic can be found in the Benefits Section, Question 2.*

There are a number of factors that increase an individual's risk for tooth decay.⁵⁴⁻⁵⁹

- Recent history of tooth decay
- Elevated oral bacteria count
- Inadequate exposures to fluorides
- Exposed roots
- Frequent intake of sugar/sugary foods and sugar-sweetened beverages
- Poor or inadequate oral hygiene
- Decreased flow of saliva
- Deep pits and fissures on the chewing surfaces of teeth

Exposure to fluoride is a key component in any recommended decay prevention strategy; however, the use of fluoride alone will not prevent all tooth decay. In formulating a decay prevention program, in addition to consuming fluoridated tap water, a number of intervention strategies may be considered such as improved daily home care, reducing sugar in the diet, placement of dental sealants and prescription strength fluoride toothpaste for home use and professionally applied topical treatments.

Ongoing Need for Water Fluoridation

Because of the risk factors for tooth decay noted previously, many individuals and communities still experience high levels of tooth decay. Although water fluoridation demonstrates an impressive record of effectiveness and safety, only 74.4% of the United States population on public water supplies in 2014 received fluoridated water containing protective levels of fluoride.⁴⁸ Unfortunately, some people continue to be confused about this effective public health measure. If the number of individuals drinking fluoridated water is to increase, the public must be accurately informed about its benefits and safety.

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Benefits

1. What is fluoride?	13	9. Discontinued?	21
2. Fluoride prevents tooth decay?	13	10. Tooth decay problem?	22
3. Water fluoridation?	14	11. Adult benefits?	24
4. Fluoride is in your water?	15	12. Fluoride supplements?	25
5. Fluoride additives?	16	13. Fluoride for children?	27
6. Natural vs. adjusted?	16	14. Alternatives?	28
7. Effectiveness?	17	15. Bottled water?	31
8. Still effective?	20	16. Home treatment systems?	32

1. What is fluoride?

Answer.

Fluoride is a naturally occurring mineral that can help prevent tooth decay.

Fact.

The element fluorine is abundant in the earth's crust as a naturally occurring fluoride compound found in rocks and soil.¹ As ground water moves through the earth, it passes over rock formations and dissolves the fluoride minerals that are present, releasing fluoride ions that are naturally occurring fluoride in the rocks. This increases the fluoride content of the water. The concentration of fluoride in ground water (e.g., wells, springs) varies according to such factors as the depth at which the water is found and the quantity of fluoride-bearing minerals in the area.

Fluoride is present at varied concentrations in all water sources including rainwater and the oceans. For example, the oceans' fluoride levels range from 1.2 to 1.4 mg/L.² In the United States, the natural level of fluoride in ground water varies from very low levels to over 4 mg/L.³ In comparison, the fluoride concentrations in surface water sources such as lakes and rivers is very low. For example, the water analysis completed by the city of Chicago for the year 2016 lists the range for Lake Michigan's natural fluoride level as 0.11 to 0.13 mg/L.⁴

2. How does fluoride help prevent tooth decay?

Answer.

Tooth decay begins when the outer layer of a tooth loses some of its minerals due to acid produced by bacteria in dental plaque breaking down the sugars that we eat. Fluoride protects teeth by helping to prevent the loss of these minerals and by restoring them with a fluoride-containing mineral that is more resistant to acid attacks. In other words, fluoride protects teeth by reducing demineralization and enhancing remineralization. Fluoride also works to hinder bacterial activity necessary for the formation of tooth decay.

Fact.

One of fluoride's main mechanism of action is its ability to prevent or delay the loss of minerals from teeth.^{5,6} Cavities start to form when minerals are lost due to acid attacks from bacteria in dental plaque (a soft, sticky film that is constantly forming on teeth). Bacteria grow rapidly by feeding on the sugars and refined carbohydrates that we consume. This process of losing minerals is called demineralization.

Fluoride's second mechanism of action is called remineralization, which is the reversal of this demineralization process.^{6,7} Teeth gain back the minerals lost during acid attacks through remineralization but with an important difference. Some of the hydroxyapatite crystal lost is replaced with fluorapatite. This fluoride-rich replacement mineral is even more resistant to acid attacks than the original tooth surface.⁶

Studies indicate fluoride has a third mechanism of action that hinders the ability of bacteria to metabolize carbohydrates and produce acids.⁵ It can also hinder the ability of the bacteria to stick to the tooth surface.⁸

Fluoride and minerals, including calcium and phosphate, are present in saliva^{6,8} and are stored in dental plaque. To halt the formation of tooth decay or rebuild tooth surfaces, fluoride must be constantly present in low concentrations in saliva and plaque.⁶ Frequent exposure to small amounts of fluoride, such as that which occurs when drinking fluoridated water, helps to maintain the reservoir of available fluoride in saliva and plaque to resist demineralization and enhance remineralization.^{6,9} In other words, drinking fluoridated water provides the right amount of fluoride at the right place at the right time. Fluoride in water and water-based beverages is consumed many times during the day, providing frequent contact with tooth structures and making fluoride available to fluoride reservoirs in the mouth. This helps explain why fluoride at the low levels found in fluoridated water helps to prevent tooth decay.⁶

Additionally, studies have concluded that fluoride ingested during tooth formation becomes incorporated into the tooth structure making the teeth more resistant to acid attacks and demineralization.¹⁰⁻¹⁴ In particular, this pre-eruptive exposure to fluoride, before the teeth come into the mouth during childhood, can play a significant role in preventing tooth decay in the pits and fissures of the chewing surfaces, particularly of molars.^{6,15,16} Sources of fluorides in the United States that provide this pre-eruptive effect include fluoridated water and dietary fluoride supplements as well as fluoride present in foods and beverages. Additionally, young children often swallow substantial percentages of the fluoride toothpaste and other fluoride-containing dental products which adds to their intake of fluoride. Originally, it was believed that fluoride's action was exclusively pre-eruptive, meaning the benefit occurred only during tooth formation, but by the mid-1950s there was growing evidence of the importance of fluoride's important roles in demineralization and remineralization.¹¹

Pre-eruptive effects are sometimes called systemic, while post-eruptive effects are called topical. These terms refer to different things. Pre- and post-eruptive refer to the timing of fluoride benefits while systemic

and topical refer to the mode of administration or source of fluoride. Defining the effects of fluoride from a specific source as solely systemic or topical is not entirely accurate. For example, water fluoridation provides both a systemic (during tooth development) and topical effect (at the time of ingestion strengthening the outside of the tooth).

Today it is understood that the maximum reduction in tooth decay occurs when both effects are combined, that is when fluoride has been incorporated into the tooth during formation and when it is available at the tooth surface during demineralization and remineralization. Water fluoridation works in both ways to prevent tooth decay.^{8,11,13,15,16}

Today it is understood that the maximum reduction in tooth decay occurs when both effects are combined, that is when fluoride has been incorporated into the tooth during formation and when it is available at the tooth surface during demineralization and remineralization. Water fluoridation works in both ways to prevent tooth decay.

3. What is water fluoridation?

Answer.

Water fluoridation is the controlled adjustment of the natural fluoride concentration in community water supplies to the concentration recommended for optimal dental health. Fluoridation helps prevent tooth decay in children and adults.

Fact.

In 2015, the U.S. Department of Health and Human Services (HHS), using the best available science, established the recommended concentration for fluoride in the water in the United States at 0.7 mg/L.¹⁷ This level effectively reduces tooth decay while minimizing dental fluorosis.

The level of fluoride in water is measured in milligrams per liter (mg/L) or parts per million (ppm). When referring to water, a concentration in milligrams per liter is identical to parts per million and the notations can be used interchangeably. Thus, 0.7 mg/L of fluoride in water is identical to 0.7 ppm. The preferred notation is milligrams per liter.

At 0.7 mg/L, there are seven-tenths of one part of fluoride mixed with 999,999.3 parts of water. While not exact, the following comparisons can be of assistance in comprehending 0.7 mg/L:

- 1 inch in approximately 23 miles
- 1 minute in approximately 1000 days
- 1 cent in approximately \$14,000.00
- 1 seat in more than 34 Wrigley Field baseball parks (seating capacity 41,268)

The following terms and definitions are used in this publication:

- **Community water fluoridation** is the controlled adjustment of the natural fluoride concentration in water up to 0.7 mg/L, the level recommended for optimal dental health. Other terms used interchangeably are water fluoridation, fluoridation and optimally fluoridated water. Optimal levels of fluoride can be present in the water naturally or by adjusted means.
- **Sub-optimally fluoridated water** is water that naturally contains less than the optimal level (below 0.7 mg/L) of fluoride. Other terms used are nonfluoridated water and fluoride-deficient water.

♦ Additional information on this topic can be found in this Section, Question 6.

The level of fluoride in water is measured in milligrams per liter (mg/L) or parts per million (ppm). When referring to water, a concentration in milligrams per liter is identical to parts per million and the notations can be used interchangeably. Thus, 0.7 mg/L of fluoride in water is identical to 0.7 ppm. The preferred notation is milligrams per liter.

4. How much fluoride is in your water?

Answer.

If your water comes from a public/community water supply, the options to learn the fluoride level of the water include contacting the local water supplier or the local/county/state health department, reviewing the Consumer Confidence Report (CCR) issued by your local water supplier, and using the Centers for Disease Control and Prevention's internet based "My Water's Fluoride." If your water source is a private well, it will need to be tested and the results obtained from a certified laboratory.

Fact.

The fluoride content of the local public or community water system can be obtained by contacting the local water supplier or the local/county/state health department. The name of your water system might not be the same as the name of your community.

In 1999, the U.S. Environmental Protection Agency (EPA) began requiring water suppliers to make annual drinking water quality reports accessible to their customers. Available prior to July 1 each year for the preceding calendar year, these Consumer Confidence Reports (CCRs), or Water Quality Reports,¹⁸ can be mailed to customers, placed in the local newspaper or made available through the internet. To obtain a copy of the report, contact the local water supplier. If the name of the community water system is unknown, contact the local health department.

There are two sites on the internet that supply information on water quality of community water systems. The online source for Water Quality Reports or CCRs is the EPA website¹⁹ at: <https://ofmpub.epa.gov/apex/safewater/f?p=136:102>. Additionally, the Centers for Disease Control and Prevention's (CDC) fluoridation website, "My Water's Fluoride,"²⁰ is available at: https://nccd.cdc.gov/DOH_MWF/Default/Default.aspx. The website allows consumers in currently participating states to learn the fluoridation status of their water system. It also provides information on the number of people served by the water system, the water source, and if the water system is naturally fluoridated or adjusts the fluoride level in the water supply.²⁰

The EPA does not have the authority to regulate private drinking water wells. However, the EPA recommends that private well water be tested once a year.²¹ For

the most accurate results, a state certified laboratory that conducts drinking water tests should be used for fluoride testing. For a list of state certified laboratories, contact the local, county or state water/health department.

The EPA does not specifically recommend testing private wells for the level of fluoride. However, if a household with a private well has children under 16 years of age, their health professionals will need to know the fluoride level of the well water prior to consideration of prescription of dietary fluoride supplements⁸ or to counsel patients about alternative water sources to reduce the risk of fluorosis if the natural fluoride levels are above 2 mg/L.

Dietary fluoride supplements (tablets, drops or lozenges) are available only by prescription and are intended for use by children ages six months to 16 years living in nonfluoridated areas and at high risk of developing tooth decay. Your dentist or physician can prescribe the correct dosage.⁸

➦ Additional information on this topic can be found in this Section, Question 12 and in the Safety Section, Questions 21, 27, 28 and 29.

5. What additives are used to fluoridate water supplies in the United States?

Answer.

Sodium fluoride, sodium fluorosilicate and fluorosilicic acid are the three additives approved for use in community water fluoridation in the United States. Sodium fluorosilicate and fluorosilicic acid are sometimes referred to as silicofluoride additives.

Fact.

The three basic additives used to fluoridate water in the United States are: 1) sodium fluoride which is a white, odorless material available either as a powder or crystals; 2) sodium fluorosilicate which is a white or yellow-white, odorless crystalline material and 3) fluorosilicic acid which is a white to straw-colored liquid.²²

Water fluoridation began in the U.S. in 1945 with the use of sodium fluoride; the use of silicofluorides began in 1946 and by 1951, they were the most commonly used additives.²³ First used in the late

1940s, fluorosilicic acid is currently the most commonly used additive to fluoridate communities in the United States.²⁴ To ensure the public's safety, regardless of where the additives are manufactured, they should meet safety standards for water treatment in the U.S.²² Specifically, additives used in water fluoridation should meet standards of the American Water Works Association (AWWA). With respect to NSF/ANSI certification, fluoride additives are considered no different than other water additives. Fluoride additives, like any other water additive should also meet NSF/ANSI Standards.²² In the United States, the authority to regulate products for use in drinking water, including additives used to fluoridate community water systems, rests with individual states. In 2013, AWWA reported that 47 states had adopted the NSF/ANSI Standard 60 which specifies the product quality with validation supplied by independent certification entities.²²

To ensure the public's safety, regardless of where the additives are manufactured, they should meet safety standards for water treatment in the U.S.

Additional information on the topic of fluoride additives can be found in the Fluoridation Practice section of this publication and at the CDC's fluoridation website, "Water Operators and Engineers" at <https://www.cdc.gov/fluoridation/engineering/index.htm>.

6. Is there a difference in the effectiveness between naturally occurring fluoridated water (at optimal fluoride levels) and water that has fluoride added to reach the optimal level?

Answer.

No. The dental benefits of optimally fluoridated water occur regardless of the fluoride's source.

Fact.

Fluoride is present in water as "ions" or electrically-charged atoms.²⁵ These ions are the same whether acquired by water as it seeps through rocks and sand or added to the water supply under carefully controlled conditions.

It has been observed that the major features of human fluoride metabolism are not affected by the three fluoride additives used in community water fluoridation nor are they affected by whether the fluoride is present naturally or added to drinking water.²⁶ In more simple terms, there is no difference chemically between natural and adjusted fluoridation.

When fluoride is added under controlled conditions to fluoride-deficient water, the dental benefits are the same as those obtained from naturally fluoridated water. Fluoridation is merely an increase of the level of the naturally occurring fluoride present in all drinking water sources to the level recommended for optimal dental health.

Fluoridation is merely an increase of the level of the naturally occurring fluoride present in all drinking water sources to the level recommended for optimal dental health.

For example, a fluoridation study conducted in the Ontario, Canada, communities of Brantford (optimally fluoridated by adjustment), Stratford (optimally fluoridated naturally) and Sarnia (fluoride-deficient), revealed much lower decay rates in both Brantford and Stratford as compared to nonfluoridated Sarnia. There was no observable difference in the decay-reducing effect between the naturally occurring fluoride and adjusted fluoride concentration water supplies, proving that dental benefits were similar regardless of the source of fluoride.²⁷

Some individuals use the term “artificial fluoridation” to imply that the process of water fluoridation is unnatural and that it delivers a foreign substance into a water supply when, in fact, all water sources contain some fluoride. The fluoride ion released in water is the same regardless of the source²⁵ and is metabolized (processed) by the body in the same way no matter what the source.²⁶ Community water fluoridation is a natural way to improve oral health.

7. Is water fluoridation effective in helping to prevent tooth decay?

Answer.

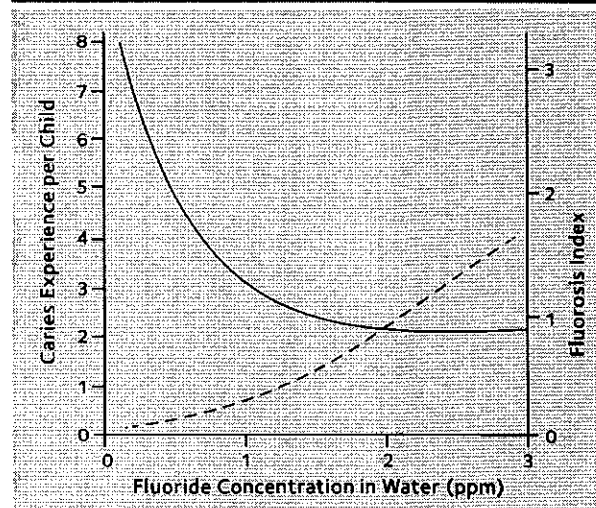
Yes. According to the best available scientific evidence, community water fluoridation is an effective public health measure for preventing, and in some cases, reversing tooth decay, in children, adolescents and adults. With hundreds of studies published in peer-reviewed, scientific journals, fluoridation is one of the most studied public health measures in history and it continues to be studied today.

Fact.

The effectiveness of fluoride in drinking water to prevent tooth decay has been documented in the scientific literature for over 70 years. Before the first community fluoridation program began in 1945, epidemiologic data from the 1930s and 1940s were collected and analyzed.²⁸⁻³⁰ What began as research to learn what caused “Colorado Brown Stain” (dental fluorosis) led to the discovery of strikingly low tooth decay rates associated with fluoride in drinking water at approximately 1 ppm (mg/L). Figure 2 shows the results of early research by Dr. H. Trendley Dean noting the relationship between children’s experience with tooth decay (solid line), dental fluorosis (dotted line) and the fluoride concentration in drinking water.^{28,29}

➦ Additional information on this topic can be found in the Introduction Section.

Figure 2. Dean’s Graph
Relationships of tooth decay experience (solid line), dental fluorosis index (dashed line) and the fluoride concentration of drinking water.^{28,29}



Since that time, hundreds of studies have been done, including a number of systematic reviews which continue to show fluoride's effectiveness in helping to prevent tooth decay. A systematic review is an analysis of studies that identifies and evaluates all of the evidence with which to answer a specific, narrowly focused question. It entails a systematic and unbiased review process that locates, assesses and combines high quality evidence from a collection of scientific studies to obtain a comprehensive, valid and reliable review on a specific topic. Systematic reviews provide the highest level of scientific evidence about a specific research question. Below is a discussion of major reviews of community water fluoridation, beginning with two systematic reviews published in 2017 and 2013, respectively, demonstrating that water fluoridation is effective in reducing tooth decay.

On November 9, 2017, the Australian Government's National Health and Medical Research Council (NHMRC) released the *NHMRC Public Statement 2017 — Water Fluoridation and Human Health in Australia*³¹ recommending community water fluoridation as a safe, effective and ethical way to help reduce tooth decay. Based on a comprehensive review of the evidence, published in 2016, and the translation of that evidence into the *NHMRC Information Paper — Water Fluoridation: Dental and Other Human Health Outcomes*,³² published in 2017, the Public Statement notes that the NHMRC found that water fluoridation reduces tooth decay by 26% to 44% in children and adolescents, and by 27% in adults. Additionally, it notes that recent Australian research found that access to fluoridated water from an early age is associated with less tooth decay in adults. The Statement notes that NHMRC supports Australian states and territories fluoridating their drinking water supplies within the range of 0.6 to 1.1 mg/L.³¹

Established by the U.S. Department of Health and Human Services in 1996, the Community Preventive Services Task Force develops and disseminates guidance on which community-based health promotion and disease prevention intervention approaches work, and which do not work, based on available scientific evidence. The Task Force issues findings based on systematic reviews of effectiveness and economic evidence. The Guide to Community Preventive Services ("The Community Guide") is a collection of evidence-based findings of the Community Preventive Services Task Force and is designed to assist decision makers in selecting

interventions to improve health and prevent disease.³³

The Community Guide reviews are designed to answer three questions:

1. What has worked for others and how well?
2. What might this intervention approach cost, and what am I likely to achieve through my investment?
3. What are the evidence gaps?³³

In a 2013 update of the evidence, the Community Preventive Services Task Force continued to recommend community water fluoridation to reduce tooth decay, noting that cavities decreased when fluoridation was implemented and that cavities increased when fluoridation was stopped, as compared to communities that continued fluoridation.³³

A summary of systematic reviews by the Oral Health Services Research Centre at the University Dental School in Cork, Ireland, published in 2009, reviewed results from three systematic reviews, all of which were published between 2000 and 2007. The summary of results concluded that the best available scientific evidence demonstrated that water fluoridation was an effective community-based method to prevent tooth decay, especially for the disadvantaged who bear the greatest burden of disease.³⁵

A meta-analysis (a type of systematic review that seeks to determine a statistical estimate of an overall benefit based on the results of the collection of studies included in the review), which was published in 2007 in the *Journal of Dental Research*, demonstrated the effectiveness of water fluoridation for preventing tooth decay in adults. Twenty studies representing over 13,500 participants were included in the analysis. Of the 20 studies, nine examined the effectiveness of water fluoridation. The review of these studies found that fluoridation prevents approximately 27% of tooth decay in adults.³⁶

Besides systematic reviews, significant additional studies conducted since the initiation of water fluoridation in 1945, also have demonstrated the effectiveness of water fluoridation in reducing the occurrence of tooth decay.

- In Grand Rapids, Michigan, the first city in the world to fluoridate its water supply, a 15-year landmark study showed that children who consumed fluoridated water from birth had 50–63% less tooth decay than children who had been examined during the original baseline survey completed in nonfluoridated Muskegon, Michigan.³⁷
- In 1985, the National Preventive Dentistry Demonstration Program³⁸ analyzed various types and combinations of school-based preventive dental services to determine the cost and effectiveness of these types of prevention programs. Ten sites from across the nation were selected. Five of the sites had fluoridated water and five did not. Over 20,000 second and fifth graders participated in the study over a period of four years. Students were examined and assigned by site to one or a combination of the following groups:
 - biweekly in class brushing and flossing plus a home supply of fluoride toothpaste and dental health lessons (ten per year);
 - in-class daily fluoride tablets (in nonfluoridated areas);
 - in-school weekly fluoride mouthrinsing;
 - in-school professionally applied topical fluoride;
 - in-school professionally applied dental sealants, and
 - a control.³⁸

After four years, approximately 50% of the original students were examined again. The study affirmed the value and effectiveness of community water fluoridation. At the sites where the community water was fluoridated, students had substantially fewer cavities, as compared to those sites without fluoridated water where the same preventive measures were implemented. In addition, while sealants were determined to be an effective prevention method, the cost of a sealant program was substantially more than the cost of fluoridating the community water, confirming fluoridation as the most cost-effective preventive option.³⁸

- In another review of studies conducted from 1976 through 1987 and published in 1989,³⁹ data for different age groups were separated into categories by the types of teeth present in the mouth. The results demonstrated a 30–60% reduction in tooth decay in primary teeth, a 20–40% reduction in the mixed dentition (having both

baby and adult teeth) and a 15%–35% reduction in the permanent dentition (adults and seniors) for those living in fluoridated communities.³⁹

- In the United States, an epidemiological survey of nearly 40,000 schoolchildren was completed in 1987.⁴⁰ Nearly 50% of the children aged 5 to 17 years who participated in the study were decay free in their permanent teeth, which was a major change from a similar survey conducted in 1980 in which approximately 37% were decay free. This dramatic decline in decay rates was attributed primarily to the widespread use of fluoride in community water supplies, toothpastes, dietary fluoride supplements and mouthrinses. Although decay rates had declined overall, data also revealed that the decay rate was 25% lower in children with continuous residence in fluoridated communities when the data were adjusted to control for exposure to dietary fluoride supplements and topical fluoride treatments.⁴⁰
- In 1993, the results of 113 studies in 23 countries (over half of the studies were from the U.S.) were compiled and analyzed.⁴¹ This review provided effectiveness data for 66 studies of primary teeth and 86 studies of permanent teeth. The analysis of the studies demonstrated a 40–49% decay reduction for primary (baby) teeth and a 50–59% decay reduction for permanent (adult) teeth for those living in fluoridated communities.⁴¹
- A comprehensive analysis of the first 50 years of community water fluoridation in the United States concluded that “Community water fluoridation is one of the most successful public health disease prevention programs ever initiated.”⁴² While noting that the difference in tooth decay between optimally fluoridated communities and fluoride-deficient communities was smaller than in the early days of fluoridation, largely due to additional sources of fluoride, the difference was still significant and the benefits for adults should be emphasized. The report ended by noting that water fluoridation is a near-ideal public health measure whose benefits can transcend racial, ethnic, socioeconomic and regional differences.⁴²

The systematic reviews and studies noted above provide science-based evidence that, for more than 70 years, fluoridation has been effective in helping to prevent tooth decay.

8. With other sources of fluoride now available, is water fluoridation still an effective method for preventing tooth decay?

Answer.

Yes. Even in an era with widespread availability of fluoride from other sources, studies show that community water fluoridation prevents at least 25% of tooth decay in children and adults throughout the life span.

Fact.

During the 1940s, studies demonstrated that children in communities with optimally fluoridated drinking water had reductions in tooth decay rates of approximately 40% to 60% as compared to those living in nonfluoridated communities.^{37,44} At that time, drinking water was the only source of fluoride other than fluoride that occurred naturally in foods.

Increase in the Number of Sources of Fluoride

Fluoride is available today from a number of sources including water, beverages, food, dental products (toothpaste, rinses, professionally applied fluoride foams, gels and varnish and dietary supplements).¹⁷ As a result of the widespread availability of these various sources of fluoride, the difference between decay rates in fluoridated areas and nonfluoridated areas is somewhat less than several decades ago, yet it is still significant.¹⁷ Studies show that community water fluoridation prevents at least 25% of tooth decay in children and adults throughout the life span.^{36,45} The benefits of fluoridation are extended to everyone in a community where they live, work, attend school or play — and it does not require a change of behavior or access to dental care.

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The Diffusion or Halo Effect

The diffusion or “halo” effect occurs because foods and beverages processed in optimally fluoridated cities generally contain higher levels of fluoride than those processed in nonfluoridated communities. This exposure to fluoride in nonfluoridated areas through the diffusion effect lessens the differences in the amount of tooth decay between communities.^{39,42,43} The best available national data demonstrate that the failure to account for the diffusion effect results in an underestimation of the total benefit of water fluoridation especially in areas where large quantities of fluoridated beverage and food products are brought into nonfluoridated communities.⁴⁶

Exposure to Fluoridation over the Life Span

Another factor in the difference between decay rates in fluoridated areas and nonfluoridated areas is the high geographic mobility of our society. On a day-to-day basis, many individuals may reside in a nonfluoridated community but spend a significant part of their day in a fluoridated community at work, school or daycare. Additionally, over their lifetime, people tend to move and reside in a number of communities, some with optimally fluoridated water and some without. This mobility makes it increasingly difficult to study large numbers of people who have spent their entire lives in one (fluoridated or nonfluoridated) community.³⁹ It also means that many individuals receive the benefit of fluoridation for at least some part of their lives. For children who have resided in fluoridated communities their entire lives, studies demonstrated they had less tooth decay than children who never lived in fluoridated communities.⁴⁰

Despite fluoride from a number of other sources, the “halo effect” and the mobility of today’s society, studies show that community water fluoridation prevents at least 25% of tooth decay in children and adults throughout the life span.^{36,45}

9. What happens if water fluoridation is discontinued?

Answer.

Tooth decay can be expected to increase if water fluoridation in a community is discontinued even if topical products such as fluoride toothpaste and fluoride mouthrinses are widely used.

Fact.

In 2013, using an updated systematic review, the Community Preventive Services Task Force, established by the U.S. Department of Health and Human Services, continued to recommend community water fluoridation to reduce tooth decay, noting that cavities decreased when fluoridation was implemented and that cavities increased when fluoridation was stopped, as compared to communities that continued fluoridation.³⁴ This confirmed the Task Force's earlier systematic review published in 2002⁴⁵ which also noted an increase in tooth decay when fluoridation was halted (a median 17.9% increase in tooth decay during 6 to 10 years of follow-up).

Historical Studies Noting an Increase in Tooth Decay after Discontinuation of Fluoridation

Antigo, Wisconsin, began water fluoridation in June 1949 and ceased adding fluoride to its water in November 1960. After five and one-half years without optimal levels of fluoride, second grade children had a 200% increase in tooth decay experience, fourth graders a 70% increase and sixth graders a 91% increase in decay experience compared with the levels of those of the same ages in 1960. Residents of Antigo re-instituted water fluoridation in October 1965 on the basis of the severe deterioration of their children's oral health.⁴⁷

A study that reported the relationship between fluoridated water and tooth decay prevalence focused on the city of Galesburg, Illinois, a community whose public water supply contained naturally occurring fluoride at 2.2 mg/L. In 1959, Galesburg switched its community water source to the Mississippi River. This alternative water source provided the citizens of Galesburg a sub-optimal level of fluoride at approximately 0.1 mg/L. In the period of time between a baseline survey conducted in 1958 and a new survey conducted in 1961, data revealed a 10% decrease in the percentage of decay free 14-year-olds (oldest group observed), and a 38% increase in mean tooth decay experience. Two years later, in

1961, the water was fluoridated at the recommended level of 1.0 mg/L.⁴⁸

Because of a government decision in 1979, fluoridation in the northern Scotland town of Wick was discontinued after eight years. The water was returned to its sub-optimal, naturally occurring fluoride level of 0.02 mg/L. Data collected to monitor the oral health of Wick children clearly demonstrated a negative health effect from the discontinuation of water fluoridation. Five years after the cessation of water fluoridation, decay in primary (baby teeth) had increased 27%. This increase in decay occurred during a period when there had been a reported overall reduction in decay nationally and when fluoride toothpaste had been widely adopted. These data suggest that decay levels in children can be expected to rise where water fluoridation is interrupted or terminated, even when topical fluoride products are widely used.⁴⁹

In a similar evaluation, the prevalence of tooth decay in 5- and 10-year-old children in Stranraer, Scotland, increased after the discontinuation of water fluoridation. This increase in tooth decay was estimated to result in a 115% increase in the mean cost of restorative dental treatment for decay. These data support the important role water fluoridation plays in the reduction of tooth decay.⁵⁰

Historical Studies and Factors Noting No Increase in Tooth Decay after Discontinuation of Fluoridation

There have been several studies from outside the United States that have not reported an increase in tooth decay following the discontinuation of fluoridation. In all of these, the discontinuation of fluoridation coincided with the implementation of other measures to prevent tooth decay.

In La Salud, Cuba, a study on tooth decay in children indicated that the rate of tooth decay did not increase after fluoridation was stopped in 1990. However, at the time fluoridation was discontinued a new preventive fluoride program was initiated where all children received fluoride mouthrinses on a regular basis and children two to five years of age received fluoride varnish once or twice a year.⁵¹

In Finland, a longitudinal study in Kuopio (fluoridated from 1959 to 1992) and Jyväskylä (with low levels of natural fluoride) showed little difference in

decay rates between the two communities that are extremely similar in terms of ethnic background and social structure.⁵² This was attributed to a number of factors. The dental programs exposed the Finnish children to intense topical fluoride regimes and dental sealant programs. Virtually all children and adolescents used the government-sponsored, comprehensive, free dental care. As a result, the effect of water fluoridation appeared minimal. Because of this unique set of factors, it was concluded that these results could not be replicated in countries with less intensive preventive dental care programs.⁵²

No significant decrease in tooth decay was seen after fluoridation was discontinued in 1990 in Chemnitz and Plauen, located in what was formerly East Germany.⁵³ The intervening factors in these communities include improvements in attitudes toward oral health behaviors, and broader availability and increased use of other preventive measures including fluoridated salt, fluoride toothpaste and dental sealants.⁵³

A similar situation was reported from the Netherlands. A study was conducted of 15-year-old children in Tiel (fluoridated 1953 to 1973) and Culemborg (nonfluoridated) comparing tooth decay rates from a baseline in 1968 through 1988. The lower tooth decay rate in Tiel after the cessation of fluoridation was attributed in part to the initiation of a dental health education program, free dietary fluoride supplements and a greater use of professionally applied topical fluorides.⁵⁴

In the preceding examples, communities that discontinued fluoridation either found higher tooth decay rates in their children or a lack of an increase that could be attributed to the availability and use of free dental services for all children or the implementation of wide-spread decay prevention programs that require significant professional and administrative support and are less cost-effective than fluoridation.

10. Is tooth decay still a serious problem in the United States?

Answer.

Yes. Tooth decay is an infectious disease that continues to be a significant oral health problem.

Fact.

Good oral health is often taken for granted by many people in the U.S. Yet, while largely preventable, tooth decay, cavities or dental caries (a term used by health professionals) remains a common, debilitating, chronic condition for many children and adults.

Tooth decay begins with a weakening and/or breakdown (loss of minerals) of the enamel (the hard outer layer of teeth) caused by acids produced by bacteria that live in plaque. Dental plaque is a soft, sticky film that is constantly forming on teeth. Eating foods or drinking beverages that contain sugars or other refined carbohydrates allow the bacteria in the plaque to produce acids that attack the enamel. The plaque helps to keep these acids in contact with the tooth surface and demineralization (loss of mineral) occurs. After repeated acid attacks, the enamel can breakdown creating a cavity. Left unchecked, bacteria and acid can penetrate the dentin (the next, inner layer of teeth) and then finally the pulp, which contains nerves and blood vessels. Once the bacteria enter the pulp, the tooth becomes infected (abscessed) and, without treatment, the infection can progress and travel into the surrounding tissues. The infection can enter the bloodstream and potentially spread the infection to other parts of the body which, in rare cases, becomes life-threatening.

💡 *Additional information on this topic can be found in this Section, Question 2.*

Tooth decay can negatively affect an individual's quality of life and ability to succeed. Tooth decay can cause pain — pain that can affect how we eat, speak, smile, learn at school or succeed at work. Children with cavities often miss more school and receive lower grades than children who are cavity-free.⁵⁵ More than \$6 billion of productivity is lost each year in the U.S, because people miss work to get dental care.⁵⁶

While cavities are often thought of as a problem for children, adults in the U.S. are keeping their teeth longer (partially due exposure to fluoridation) and this increased retention of teeth means more adults are at risk for cavities — especially decay of exposed root surfaces.^{57,58} Tooth root surfaces are covered with cementum (a softer surface than the enamel) and so are susceptible to decay. As Baby Boomers age, root decay experience is expected to increase in future years possibly to the point where older adults experience similar or higher levels of new cavities than do school children.⁵⁷

💡 *Additional information on this topic can be found in this Section, Question 11.*

Additionally, once an individual has a cavity repaired with a filling (restoration), that filling can break down over time especially around the edges. These rough edges (or margins) can harbor bacteria that start the cavity process over again or leak which allows the bacteria to enter the tooth below the existing filling. These fillings often need to be replaced — sometimes multiple times over decades — each time growing larger to the point where the best restoration for the tooth is a crown that covers the entire tooth surface. Preventing cavities and remineralizing teeth at the earliest stages of decay is very important not only in saving tooth structure but also in reducing the cost for dental care. Community water fluoridation is an effective public health measure that is a cost-saving and cost-effective approach to preventing tooth decay.

💡 *Additional information on this topic can be found in the Cost Section, Question 68.*

Oral health disparities exist in the United States and have been documented through extensive studies and reviews.⁵⁹⁻⁶¹ Despite the fact that millions of people in the U.S. enjoy good dental health, disparities exist for many racial and ethnic groups, as well as by socioeconomic status, sex, age and geographic location.⁶² Water fluoridation helps to reduce the disparities in oral health at the community level as it benefits all residents served by community water supplies. In his 2001 Statement on Community Water Fluoridation,⁶³ former Surgeon General Dr. David Satcher noted:

...community water fluoridation continues to be the most cost-effective, practical and safe means for reducing and controlling the occurrence of

dental decay in a community...water fluoridation is a powerful strategy in efforts to eliminate health disparities among populations.⁶³

💡 *Additional information on this topic can be found in the Public Policy Section, Question 59.*

Today, the major focus for achieving and maintaining oral health is on prevention. Established by the U.S. Department of Health and Human Services, Healthy People 2020⁶⁴ provides a science-based, comprehensive set of ambitious, yet achievable, ten-year national objectives for improving the health of the public. Included under oral health is an objective to expand the fluoridation of public water supplies. Objective 13 states that at least 79.6% of the U.S. population served by community water systems should be receiving the benefits of optimally fluoridated water by the year 2020.⁶⁵ Data from the CDC indicate that, in 2014, 74.4% of the U.S. population on public water systems, or a total of 211.4 million people, had access to fluoridated water.⁶⁶ Conversely, approximately 25% or more than 72.7 million people on public water systems do not receive the decay preventing benefits of fluoridation.

While cavities are often thought of as a problem for children, adults in the U.S. are keeping their teeth longer (partially due exposure to fluoridation) and this increased retention of teeth means more adults are at risk for cavities — especially decay of exposed root surfaces.

11. Do adults benefit from fluoridation?

Answer.

Yes. Fluoridation plays a protective role against tooth decay throughout life, benefiting both children and adults.

Fact.

While the early fluoridation trials were not designed to study the possible benefits fluoridation might have for adults, by the mid-1950s, it became evident from the results of the first fluoridation trial in Grand Rapids, Michigan, that the beneficial effects of fluoridation were not confined to children drinking the fluoridated water from birth. The fact that a reduction in tooth decay was observed for teeth which had already been calcified or were erupted when fluoridation was started indicated that a beneficial effect could be gained by older age groups.^{67, 68} Today it is understood that the maximum reduction in tooth decay occurs when fluoride has been incorporated into the tooth during formation and when it also is available at the tooth surface during demineralization and remineralization. Fluoridation works in both ways to prevent tooth decay.^{9, 12, 14, 16, 17}

Fluoride and minerals, including calcium and phosphate, are present in saliva^{7, 9} and are stored in dental plaque (a soft, sticky film that is constantly forming on teeth). To halt the formation of tooth decay or rebuild tooth surfaces, fluoride must be constantly present in low concentrations in saliva and plaque.⁷ Frequent exposure to small amounts of fluoride, such as occurs when drinking fluoridated water, helps to maintain the reservoir of available fluoride in saliva and plaque to resist demineralization and enhance remineralization.^{7, 10} In other words, drinking fluoridated water provides the right amount of fluoride at the right place at the right time. Fluoride in water and water-based beverages is consumed many times during the day, providing frequent contact with tooth structures and making fluoride available to fluoride reservoirs in the mouth. This helps explain why fluoride at the low levels found in fluoridated water helps to prevent tooth decay in teeth after they have erupted.⁷

 *Additional information on this topic can be found in this Section, Question 2.*

While teeth already present in the mouth when exposure to water fluoridation begins receive the benefit of decay protection, studies have indicated

that adults who have consumed fluoridated water continuously from birth receive the maximum protection against tooth decay.¹⁰⁻¹⁴

An Australian study published in 2008 investigating decay experience among Australian Defense Force personnel showed that a longer period of exposure to water fluoridation was associated with lower decay rates in adults between the ages of 17 and 44. Adults who lived at least 90% of their lifetime in communities with fluoridated water had 24% less decay than adults who lived in fluoridated areas for less than 10% of their lifetimes.⁶⁹

A meta-analysis published in 2007 examining the effectiveness of fluoridation for adults found that fluoridation prevents approximately 27% of tooth decay in adults. It included only studies that were published after 1979. The studies were limited to participants who were lifelong residents of communities with fluoridated water and a control group of lifelong residents of communities without fluoridated water.⁵⁷

A study published in 2002 examined the differences in tooth decay patterns between two cohorts of young adults: the first grew up before fluoridation was widely available and the second after fluoridation became more widespread. Comparing data from two different U.S. National Health and Nutrition Examination Surveys (NHANES), NHANES I (1971-1974) and NHANES III (1988-84), results indicated that total tooth decay declined among people aged 45 years and younger. No decline was observed in people aged 46 to 65, a cohort that grew up during the late 40s and early 50s before fluoridation was widely available. This was identified as the major reason this older cohort did not show a decline in tooth decay.⁷⁰

In 1989, a study conducted in the state of Washington found that adults (20-34 years of age) who had a continuous lifetime exposure to fluoridation water had 31% less tooth decay experience compared to similar aged adults with no exposure to fluoridated water. It also concluded that exposure to fluoridation only during childhood has lifetime benefits since adults exposed to fluoridated water only during childhood had decay experience similar to those adults exposed to fluoridated water only after age 14.⁷¹

An important issue for adults is the prevention of root decay.^{57, 58} People in the United States are living longer and retaining more of their natural teeth than ever

before — in part due to water fluoridation. Adults with gum recession are at risk for root decay because the root surface, a much softer tooth surface than enamel, becomes exposed to decay-causing bacteria in the mouth as gums recede. Data from the ongoing NHANES survey indicate that root decay experience has declined in recent years among older adults with teeth (ages 65-years and older), decreasing from 46% (NHANES 1988-1994) to 36% (NHANES 1999-2004). However, the prevalence of root decay increases markedly as adults age and escalates more rapidly after age 65. Specifically, the 75-years and older group had 23% greater prevalence of root surface decay than did the 65- to 74-years-old age group.⁷² While most studies related to the prevention of root decay focus on professional fluoride treatments such as fluoride varnish, there is evidence that demonstrates fluoridation may have an impact on root decay.⁷³⁻⁷⁵ For example, in Ontario, Canada, lifelong residents of the nonfluoridated community of Woodstock had a 21% higher root surface decay experience than those living in the naturally fluoridated (1.6 ppm) matched community of Stratford.⁷⁴ Similarly, Iowa residents more than 40 years of age living long-term in fluoridated communities had significantly less root decay than lifelong residents of nonfluoridated communities (0.56 versus 1.11 surfaces).⁷⁵

Adults in the U.S. are keeping their natural teeth longer — partially due to exposure to water fluoridation. But as adults age with their teeth, it means more teeth will be at risk for tooth decay. It has been suggested in the literature that decay experience for adults could increase to the point where older adults experience similar or higher levels of new cavities than do school children.^{35,76,77} It continues to be important to document and acknowledge the effectiveness of fluoridation in preventing tooth decay in adults because virtually all primary preventive dental programs target children and adolescents — with one exception — community water fluoridation. Fluoridation is unique in that it remains the one dental public health measure that reaches all members of a community including young, middle-aged and older adults.⁵⁶

Fluoridation is unique in that it remains the one dental public health measure that reaches all members of a community including young, middle-aged and older adults.

12. Are dietary fluoride supplements effective in helping to prevent tooth decay?

Answer.

Yes. Dietary fluoride supplements can be effective in preventing tooth decay.

Fact.

Dietary fluoride supplements are available only by prescription in the United States and are intended for use by children who are at high risk for developing tooth decay and living in areas where the primary source of water is deficient in fluoride.⁸

Recommendations for health professionals seeking to prescribe dietary fluoride supplements are found in *The Evidence-Based Clinical Recommendations on the Prescription of Dietary Fluoride: A Report of the American Dental Association Council on Scientific Affairs* published in 2010.⁸ The report and a *Chairside Guide: Dietary Fluoride Supplements: Evidence-based Clinical Recommendations* can be accessed at <http://ebd.ADA.org/en/evidence/guidelines/fluoride-supplements>. The current dietary fluoride supplement schedule appears in this section as Table 1.

 Additional information on this topic can be found in this Section, Question 13.

As noted in Table 3 of the report, “Clinical recommendations for the use of dietary fluoride supplements:”

The expert panel convened by the American Dental Association Council on Scientific Affairs developed the following recommendations. They are intended as a resource for dentists and other health care providers. The recommendations must be balanced with the practitioner’s professional judgment and the individual patient’s needs and preferences.

Children are exposed to multiple sources of fluoride. The expert panel encourages health care providers to evaluate all potential fluoride sources and to conduct a caries risk assessment before prescribing fluoride supplements.

As noted in the recommendations, prior to prescribing dietary fluoride supplements, accurate assessment of the fluoride content of the patient’s primary drinking water source(s) should be conducted.⁸ The identification of the “primary” sources is sometimes

difficult due to the fact that some patients have multiple sources of drinking water during a typical day. For example, while a patient may have access to drinking water in the home, they often also spend a large part of their day accessing drinking water at day care or school, which could be a different water system. It might be necessary to contact the local, county or state health departments for information on the fluoride content of public water sources or to be referred to a certified laboratory that can provide a fluoride test for private wells.

◆ Additional information on this topic can be found in this Section, Question 4.

The ADA offers information on caries risk assessment⁷⁸ on the web at <http://www.ADA.org/en/member-center/oral-health-topics/caries-risk-assessment-and-management>. It should be noted that dietary fluoride supplements are recommended only for children at high risk for tooth decay.⁸ Caries risk assessments should be completed for patients on a regular basis to determine their risk for tooth decay which can change over time.

Dietary fluoride supplements can be effective in helping to prevent tooth decay. To receive the optimal benefit from fluoride supplements, the use of supplements should begin at six months of age and continue daily until the child is 16 years old.⁸ However, individual patterns of compliance can vary greatly.

For that reason, the report suggests that providers carefully monitor the adherence to the schedule to maximize the therapeutic benefit of supplements in caries prevention. If the health care provider has concerns regarding a lack of compliance to the schedule, it might be best to consider other sources of fluoride exposure for the patient, such as bottled water with fluoride.⁸

While dietary fluoride supplements can be effective in reducing tooth decay, there are a number of factors that can impede their use and resulting therapeutic value:

- Patients/parents/caregivers must have access to a professional health care provider who can provide the necessary assessments and provide prescriptions for the supplements — often repeatedly over time.
- The supplements must be obtained through a pharmacy/pharmaceutical service and refilled as necessary.
- The cost of supplements can be a financial hardship for some individuals.
- The compliance required (a child should take the supplement every day until 16 years of age) to obtain the optimal therapeutic affect often is difficult to achieve.

Table 1. Dietary Fluoride Supplement Schedule for Children at High Caries Risk⁸

Age	Fluoride ion level in drinking water (ppm)*		
	<0.3 ppm	0.3-0.6 ppm	>0.6 ppm
Birth - 6 months	None	None	None
6 months - 3 years	0.25 mg/day**	None	None
3-6 years	0.50 mg/day	0.25 mg/day	None
6-16 years	1.0 mg/day	0.50 mg/day	None
* 1.0 part per million (ppm) = 1 milligram/liter (mg/L) **2.2 mg sodium fluoride contains 1 mg fluoride ion.			

Noting the potential obstacles listed above, where feasible, community water fluoridation offers proven decay prevention benefits without the need for access to a health care professional or a change in behavior on the part of the individual. Simply by drinking water at home, school, work or play everyone in the community benefits regardless of socioeconomic status, educational attainment or other social variables.⁷⁹ While dietary fluoride supplements can reduce a child's risk of tooth decay, fluoridation extends that benefit to adults in the community. Additionally, the cost of dietary fluoride supplements over an extended period of time can be an economic concern to a family. In looking at overall costs, consideration should be given to the cost per person and the number of people who can benefit from a dietary fluoride supplement or community fluoridation program.⁷⁷

13. The ADA Dietary Fluoride Supplements Schedule 2010 contains the word "none" in specific boxes. Does this mean the ADA does not recommend fluoride for children?

Answer.

No, that would be a misinterpretation of the purpose of the schedule. The schedule reflects the recommended dosage of fluoride supplements based on age and the fluoride level of the child's primary source of drinking water, in addition to what would be consumed from other sources.

Fact.

The dietary fluoride supplement schedule⁸ (Table 1.) is just that — a supplement schedule. Children residing in areas where the drinking water is not fluoridated will receive some fluoride from other sources such as foods and beverages. Dietary fluoride supplements are designed for children over six months of age who do not receive a sufficient amount of fluoride from those sources. The dosage amounts in the table reflect the additional amount of supplemental fluoride intake necessary to achieve an optimal anti-cavity effect. To reduce the risk of dental fluorosis, children under six months of age should not take dietary fluoride supplements.

⚡ *Additional information on this topic can be found in the Safety Section, Question 29.*

The dietary fluoride supplement schedule should not be viewed as a recommendation of the absolute upper limits of the amount of fluoride that should be ingested each day. In 2011, the Food and Nutrition Board of the Institute of Medicine developed Dietary Reference Intakes, a comprehensive set of reference values for dietary nutrient values. The values present nutrient requirements to optimize health and, for the first time, set maximum-level guidelines to reduce the risk of adverse effects from excessive consumption of a nutrient. In the case of fluoride, levels were established to reduce tooth decay without causing moderate dental fluorosis.⁸⁰

For example, the dietary fluoride supplement schedule recommends that a two-year-old child at high risk for tooth decay living in a nonfluoridated area (where the primary water source contains less than 0.3 ppm fluoride) should receive 0.25 mg of supplemental fluoride per day. This does not mean that this child should ingest exactly 0.25 mg of fluoride per day total. Instead, a two-year-old child could receive important anti-cavity benefits by taking 0.25 mg of supplemental fluoride a day without causing any adverse effects on health. This child would most probably be receiving fluoride from other sources (foods and beverages) even in a nonfluoridated area and the recommendation of 0.25 mg of fluoride per day takes this into account. In the unlikely event the child did not receive any additional fluoride from food and beverages, the 0.25 mg per day could be inadequate fluoride supplementation to achieve an optimal anti-cavity effect.

⚡ *Additional information on this topic can be found in the Safety Section, Question 23.*

The following statement is correct. "Fluoride supplement dosage levels have been lowered in the past as exposure to fluoride from other sources has increased." Rather than being a problem, as those opposed to the use of fluoride might imply, this is evidence that ADA policy is based on the best available science. The ADA periodically reviews the dosage schedule and issues updated recommendations based on the best available science.

In 1994, a Dietary Fluoride Supplement Workshop, co-sponsored by the ADA, the American Academy of Pediatric Dentistry and the American Academy of Pediatrics, was held in Chicago. Based on a review of scientific evidence, a consensus was reached on a

new dosage schedule developed acknowledging that numerous sources of topical and systemic fluoride are available today that were not available many years ago.⁸¹

The supplement schedule was reviewed and reissued in December 2010. At that time, the American Dental Association Council on Scientific Affairs (CSA) published evidence-based clinical recommendations for the schedule of dietary fluoride supplements.⁸ The evidence-based review recommended that the age stratification established in the ADA's 1994 supplement schedule remain unchanged. The review also recommended that prior to prescribing fluoride supplements, the prescribing provider should assess the patient's risk for cavities and only those at high risk should receive supplements.⁸ If at high risk, then the fluoride level of the patient's primary drinking water source should be assessed.⁸ It should be noted that an accurate assessment of the patient's primary drinking water source can be difficult due to the various sources of fluoridated water. For example, the patient might not have access to fluoridated water in the home, but may drink fluoridated water while at day care or school. The current dietary fluoride supplement schedule appears as Table 1.⁸

◆ *Additional information on this topic can be found in this Section, Question 12.*

14. What are salt and milk fluoridation and where are they used?

Answer.

Salt and milk fluoridation are fluoridation methods used to provide community-based fluoridation in countries outside of the United States where various political, geographical, financial or technical reasons prevent the use of water fluoridation.

Fact.

The practice of salt fluoridation began in the 1950s, approximately 10 years after water fluoridation was initiated in the United States.⁸² Based on the success several decades earlier of the use of iodized salt for the prevention of goiter, fluoridated salt was first introduced in Switzerland in 1956.⁸³

According to a review published in 2013, salt fluoridation is available in a number of countries in Europe but its coverage varies greatly.⁸² Germany

and Switzerland have attained a coverage exceeding two-thirds of their populations (67% and 85% respectively). In other European countries including Austria, the Czech Republic, France, Slovakia and Spain, salt fluoridation is reportedly used on a very limited scale.⁸² Additional countries, such as Hungary, Romania, Slovenia, Croatia and Poland, have considered salt fluoridation but have failed to take action.⁸⁴

European regulations (current as of 2017) permit the addition of fluoride to salt and water.⁸² However, it appears that the majority of European countries favor the twice daily use of fluoride toothpaste as the most important measure for improving the public's dental health.⁸⁴ In Europe, toothpaste sold over the counter typically contains 1,500 ppm fluoride,⁸⁵ while toothpaste in the United States typically contains 1,000 to 1,100 ppm fluoride.⁸⁶

On a historical note, prior to the political changes that occurred in the late 1980s and early 1990s in Europe, water fluoridation was widely available in the German Democratic Republic and the Czechoslovak Republic and to a lesser extent in Poland. With the end of the Communist regimes, efforts related to public health dentistry were largely discontinued. While fluoridation continued in several small towns until 1993, in general, it was abandoned.⁸⁴

In North and South America, salt fluoridation is available in Belize, Bolivia, Colombia, Costa Rica, Dominican Republic, Ecuador, Mexico, Peru, Uruguay and Venezuela. Like in Europe, the extent of salt fluoridation varies between countries. Columbia, Costa Rica, Jamaica, Mexico and Uruguay provide fluoridated salt to nearly their entire populations while there is less coverage in other countries.⁸²

In 2013, it was estimated that approximately 60 million people in Europe and 160 million in the Americas had access to fluoridated salt.⁸²

The Pan American Health Organization (PAHO), a regional division of the World Health Association (WHO) with responsibilities for health matters in North, South and Central America and the Caribbean, has been active in developing strategies to implement decay prevention programs in the regions of the Americas using water and salt fluoridation.⁸⁷ In order to achieve the greatest reduction in tooth decay while minimizing the risk of dental fluorosis, it is advisable that a country implement only one of these two

public health measures — either community water fluoridation or salt fluoridation. The United States has implemented water fluoridation. The U.S. Food and Drug Administration has not approved fluoridated salt for use in the U.S.

Early studies evaluating the effectiveness of salt fluoridation conducted in Columbia, Hungary and Switzerland indicated that fluoride delivered via salt might produce a reduction in tooth decay similar to that seen with optimally fluoridated water.^{88,89} When all salt destined for human consumption (both domestic salt and bulk salt that is used by commercial bakeries, restaurants, institutions, and industrial food production) is fluoridated, the decay-reducing effect could be comparable to that of water fluoridation over an extended period of time.^{88,89} When only domestic salt is fluoridated, the decay-reducing effect is diminished.⁸⁸ Studies conducted in Costa Rica, Jamaica and Mexico in the 1980s and 1990s also showed significant reductions in tooth decay. However, it was noted that these studies did not include other variables that could have contributed to the reductions.⁸⁸

The fact that salt fluoridation does not require a centralized piped water system is of particular value in countries that do not have such water systems. Fluoridated salt is also a very cost-effective public health measure. For example, in Jamaica, where all salt destined for human consumption is fluoridated, the use of fluoridated salt was reported to reduce tooth decay by as much as 84% at a cost of 6 cents per person per year.⁸⁷ In some cases, the cost to produce fluoridated salt is so low that for consumers, the cost of fluoridated salt is the same as for nonfluoridated salt.⁹⁰

The implementation of salt fluoridation has unique challenges not incurred with water fluoridation. Sources of salt, the willingness of local manufacturers to produce fluoridated salt or the need to import fluoridated salt would need to be studied. Because fluoridated salt should only be consumed by the public in areas with a naturally low level of fluoride, it would be necessary to completely map the naturally occurring levels of fluoride and devise a plan to keep fluoridated salt out of the areas with moderate to high naturally occurring fluoride (to aid in reducing the risk of dental fluorosis). Additionally, a plan would need to be developed to monitor the fluoride level in urine of those consuming fluoridated salt starting with a baseline before implementation

and including follow-up testing on a regular basis. While salt fluoridation typically is not implemented through a public vote, it would be necessary to gain the cooperation of salt manufacturers and institutions of all kinds that would use salt in their food preparation.⁸⁹ Additionally, educational efforts would need to be directed at health professionals and health authorities to avoid referendum approaches and identify enabling regulations.⁸³

In a number of European countries, consumers have a choice of purchasing either fluoridated or nonfluoridated salt for use in the home. While it has been argued that, unlike water fluoridation, this option to purchase fluoridated or nonfluoridated salt allows for personal choice, studies indicate that fluoridated salt is not as effective a public health measure when only a small portion of the population opts to purchase and use the product.⁸⁹ For example, in France, fluoridated salt for home use became available to the consumer by decree in 1986, while nonfluoridated salt remained available for purchase. By 1991, with an aggressive public health campaign, the market share of fluoridated salt was 50% and it reached a high of 60% in 1993. Then the public health campaign ended. By 2003, the market share had decreased to 27%.^{82,91} It has been suggested that, in order to be a successful public health measure that effectively reaches those who are disadvantaged, approximately 70% of the population needs to use fluoridated salt. Conversely, usage rates less than 50% should be considered as having minimal effect on public health.⁸² While the situation described in Europe allows for personal choice, salt programs in the Americas where all salt destined for human consumption is fluoridated would seem at odds with the issue of personal choice, yet the program is apparently working well with fluoridated salt well accepted by the public.⁹²

A number of studies have shown an increase in the occurrence of dental fluorosis in areas where salt fluoridation programs have been implemented. For example, a 2006 cohort study examined the prevalence and severity of dental fluorosis in children before and after the implementation of salt fluoridation in Campeche, Mexico, in 1991.⁹³ The study showed, that while 85% of the dental fluorosis identified was categorized as very mild, children born in 1990-1992 were more likely to have dental fluorosis than those born in the period 1986-1989.⁹³ A study published in 2009 of children in Jamaica

showed similar results.⁹⁴ Jamaica began a fluoridated salt program in 1987. In 1999, an area around St. Elizabeth was found to have a high prevalence of dental fluorosis. Examiners returned in 2006 to re-evaluate students in the area. While their results indicated a slightly reduced tooth decay experience for 6-year-olds in 2006 compared to 6-year-olds in 1999, they also found that 6-year-olds also had a higher prevalence of dental fluorosis in 2006 than the 6-year-olds examined in 1999. In addition to the implementation of salt fluoridation, other factors including the use of increased use of fluoridated toothpaste and mouthrinses could have played a role.⁹⁴ However, both of these studies point out the need to carefully monitor fluorides from multiple sources especially when implementing fluoridated salt programs.

Fluoridated milk has been suggested as another alternative to community water fluoridation in countries outside the United States. Studies on the effectiveness of milk fluoridation have been carried out in numerous countries, including but not limited to, Brazil, Bulgaria, China, Israel, Japan, Russia and the United Kingdom.⁹⁵ Many of these studies have found milk fluoridation programs to be an efficient and cost-effective method to prevent cavities.⁹⁵ For example, a 2001 study of Chilean preschoolers using fluoridated powdered milk and milk derivatives resulted in a 41% reduction in the number of primary decayed missing and filled tooth surfaces as compared to the control group that did not receive fluoridated milk.⁹⁶ Additionally, in the same study, the proportion of decay free children increased from 22% to 48% in the study group after four years of implementing the program.⁹⁶

In 2004, the dental health of school children from the northwest of England, who were enrolled in the school milk fluoridation program, was compared to children with similar characteristics who were not consuming fluoridated milk.⁹⁷ The average age of the children in the study was 11 years old. In order to participate in the study, participants chosen for the test group were required to have been receiving fluoridated milk for a minimum of 6 years. First permanent molars were examined for tooth decay experience. Results from the study indicated that children consuming fluoridated milk had less tooth decay experience (1.01 DMFT) than the children who did not receive fluoridated milk (1.46 DMFT).⁹⁷

A study of community milk programs in Bulgaria examined children at age 3 and again at age 8.⁹⁸ The study indicated that tooth decay experience was substantially lower in the cohort of children who had received fluoridated milk in school for five years compared with the cohorts of children who had received milk in school without fluoride added. At the end of the five-year trial in 2009, tooth decay experience was lower in children who received fluoridated milk (5.61 dmfs and 0.48 DMFS) than in the control community children who received milk with no fluoride (9.41 dmfs and 1.24 DMFS).⁹⁸

In these two examples “dmfs” is the mean number of decayed, missing or filled tooth surfaces on primary (or baby) teeth while “DMFS” is the mean number of decayed missing or filled tooth surfaces on permanent teeth.

Studies completed on milk fluoridation to date largely target children. There has been only a very small number that have looked at the role fluoridated milk might play for adults. These studies have largely examined fluoridated milk and its possible effect on root decay. For example, a study published in 2011 and conducted in Sweden indicated that fluoridated milk could be of value in remineralizing early tooth decay in root surfaces.⁹⁹

It was estimated that as of 2013, more than one million children worldwide were receiving fluoridated milk.⁹⁴ The majority of studies conducted have indicated that fluoridated milk is effective in preventing tooth decay under certain conditions. It is most effective if the consumption of fluoridated milk starts before 4 years of age and continues until the permanent teeth are present in the mouth. Most successful programs are conducted through schools where the natural fluoride levels in water are low and children are able to consume fluoridated milk for a minimum of 200 days a year.⁹⁵ While these conditions prevent fluoridated milk from being recommended as a public health measure for an entire community, fluoridated milk might be the most appropriate and effective means of fluoride exposure for children in some circumstances.

15. Can the consistent use of bottled water result in individuals missing the benefits of optimally fluoridated water?

Answer.

Yes. The majority of bottled waters on the market do not contain optimal levels (0.7 mg/L) of fluoride.

Fact.

There is not a large body of research regarding the risk for tooth decay associated with the consumption of bottled water. However, a lack of exposure to fluoride could increase an individual's risk for tooth decay. The vast majority of bottled waters do not contain significant amounts of fluoride.¹⁰⁰ Individuals who drink bottled water as their primary source of water could be missing the decay preventive effects of optimally fluoridated water available from their community water supplies. These consumers should seek advice from their dentists about their risk for tooth decay and specific fluoride needs.

While drinking water from the tap is regulated by the U.S. Environmental Protection Agency (EPA), bottled water is regulated by the U.S. Food and Drug Administration (FDA).¹⁰¹ The FDA has established maximum allowable levels for physical, chemical, microbiological, and radiological contaminants in bottled water.¹⁰²

Individuals who drink bottled water as their primary source of water could be missing the decay preventive effects of optimally fluoridated water available from their community water supplies.

Noting that fluoride can occur naturally in source waters used for bottled water or can be added by a bottled water manufacturer, the FDA has approved standards for the fluoride content of bottled water.¹⁰² However, the FDA regulations require the fluoride content of bottled water to be listed on the label only if fluoride is added during processing.¹⁰³ If the fluoride level is not shown on the label of the bottled water, the company can be contacted, or the water can be tested to obtain this information. Most consumers are unaware that the vast majority of bottled waters, especially those treated by distillation or reverse

osmosis, are largely fluoride-free. Unknowingly, individuals who drink bottled water as their primary source of water could be missing the decay preventive effects of optimally fluoridated water available from their community water supplies. The American Dental Association supports the labeling of bottled water with the fluoride content to aid consumers in making informed decisions about choices of drinking water.¹⁰⁴

Recognizing the benefit of fluoride in drinking water, in 2006 the FDA issued the "FDA Health Claim Notification for Fluoridated Water and Reduced Risk of Dental Caries"¹⁰⁵ which states that bottled water meeting the specific standards of identity and quality set forth by FDA, and containing greater than 0.6 mg/L up to 1.0 mg/L total fluoride, can be labeled with the following health claim: "Drinking fluoridated water may reduce the risk of [dental caries or tooth decay]." This health claim is not intended for use on bottled water products specifically marketed for use by infants.¹⁰⁵

💡 *Additional information on this topic can be found in the Safety Section, Question 28.*

According to a 2017 press release from the Beverage Marketing Corporation,¹⁰⁶ bottled water surpassed carbonated soft drinks in 2016 to become the largest beverage category by volume in the United States. Per capita consumption of bottled water was approximately 39.3 gallons in 2016, while the average consumption of carbonated soft drinks was approximately 38.5 gallons per person per year. The majority (67.3%) of U.S. bottled water is sold in single-serving PET (polyethylene terephthalate or plastic resin¹⁰⁷) bottles. Bottled water is also sold via bulk deliveries to homes and offices (approximately 11%) and by retail sales in different sizes of gallon containers (approximately 9%).¹⁰⁶

Individuals choose to drink bottled water for various reasons. Some find it a calorie-free substitute for carbonated soft drinks or other sugary beverages. Others dislike the taste of their tap water or have concerns about the possible contaminants in their local water supply.

In a small study published in 2012, a convenience sample of caretakers and adolescents at an urban clinic found that 17% drank tap water exclusively, 38% drank bottled water exclusively and 42% drank both. Bottled water was ranked significantly higher

in taste, clarity, purity and safety than tap water. Only 24% of caretakers of children and adolescents knew whether or not fluoride was in their drinking water. The authors concluded that perception of the qualities of water were responsible for choices of drinking water.¹⁰⁸ Similar findings have been echoed in earlier studies.¹⁰⁹⁻¹¹¹ Additionally, cultural influences can affect drinking water preferences. In some Latino communities, parents were less likely to give tap water to their children because they believed tap water would make them sick based in part on the fact that many have come to the U.S. from places with poor water quality where water-borne illness was common.¹¹¹ Besides missing the decay preventive effects of fluoridated tap water, it has been determined that families spend hundreds of dollars more each year on purchasing water than if they were to consume tap water.^{109,111}

16. Can home water treatment systems such as water filters, reverse osmosis and water softeners remove fluoride from drinking water?

Answer.

Some types of home water treatment systems can reduce the fluoride levels in water supplies. Individuals who drink water processed by home water treatment systems as their primary source of water could be losing the decay preventive effects of optimally fluoridated water available from their community water supply.

Fact.

There are many kinds of home water treatment systems including reverse osmosis systems, distillation units, water softeners and water filters such as carafe filters, faucet filters, under the sink filters and whole house filters. There has not been a large body of research regarding the extent to which these treatment systems affect the fluoride content of optimally fluoridated water.

However, it has been consistently documented that reverse osmosis systems and distillation units remove significant amounts of fluoride from the water supply.^{112,113} Studies regarding water softeners show clearly that the water softening process does not significantly change fluoride levels.^{114,115}

With water filters, the fluoride concentration remaining in the water depends on the type and quality of the filter being used, the status of the filter and the filter's age. Most carbon filters do not remove fluoride. However, some filters containing activated alumina can remove significant amounts of the fluoride. Additionally, some filters containing bone char also can remove significant amounts of fluoride.^{113,116} Accordingly, each type of filter should be assessed individually.

Individuals who drink water processed by home water treatment systems as their primary source of water could be losing the decay preventive effects of optimally fluoridated water available from their community water supply. Therefore, it might be necessary to contact the installer, distributor or manufacturer of the water treatment system or water filter in question to determine whether the item removes fluoride. Information regarding the existing level of fluoride in a community's public water system can be obtained by asking a local dentist or contacting the local or state health department or the local water supplier. If the consumer is using a private well, it is suggested that it be tested yearly for fluoride levels.

⚠ *Additional information on this topic can be found in this Section, Question 4.*

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Safety

17. Harmful to humans?.....	37	32. Cancer?.....	56
18. More studies needed?.....	38	33. Osteosarcoma?.....	57
19. Recommended level?.....	39	34. Enzyme effects?.....	58
20. EPA maximum?.....	40	35. Thyroid?.....	59
21. EPA secondary level?.....	41	36. Pineal gland?.....	60
22. Total intake?.....	43	37. Allergies?.....	60
23. Daily intake?.....	44	38. Genetic risk?.....	61
24. Prenatal dietary fluoride supplements?.....	46	39. Fertility?.....	61
25. Body uptake?.....	47	40. Down Syndrome?.....	62
26. Bone health?.....	47	41. Neurological impairment/IQ?.....	62
27. Dental fluorosis?.....	49	42. Lead poisoning?.....	64
28. Fluoridated water for infant formula?.....	52	43. Alzheimer's disease?.....	65
29. Prevent fluorosis?.....	52	44. Heart disease?.....	66
30. Warning Label?.....	54	45. Kidney disease?.....	67
31. Acute and chronic toxicity?.....	55	46. Erroneous health claims?.....	68

17. Does fluoride in the water supply, at the levels recommended for the prevention of tooth decay, adversely affect human health?

Answer.

The overwhelming weight of scientific evidence supports the safety of community water fluoridation.

Fact.

For generations, millions of people have lived in areas where fluoride is found naturally in drinking water in concentrations as high or higher than the optimal level recommended to prevent tooth decay. Research conducted among these persons confirms the safety of fluoride in the water supply.¹⁻⁵

As with other nutrients, fluoride is safe and effective when used and consumed as recommended. No charge against the benefits and safety of fluoridation has ever been substantiated by generally accepted scientific knowledge. A number of reviews on fluoride in drinking water have been issued over the years. For example, in 1951⁶ the National Research Council (NRC), of the National Academies,

issued its first report stating fluoridation was safe and effective. Additional reviews by the NRC followed in 1977⁷ and 1993⁸ with the most recent NRC review completed in 2006.⁹ Additional reviews completed over the ten year period from 2007-2017 include:

- 2017 Australian Government, National Health and Medical Research Council (NHMRC). *Information Paper — Water Fluoridation: Dental and Other Human Health Outcomes*.¹⁰
- 2016 O'Mullane DM, Baez RJ, Jones S, Lennon MA, Petersen PE, Rugg-Gunn AJ, Whelton H, Whitford GM. *Fluoride and Oral Health*.¹¹
- 2016 American Water Works Association. *Water Fluoridation Principles and Practices*. AWWA Manual M4. Sixth edition.¹²
- 2015 Water Research Foundation. *State of the Science: Community Water Fluoridation*.¹³
- 2015 The Network for Public Health Law. *Issue Brief: Community Water Fluoridation*.¹⁴

- 2015 Ireland Health Research Board. *Health Effects of Water Fluoridation: An Evidence Review*.¹⁵
- 2015 U.S. Department of Health and Human Services Federal Panel on Community Water Fluoridation. *U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries*.¹⁶
- 2014 Public Health England. *Water Fluoridation: Health Monitoring Report for England*.¹⁷
- 2014 Royal Society of New Zealand and the Office of the Prime Minister's Chief Science Advisor. *Health Effects of Water Fluoridation: a Review of the Scientific Evidence*.¹⁸
- 2013 U.S. Community Preventive Services Task Force. The Guide to Community Preventive Services. *Preventing Dental Caries: Community Water Fluoridation*.¹⁹
- 2011 European Commission of the European Union Scientific Committee on Health and Environmental Risks (SCHER). *Fluoridation*.²⁰
- 2008 Health Canada. *Findings and Recommendations of the Fluoride Expert Panel*.²¹
- 2007 Australian Government National Health and Medical Research Council A Systematic Review of the Efficacy and Safety of Fluoridation; Part A: Review Methodology and Results.²²

The overwhelming weight of scientific evidence supports the safety of community water fluoridation.

18. Are additional studies being conducted to determine the effects of fluorides in humans?

Answer.

Yes. Since its inception, fluoridation has undergone a nearly continuous process of re-evaluation. As with other areas of science, additional studies on the effects of fluorides in humans can provide insight as to how to make effective choices for the use of fluoride. The American Dental Association and the U.S. Public Health Service support this on-going research.

Fact.

For more than 70 years, detailed reports have been published on multiple aspects of fluoridation. The accumulated dental, medical and public health evidence concerning fluoridation has been reviewed and evaluated numerous times by academicians, committees of experts, special councils of governments and most of the world's major national and international health organizations. The consensus of the scientific community is that water fluoridation, at the level recommended to prevent tooth decay, safely provides oral health benefits which in turn supports improved general health. The question of possible secondary health effects caused by fluorides consumed in optimal concentrations throughout life has been the object of thorough medical investigations which have failed to show any impairment of general health throughout life.¹⁰⁻²²

The consensus of the scientific community is that water fluoridation, at the level recommended to prevent tooth decay, safely provides oral health benefits which in turn supports improved general health.

In scientific research, there is no such thing as "final knowledge." New information is continuously emerging and being disseminated. Government agencies, such as the U.S. National Institutes of Health, National Institute of Dental and Craniofacial Research, and others continue to fund fluoride research. One example is the National Toxicology Program's systematic review using animal studies to evaluate potential neurobehavioral effects from exposure to fluoride during development which began in 2015 and continues in 2017.²³

In 2011, the U.S. Department of Health and Human Services and the U.S. Environmental Protection Agency (EPA) issued a joint press release²⁴ outlining important steps the respective agencies were taking to ensure that standards and guidelines on fluoride in drinking water continue to ensure the safety of the public while supporting good dental health, especially in children. Those actions resulted in the 2015 report issued by the U.S. Public Health Service¹⁶ regarding the recommended level of fluoride in drinking water and the EPA activity was informational to the 2016 EPA Six-Year Review³²⁵ in which the Agency completed a detailed review of drinking water regulations including the regulation for naturally occurring fluoride in water.

19. Why did the U.S. Public Health Service issue a report in 2015 recommending 0.7 milligrams per liter (mg/L) as the optimal level for fluoride in drinking water for all temperature zones in the U.S.?

Answer.

The U.S. Public Health Service (USPHS) updated and replaced its 1962 Drinking Water Standards related to community water fluoridation to establish a single value of 0.7 mg/L as the optimal concentration of fluoride in drinking water. This concentration provides the best balance of protection from tooth decay while limiting the risk of dental fluorosis.¹⁶

Fact.

The previous U.S. Public Health Service recommendations for optimal fluoride concentrations were based on average ambient air temperatures of geographic areas and ranged from 0.7–1.2 mg/L. In 2011, the U.S. Department of Health and Human Services (HHS) issued a notice of intent in the *Federal Register*²⁶ proposing that community water systems adjust the amount of fluoride to 0.7 mg/L to achieve an optimal fluoride level.

The new guidance was based on several considerations that included:

- Scientific evidence related to effectiveness of water fluoridation on caries prevention and control across all age groups.
- Fluoride in drinking water as one of several available fluoride sources.

- Trends in the prevalence and severity of dental fluorosis.
- Current evidence on fluid intake in children across various ambient air temperatures.

As part of the process leading to the notice of intent, the U.S. Department of Health and Human Services (HHS) convened a federal interdepartmental, interagency panel of scientists to review the scientific evidence relevant to the 1962 USPHS Drinking Water Standards for fluoride concentrations in drinking water in the United States and to update these recommendations based on current science. Panelists included representatives from the Centers for Disease Control and Prevention, the National Institutes of Health, the U.S. Food and Drug Administration, the Agency for Healthcare Research and Quality, the Office of the Assistant Secretary for Health, U.S. Environmental Protection Agency, and the U.S. Department of Agriculture.¹⁶

A public comment period followed the publication of the notice of intent during which time more than 19,000 comments were received. The vast majority (more than 18,000) were variations on a letter submitted by an organization opposing community water fluoridation. Comments received were summarized and reported to the full federal panel. The panel then spent several years reviewing each comment in light of the best available science. After completing their extensive review, the panel did not alter the recommendation based on the following:

- Community water fluoridation remains an effective public health strategy for delivering fluoride to prevent tooth decay and is the most feasible and cost-effective strategy for reaching entire communities.
- In addition to drinking water, other sources of fluoride exposure have contributed to the prevention of dental caries and an increase in dental fluorosis prevalence.
- Caries preventive benefits can be achieved and the risk of dental fluorosis reduced at 0.7 mg/L.
- Recent data do not show a convincing relationship between water intake and outdoor air temperature. Thus, recommendations for water fluoride concentrations that differ based on outdoor temperature are unnecessary.¹⁶

In 2015 the USPHS published a final report establishing guidance for water systems that are actively fluoridating or those that may initiate fluoridation in the future.¹⁶ For community water systems that add fluoride to their water, the USPHS recommends a uniform fluoride concentration of 0.7 mg/L (parts per million [ppm]) for the entire United States to maintain caries (tooth decay) prevention benefits and reduce the risk of dental fluorosis.

The USPHS further noted that surveillance of dental caries (tooth decay), dental fluorosis, and fluoride intake through the National Health and Nutritional Examination Survey will be done to monitor changes that might occur following implementation of the recommendation.¹⁶

20. What is the recommendation for the maximum level of naturally occurring fluoride in drinking water contained in the 2016 EPA Six-Year Review 3?

Answer.

As established by the U.S. EPA, the maximum allowable level of naturally occurring fluoride in drinking water is 4 milligrams/liter (mg/L or ppm). Under the Maximum Contaminant Level (MCL) standard, if the naturally occurring level of fluoride in a public water supply exceeds the MCL, the water supplier is required to lower the level of fluoride below the MCL — a process called defluoridation. The MCL is a federally enforceable standard.²⁷ (Additional details regarding the EPA maximum contaminant standards can be found in the Figure 3.)

Fact.

Under the Safe Drinking Water Act (SDWA),²⁷ the EPA is required to periodically review the existing National Primary Drinking Water Regulations (NPDWRs) “not less often than every 6 years.” This review is a routine part of the EPA’s operations as dictated by the SDWA.

In April 2002, the EPA announced the results of its preliminary revise/not revise decisions for 68 chemical NPDWRs as part of its first Six-Year Review of drinking water standards.²⁸ Fluoride was one of the 68 items reviewed. While the EPA determined that it fell under the “Not Appropriate for Revision at this Time” category, the agency asked the National Academies (NA) to update the risk assessment for fluoride. Prior to this time, the National Academies’ National Research Council (NRC) completed a review

of fluoride for the EPA which was published as “Health Effects of Ingested Fluoride” in 1993.⁸

The National Research Council’s Committee on Toxicology created the Subcommittee on Fluoride in Drinking Water⁹ which reviewed toxicologic, epidemiologic, and clinical data published since 1993, and exposure data on orally ingested fluoride from drinking water and other sources (e.g., food, toothpaste, dental rinses). Based on these reviews, the Subcommittee evaluated independently the scientific and technical basis of the U.S. Environmental Protection Agency’s (EPA) maximum contaminant level goal (MCLG) of 4 milligram per liter (mg/L or ppm) and secondary maximum contaminant level (SMCL) of 2 mg/L in drinking water.

On March 22, 2006, almost three years after work began, the NRC issued a 500-page report titled *Fluoride in Drinking Water — A Scientific Review of the EPA’s Standards*⁹ to advise the EPA on the adequacy of its fluoride MCLG (maximum contaminant level goal) and SMCL (secondary maximum contaminant level) to protect children and others from adverse effects. (For additional information on the EPA maximum contaminant standards, please refer to Figure 3.) The report contained two major recommendations related to the MCLG:

In light of the collective evidence on various health end points and total exposure to fluoride, the committee concludes that EPA’s MCLG of 4 mg/L should be lowered. Lowering the MCLG will prevent children from developing severe enamel fluorosis and will reduce the lifetime accumulation of fluoride into bone that the majority of the committee concludes is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis, which are particular concerns for subpopulations that are prone to accumulating fluoride in their bones.⁹

To develop an MCLG that is protective against severe enamel fluorosis, clinical stage II skeletal fluorosis, and bone fractures, EPA should update the risk assessment of fluoride to include new data on health risks and better estimates of total exposure (relative source contribution) for individuals. EPA should use current approaches for quantifying risk, considering susceptible subpopulations, and characterizing uncertainties and variability.⁹

The 2006 NRC report⁹ contained one major recommendation related to the Secondary Maximum Contaminant Level (SMCL):

The prevalence of severe enamel fluorosis is very low (near zero) at fluoride concentrations below 2 mg/L. From a cosmetic standpoint, the SMCL does not completely prevent the occurrence of moderate enamel fluorosis. EPA has indicated that the SMCL was intended to reduce the severity and occurrence of the condition to 15% or less of the exposed population. The available data indicate that fewer than 15% of children will experience moderate enamel fluorosis of aesthetic concern (discoloration of the front teeth) at that concentration. However, the degree to which moderate enamel fluorosis might go beyond a cosmetic effect to create an adverse psychological effect or an adverse effect on social functioning is not known.⁹

Additionally, the Subcommittee identified data gaps and made recommendations for future research relevant to future revisions of the MCLG and SMCL for fluoride.⁹

It should be emphasized that the 2006 NRC report was not a review of fluoride as used in community water fluoridation. In fact, the 2006 NRC Report in Brief²⁹ states: "The committee did not evaluate the risks or benefits of the lower fluoride concentrations (0.7 to 1.2 mg/L) used in water fluoridation. Therefore, the committee's conclusions regarding the potential for adverse effects from fluoride at 2 to 4 mg/L in drinking water do not apply at the lower water fluoride levels commonly experienced by most U.S. citizens."²⁹

In response to the recommendations noted above from the NRC report, in 2011, the EPA completed and peer-reviewed a quantitative dose-response assessment based on the available data for severe dental fluorosis as recommended by the NRC.³⁰ Additionally, the EPA completed and peer-reviewed a document on the environmental exposure of children and adults to fluoride and the relative source contribution for water which is needed in order to derive the MCLG from the dose-response assessment.³⁰ These efforts were being undertaken during Six-Year Review 2 and so no action on fluoride was taken during Six-Year Review 2.

In December 2016, the EPA announced the review results for the Agency's third Six-Year Review (called Six-Year Review 3),²⁵ in which the Agency completed a detailed review of 76 national primary drinking water regulations. The regulation for naturally occurring fluoride in water was examined as part of this review and is included among the list of regulated contaminants considered to be "Low priority and/or

no meaningful opportunity" under "Not Appropriate for Revision at this Time."²⁵

The announcement of the results of the EPA's Six-Year Review 3 in the *Federal Register*³¹ indicates that, with the reviews of fluoride conducted since the first Six-Year Review (including but not limited to the 2006 NRC report and the EPA Fluoride Risk Assessment and Relative Source Contribution) and noting that other contaminants are of much greater concern, the EPA is recommending that no further action be taken at this time to change the current MCL/MCLG of 4 mg/L (the maximum level of naturally occurring fluoride allowed in drinking water).³¹

21. What is the Secondary Maximum Contaminant Level (SMCL) for naturally occurring fluoride in drinking water established by the EPA?

Answer.

The Secondary Maximum Contaminant Level (SMCL) for naturally occurring fluoride in water is 2 mg/L (or ppm). This is a non-enforceable federal standard.

Fact.

In addition to the MCL, the EPA has established a Secondary Maximum Contaminant Level (SMCL) of 2.0 mg/L and requires consumer notification by the water supplier if the naturally occurring fluoride level exceeds 2.0 mg/L. The SMCL, while not federally enforceable, is intended to alert families that regular consumption of water with natural levels of fluoride greater than 2.0 mg/L by young children could cause moderate to severe dental fluorosis in the developing permanent teeth.³² The notice to be used by water systems that exceed the SMCL must contain the following points:

1. The notice is intended to alert families that children under nine years of age who are exposed to levels of fluoride greater than 2.0 mg/liter may develop dental fluorosis.
2. Adults are not affected because dental fluorosis occurs only when developing teeth are exposed to elevated fluoride levels.
3. The water supplier can be contacted for information on alternative sources or treatments that will insure the drinking water would meet all standards (including the SMCL).³²

Figure 3. USEPA Standards and USPHS Recommendation for Fluoride in Drinking Water

U.S. Environmental Protection Agency (EPA) Standards for Fluoride in Drinking Water

The EPA standards for fluoride in drinking water apply to the **naturally occurring** fluoride in water. They are the:

- Maximum Contaminant Level Goal (**MCLG**) – 4 mg/L
- Maximum Contaminant Level (**MCL**) – 4 mg/L
- Secondary Maximum Contaminant Level (**SMCL**) – 2 mg/L

MCLG — The MCLG is the level of contaminants in drinking water at which no adverse health effects are likely to occur. This health goal is based solely on possible health risks and exposure over a lifetime with an adequate margin of safety. The current MCLG for fluoride is 4 mg/L and is set at this level to provide protection against the increased risk of crippling skeletal fluorosis.

MCL — The MCL is an enforceable standard which is set as close to the health goal as possible, considering the benefit to the public, the ability of public water systems to detect and remove contaminants using suitable treatment technologies and cost. In the case of fluoride, the MCL is set at the MCLG.

Under the MCL standard, if the naturally occurring level of fluoride in a public water supply exceeds 4 mg/L, the water supplier is required to lower the level of fluoride or defluoridate. Community water systems that exceed the fluoride MCL of 4 mg/L must notify persons served by that system as soon as practical, but no later than 30 days after the system learns of the violation.

SMCL — Secondary standards are non-enforceable guidelines regulating contaminants that may cause cosmetic effects (such as tooth discoloration). The EPA recommends secondary standards to water systems but does not require systems to comply. However, states may choose to adopt them as enforceable standards. Tooth discoloration and/or pitting is caused by excess fluoride exposures during the formative period prior to eruption of the teeth in children. The level of the SMCL was set based upon a balancing of the beneficial effects of protection from tooth decay and the undesirable effects of excessive exposures leading to discoloration.

Under the SMCL, if water exceeds 2 mg/L, the water system is to notify consumers that regular consumption of water with fluoride above 2 mg/L may increase the risk for fluorosis in young (under 9 years of age) children. Community water systems that exceed the fluoride secondary standard of 2 mg/L must notify persons served by that system as soon as practical but no later than 12 months from the day the water system learns of the exceedance.

U.S. Public Health Service (USPHS) Recommendation for Fluoride in Drinking Water

In 2015, the USPHS published a final report establishing guidance for water systems that are actively fluoridating or those that may initiate fluoridation in the future. For community water systems that add fluoride to their water, the USPHS recommends a uniform fluoride concentration of 0.7 mg/L for the entire United States to maintain caries (tooth decay) prevention benefits and reduce the risk of dental fluorosis.

Why is the EPA MCL of 4 mg/L different from the USPHS recommendation of 0.7 mg/L?

The two benchmarks have different purposes and are set under different authorities. The EPA MCL of 4 mg/L is set to protect against risks from exposure to too much fluoride. The USPHS recommended level of fluoride of 0.7 mg/L is set to promote the benefit of fluoride in preventing tooth decay while minimizing the chance for dental fluorosis.

Information Source: EPA Fact Sheet: Questions and Answers on Fluoride, 2011. Available at <https://www.epa.gov/dwsixyearreview/fact-sheet-questions-and-answers-fluoride>

➦ Additional information on these topics can be found in this Section, Questions 19, 20 and 21.

22. Does the total intake of fluoride from air, water and foods in a community in the United States with drinking water fluoridated at the recommended level pose significant health risks?

Answer.

The total intake of fluoride from air, water and foods in a community in the United States with drinking water fluoridated at the recommended level does not pose significant health risks.

Fact.

Fluoride from the Air

The atmosphere normally contains negligible concentrations of airborne fluorides. Studies reporting the levels of fluoride in air in the United States suggest that ambient fluoride contributes very little to a person's overall fluoride intake.^{9,30}

Fluoride from Water

For generations, millions of people have lived in areas where fluoride is found naturally in drinking water in concentrations as high as or higher than those recommended to prevent tooth decay. Research conducted among these people confirms the safety of fluoride in the water supply.¹⁻⁵

A ten-year comparison study of long-time residents of Bartlett and Cameron, Texas, where the water supplies contained 8.0 and 0.4 mg/L of fluoride, respectively, included examinations of organs, bones and tissues. Other than a higher prevalence of dental fluorosis in the Bartlett residents (8.0 mg/L fluoride), the study indicated that long-term consumption of fluoride from water and food sources (resident average length of fluoride exposure was 36.7 years), even at these levels more than 10 times higher than recommended for tooth decay prevention, resulted in no clinically significant physiological or functional effects.⁵

In the United States, the natural level of fluoride in ground water varies from very low levels to over 4 mg/L. Public water systems in the U.S. are monitored by the Environmental Protection Agency (EPA), which requires that public water systems not exceed a naturally occurring fluoride level of 4 mg/L.³¹ The recommended level for fluoride in drinking water in the United States has been established at 0.7 mg/L by the U.S. Public Health Service.¹⁶ This level has been

established to reduce tooth decay while minimizing the occurrence of dental fluorosis.

Individuals living in a community with water fluoridation get a portion of their daily fluoride intake from fluoridated water and a portion from dietary sources which would include foods and other beverages. Water and water-based beverages are the chief source of dietary fluoride intake. Conventional estimates are that approximately 75% of dietary fluoride comes from water and water-based beverages.^{33,34} When considering water fluoridation, an individual consuming one liter of water fluoridated at 0.7 mg/L receives 0.7 milligram of fluoride.

Fluoride in Foods

In looking at the fluoride content of foods and beverages over time, it appears that fluoride intake from dietary sources has remained relatively constant.³⁵ Except for products prepared (commercially or by the individual) or cooked with fluoridated water, the fluoride content of most foods and beverages is not significantly different between fluoridated and nonfluoridated communities. When fluoridated water is used to prepare or cook the samples, the fluoride content of foods and beverages is higher. This difference has remained relatively constant over time.^{33,35}

Launched in 2004 and updated in 2005, the National Fluoride Database is a comprehensive, nationally representative database of the fluoride concentration in 427 foods across 27 food groups and beverages consumed in the United States.³⁴ This database for fluoride was designed for use by epidemiologists and health researchers to estimate fluoride intake and to assist in the investigation of the relationships between fluoride intake and human health. The database contains fluoride values for beverages, water, and some lower priority foods.³⁴

The fluoride content of fresh solid foods in the United States generally ranges from 0.01 to 1.0 part per million.³⁵ The foods highest in fluoride are fish and shellfish, reflective of the fluoride found in ocean water, and the presence or absence of bone fragments such as those in sardines.³⁵ (Fluoride has an affinity for calcified tissues such as bones.) Cereals, baked goods, breads, and other grain products were estimated to have fluoride concentrations between 0.06 and 0.72 ppm. The majority of vegetables (leafy, root, legumes, green or yellow) have a relatively low fluoride concentration (ranging from 0.01 to 0.5 ppm)

with fruits generally having lower concentrations (ranging from 0.01 to 0.2 ppm) than in vegetables. Raisins are one exception in the fruit category with a higher fluoride concentration due to the use of certain pesticides and concentration through drying.³⁵

Brewed teas can contain fluoride concentrations of 1 ppm to 6 ppm depending on the amount of dry tea used, the water fluoride concentration and the brewing time.³⁶ The fluoride value for unsweetened instant tea powder appears very high when reported as a dry powder because this product is extremely concentrated. However, when one teaspoon of the unsweetened tea powder is added to an eight ounce cup of tap water, the value for prepared instant tea is similar to the values reported for regular brewed tea.³⁴

Foods and beverages commercially processed (cooked or reconstituted) in cities fluoridated to the recommended level generally contain higher levels of fluoride than those processed in nonfluoridated communities. These foods and beverages are consumed not only in the city where processed, but also are often distributed to and consumed in nonfluoridated areas.³⁷ This "halo" or "diffusion" effect results in increased fluoride intake by people in nonfluoridated communities, providing them increased protection against tooth decay.^{38,39} As a result of the widespread availability of these various sources of fluoride, the difference between tooth decay rates in fluoridated areas and nonfluoridated areas is somewhat less than several decades ago but this difference is still significant. Failure to account for the diffusion effect results in an underestimation of the total benefit of water fluoridation especially in areas where large amounts of fluoridated products are brought into nonfluoridated communities.³⁸

The average daily dietary intake of fluoride (expressed on a body weight basis) by children residing in communities with water fluoridated at 1.0 mg/L is 0.05 mg/kg/day (milligram per kilogram of body weight per day).⁴⁰ In communities without optimally fluoridated water, average intakes for children are about 50% lower.⁴⁰ Dietary fluoride intake by adults in communities where water is fluoridated at 1.0 mg/L averages 1.4 to 3.4 mg/day, and in nonfluoridated areas averages 0.3 to 1.0 mg/day.⁴⁰ With the 2015 recommendation that drinking water be fluoridated at 0.7 mg/L, average intakes would be 30% lower in fluoridated communities than when they were fluoridated at 1.0 mg/L.

23. How much fluoride is recommended to maximize the tooth decay prevention benefits of fluoride?

Answer.

As with all nutrients, the appropriate amount of daily fluoride intake varies with age and body weight. Fluoride is safe and effective when used and consumed properly.

Fact.

In 1997, the Food and Nutrition Board of the Institute of Medicine developed a comprehensive set of reference values for dietary nutrient intakes.⁴⁰ These new reference values, the Dietary Reference Intakes (DRI), replace the Recommended Dietary Allowances (RDA) which had been set by the National Academy of Sciences since 1941. The new values present nutrient requirements to optimize health and, for the first time, set maximum-level guidelines to reduce the risk of adverse effects from excessive consumption of a nutrient. Along with calcium, phosphorous, magnesium and vitamin D, DRIs for fluoride were established because of its proven preventive effect on tooth decay. (See Table 2 in this Question.)

The Adequate Intake (AI) establishes a goal for intake to sustain a desired indicator of health without causing side effects. In the case of fluoride, the AI is the daily intake level required to reduce tooth decay without causing moderate dental fluorosis. The AI for fluoride intake from all sources (fluoridated water, foods, beverages, fluoride dental products and dietary fluoride supplements) is set at 0.05 mg/kg/day. Using the established AI of 0.05 mg/kg, the amount of fluoride for optimal health to be consumed each day has been calculated by sex and age group (expressed as average weight).⁴⁰

The Tolerable Upper Intake Level (UL) establishes a maximum guideline. The UL is higher than the AI and is not the recommended level of intake. The UL is the estimated maximum intake level that should not produce unwanted effects on health. The UL for fluoride intake from all sources (fluoridated water, foods, beverages, fluoride dental products and dietary fluoride supplements) is set at 0.10 mg/kg/day (milligram per kilogram of body weight per day) for infants, toddlers, and children through eight years of age. For older children and adults, who are no longer at risk for dental fluorosis, the UL for fluoride is set at

Table 2. Reference Intakes for Fluoride**Food and Nutrition Board of the Institute of Medicine 1997⁴⁰**

Age Group	Reference Weights kg (lbs)*	Adequate Intake (mg/day)	Tolerable Upper Intake (mg/day)
Infants 0-6 months	7 (16)	0.01	0.7
Infants 7-12 months	9 (20)	0.5	0.9
Children 1-3 years	13 (29)	0.7	1.3
Children 4-8 years	22 (48)	1.0	2.2
Children 9-13 years	40 (88)	2.0	10.0
Boys 14-18 years	64 (142)	3.0	10.0
Girls 14-18 years	57 (125)	3.0	10.0
Males 19 years and over	76 (166)	4.0	10.0
Females 19 years and over	61 (133)	3.0	10.0

* Value based on data collected during 1988-94 as part of the Third National Health and Nutrition Examination Survey (NHANES III) in the United States.⁴⁰

10 mg/day regardless of weight. Using the established ULs for fluoride, the amount of fluoride that can be consumed each day to reduce the risk of moderate enamel fluorosis for children through age eight, has been calculated by sex and age group (expressed as average weight).⁴⁰ (See Table 2.)

As a practical example, daily intake of 2 mg of fluoride is adequate for a 9- to 13-year-old child weighing 88 pounds (40 kg). This was calculated by multiplying 0.05 mg/kg/day (AI) times 40 kg (weight) to equal 2 mg. At the same time, that 88 pound (40kg) child could consume 10 mg of fluoride a day as a tolerable upper intake level.

Children living in a community with water fluoridation get a portion of their daily fluoride intake from fluoridated water and a portion from dietary sources which would include foods and other beverages. When considering water fluoridation, an individual must consume one liter of water fluoridated at 0.7 mg/L to receive 0.7 milligrams (0.7 mg) of fluoride. Children under six years of age, on average, consume less than one-half liter of drinking water a day.³⁵ Therefore, children under six years of age would consume, on average, less than 0.35 mg of fluoride a day from drinking optimally fluoridated water (at 0.7 mg/L).

If a child lives in a nonfluoridated area and is determined to be at high risk for tooth decay, the dentist or physician may prescribe dietary fluoride supplements.⁴¹ As shown in Table 1 "Dietary Fluoride Supplement Schedule" (See Benefits Section, Question 12.), the current dosage schedule recommends supplemental fluoride amounts that are below the AI for each age group.⁴² The dosage schedule was designed to offer the benefit of decay reduction with a margin of safety to prevent mild to moderate enamel fluorosis. For example, the AI for a child 3 years of age is 0.7 mg/day. The recommended dietary fluoride supplement dosage for a child 3 years of age in a nonfluoridated community is 0.5 mg/day. This provides leeway for some fluoride intake from processed foods and beverages, and other sources.

Tooth decay rates are declining in many population groups because children today are being exposed to fluoride from a wider variety of sources than decades ago.¹⁶ Many of these sources are intended for topical use only; however, some fluoride is ingested inadvertently by children.^{42,43} By reducing the inappropriate ingestion of fluoride from toothpaste, the risk of dental fluorosis can be reduced without jeopardizing the benefits to oral health.

For example, it has been reported in a number of studies that young children inadvertently swallow an average of 0.30 mg of fluoride from fluoride toothpaste at each brushing.⁴⁴⁻⁴⁸ If a child brushes twice a day, 0.60 mg of fluoride could be ingested inappropriately. This could slightly exceed the Adequate Intake (AI) values from Table 2. The 0.60 mg consumption is 0.10 mg higher than the AI value for children 6 to 12 months and is 0.10 mg lower than the AI for children from 1-3 years of age.⁴⁰ Although toothpaste is not meant to be swallowed, children could consume the daily recommended Adequate Intake amount of fluoride from toothpaste alone. In order to decrease the risk of dental fluorosis, the American Dental Association (ADA) recommends:⁴⁹

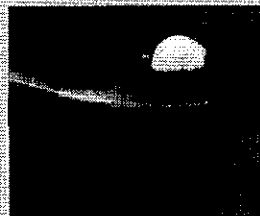
- For children younger than 3 years, caregivers should begin brushing children's teeth as soon as they begin to come into the mouth by using fluoride toothpaste in an amount no more than a smear or the size of a grain of rice (Figure 4). Brush teeth thoroughly twice per day (morning and night) or as directed by a dentist or physician. Supervise children's brushing to ensure that they use the appropriate amount of toothpaste.
- For children 3 to 6 years of age, caregivers should dispense no more than a pea-sized amount (Figure 4) of fluoride toothpaste. Brush teeth thoroughly twice per day (morning and night) or as directed by a dentist or physician. Supervise children's brushing to minimize swallowing of toothpaste.⁴⁹

⚡ Additional information on this topic can be found in this Section, Question 29.

Figure 4. Examples of Toothpaste Amounts for Children⁴⁹



For children under three years old, use no more than a smear or grain-of-rice-sized amount of fluoride toothpaste.



For children three to six years old, use only a pea-sized amount of fluoride toothpaste.

It should be noted that the amounts of fluoride discussed here are intake, or ingested, amounts. When fluoride is ingested, a portion is retained in the body and a portion is excreted.

⚡ Additional information on this topic can be found in this Section, Question 25.

24. Is there a need for prenatal dietary fluoride supplementation?

Answer.

There is no scientific basis to suggest any need to increase a woman's daily fluoride intake during pregnancy or breastfeeding to protect her health. At this time, scientific evidence is insufficient to support the recommendation for prenatal fluoride supplementation for decay prevention for infants.

Fact.

The Institute of Medicine determined that, "No data from human studies document the metabolism of fluoride during lactation. Because fluoride concentrations in human milk are very low (0.007 to 0.011 ppm) and relatively insensitive to differences in the fluoride concentrations of the mother's drinking water, fluoride supplementation during lactation would not be expected to significantly affect fluoride intake by the nursing infant or the fluoride requirement of the mother."⁴⁰

A 2005 a randomized, double blind study⁵⁰ compared the amount of fluoride incorporated into primary teeth exposed to prenatal and postnatal fluoride supplements to primary teeth that were exposed to only postnatal fluoride. The study concluded that teeth exposed to prenatal and postnatal fluoride supplements had no additional measurable fluoride other than that attributable to postnatal fluoride alone.⁵⁰ This study confirmed the findings of a 1997 randomized, double blind study that evaluated the effectiveness of prenatal dietary supplementation which concluded that the data did not support the hypothesis that prenatal fluoride had a strong decay preventive effect on primary teeth.⁵¹

25. When fluoride is ingested; where does it go?

Answer.

Much of the ingested fluoride is excreted. Of the fluoride retained, almost all is found in calcified (hard) tissues, such as bones and teeth.

Fact.

After ingestion of fluoride, such as drinking a glass of fluoridated water, the majority of the fluoride is absorbed from the stomach and small intestine into the blood stream. This causes a short-term increase in fluoride levels in the blood. Fluoride is distributed through the body by plasma (a component of blood) to hard and soft tissues. Following ingestion, the fluoride plasma levels increase quickly and reach a peak concentration within 20–60 minutes. The concentration declines rapidly, usually approximating the baseline levels within three to six hours, due to the uptake of fluoride by calcified tissues and excretion in urine. In adults, approximately 50% of the fluoride absorbed each day becomes associated with calcified tissues within 24 hours while the remainder is excreted in the urine. Approximately 99% of the fluoride present in the body is in calcified tissues (mainly bone).⁵²

Ingested or systemic fluoride becomes incorporated into forming tooth structures. Fluoride ingested regularly during the time when teeth are developing is deposited throughout the tooth structure and contributes to long lasting protection against tooth decay.^{53–57}

◆ *Additional information on this topic can be found in the Benefits Section, Question 2.*

An individual's age and stage of skeletal development will affect the rate of fluoride retention. The amount of fluoride taken up by bone and retained in the body is inversely related to age. A greater percentage of fluoride is absorbed in young bones than in the bones of older adults.⁵² However, once fluoride is absorbed into bones, it is released back into plasma (a component of blood) when fluoride levels in plasma fall. This absorption and release cycle continues throughout the life span.⁵²

26. Will drinking water that is fluoridated at the recommended level adversely affect bone health?

Answer.

According to the best available science, drinking water that has been fluoridated at the recommended level does not have an adverse effect on bone health.

Fact.

Several systematic reviews have concluded that fluoride at the level used in community water fluoridation has no adverse effect on bone health. A systematic review published in 2000 concluded that there was no clear association between water fluoridation and hip fracture.⁵⁹ Twenty-nine studies that looked at the association between bone fracture/ bone development and water fluoridation were included in the review. The evidence regarding other types of bone fractures was similar.⁵⁹ A systematic review published in 2017¹⁰ concurred with the earlier review concluding that there is evidence that fluoridated water at recommended levels is not associated with bone fracture.¹⁰

In addition to the systematic reviews, a number of individual studies have investigated the bone health of individuals residing in communities with fluoride in drinking water at the recommended levels and higher than recommended levels. Most of these studies have focused on whether there exists a possible link between fluoride and bone fractures. Additionally, the possible association between fluoride and bone cancer has been studied. None of the studies provide a legitimate reason for altering public health policy regarding fluoridation and bone health concerns.

The following studies, listed in chronological order, add to the body of evidence indicating that there is no association between consumption of optimally fluoridated water and bone fracture.

The Iowa Fluoride Study/Iowa Bone Development Study⁶⁰ looked at the association of fluoride intake with bone measures (bone mineral content and bone mineral density) in a cohort of Iowa children. Assessment of the participants' dietary fluoride intake had been ongoing since birth with parents completing detailed fluoride questionnaires at numerous time periods through 15 years of age. These children had combined fluoride intake estimated from a number of sources including water, other beverages, selected

foods, dietary fluoride supplements and fluoride toothpaste. Estimated fluoride intake was noted during different time periods and cumulatively from birth to 15 years of age. The findings indicate that fluoride exposures at typical levels for most U.S. adolescents in fluoridated areas do not have significant effects on bone mineral measures. These findings are generally comparable with those from the analyses of this cohort at age 11 years.⁶¹ During the intervening 4 years, cohort members generally experienced a substantial increase in bone mass accrual. For example, mean whole-body bone mineral content showed mean increases of approximately 61% in females and 96% in males. Despite the acceleration of bone growth near puberty, the associations between fluoride intake and bone outcome measures remained weak and none was significant after adjustment for other variables.⁶⁰

In one of the largest studies of its kind with nearly half a million subjects, Swedish researchers looked at residents' chronic consumption of various levels of fluoride and the risk of hip fracture. All individuals born in Sweden between January 1, 1900 and December 31, 1919, alive and living in their municipality of birth at the time of the start of follow-up, were eligible for the study. Information on the study population was linked to the Swedish health registers. Estimated individual drinking water fluoride exposure was stratified into 4 categories: very low, < 0.3 mg/L; low, 0.3 to 0.69 mg/L; medium, 0.7 to 1.49 mg/L; and high, $\geq$ 1.5 mg/L. Published in 2013, the researchers found Swedish residents chronically exposed to various levels of fluoride in drinking water did not show any differences in rates of either hip fracture or low-trauma osteoporotic hip fracture due to fluoride exposure.⁶²

A study published in 2005 evaluated the bone mineral density levels and rate of bone fracture of 1,300 women living in three separate communities. To be included in the study, the women had to be ambulatory. The ages of the women ranged from 20 years to 92 years. The size and demographics of the three communities were similar. One part of the study looked at whether fluoride was associated with adverse bone-related outcomes. The study measured fluoride serum levels, fluoride exposure, and bone metabolism as related to fluoride exposure and fluoride's interaction with other important bone factors including age, menopause status and medications. The study concluded that long-term exposure to fluoride was not associated with adverse effects on bone health.⁶³

A study published in 2001⁶⁴ examined the risk of bone fractures, including hip fractures associated with long-term exposure to fluoridated water in six Chinese populations. The water fluoride concentrations ranged from 0.25 to 7.97 mg/L. A total of 8,266 male and female subjects, all of whom were 50 years old or older participated in the study. The results showed an interesting and potentially important finding regarding overall bone fractures. Whereas there appeared to be a trend for higher fracture rates from 1.00 to 4.00 mg/L, the fracture rate in the 1.00 to 1.06 mg/L category was lower than the rate in the category with the lowest fluoride intake (0.25 to 0.34 mg/L). The study concluded that long-term fluoride exposure from drinking water containing 4.32 mg/L or more increases the risk of overall bone fracture, as well as hip fracture, while water fluoride levels of 1.0 to 1.06 mg/L decreased the risk of overall fractures relative to negligible fluoride in water.⁶⁴ (Note that 4.32 mg/L is more than six times the fluoride level currently recommended for community water fluoridation in the United States).

While a number of studies reported findings at a population level, both the Hillier and Phipps studies published in 2000, examined risk on an individual, rather than a community basis, taking into account other risk factors such as medications, age of menopause, alcohol consumption, smoking, dietary calcium intake and physical activity. Using these more rigorous study designs, these two studies reported no effect of the risk of hip fracture⁶⁵ and no increase in the risk of hip fracture in those drinking fluoridated water,⁶⁶ respectively.

According to the best available science, drinking water that has been fluoridated at the recommended level does not have an adverse effect on bone health.

27. What is dental fluorosis or enamel fluorosis?

Answer.

Dental fluorosis is a change in the appearance of the tooth enamel that only occurs when younger children consume too much fluoride, from all sources, over long periods when teeth are developing under the gums.³⁶ In the United States, most commonly these changes are not readily apparent to the affected individual or casual observer and require a trained specialist to detect. This type of dental fluorosis found in the United States has no effect on tooth function and can make the teeth more resistant to decay.⁶⁷ Photographs of mild dental fluorosis can be viewed at <https://www.ADA.org/en/member-center/oral-health-topics/fluoride-topical-and-systemic-supplements>. (Note that mild dental fluorosis is generally less evident than on these photographs. This is because the teeth were dried very well to improve the photography and this makes the mild dental fluorosis stand out, but if the tooth had saliva on it as it usually does, then it would be less noticeable.)

Fact.

The crown of the tooth (the part covered in enamel) is formed under the gums before the teeth erupt. Enamel formation of permanent teeth, other than third molars (wisdom teeth), occurs from about the time of birth until approximately eight years of age.⁶⁸ Because dental fluorosis occurs only while teeth are forming under the gums, teeth that have erupted are not at risk for dental fluorosis; therefore, older children and adults are not at risk for the development of dental fluorosis.⁶⁹ It should be noted that there are many other developmental changes that affect the appearance of tooth enamel which are not related to fluoride intake. In other words, not all opaque or white blemishes on teeth are caused by fluoride. Furthermore, dental fluorosis occurs among some people in all communities, even in communities that do not have community water fluoridation, or that have a low natural concentration of fluoride in their drinking water.⁷⁰⁻⁷²

Classification of Dental Fluorosis

Dental fluorosis has been classified in a number of ways. One of the most widely used classifications was developed by Dean in 1942.⁷³ (See Table 3.)

In using Dean's Fluorosis Index, each tooth in an individual's mouth is rated according to the fluorosis

index in Table 3. The individual's dental fluorosis score is based upon the most severe form of fluorosis recorded for two or more teeth. Dean's Fluorosis Index, which has been used since 1942, remains popular for prevalence studies in large part due to its simplicity and the ability to make comparisons with findings from a number of earlier studies.⁷⁴

In 2010, a report by the U.S. National Center for Health Statistics described the prevalence and changes in prevalence and severity of dental fluorosis in the United States and among adolescents between 1986–1987 and 1999–2004.⁷⁵ According to the report, in 1999 to 2004, 40.7% of adolescents had dental fluorosis. It should be noted that dental fluorosis can occur not only from fluoride intake from water but also from fluoride products, such as toothpaste, mouthrinses and excessive use of fluoride supplements during the ages when teeth are forming. A 1994 analysis of five studies showed that the amount of dental fluorosis attributable to water fluoridation at 1.0 mg/L was approximately 13%.⁷⁶ In other words, at that time the amount of dental fluorosis would have been reduced by only 13% if water was not fluoridated. Now it would be less of a reduction, since fluoridation uses the lower level of 0.7 mg/L. The majority of dental fluorosis in the U.S. is caused by the inappropriate ingestion of fluoride products.⁷⁶

The vast majority of dental fluorosis in the United States is the very mild or mild type. This type of dental fluorosis is not readily apparent to the affected individual or casual observer and often requires a trained specialist to detect. In contrast, the moderate and severe forms of dental fluorosis, characterized by esthetically (cosmetically) objectionable changes in tooth color and surface irregularities, respectively, are not common in the United States. Most investigators regard even the more advanced forms of dental fluorosis as a cosmetic effect rather than a functional adverse effect.⁴⁰ In 1993, the U.S. Environmental Protection Agency, in a decision supported by the U.S. Surgeon General, determined that objectionable dental fluorosis is a cosmetic effect with no known health effects.⁷⁷ However, in 2003, the EPA requested that the National Research Council (NRC) evaluate the adequacy of its MCLG for fluoride to protect public health. A committee was convened to review recent evidence and eventually developed the 2006 report titled, *Fluoride in Drinking Water — A Scientific Review of the EPA's Standards*.⁹ As part of that report, a majority of the committee members found severe dental fluorosis to be an adverse health

effect based on suggestive but inconclusive evidence that severe dental fluorosis (characterized by pitting of the enamel) increased the risk of tooth decay. All members of the committee agreed that the condition damages the tooth and that the EPA standard should prevent the occurrence of this unwanted condition. The prevalence of severe enamel fluorosis is very low below 2 mg/L of fluoride in drinking water in the U.S.⁹

◆ Additional information on this topic can be found in this Section, Questions 20 and 21.

The vast majority of dental fluorosis in the United States is the very mild or mild type. This type of dental fluorosis is not readily apparent to the affected individual or casual observer and often requires a trained specialist to detect.

Limited research on the psychological effects of dental fluorosis on children and adults has been conducted. However, a 2009 literature review that assessed the relationships between perceptions of dental appearance/oral health related quality of life (OHRQoL) and dental fluorosis concluded that very mild to mild dental fluorosis has little impact and in some cases evidence suggested enhanced quality of life with mild dental fluorosis.⁷⁸ When evaluating the oral health related quality of life of children by tooth decay (cavities) and dental fluorosis experience, a 2007 study concluded that cavities were associated with a negative impact while mild dental fluorosis had a positive impact on children's and parents' quality of life.⁷⁹

Very mild to mild dental fluorosis has no effect on tooth function and can make the tooth enamel more resistant to decay. A study published in 2009⁶⁷ investigated the relationship between dental fluorosis and tooth decay in U.S. schoolchildren. The study concluded that teeth with dental fluorosis were more resistant to tooth decay than were teeth without dental fluorosis. Not only should the cavity preventive benefits of fluoridation be considered when evaluating policy to introduce or retain water fluoridation, but the cavity preventive benefits of mild dental fluorosis should also be considered.⁶⁷

Very mild to mild dental fluorosis has no effect on tooth function and can make the tooth enamel more resistant to decay.

A report published in 2010⁷⁵ described the prevalence (total percentage of cases in a population) of dental fluorosis in the United States and discussed the changes in the prevalence and severity of dental fluorosis among adolescents between 1986-1987 and 1999-2004. The report used data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004 and the 1986-1987 National Survey of Oral Health in U.S. School Children. The data represented persons from 6 to 49-years of age and varied races and ethnicities including non-Hispanic black and Mexican-American persons. The oral exams for both surveys were conducted by trained dental examiners and included a dental fluorosis assessment of permanent teeth. The Dean's Fluorosis Index was used to determine the prevalence and severity of dental fluorosis.

The data published in 2010⁷⁵ showed that less than one-quarter of persons aged 6-49 in the United States had some form of dental fluorosis. For the remaining three-quarters of persons in this age group, 60.6% were unaffected by dental fluorosis and 16.5% were classified as having questionable dental fluorosis. The percent distribution of the types of dental fluorosis in persons aged 6-49 years observed was:

Very mild fluorosis	16.0%
Mild fluorosis	4.8%
Moderate fluorosis	2.0%
Severe fluorosis	less than 1%

While moderate and severe dental fluorosis comprise less than 3% of dental fluorosis in all persons aged 6-49, the prevalence of moderate or severe dental fluorosis in this age group comprised a very small portion (less than 10%) of the total number of all cases of dental fluorosis. In other words, approximately 90% of all dental fluorosis observed was very mild to mild form.⁷⁵

In regards to dental fluorosis in adolescents, children aged 12-15 years in 1999-2004 had higher prevalence of dental fluorosis compared with the same aged children in 1986-1987.⁷⁵

In reviewing this report,⁷⁵ it should be noted that dental fluorosis was not assessed in NHANES 1988–1994 and so it was not possible to compare the NHANES 1999–2002 to the earlier NHANES report. The only other previously collected national data on dental fluorosis were the 1986–1987 National Institute of Dental Research (NIDR) National Survey of Oral Health in U.S. School Children. Differences in study design between NIDR 1986–1987 and NHANES 1999–2002 should be considered when drawing inferences about changes in prevalence and severity of enamel fluorosis.⁷⁵ Examples of differences in these two surveys include but are not limited to:

- NIDR survey is a school-based survey while the NHANES is a household survey.
- NHANES did not collect residential histories; NIDR did gather residential histories but it is unknown if NIDR reported dental fluorosis data only for those with a single residence history.
- NIDR collected water samples from schools for fluoride analysis; NHANES did not collect water samples for analysis until the 2013–14 survey cycle.

As defined in Table 3, very mild dental fluorosis is characterized by small opaque, paper-white areas covering less than 25% of the tooth surface. The risk of teeth forming with the very mildest form of dental fluorosis must be weighed against the benefit that the individual will have fewer cavities thus saving dental treatment costs, avoiding patient discomfort and reducing tooth loss.^{81,82} In addition, the risk of dental fluorosis can be viewed as an alternative to having tooth decay,⁸³ which is a disease that causes cosmetic problems, pain, missed school and work, and can lead to infection and, in advanced cases, life-threatening health effects. This is in contrast to dental fluorosis which is not a disease and is not life-threatening.

The risk of teeth forming with the very mildest form of dental fluorosis must be weighed against the benefit that the individual will have fewer cavities thus saving dental treatment costs, avoiding patient discomfort and reducing tooth loss.

Table 3. Dental Fluorosis Classification by H.T. Dean – 1942⁷⁵

Classification	Criteria-Description of Enamel
Normal	Smooth, glossy, pale creamy-white translucent surface
Questionable	A few white flecks or white spots
Very Mild	Small opaque, paper-white areas covering less than 25% of the tooth surface
Mild	Opaque white areas covering less than 50% of the tooth surface
Moderate	All tooth surfaces affected; marked wear on biting surfaces; brown stain may be present
Severe	All tooth surfaces affected; discrete or confluent pitting; brown stain present

28. Is it safe to use fluoridated water to reconstitute infant formula?

Answer.

It is safe to use fluoridated water to reconstitute infant formula.

Fact.

Fluoridated water can be used to prepare infant formula. However, if the child is exclusively consuming infant formula reconstituted with fluoridated water, there could be an increased chance of mild dental fluorosis.⁸⁶ To lessen this chance, parents can use low-fluoride bottled water some of the time to mix infant formula. These bottled waters are labeled as de-ionized, purified, demineralized, or distilled. However, parents should be aware that using these types of waters exclusively means an infant does not receive the amount of fluoride the Institute of Medicine indicated is required to prevent tooth decay.⁴⁰ On the other hand, the exclusive use of nonfluoridated water to reconstitute infant formula will not guarantee that an infant will not develop dental fluorosis. The chance of development of dental fluorosis exists through approximate eight years of age when the permanent teeth are still forming under the gums. Fluoride intake from other sources during this time such as toothpaste, mouthrinse and dietary fluoride supplements also contributes to the chance of dental fluorosis for children living in nonfluoridated and fluoridated communities.⁸⁴

In response to the report of the National Research Council (NRC) *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*⁹ in November 2006, and with an abundance of caution, the ADA issued the *Interim Guidance on Fluoride Intake for Infants and Young Children* (Interim Guidance). **The Interim Guidance is no longer current and has been replaced.** Unfortunately, those opposed to fluoridation continue to publicize and use the Interim Guidance in efforts to halt fluoridation.

The *Interim Guidance* was replaced in January 2011 by the ADA *Evidence-Based Clinical Recommendations Regarding Fluoride Intake From Reconstituted Infant Formula and Enamel Fluorosis A Report of the American Dental Association Council on Scientific Affairs*.⁸⁴ The report encourages clinicians to follow the American Academy of Pediatrics guidelines for infant nutrition which advocates exclusive breastfeeding until the child is aged 6 months and continued breastfeeding until the

child is at least 12 months of age, unless specifically contraindicated. Additionally, the ADA report, designed for use by clinical practitioners, offers the following suggestions to practitioners to use in advising parents and caregivers of infants who consume powdered or liquid concentrate infant formula as the main source of nutrition:⁸⁴

- Suggest the continued use of powdered or liquid concentrate infant formulas reconstituted with optimally fluoridated drinking water while being cognizant of the potential risk of enamel fluorosis development.⁸⁹
- When the potential risk of enamel fluorosis development is a concern, suggest ready-to-feed formula or powdered or liquid concentrate formula reconstituted with water that either is fluoride free or has low concentrations of fluoride.⁸⁴

It should be noted that the Centers for Disease Control and Prevention,⁸⁵ as well as other agencies, such as the U.S. Department of Health and Human Services,⁸⁶ American Public Health Association,⁸⁷ and health departments such as the New York State Health Department⁸⁸ provide similar information regarding the use of fluoridated water to reconstitute infant formula.

29. What can be done to reduce the occurrence of dental fluorosis in the U.S.?

Answer.

The vast majority of enamel fluorosis in the United States can be prevented by limiting the ingestion of topical fluoride products (such as toothpaste) and recommending the appropriate use of dietary fluoride supplements — without denying young children the decay prevention benefits of community water fluoridation.

Fact.

Tooth decay has decreased substantially in the United States because more children today are benefitting from access to fluoride which is available from a wider variety of sources than decades ago. Many of these sources are intended for topical use only; however, when they are used, some fluoride is inadvertently swallowed by children.^{42,43,89} Inappropriate ingestion of topical fluoride can be minimized, thus reducing the risk for dental fluorosis without reducing decay prevention benefits.

Fluoride Toothpaste

Fluoride toothpastes are effective in helping to prevent tooth decay but have been identified as a major risk factor for enamel fluorosis when used inappropriately.^{42,43,89}

In order to decrease the risk of dental fluorosis, the American Dental Association (ADA) recommends:⁴⁹

- For children younger than 3 years, caregivers should begin brushing children's teeth as soon as they begin to come into the mouth by using fluoride toothpaste in an amount no more than a smear or the size of a grain of rice. (See Figure 4 in Question 23.) Brush teeth thoroughly twice per day (morning and night) or as directed by a dentist or physician. Supervise children's brushing to ensure that they use the appropriate amount of toothpaste.
- For children 3 to 6 years of age, caregivers should dispense no more than a pea-sized amount (Figure 4) of fluoride toothpaste. Brush teeth thoroughly twice per day (morning and night) or as directed by a dentist or physician. Supervise children's brushing to minimize swallowing of toothpaste.

The reason for including age information on directions for use for fluoride toothpaste is because it takes into account the ages during which teeth are most susceptible to dental fluorosis (during the time when the teeth are forming under the gums). Additionally, until approximately six years of age, children have not developed the full ability to spit and not swallow toothpaste. Inadvertently swallowing toothpaste during brushing can increase the risk of dental fluorosis. After age eight, the enamel formation of permanent teeth (with the exception of the third molars) is basically complete;⁶⁸ therefore, the risk of developing dental fluorosis is over. Because dental fluorosis occurs while teeth are forming under the gums, individuals whose teeth have erupted are not at risk for enamel fluorosis.

⚡ *Additional information on this topic can be found in this Section, Question 27.*

Numerous studies have established a direct relationship between young children brushing with more than a pea-sized amount of fluoride toothpaste and the risk of very mild or mild dental fluorosis in both fluoridated and nonfluoridated communities.^{42,43,48,71,89} It was noted that 34% of the dental fluorosis cases in a nonfluoridated community were explained by children having brushed with fluoride toothpaste more than

once per day during the first two years of life.⁹⁰ In the optimally fluoridated community, 68% of the fluorosis cases were explained by the children using more than a pea-sized amount of toothpaste during the first year of life.⁹⁰ However, recognizing that the risk tooth decay can start before a child's first birthday, it is considered important to begin using a fluoride toothpaste when the child's first tooth appears in the mouth.⁴⁹

Dietary Fluoride Supplements

A systematic review published in 2006 concluded that the use of supplements during the first six years of life, and especially during the first three years, is associated with a significant increase in dental fluorosis.⁹¹

Dietary fluoride supplements should only be prescribed for children at high risk for tooth decay who live in nonfluoridated areas.⁴¹

Dietary fluoride supplements should be prescribed according to the dosage schedule found in the *Evidence-based Clinical Recommendations on the Prescription of Dietary Fluoride Supplements for Caries Prevention: A Report of the American Dental Association Council on Scientific Affairs* published in 2010.⁴¹ The current dietary fluoride supplement schedule⁴¹ is shown in the Benefits Section, Question 12, Table 1.

Determination of the level of risk for tooth decay is accomplished through the use of a professional caries risk assessment that assists the health provider identify and assess factors that could contribute to the development of cavities.⁴¹ A child's caries (cavity) risk should be assessed on a routine basis because risk status can be affected by changes in the child's development, home conditions, dietary regimen and oral hygiene practices. Additional information on caries risk assessments can be found on the ADA website.⁹² Because of the many sources of fluoride in the diet, proper prescribing of fluoride supplements can be complex. It is suggested that all sources of fluoride be evaluated with a thorough fluoride history before supplements are prescribed for a child.⁴¹ This evaluation should include testing of the home water supply if the fluoride concentration is unknown. Families on community water systems should contact their water supplier to ask about the fluoride level. Consumers with private wells should have the water tested yearly to accurately determine the fluoride content.

⚡ *Additional information on this topic can be found in the Benefits Section, Question 4.*

Dietary fluoride supplements can be considered for infants and children aged 6 months to 16 years. Compliance with the daily administration of the supplement will enhance the cavity prevention benefits. Providers should consider and monitor the ability of the caregiver and child to adhere to the schedule. If compliance is an issue, another mode of fluoride delivery should be considered.⁴¹

Use of Over the Counter Fluoride-Containing Dental Products in the Home
Parents, caretakers and health care professionals should judiciously monitor use of all fluoride-containing dental products by children under age six. As is the case with any therapeutic product, more is not always better. The same is true for most products found in the medicine cabinet; care should be taken to adhere to label directions on fluoride prescriptions and over-the-counter products (e.g., fluoride toothpastes and rinses).

The ADA recommends the use of fluoride mouthrinses, but not for children less than six years of age because they may swallow the rinse.⁹³ These products should be stored out of the reach of children. Additional information regarding the use of mouthrinses can be found on the ADA website.⁹³

Drinking Water That Has Been Fluoridated at the Recommended Levels

In 2015, the U.S. Public Health Service made a recommendation on the level of fluoride to be used in water fluoridation (0.7mg/L) to provide the best balance of protection from tooth decay while limiting the risk of dental fluorosis.¹⁶

⚡ *Additional information on this topic can be found in this Section, Question 19.*

Drinking Water With High Levels of Naturally Occurring Fluoride

In areas where naturally occurring fluoride levels in ground water are higher than 2 mg/L, the U.S. EPA has recommended that consumers should consider action to lower the risk of dental fluorosis for young children such as providing drinking water from an alternative source.³²

Families with young children on community water systems should contact their water suppliers to ask about the fluoride level in their drinking water. Consumers with private wells should have the water tested yearly to accurately determine the fluoride content. Consumers should consult with their dentist regarding water-testing results and discuss appropriate dental health care measures.

In homes where young children (with developing permanent teeth) are faced with consuming water with a fluoride level greater than 2 mg/L, families should use an alternative primary water source that contains the recommended level of fluoride for drinking and cooking.³²

⚡ *Additional information on this topic can be found in this Section, Question 21.*

30. Why is there a warning label on a tube of fluoride toothpaste?

Answer.

The U.S. Food and Drug Administration (FDA) has established regulations for warning labels for a number of over-the-counter items it considers safe and effective including fluoride toothpaste.

Fact.

The FDA has published regulations regarding warning labels for over-the-counter (OTC) drugs in the Code of Federal Regulations (CFR).⁹⁴ All the non-prescription drugs covered by these regulations must display the general warning "Keep out of the reach of children" in bold type. The regulations outline three additional warning statements (based on the most likely route of exposure) to be listed on the label in the event the drug is misused. While they vary slightly, they all include the following language: "...get medical help or contact a Poison Control Center right away."⁹⁴

In the CFR, the FDA has outlined the drug categories to be covered by these warning labels.⁹⁵ Some of the 26 categories include antacids, allergy treatment products, antiperspirants, cold remedies, ophthalmic products and dentifrices and dental products such as analgesics, antiseptics, etc.⁹⁵

A specific FDA regulation⁹⁶ applies to "Anticaries Drug Products for Over-The-Counter Human Use" which provides the exact language for the warning label to be used on "fluoride dentifrice (gel, paste, and powder) products." The regulation requires the following language appear on these products under the heading "Warning":

"Keep out of reach of children under 6 years of age. [highlighted in bold type] If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away."⁹⁶

The over-the-counter (OTC) drugs listed in these regulations are generally recognized as safe and effective by the FDA.⁹⁴ Fluoride toothpaste is just one of a long list of OTC products that carries a warning label.

The over-the-counter (OTC) drugs listed in these regulations are generally recognized as safe and effective by the FDA. Fluoride toothpaste is just one of a long list of OTC products that carries a warning label.

While the FDA has required such label language since 1997, the ADA has required manufacturers seeking the ADA Seal of Acceptance to place a label on fluoride toothpaste since 1991 to help ensure proper use and thereby reduce the risk of dental fluorosis. At that time, the ADA required the label to include: "Do not swallow. Use only a pea-sized amount for children under six. To prevent swallowing, children under six years of age should be supervised in the use of toothpaste."

Additionally, to ensure children's safety, the ADA limits the total amount of fluoride allowed in any one tube of ADA-Accepted toothpaste. If a child were to ingest an entire tube of fluoride toothpaste at one time, the total fluoride content of a single tube is not enough to cause a fatal event. In fact, because of some of the (non-fluoride) additives in toothpaste, a child attempting to ingest a tube of toothpaste would most likely vomit before they could eat enough to become seriously ill.

31. Is fluoride, as provided by community water fluoridation, a toxic substance?

Answer.

No. Fluoride in water at the recommended level is not toxic according to the best available scientific evidence.

Fact.

Toxicity is related to dose. While large doses of fluoride could be toxic, it is important to recognize the difference between the effect of a massive dose of an extremely high level of fluoride versus the fluoride level currently recommended for public water systems. Like many common substances essential to life and good health — salt, iron, vitamins A and D, chlorine, oxygen and even water itself — fluoride can be toxic in massive quantities. Fluoride at the much lower recommended concentrations (0.7 mg/L) used in community water fluoridation is not harmful or toxic.¹⁶

Fluoride at the much lower recommended concentrations (0.7 mg/L) used in community water fluoridation is not harmful or toxic.

The single dose (consumed all at one time) of fluoride that could cause acute fluoride toxicity is 5 mg/kg of body weight (11mg/kg of body weight of sodium fluoride).⁹⁷ This dose is considered the probably toxic dose (PTD) which "is defined as the minimum dose that could cause serious or life-threatening systemic signs and symptoms and that should trigger immediate therapeutic intervention and hospitalization."⁹⁷ Acute fluoride toxicity occurring from the ingestion of optimally fluoridated water is impossible.⁹⁷ With water fluoridated at 1 mg/L, an individual would need to drink five (5) liters of water for every kilogram of body weight. For example, for an adult male (155 pound/70.3 kilogram man), it would require that he consume more than 350 liters (nearly 93 gallons) of water at one time to reach an acute fluoride dose. With optimally fluoridated water now set at 0.7 mg/L, it would take almost 30% more, or nearly 120 gallons (more than 1,900 eight ounce glasses) of water at one time to reach the acute dose.

Chronic fluoride toxicity can develop after 10 or more years of exposure to very high levels of fluoride, levels much higher than what is associated with drinking water fluoridated at recommended levels. The primary functional adverse effect associated with long-term excess fluoride intake is skeletal fluorosis.^{40,58} The development of skeletal fluorosis and its severity is directly related to the level and duration of fluoride intake. For example, the ingestion of water naturally fluoridated at approximately 5 mg/L or greater for 10 years or more is needed to produce clinical signs of osteosclerosis (a mild form of skeletal fluorosis that can be seen as a change in bone density on x-rays) in the general population. In areas naturally fluoridated at 5 mg/L, daily fluoride intake of 10 mg/day would not be uncommon.⁴⁰ A survey of X-rays from 170,000 people in Texas and Oklahoma whose drinking water had naturally occurring fluoride levels of 4 to 8 ppm revealed only 23 cases of osteosclerosis and no cases of crippling skeletal fluorosis.⁹⁸ Evidence of advanced skeletal fluorosis, or crippling skeletal fluorosis, was not seen in communities in the United States where water supplies contained up to 20 mg/L of naturally occurring fluoride.^{40,99} In these communities, "daily fluoride intake of 20 mg/day would not be uncommon."⁴⁰ Crippling skeletal fluorosis is extremely rare in the United States and is not associated with water fluoridated at the recommended level.^{40,58}

◆ Additional information on this topic can be found in this Section, Question 26.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the Superfund: National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities.¹⁰⁰ The Agency for Toxic Substances and Disease Registry (ATSDR) prepares toxicological profiles for hazardous substances that describe the effects of exposure from chemicals found at these sites and acute releases of these hazardous substances.¹⁰¹ The ATSDR provides answers to the most frequently asked questions about exposure to hazardous substances found around hazardous waste sites and the effects of exposure on human health. The Toxicological Profile for Fluorides, Hydrogen Fluoride and Fluorine indicates that subsets of the population could be unusually susceptible to the toxic effects of fluoride and its compounds at high doses, such as what might be encountered in the cleanup of a chemical spill. However, there are no data to suggest that exposure to the low levels of fluoride associated with community

water fluoridation would result in adverse effects in these potentially susceptible populations.¹⁰¹ The ATSDR's Public Health Statement on Fluorides states that "when used appropriately, fluoride is effective in preventing and controlling dental caries."¹⁰²

While large doses of fluoride could be toxic, it is important to recognize the difference in the effect of a massive dose of an extremely high level of fluoride versus the recommended amount of fluoride found in optimally fluoridated water. The implication that fluoride in large doses and fluoride in trace amounts have the same effect is completely unfounded. Many substances in widespread use are very beneficial in small amounts while toxic in large quantities.

The possibility of adverse health effects from continuous low level consumption of fluoride over long periods has been studied extensively. As with other nutrients, fluoride is safe and effective when used and consumed properly. No charge against the safety of fluoridation has ever been substantiated by generally accepted scientific knowledge. After more than 70 years of research and practical experience, the best available scientific evidence indicates that fluoridation of community water supplies is safe.

After more than 70 years of research and practical experience, the best available scientific evidence indicates that fluoridation of community water supplies is safe.

32. Does drinking water fluoridated at the recommended levels cause or accelerate the growth of cancer?

Answer.

According to the best available scientific evidence, there is no association between cancer rates in humans and drinking water that is fluoridated at the recommended levels.

Fact.

Since community water fluoridation was introduced in 1945, more than 50 epidemiologic studies in different populations and at different times have failed to demonstrate an association between fluoridation and the risk of cancer.¹ Studies have been conducted

in the United States,¹⁰³⁻¹⁰⁸ Japan,¹⁰⁹ the United Kingdom,¹¹⁰⁻¹¹² Canada¹¹³ and Australia.¹¹⁴ In addition, over the years, a number of independent bodies from around the world have conducted extensive reviews of the scientific literature and concluded that there is no relationship between fluoridation and cancer.^{1,2,4,59,115} At the beginning of the Safety Section in Question 17, a number of recent reviews are listed that have also concluded there is no relationship between fluoridation and cancer.^{10,11,13,15-18,20,21} Clearly, the best available science indicates there is no association between fluoridation and cancer.

Clearly, the best available science indicates there is no association between fluoridation and cancer.

Many of the questions about a possible association between fluoride and cancer center around a form of bone cancer called osteosarcoma. This topic is covered in the next question.

In October 2011, the California Office of Environmental Health Hazard Assessment (OEHHA) through its Carcinogen Identification Committee (CIC) determined that fluoride does not cause cancer. The review was part of California's Proposition 65 listing process.¹¹⁶ Proposition 65 was enacted in 1986 with the intent to protect California citizens and the State's drinking water sources from chemicals known to cause cancer, birth defects or other reproductive harm and to inform citizens about exposure to such chemicals. It requires the Governor to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity. The OEHHA administers meetings of the CIC and the list of items to be reviewed through the Proposition 65 process. On May 29, 2009, fluoride was selected by OEHHA for review by the CIC. Due to widespread exposure to fluoride, it was identified as one of five high priority chemicals to be evaluated. A public comment period followed. On July 8, 2011, as the next step in the Proposition 65 process, the CIC released a hazard identification document, "Evidence on the Carcinogenicity of Fluoride and its Salts". It was used by the CIC in its deliberations on whether fluoride should be listed as a carcinogen under Proposition 65. A second public comment period followed. At a public meeting on October 12, 2011, the CIC

heard additional testimony and then voted on the question, "Do you believe that it has been clearly shown, through scientifically valid testing according to generally accepted principles, that fluoride causes cancer?" The CIC's vote was unanimous (6-0) that fluoride had not been clearly shown to cause cancer.¹¹⁷

On its website, the American Cancer Society (ACS) provides a page titled, "Water Fluoridation and Cancer Risk."¹¹⁸ In question and answer format, the ACS provides basic information regarding fluoridation as well as information on a number of studies that examined the possible association between fluoridation and cancer — many of which are referenced in the opening paragraph of this Safety Section. Near the bottom of the ACS web page, under the header "Assessments by Expert Groups" is this paragraph:

The general consensus among the reviews done to date is that there is no strong evidence of a link between water fluoridation and cancer. However, several of the reviews noted that further studies are needed to clarify the possible link.¹¹⁸

33. Does fluoridated water cause osteosarcoma?

Answer.

No. The best available scientific evidence shows that fluoridated water does not cause osteosarcoma.

Fact.

In 2016, the American Society of Clinical Oncology estimated that a total of 1,000 people, including 450 children and teens younger than 20, would be diagnosed with osteosarcoma (a form of bone cancer) in the United States during the year. About 2% of all childhood cancers are osteosarcoma which most often affects those between the ages of 10 and 30. Osteosarcoma is about 50% more common in boys than girls. The 5-year survival rate for children and teens with osteosarcoma that is only in one place at the time of diagnosis is 70%.¹¹⁹

In 2014, researchers from England published the largest study ever conducted examining the possible association between fluoride in drinking water and risk of osteosarcoma or Ewing sarcoma. Analyzing 2,566 osteosarcoma cases and 1,650 Ewing's sarcoma cases from 1980 to 2005, the study found that higher

levels of natural or adjusted fluoride in drinking water in Great Britain (England, Scotland and Wales) had no impact on the incidence of either osteosarcoma or Ewing's sarcoma in people aged 0-49. Water fluoride levels ranged from near zero to a maximum of approximately 1.26 ppm.¹²⁰

A case-control study¹²¹ published in 2011 found no significant association between the fluoride levels in bone and osteosarcoma risk. Led by a Harvard researcher, the study analyzed fluoride levels in bone samples from 137 patients with primary osteosarcoma and bone samples from 51 patients with other newly-diagnosed malignant bone tumors who served as a control group. Conducted in nine U.S. hospitals over an eight-year period (1993 and 2000), the study was considered the most extensive to date on the issue. The vast majority of fluoride in the body is located in calcified tissue such as bone. The study hypothesized that if chronic exposure to fluoride was a risk factor for osteosarcoma, then those cases would have a significantly higher level of fluoride in bone than the controls. This was not the case. The major advantage of this study was the ability to use actual bone fluoride levels as a measure of fluoride intake rather than estimating fluoride exposure. Focusing on fluoride intake from water as a primary source of fluoride, in earlier studies^{122,123} members of the research team noted the difficulty in obtaining accurate information on fluoride levels of drinking water at the subjects' homes. Even when accurate information could be obtained, that information did not reflect actual consumption of water by the study subjects. Funding for the study came from three agencies of the National Institutes of Health — the National Cancer Institute, the National Institute of Environmental Health Sciences and the National Institute of Dental and Craniofacial Research.¹²¹

The best available scientific evidence shows that fluoridated water does not cause osteosarcoma (a form of bone cancer).

34. Does fluoride, as provided by community water fluoridation, inhibit the activity of enzymes in humans?

Answer.

The best available scientific evidence demonstrates that the recommended levels of fluoride in drinking water, has no effect on human enzyme activity.

Fact.

Enzymes are organic compounds that promote chemical change in the body. The best available scientific evidence has not indicated that water fluoridated at the recommended levels has any influence on human enzyme activity. There are no available data to indicate that, in humans drinking water fluoridated at the recommended levels, the fluoride affects enzyme activities with toxic consequences.¹²⁴ The World Health Organization report, *Fluorides and Human Health* states, "No evidence has yet been provided that fluoride ingested at 1 ppm in the drinking water affects intermediary metabolism of food stuffs, vitamin utilization or either hormonal or enzymatic activity."¹²⁵

In 2006, the National Research Council Report stated that the available data were not sufficient to draw any conclusions about potential effects or risks to liver enzymes from low-level long-term fluoride exposures such as those seen with community water fluoridation.⁹

The concentrations of fluoride used in laboratory studies to produce significant inhibition of enzymes are hundreds of times greater than the concentration present in body fluids or tissues.¹²⁶ While fluoride could affect enzymes in an artificial environment outside of a living organism in the laboratory, it is unlikely that adequate cellular levels of fluoride to adversely alter enzyme activities would be attainable in a living organism. The two primary physiological mechanisms that maintain a low concentration of fluoride ion in body fluids are the rapid excretion of fluoride by the kidneys and the uptake of fluoride by calcified tissues.⁵²

35. Does the ingestion of optimally fluoridated water adversely affect the thyroid gland or its function?

Answer.

The best available scientific evidence indicates optimally fluoridated water does not have an adverse effect on the thyroid gland or its function.

Fact.

A number of systematic reviews completed in the last ten years have looked at a possible association between exposure to fluoride and thyroid function.

In 2017, the Australian National Health and Medical Research Council's systematic review *Information Paper — Water Fluoridation: Dental and Other Human Health Outcomes*¹⁰ concluded, "There is no reliable evidence of an association between water fluoridation and current Australian levels and thyroid function." (Current recommendations for fluoride levels in drinking water in Australia are a range of 0.6 to 1.1 mg/L depending on climate.)¹⁰

A scientific evaluation of fluoridating agents of drinking water was done by the Scientific Committee on Health and Environmental Risks (SCHER) as requested by the European Commission (EC). The EC is the European Union's (EU) executive body with responsibility to manage EU policy. The final report, *Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water*, was released in 2011. It stated that "A systematic evaluation of the human studies does not suggest a potential thyroid effect at realistic exposures to fluoride."²⁰

In 2015, the U.S. Public Health Service Recommendation for Fluoride Concentration in Drinking Water for the Prevention of Dental Caries¹⁶ was released. It referred to the 2006 National Research Council's report, *Fluoride in Drinking Water — A Scientific Review of the EPA's Standards*,⁹ stating:

The 2006 NRC review considered a potential association between fluoride exposure (2–4 mg/L) and changes in the thyroid, parathyroid, and pineal glands in experimental animals and humans. The report noted that available studies of the effects of fluoride exposure on endocrine function have limitations. For example, many studies did not measure actual hormone concentrations, and several

studies did not report nutritional status or other factors likely to confound findings. The NRC called for better measurement of exposure to fluoride in epidemiological studies and for further research "to characterize the direct and indirect mechanisms of fluoride's action on the endocrine system and factors that determine the response, if any, in a given individual."⁹

On March 22, 2006, during the press webcast¹²⁷ for the release of the 2006 National Research Council (NRC) Report,⁹ John Doull, M.D., Ph.D., Professor Emeritus of Pharmacology and Toxicology, University of Kansas Medical Center, Kansas City and Chair of the NRC Committee was asked about the conclusions reached on fluoride and the endocrine system (which includes the thyroid). Dr. Doull replied:

The Endocrine Chapter (of the NRC Report) is a relatively new chapter. It has not been extensively reviewed previously and our feeling was that we needed to provide a baseline of all the adverse effects and a lot of the systems that hadn't really been looked at very closely. We have a chapter for example on the central nervous system which has not been reviewed in detail previously. We went through all those effects in the endocrine chapter, the thyroid effect, the parathyroid effect, calcitonin to see whether there were sufficient evidence for us to include any of those effects as specific adverse effects at 4 mg/L and the conclusion of our Committee was that those were all things we needed to worry about. Those were all things that we made recommendations for additional research. **But, none of them reached the level where we considered them to be signs of adverse effects at the 4 mg/L level.** (Emphasis added.)¹²⁷

A population-based Canadian study¹²⁸ was released in 2017 that examined the association between fluoride exposure and thyroid conditions. Data for the analysis came from Cycles 2 (2009–2011) and 3 (2012–2013) of Statistics Canada's Canadian Health Measures Survey (CHMS). The CHMS' target population is all Canadian residents between the ages of 3 and 79 living in all ten Canadian provinces. It collects health information by an individual in-home interview followed by a clinical exam conducted in a mobile clinic. The researchers' reported findings suggest that, at the population level in Canada, fluoride exposure does not contribute to impaired thyroid functioning during a time when multiple sources of fluoride exposure, including community water

fluoridation, exist. It was additionally noted that the findings could be broadly relevant to other countries with similar populations and water fluoridation.¹²⁸

In 2015, a study was published in which the authors claimed to have found a positive association between fluoride levels in drinking water and hypothyroidism. Drawing immediate criticism, the published critiques noted that a major weakness of this study was the failure to consider a number of potential confounding factors. The only confounders taken into consideration were age, sex and socioeconomic status. While acknowledging that iodine intake is associated with thyroid health, the authors failed to consider iodine as a factor along with the impacts of smoking and medications. The strong conclusion of the paper was not supported by the work of the authors or other published literature.¹³⁰⁻¹³³

In addition, two studies have explored the association between fluoridated water and cancer of the thyroid gland. Both studies found no association between optimal levels of fluoride in drinking water and thyroid cancer.^{106,110}

36. Does water fluoridation affect the pineal gland causing the early onset of puberty?

Answer.

The best available scientific evidence indicates that water fluoridation does not cause the early onset of puberty.

Fact.

The pineal gland is an endocrine gland located in the brain which produces melatonin.¹³³ Endocrine glands secrete their products into the bloodstream and body tissues and help regulate many kinds of body functions. The hormone, melatonin, plays a role in sleep, aging and reproduction.¹³⁴

A single researcher has published one study in a peer-reviewed scientific journal regarding fluoride accumulation in the pineal gland. The purpose of the study was to discover whether fluoride accumulates in the pineal gland of older adults. This limited study, conducted on only 11 cadavers whose average age at death was 82 years, indicated that fluoride deposited in the pineal gland was significantly linked to the amount of calcium in the pineal gland.¹³⁵ It would not be unexpected to see higher levels of calcium in the pineal gland of

older individuals as this would be considered part of a normal aging process. As discussed in Question 25, approximately 99% of the fluoride present in the body is associated with hard or calcified tissues.⁵² The study concluded fluoride levels in the pineal gland were not indicators of long-term fluoride exposure.¹³⁵

The same researcher had theorized in her 1997 dissertation, portions of which are posted on numerous internet sites opposed to fluoridation, that the accumulation of fluoride in children's pineal glands leads to an earlier onset of puberty. However, the researcher notes in the dissertation that there is no verification that fluoride accumulates in children's pineal glands. Moreover, a study conducted in Newburgh (fluoridated) and Kingston (nonfluoridated), New York found no statistically significant difference between the onset of menstruation for girls living in a fluoridated versus nonfluoridated area.¹³⁶ The National Research Council's 2006 report, *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*, stated that a connection between fluoride pineal function in humans remains to be demonstrated.⁹

37. Can fluoride, at the levels found in drinking water that is fluoridated to the recommended levels, alter immune function or produce an allergic reaction (hypersensitivity)?

Answer.

There is no scientific evidence of any adverse effect from fluoridation on any specific immunity, nor have there been any medically confirmed reports of allergic reaction from drinking or being in contact with optimally fluoridated water.

Fact.

There is no scientific evidence linking health conditions related to immune function such as HIV or AIDS (acquired immune deficiency syndrome) with community water fluoridation.¹³⁷

There are no confirmed cases of allergy to fluoride, or of any positive skin testing in human or animal models.¹³⁸ A committee of the National Academy of Sciences evaluated clinical reports of possible allergic responses to fluoride in 1977 and stated, "The reservation in accepting (claims of allergic reaction) at face value is the lack of similar reports in much larger numbers of people who have been exposed to considerably more fluoride than was involved in the

original observations.”⁷ The World Health Organization also judged these cases to represent “a variety of unrelated conditions” and found no evidence of allergic reactions to fluoride.^{139,140}

38. Is fluoride, as provided by community water fluoridation, a genetic hazard?

Answer.

The best available scientific evidence indicates that drinking water fluoridated at the recommended levels is not a genetic hazard.

Fact.

Chromosomes are the DNA-containing bodies of cells that are responsible for the determination and transmission of hereditary characteristics. A single chromosome contains many genes which are the functional hereditary units that occupy a fixed location on a chromosome. Many studies have examined the possible effects of fluoride on chromosome damage.

In 1993, the National Research Council (NRC) of the National Academies issued a report⁸ that supported the conclusion that drinking optimally fluoridated water is not a genetic hazard. In a statement summarizing its research⁸, the NRC stated, “in vitro data indicate that:

1. the genotoxicity of fluoride is limited primarily to doses much higher than those to which humans are exposed,
2. even at high doses, genotoxic effects are not always observed, and
3. the preponderance of the genotoxic effects that have been reported are of the types that probably are of no or negligible genetic significance.”⁸

The lowest dose of fluoride reported to cause chromosomal changes in mammalian cells was approximately 170 times that normally found in human cells in areas where drinking water was fluoridated at 1.0 mg/L, which indicates a large margin of safety.⁸ (Note that this would be 242 times greater with fluoridation now set at 0.7 mg/L.)

In its subsequent 2006 report,⁹ the NRC stated after reviewing the evidence available since its 1993 report, that the weight of evidence from studies on rodents indicated a very low probability that fluoride presents a risk of genetic mutation for humans.⁹

In addition, the 2006 NRC report⁹ indicated that the results of human studies related to fluoride and its effect on genotoxicity since its 1993 report are inconsistent and do not strongly indicate the presence or absence of genotoxic potential for fluoride. Continued research and evaluation are recommended.⁹

39. Does fluoride at the levels found in water fluoridation affect human reproduction, fertility or birth rates?

Answer.

According to the best available scientific evidence, water fluoridation does not have an adverse effect on human reproduction, fertility or birth rates.

Fact.

In 2011, the European Commission requested the European Scientific Committee on Health and Environmental Risks (SCHER) perform a critical review of fluoridating agents of drinking water. A portion of that report looked at reproductive issues. The report concluded that there is no new evidence from human studies indicating that fluoride in drinking water influences male and female reproductive capacity.²⁰

In its 2006 report,⁹ the National Research Council (NRC) indicated that since 1990, the quality and number of reproductive and developmental studies using laboratory animals have improved significantly. These high-quality studies indicate adverse reproductive and developmental effects occur only at levels of fluoride much higher than 4 mg/L.⁹ The NRC also indicated that a few studies conducted with human populations have suggested that fluoride might be associated with alterations in reproductive hormones and fertility. However, the report continued on to explain that limitations in study design, such as the lack of control of reproductive variables, make these studies of little value for risk evaluation.⁹

A study examining the relative risk of stillbirths and congenital abnormalities (facial clefts, Down syndrome and neural tube defects) found no evidence that fluoridation had any influence on the rates of congenital abnormalities or stillbirths.¹⁴¹ The study, conducted in 2003, analyzed data from two population based registries to identify all stillbirths and congenital abnormalities occurring in northeastern England between 1989 and 1998 and compared the rates of stillbirths and

specific congenital abnormalities in fluoridated and nonfluoridated communities. The study found no significant association between the occurrence of stillbirths or specific congenital abnormalities and fluoride levels in drinking water.¹⁴¹

40. For women, does drinking water fluoridated at the recommended levels create a risk for their children to be born with Down syndrome?

Answer.

There is no known association between the consumption of drinking water fluoridated at the recommended levels and Down syndrome.

Fact.

All people with Down syndrome have an extra, critical portion of chromosome 21 present in all or some of their cells. This additional genetic material alters the course of development and causes the characteristics associated with Down syndrome. The cause of the extra full or partial chromosome is still unknown. Maternal age is the major factor that has been linked to an increased chance of having a baby with Down syndrome. There is no definitive scientific research that indicates that Down syndrome is caused by environmental factors or the parents' activities before or during pregnancy.¹⁴²

However, those opposed to fluoridation sometimes still assert that consuming fluoridated tap water can cause Down syndrome.

In 2014, the systematic review published by Public Health England reviewed the literature and concluded that there was no evidence of a difference in the rate of Down syndrome in fluoridated and nonfluoridated areas.¹⁷

A number of studies have looked at this issue in the past. Several are summarized below.

A detailed study of approximately 2,500 children born with Down syndrome was conducted in Massachusetts. A rate of 1.5 cases per 1,000 births was found in both fluoridated and nonfluoridated communities, providing strong evidence that fluoridation does not increase the risk of Down syndrome.¹⁴³

Another large population-based study with U.S. national data relating to nearly 1.4 million births showed no association between water fluoridation and the incidence of congenital malformations including Down syndrome.¹⁴⁴

A comprehensive study of Down syndrome births was conducted in 44 U.S. cities over a two-year period. Rates of Down syndrome were comparable in both fluoridated and nonfluoridated cities.¹⁴⁵

41. Does ingestion of water fluoridated at recommended levels have any effect on intelligence (IQ) in children or neurological impact?

Answer.

The best available science-based evidence does not establish a causal relationship between consumption of water fluoridated at recommended levels and lowered intelligence (IQ) or behavioral disorders in children.

Fact.

A number of systematic reviews and individual studies provide evidence that consumption of optimally fluoridated water at levels recommended in the U.S. (0.7 mg/L) does not lower IQ or cause behavior problems in children. The following conclusions from a number of systematic reviews and individual studies support the safety of community water fluoridation.

A number of systematic reviews and individual studies provide evidence that consumption of optimally fluoridated water at levels recommended in the U.S. (0.7 mg/L) does not lower IQ or cause behavior problems in children.

In 2017, the Australian National Health and Medical Research Council's systematic review *Information paper — Water Fluoridation: Dental and Other Human Health Outcomes*¹⁰ concluded, "The evidence from a single study of acceptable quality shows that there is no association between water fluoridation at current Australian levels and the cognitive function of children or adults." (Current recommendations for fluoride levels in drinking water in Australia are a range of 0.6 to 1.1 mg/L depending on climate.)¹⁰

The report, *Health Effects of Water Fluoridation: An Evidence Review*, issued in 2015 by the Ireland Health Research Board noted,¹⁵ "There was only one study carried out in a non-endemic or CWF area (like Ireland) that examined fluoride and IQ. This was a prospective cohort study (whose design is appropriate to infer causality) in New Zealand. The study concluded that there was no evidence of a detrimental effect on IQ as a result of exposure to CWF (community water fluoridation)."¹⁵

In 2014, a scientific review, *Health effects of water fluoridation: A review of the scientific evidence*,¹⁸ commissioned by the New Zealand Prime Minister's Chief Science Advisor and the President of the Royal Society of New Zealand concluded: "There is no convincing evidence of neurological effects at fluoride concentrations achieved by CWF."¹⁸

At the request of the European Commission, the Scientific Committee on Health and Environmental Risks (SCHER) conducted a critical review²⁰ of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water. Their report of May 2011 reviewed animal and human studies concluding that "there is not enough evidence to conclude that fluoride in drinking water at concentrations permitted in the EU may impair the IQ of children. SCHER also agreed that a biological plausibility for the link between fluoridated water and IQ has not been established."²⁰

As noted in the preceding paragraphs, at least three systematic reviews^{10,15,18} indicated that there was only one high-quality prospective cohort study that addressed the issue of IQ. Published in 2014, a study¹⁴⁶ conducted in New Zealand followed a group of more than 1,000 people born in the early 1970s and measured childhood IQ at the ages of 7, 9, 11 and 13 years and adult IQ at the age of 38 years. Early life exposure to fluoride from a variety of sources was recorded and adjustments were made for factors potentially influencing IQ. Childhood factors associated with IQ variation included socio-economic status of parents, birth weight and breastfeeding, as well as secondary and tertiary educational achievement, which is associated with adult IQ. This detailed study revealed no evidence that exposure to water fluoridation in New Zealand affects neurological development or IQ. (Recommended levels of fluoride used in New Zealand's fluoridation program range from 0.7 mg/L to 1.0 mg/L.)¹⁴⁶

Those opposed to water fluoridation have promoted studies that reportedly show fluoridation causes lower intelligence (IQ) in children. The studies cited are often from China, Mexico, India or Iran where social, nutritional and environmental conditions are significantly different from those in the United States. The vast majority of these studies have not been published in peer-reviewed English language journals. The consensus of those who have reviewed these studies is that the quality of these studies does not stand up to scientific scrutiny. The studies are of low quality, have a high risk of bias and use a study design unsuited to prove or disprove theories. They take no or little account of other factors that are known to cause a lowering of IQ (also called confounders) such as nutritional status, socioeconomic status, iodine deficiency and consumption of other harmful elements in ground water (arsenic or lead).

At the request of the U.S. EPA, a report on fluoride in drinking water issued in 2006 by the National Research Council⁹ noted that the significance of the Chinese studies reviewed was "uncertain." "Most of the papers were brief reports and omitted important procedural details...Most of the studies did not indicate whether the IQ tests were administered in a blinded manner. Some of the effects noted in the studies could have been due to stress induced by the testing conditions. Without detailed information about the testing conditions and the tests themselves, the committee was unable to assess the strength of the studies."⁹

In England in 2009, the South Central Strategic Health Authority requested an independent critical appraisal of 19 papers and one abstract that reported an association between fluoride in drinking water and IQ in countries outside England. The appraisal¹⁴⁷ noted that the study design and methods used by many of the researchers in these studies had serious limitations. The researchers also exhibited a lack of a thorough consideration of confounding factors as a source of bias in the results. From these studies alone, it was "uncertain how fluoride was responsible for any impairment in intellectual development." Significant differences were noted in conditions between the communities studied and conditions in England. For example, some studies noted high levels of naturally occurring fluoride in drinking water and exposure to fluoride from other sources including the practice of burning high fluoride coal to heat poorly ventilated homes in China. Additionally, in many cases, there were stark differences in other environmental conditions and socioeconomic characteristics.¹⁴⁷

In November 2016, those opposed to fluoridation filed a legal petition¹⁴⁸ with the U.S. Environmental Protection Agency (EPA) in Washington, D.C. calling for the EPA to ban the addition of fluoridating chemicals to public drinking water on the grounds that a large body of animal, cellular, and human research showed that fluoride is neurotoxic at doses within the range now seen in fluoridated communities in the U.S. (0.7 mg/L). The EPA responded to the petition in February 2017 noting, "After careful consideration, EPA denied the TSCA section 21 petition, primarily because EPA concluded that the petition has not set forth a scientifically defensible basis to conclude that any persons have suffered neurotoxic harm as a result of exposure to fluoride in the U.S. through the purposeful addition of fluoridation chemicals to drinking water or otherwise from fluoride exposure in the U.S."¹⁴⁸ As allowed under the TSCA process, the petitioners filed a lawsuit challenging the EPA ruling in April 2017 in the U.S. District Court for the Northern District of California at San Francisco. In late 2017, a federal judge denied an EPA motion to dismiss the lawsuit.

In 2017 a study from Mexico City¹⁴⁹ received some coverage in the popular press. The authors concluded higher urinary fluoride levels of pregnant women were associated with lower scores on tests of cognitive function in their children. This was an observational study that by definition could only show a possible association between fluoride exposure and IQ — not cause and effect. This small study did not adequately address a number of potential confounders that might explain the possible association such as breast feeding, maternal age, gestational age, birth weight and education as well as exposures to lead, mercury, arsenic and iodine that affect IQ and other measures of cognitive ability. Unlike conditions in the U.S., the pregnant women participating in the study were exposed to varied fluoride levels from naturally occurring fluoride in the water supply (in some cases at levels almost twice as high as the level recommended for community water fluoridation in the U.S.) and fluoridated salt.¹⁴⁹

Additional research on this topic is underway through the National Toxicology Program's systematic review using animal studies to evaluate potential neurobehavioral effects from exposure to fluoride during development. Initiated in 2015, work continued in 2017.²³

42. Does drinking fluoridated water increase the level of lead in the blood or cause lead poisoning in children?

Answer.

The best available scientific evidence has not shown any association between water fluoridation and blood lead levels.

Fact.

A number of reviews and data analyses indicate no association between water fluoridation and blood lead levels.

In 2011, the European Commission requested that the European Scientific Committee on Health and Environmental Risks (SCHER) perform a critical review of fluoridating agents of drinking water. The committee concluded that "it is highly unlikely that there would be an increased release of lead from pipes due to hexafluorosilicic acid."²⁰ Hexafluorosilicic acid is another name for fluorosilicic acid which is one of the additives used to fluoridate water in the U.S.

 *Additional information on this topic can be found in the Fluoridation Practice Section, Question 49.*

A 2006 study analyzed data from the Third National Health and Nutrition Examination Survey (1988–1994) and the 1992 Fluoridation Census to evaluate the relationship between water fluoridation and lead concentrations in children. The study concluded that the results did not support that the silicofluorides used in community water systems caused higher lead concentrations in children.¹⁵⁰

According to the Centers for Disease Control and Prevention,¹⁵¹ the average blood lead levels of young children in the U.S. have continued to decline since the 1970s primarily due to lead poisoning prevention laws such as the phase-out of leaded paint and leaded gasoline. The primary remaining sources of childhood lead exposure are deteriorated leaded paint, house dust contaminated by leaded paint and soil contaminated by leaded paint and/or decades of industrial and motor vehicle emissions. Besides exposure to lead paint in older homes, lead water pipes and fixtures also can be found in homes built before 1978. In some areas of the country, folk remedies and pottery also add to lead exposure.¹⁵¹ Findings from the National Health and Nutrition

Examination Surveys (NHANES) from 1976–1980 to 2003–2008 show that the percentage of children aged 1- to 5-years-old having high lead blood levels ($\geq 10 \mu\text{g/dL}$) declined dramatically from 88.2% to 0.9%.¹⁵² During that same time period (1976 to 2008), the percentage of the U.S. population receiving fluoridated water rose from approximately 48.8% to 64.3%.¹⁵³ Moreover, in the 1991–1994 NHANES, the overall (all age groups) prevalence of high lead blood levels ($\geq 10 \mu\text{g/dL}$) was 2.2% but decreased to 0.7% by the 1999–2002 survey.¹⁵¹ While antifluoridationists claim that fluoridated water increases lead blood levels in children, the fact is that since 1976 while the use of water fluoridation has increased, the percentage of children in the U.S. with high lead blood levels actually has continued to decrease substantially. This demonstrates that the claim made by those opposed to water fluoridation that fluoride in water increases lead concentrations in children is unfounded. It should be noted that approximately 95% of the primary sources of adult lead exposure are occupational.¹⁵⁴ In general, adult blood lead levels have continued to decline over recent decades due largely to improved prevention measures in the workplace and changes in employment patterns.¹⁵⁴

Those opposed to water fluoridation sometimes claim that there is an increase in acidity when fluoride is added to water and that the acidic water in the system leaches lead from pipes and fixtures. The process of adding fluoride to water has minimal impact on the acidity or pH of drinking water. Under some water quality conditions, a small increase in the acidity of drinking water that is already slightly acidic can be observed after treatment with alum, chlorine, fluorosilicic acid or sodium fluorosilicate. In such cases, additional water treatment to adjust the pH to neutralize the acid in water distribution systems is standard practice in water plants.¹⁵⁵ Water facilities typically maintain a pH of between 7.0 and 8.0 as standard practice indicating that the water leaving the plant is slightly alkaline and non-acidic.¹⁵⁶

Despite this information, antifluoridationists continue to exploit their unfounded claims that fluoridation can lead to an increased uptake of lead by children. A 1999 study¹⁵⁷ charged that fluorosilicic acid and sodium silicofluoride did not disassociate completely when added to water systems and could be responsible for lower pH (more acidic) levels of drinking water, leaching lead from plumbing systems

and increasing lead uptake by children. In response to the study, scientists from the EPA reviewed the basic science that was the foundation for the claim that silicofluorides leach lead from water pipes and found that many of the chemical assumptions made in the original ecological study were scientifically unjustified.¹⁵⁸ Fluoride additives do disassociate very quickly and completely release fluoride ions into the water. The research from the 1999 study was inconsistent with accepted scientific knowledge and the authors of that study failed to identify or account for those inconsistencies. The EPA scientists discounted the 1999 study and said there were no credible data to suggest any link between fluoridation and lead. Overall, the EPA scientists concluded that “...no credible evidence exists to show that water fluoridation has any quantifiable effects on the solubility, bioavailability, bioaccumulation, or reactivity of lead compounds.”¹⁵⁸

43. Does drinking water fluoridated at recommended levels cause Alzheimer's disease?

Answer.

The best available scientific evidence has not indicated an association between drinking optimally fluoridated water and Alzheimer's disease.

Fact.

Scientists believe the causes of late-onset Alzheimer's, the most common form of the disease, include a combination of age-related brain changes, genetic, lifestyle, and environmental factors. The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's could differ from person to person. Early-onset Alzheimer's is less common (fewer than 10% of Alzheimer's cases) with the first signs of the disease typically appearing between an individual's 30s and mid-60s. It is believed to be caused primarily by gene changes passed down from parent to child.¹⁵⁹

A study published in 1998¹⁶⁰ raised concerns about the potential relationship between fluoride, aluminum and Alzheimer's disease. However, several flaws in the study's experimental design precluded any definitive conclusions from being drawn.¹⁶¹ Concerns were noted about a number of aspects of the protocol including, but not limited to, the high percentage of the test rodents dying during the study and that

the researchers failing to account for the high levels of aluminum and fluoride in the chow fed to all test rodents.¹⁶¹ For decades, a small number of researchers have implicated aluminum in the development of late-onset Alzheimer's disease. However, the "Aluminum Hypothesis" has been abandoned by the majority of mainstream scientists.¹⁶²

In 2000, a study¹⁶³ investigated the relationships between trace elements in drinking water and the thought processes of 1,016 subjects over the age of 65 living in two rural areas of China. In today's U.S. society, people are very mobile and tend to live in multiple places during their lifetimes. In contrast, the rural residents of China rarely move and so in this study the researchers were able to assume that this elderly population had used the same water and food sources throughout their lifetimes. The researchers evaluated the effects on thought processes of seven elements (cadmium, calcium, fluoride, iron, lead, selenium and zinc) found in the water sources at the two study sites. The study assessed thought processes in three areas (memory, language and attention) using a Chinese translation of the Community Screening Interview for Dementia. Taking into account the effects of the seven trace elements, the authors concluded that fluoride is not significantly related to impairment of thought processes such as is seen in Alzheimer's disease.¹⁶³

44. Does drinking water fluoridated at recommended levels cause or contribute to heart disease?

Answer.

Drinking water fluoridated at recommended levels is not a risk factor for heart disease.

Fact.

The American Heart Association identifies aging, male gender, heredity, cigarette and tobacco smoke, high blood cholesterol levels, high blood pressure, physical inactivity, obesity and diabetes mellitus as major risk factors for cardiovascular disease.¹⁶⁴

The American Heart Association's website notes: "No evidence exists that adjusting the fluoride content of public water supplies to a level of about one part per million has any harmful effect on the cardiovascular system."¹⁶⁵

A number of historical studies have evaluated urban mortality in relation to fluoridation status. Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health examined a wide range of data from communities that had naturally high levels, optimal levels and low levels of fluoride in water. The results of their analysis published in 1972¹⁶⁶ concluded, "Thus, the evidence from comparison of the health of fluoridating and nonfluoridating cities, from medical and pathological examination of persons exposed to a lifetime of naturally occurring fluorides or persons with high industrial exposures, and from broad national experience with fluoridation all consistently indicate no adverse effect on cardiovascular health."¹⁶⁶ Two additional studies were published in 1978. In the first study,¹⁶⁴ the mortality trends from 1950-70 were studied for 473 cities in the United States with populations of 25,000 or more. Findings showed no relationship between fluoridation and heart disease death rates over the 20-year period.¹⁶⁴ In the second study,¹⁶⁵ the mortality rates for approximately 30 million people in 24 fluoridated cities were compared with those of 22 nonfluoridated cities for two years. No evidence was found of any harmful health effects, including heart disease, attributable to fluoridation.¹⁶⁵

The misinterpretation of the results of a study by those opposed to fluoridation¹⁶⁷ led the opposition to claim that "research highlights the fact that mass fluoride exposure may be to blame for the cardiovascular disease epidemic that takes more lives each year than cancer."¹⁶⁷ In fact, the study published in Nuclear Medicine Communications in January 2012¹⁶⁸ examines the possible benefits of using a sodium fluoride isotope marker in testing to determine the presence of atherosclerosis and risk for coronary disease. In this case, fluoride's affinity for calcified tissue aided in the location of calcium deposited in arterial walls which could be associated with an increased risk of coronary artery disease. The study made no reference to any relationship between the consumption of fluoridated water and heart disease.¹⁶⁸

45. Is the consumption of water fluoridated at recommended levels harmful to kidneys?

Answer.

Consuming water fluoridated at recommended levels has not been shown to cause or worsen kidney disease.

Fact.

Approximately 60% of the fluoride absorbed daily by adults (45% for children) is removed from the body by the kidneys.⁵² Because the kidneys are constantly exposed to various fluoride concentrations, any health effects caused by fluoride would likely manifest themselves in kidney cells. However, several large community-based studies of people with long-term exposure to drinking water with fluoride concentrations up to 8 ppm have failed to show an increase in kidney disease.^{5,136,169}

In a report issued in 1993 by the National Research Council (NRC), the Subcommittee on Health Effects of Ingested Fluoride stated that the threshold dose of fluoride in drinking water which causes kidney effects in animals is approximately 50 ppm — more than 12 times the maximum level allowed in drinking water by the Environmental Protection Agency. Therefore, they concluded that “ingestion of fluoride at currently recommended concentrations is not likely to produce kidney toxicity in humans.”⁸ Furthermore, the NRC report on fluoride in drinking water issued in 2006 concluded that there were no published studies that demonstrate that drinking water fluoridated at recommended levels can damage kidneys. The report further concluded that fluoride concentrations need to be higher than 4 ppm to affect kidney tissues and function.⁹

A review of scientific studies completed in 2007 for Kidney Health Australia (KHA),¹⁷⁰ summarized findings from the recent literature related to the health effects of fluoridated water for people with chronic kidney disease (CKD). The purpose of the review was to provide an up to date summary of studies on the topic so that KHA, the leading organization in Australia that promotes kidney and urinary tract health, could develop a fluoride position paper. The review concluded that while studies on the topic are limited, “there is no evidence that consumption of optimally fluoridated drinking water increases the risk of developing CKD.” For those people who have CKD, the report stated that “there is no evidence that

consumption of optimally fluoridated drinking water poses any health risks for people with CKD, although only limited studies addressing this issue are available.” There is limited evidence that people with advanced CKD (stages 4 or 5) “who ingest substances with a high concentration of fluoride may be at risk of fluorosis.” Accordingly, the report recommended that it would be “prudent” for patients with advanced CKD to monitor fluoride intake and avoid fluoride-rich substances. These conclusions are the basis for KHA’s position statement on fluoride which was released in 2007.¹⁷⁰ The position statement was updated in 2011 and concluded that “there has been no new published evidence to contradict the 2007 KHA Position Statement.”¹⁷¹

According to information on their website, the National Kidney Foundation is the leading organization in the U.S. dedicated to the awareness, prevention and treatment of kidney disease. A paper titled *Fluoride Intake in Chronic Kidney Disease* dated April 15, 2008,¹⁷² developed by the National Kidney Foundation (NKF) and posted on the NKF website includes the following points under the header “Analysis and Recommendations”:

- Dietary advice for patients with CKD should primarily focus on established recommendations for sodium, potassium, calcium, phosphorus, energy/calorie, protein, fat, and carbohydrate intake. Fluoride intake is a secondary concern.
- Individuals with CKD should be notified of the potential risk of fluoride exposure by providing information on the NKF website including a link to the Report in Brief of the National Research Council and the Kidney Health Australia position paper. The risk is likely greatest in areas with naturally high water fluoride levels.
- The NKF has no position on the optimal fluoridation of water. The oral health of people with CKD is certainly of interest to the NKF, but balancing the overall benefits and risks of fluoride exposure is the primary concern.¹⁷²

Many people with kidney failure depend on hemodialysis (treatment with an artificial kidney machine) for their survival. During hemodialysis, the patient’s blood is exposed to large amounts of water each week (280–560 quarts). Therefore, procedures have been designed to ensure that the water utilized in the process contain a minimum of dissolved substances that could diffuse indiscriminately into

the patient's bloodstream.¹⁷³ Both KHA and the NKF recommend careful monitoring of hemodialysis systems to ensure proper mechanical function.^{170,172} Since the composition of water varies in different geographic locations in the United States, the U.S. Public Health Service recommends dialysis units use techniques such as reverse osmosis and de-ionization to remove excess iron, magnesium, aluminum, calcium, and other minerals, as well as fluoride, from tap water before the water is used for dialysis.¹⁷³

46. What are some of the erroneous health claims made against water fluoridation?

Answer.

From sources such as the internet, newsletters, social media and personal anecdotes in emails, it is frequently claimed that community water fluoridation causes the following adverse health effects:

- AIDS
- Allergic Reactions (e.g., loss of hair, skin that burns and peels after contact with fluoridated water)
- Accelerated Aging
- Alzheimer's disease
- Arthritis
- Asthma
- Autism
- Behavioral Problems (e.g., attention deficit disorders)
- Bone Disease (e.g., osteoporosis – increased bone/hip fractures)
- Cancer (all types including osteosarcoma or bone cancer)
- Chronic Bronchitis
- Colic (acute abdominal pain)
- Cystic Fibrosis
- Down Syndrome
- Emphysema
- Enzyme Effects (gene-alterations)
- Flatulence (gas)
- Gastrointestinal Problems (irritable bowel syndrome)
- Harmful Interactions with Medications
- Heart Disease
- Increased Infant Mortality
- Low Birth Weight for Infants
- Kidney Disease
- Lead Poisonings
- Lethargy (lack of energy)
- Lower IQ scores

- Malpositioned Teeth
- Parkinson's Disease
- Calcification of the Pineal Gland (causing early puberty) (chronic insomnia);
- Reproductive issues (damaged sperm) (reduced fertility)
- Skin Conditions (redness, rash/welts, itching)
- Sudden Infant Death Syndrome (SIDS)
- Thyroid Problems (goiter and obesity due to hypothyroidism)

AND

- Tooth Decay

Fact.

As discussed throughout this document, the best available scientific evidence consistently has indicated that fluoridation of community water supplies is safe and effective. The possibility of any adverse health effects from continuous low-level consumption of fluoride has been and continues to be studied extensively. Of the thousands of credible scientific studies on fluoridation, none has shown health problems associated with the consumption of optimally fluoridated water.

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Fluoridation Practice

47. Who regulates?	75	52. System safety concerns?	79
48. Standards for additives?	76	53. Engineering?	80
49. Lead, arsenic and other contamination?	77	54. Corrosion of water pipes?	81
50. Additives safety?	78	55. Damage to water facilities?	81
51. Source of additives?	78	56. Environment?	82

47. Who regulates drinking water additives in United States?

Answer.

The United States Environmental Protection Agency (EPA) regulates drinking water additives.

Fact.

In 1974, Congress passed the Safe Drinking Water Act (SDWA) which protects the public's health by regulating the nation's public drinking water supply.¹ The SDWA, as amended in 1986 and 1996,¹ requires the Environmental Protection Agency (EPA) to ensure the public is provided with safe drinking water.¹ On June 22, 1979, the Food and Drug Administration (FDA) and the EPA entered into a Memorandum of Understanding (MOU) to clarify their roles and responsibilities in water quality assurance.² The stated purpose of the MOU is to "avoid the possibility of overlapping jurisdiction between the USEPA and FDA with respect to control of drinking water additives." The two agencies agreed that the Safe Drinking Water Act's passage in 1974 implicitly repealed FDA's jurisdiction over drinking water as a 'food' under the Federal Food, Drug and Cosmetic Act (FFDCA). Under the MOU, EPA enjoys exclusive regulatory authority over drinking water provided by public water systems, including any additives in such water. FDA retains jurisdiction over bottled drinking water under Section 410 of the FFDCA and "over water (and substances in water) used in food or food processing once it enters the food processing establishment."²

While drinking water from the tap is regulated by the EPA, bottled water is regulated by the FDA which has established standards for its quality.² The FDA has noted that fluoride can occur naturally in source waters used for bottled water or may be added by a

bottled water manufacturer. Recognizing the benefit of fluoride in water, the FDA has stated that bottled water that meets specific standards of identity and quality set forth by FDA, and the provisions of the authorized health claim related to fluoride, may be labeled with the following health claim: "Drinking fluoridated water may reduce the risk of [dental caries or tooth decay]."³

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From time to time, states and communities have had to deal with legislation or ballot initiatives aimed at requiring the approval of the FDA before any agent can be added to community water systems. Often referred to as the Fluoride Product Quality Control Act, Water Product Quality Ordinance or Pure Water Ordinance, the legislation is specifically used by those opposed to water fluoridation as a tool to prevent water systems from providing community water fluoridation. Often this legislation does not specifically

mention fluoride or fluoridation. Those supporting this type of legislation may claim that they are not against water fluoridation but are proponents of pure water and do not want anything added to water that has not been approved by the FDA. On the surface, this may appear to be a "common sense" approach. However, its only real purpose is to defeat efforts to provide water fluoridation. That is because this proposed legislation would require the FDA — which does NOT regulate public water systems — to approve any water additive. By mistakenly (and perhaps craftily) naming the wrong federal agency, the probable outcome is to stop or prevent water fluoridation.

48. What standards have been established to ensure the safety of fluoride additives used in community water fluoridation in the United States?

Answer.

The three fluoride additives used in the U.S. to fluoridate community water systems (sodium fluoride, sodium fluorosilicate, and fluorosilicic acid) meet safety standards established by the American Water Works Association (AWWA) and NSF International (NSF).⁴

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Fact.

Additives used in water treatment meet safety standards prepared in response to a request by the Environmental Protection Agency to establish minimum requirements to ensure the safety of products added to water for its treatment, thereby ensuring the public's health.⁴ Specifically, fluoride additives used in water fluoridation meet standards established by the American Water Works Association (AWWA) and NSF International (NSF).⁴ Additionally, the American National Standards Institute (ANSI) endorses both AWWA and NSF standards for fluoridation additives and includes its name on these standards.⁴

The American Water Works Association⁵ is an international nonprofit scientific and educational society dedicated to providing total water solutions to assure the effective management of water. Founded in 1881, the AWWA is the largest organization of water supply professionals in the world. The membership represents the full spectrum of the water community: public water and wastewater systems, environmental advocates, scientists, academicians, and others who hold a genuine interest in water. AWWA unites the diverse water community to advance public health, safety, the economy, and the environment.⁵

NSF International,⁶ an independent, accredited organization, is dedicated to being the leading global provider of public health and safety-based risk management solutions. Manufacturers, regulators and consumers look to NSF to develop public health standards and certifications that help protect food, water, consumer products and the environment. Its professional staff includes microbiologists, toxicologists, chemists, engineers, and environmental and public health professionals. Founded in 1944 as the National Sanitation Foundation, NSF's mission is to protect and improve global human health.⁶

The American National Standards Institute (ANSI)⁷ is a private, non-profit organization that administers and coordinates the U.S. voluntary standardization and conformity assessment system. The Institute's mission is to enhance both the global competitiveness of U.S. business and the U.S. quality of life by promoting and facilitating voluntary consensus standards and conformity assessment systems, and safeguarding their integrity.⁷

The AWWA documents provide manufacturers, suppliers and purchasers with standards for the manufacturing, quality and verification for each of the three fluoride additives listed below. The AWWA standards set the physical, chemical and impurities standards including information on verification of the standard requirements and requirements for delivery.⁴

- ANSI/AWWA B701 Sodium Fluoride
- ANSI/AWWA B702 Sodium Fluorosilicate
- ANSI/AWWA B703 Fluorosilicic Acid⁴

NSF/ANSI Standard 60^{4,6} provides for purity of drinking water additives as it limits an additive's contribution of harmful contaminants to drinking water. The Standard also provides for safety assurances from production through distribution to ensure product quality is maintained. Additionally, the Standard requires documentation of the purity of the additives including specific criteria for products imported from other countries. NSF/ANSI Standard 61^{4,6} is a related standard that provides guidance for equipment/products used in water treatment plants that come in contact with drinking water. Both NSF/ANSI standards were developed by a consortium of associations including NSF, AWWA, the Association of State Drinking Water Administrators and the Conference of State Health and Environmental Managers with support from the U.S. Environmental Protection Agency.⁴

Fluoride additives, like all of the more than 40 additives typically used in water treatment, are "water grade" additives. All additives used at the water plant are classified as water grade additives meeting NSF Standard 60 requirements. Examples of other "water grade" additives which are commonly used in water plant operations are chlorine (gas), ferrous sulfate, hydrochloric acid, sulfur dioxide and sulfuric acid.⁸

Sometimes antifluoridationists express the view that they are not really opposed to fluoridation, but are opposed to the use of "industrial grade" fluoride additives. They may even go so far as to state that they would support fluoridation if the process was implemented with pharmaceutical grade fluoride additives that were approved by the U.S. Food and Drug Administration (FDA). On the surface, this may appear to be a "common sense" approach. In fact, this is usually a ploy whose only real purpose is to stop fluoridation. First, the EPA, not the FDA, has regulatory authority for additives used in public water systems. Second, and perhaps most importantly, the U.S. Pharmacopeia (USP) monograph on sodium fluoride does not provide for certification of quality by an independent credentialing body.^{4,9} Third, the USP and The National Formulary (USP-NF) standards used to formulate prescription drugs are not appropriate for water fluoridation additives as they could actually allow higher levels of contaminants to be introduced into drinking water than is allowed by the current EPA standards.^{4,9} According to the CDC:⁹

The USP does not provide specific protection levels for individual contaminants, but establishes a relative maximum exposure level for a group of related contaminants. Some potential impurities have no restrictions by the USP, including arsenic, some heavy metals regulated by the U.S. EPA, and radionuclides. Given the volumes of chemicals used in water fluoridation, a pharmaceutical grade of sodium fluoride for fluoridation could potentially contain much higher levels of arsenic, radionuclides, and regulated heavy metals than an NSF/ANSI Standard 60-certified product.

⚡ *Additional information about this topic can be found in this Section, Question 49.*

Lastly, USP-grade sodium fluoride product is more likely to result in water plant personnel being exposed to fluoride dust as it is more powder-like than the preferred AWWA-grade sodium fluoride which is crystalline and so minimizes dusting when handled.⁴

⚡ *Additional information about this topic can be found in this Section, Question 52.*

49. Does fluoridating the community water supply raise concerns about lead, arsenic and other toxic contaminants to the water supply?

Answer.

No. The concentrations of contaminants in drinking water as a result of fluoridation do not exceed, but are in fact, well below regulatory standards set to ensure the public's safety.

Fact.

Fluorosilicic acid is used to fluoridate the majority of community water systems in the United States.¹⁰ Because the additive is derived from ore mined from the earth, fluorosilicic acid may contain minute amounts of contaminants such as lead and arsenic. However, existing regulations and standards require that these contaminants, and others, be at levels considered acceptable by the U.S. Environmental Protection Agency when the fluorosilicic acid or other fluoridation additives are diluted to produce optimally fluoridated water.⁶ NSF International and the American National Standards Institute (NSF/ANSI) Standard 60 as well as AWWA standards are applicable to all fluoride additives.^{4,6}

Testing of fluoride additives provides evidence that the levels of these contaminants do not exceed, but are in fact, well below regulatory standards set to ensure the public's safety. NSF has prepared a detailed fact sheet, *NSF Fact Sheet on Fluoridation Products* (2013)¹¹ that provides the documented quality of fluoride additives based on product samples analyzed. The NSF reports that the majority of fluoridation products as a class, based on NSF test results, do not add measurable amounts of arsenic, lead, or other heavy metals, or radionuclides to drinking water.^{9,11}

50. Have fluoride additives been tested for safety?

Answer.

The claim is sometimes made that no studies on safety exist on the additives used in water fluoridation. This statement is a ruse because the scientific community does not study the health effects of the concentrated additives; studies are done on the health effects of the treated water.

Fact.

A 1999 study¹² charged that fluorosilicic acid and sodium silicofluoride did not disassociate (break down) completely when added to water systems and may be responsible for lower pH (acid) levels of drinking water, leaching lead from plumbing systems and increasing lead uptake by children. Scientists from the U.S. Environmental Protection Agency (EPA) evaluated the disassociation of fluoride additives¹³ and concluded that at the typical pH level of drinking water (which is normally slightly alkaline) and the fluoride levels used in drinking water, the fluoride additives quickly and completely broke down to fluoride ions and silica.

Published in 2006,¹⁴ researchers at the University of Michigan verified for the EPA that theoretical predictions that hexafluorosilicate completely hydrolyzed (broke down) when added to water separating into free fluoride ions and silica ions were confirmed. The research demonstrated that there was no hexafluorosilicate that could be measured in the finished water.¹⁴

While sodium fluoride was the first additive used in water fluoridation, the use of silicofluoride additives (sodium fluorosilicate and fluorosilicic acid) began in the late 1940s. By 1951, silicofluorides had become

the most commonly used fluoride additives in water fluoridation.¹⁵ Many of the early studies on the health effects of fluoridation were completed in communities that were using the silicofluoride additives, most generally fluorosilicic acid.¹⁶⁻²¹ However, at that time, the additives used to fluoridate were not always identified in research reports. As the body of research on fluoridation grew, it became evident that there were no adverse health effects associated with water fluoridation regardless of which fluoride additive was used. Additionally, over time, a number of comprehensive reviews of the health effects of fluoridation were published. These reviews which support the safety of water fluoridation include many studies conducted in large fluoridated communities which used the silicofluoride additives.²²⁻²⁹

There is now more than 70 years of practical experience that lends additional credence to the best available science that concludes that fluoridation is safe.

51. What is the source of the additives used to fluoridate water supplies in the United States?

Answer.

The majority of fluoridation additives used in the United States are derived from the mineral apatite (a component of calcium phosphate).

Fact.

About 95% of the fluoridation additives used in water fluoridation are by-products which come from the processing of calcium phosphate into phosphate fertilizer. About 4% are derived from the processing of calcium fluoride and the remaining 1% derived from the production of high-purity silica.*

In the production of phosphate fertilizer, calcium phosphate ore (which contains apatite) is mixed with sulfuric acid resulting in a calcium sulfate (gypsum) slurry. The gaseous phosphoric acid released from this process is collected by vacuum extraction, condensed and then desiccated (dried) and formed into phosphate fertilizer pellets. Fluoride is a trace constituent (3-7%) of the mineral apatite found in calcium phosphate ore. Silica tetrafluoride is also released as a gas in the creation of the calcium sulfate slurry and is collected by vacuum extraction along with the gaseous phosphoric acid. In about half the phosphate fertilizer plants in the U.S., the silica tetrafluoride gas is condensed and

processed along with the phosphoric acid and becomes a trace component of the phosphate fertilizer. In the other plants, the silica tetrafluoride gas is separated from the phosphoric acid. Roughly 60% of the fluoride recovered from processing calcium phosphate ore is sold for use as fluoridation additives. The fluoridation additive produced by this process is fluorosilicic acid. While most of the product is sold as fluorosilicic acid, some of the product is partially neutralized to sodium fluorosilicate salt and some is fully neutralized to sodium fluoride salt. In the U.S., 77% of the fluoridation additives used are fluorosilicic acid, 15% are sodium fluorosilicate and 8% are sodium fluoride.*

About 4% of the fluoridation additives used are derived from the processing of calcium fluoride into hydrogen fluoride using a gas separation technique to recover the fluorosilicic acid from the hydrogen fluoride.*

About 1% of the fluoridation additives used are derived from the production of high-purity silica. Fluorosilicic acid is produced as part of the purification of the silica.*

**The preceding paragraphs were developed using references 4, 30 through 35 and personal communication from Mr. Kip Duchon, P.E., national fluoridation engineer, CDC.*

From time to time, opponents of fluoridation allege that fluoridation additives are by-products of the phosphate fertilizer industry in an effort to suggest the additives are not safe. By definition, by-products are materials produced as a result of producing something else. In the chemical industry, a byproduct (secondary product) is anything other than the principal product produced. The fact that a product is a secondary product of a manufacturing process should not suggest the item is bad, harmful or a waste product. On the contrary, by-products may have certain characteristics which make them valuable resources. In the production of phosphate fertilizer, the fluoridation additive, fluorosilicic acid, is a by-product along with gypsum.³⁶ Gypsum is commonly used in manufacturing wall board used in construction. The production of orange juice provides another example of valuable by-products. In addition to orange juice, various by-products are obtained from oranges during juice production that are used in cleaners, fragrances and flavorings.³⁷

Fluoridation additives are valuable by-products produced as a result of producing phosphate fertilizer. To ensure the public's safety, additives used in water fluoridation meet standards of the American Water Works Association (AWWA) and NSF International (NSF).⁴

52. Does the process of water fluoridation present unusual safety concerns for water systems and water facility operators?

Answer.

No. With proper monitoring, maintenance, water facility operator training and systems planning, water fluoridation is a safe and reliable process.

Fact.

Water facilities and water facility operators perform a valuable public service by carefully adjusting the level of fluoride in water to improve the oral health of the community. Facilities and personnel are subject to a number of regulations designed to ensure safety.

Employers must conform to Occupational Safety and Health Administration (OSHA) requirements.³⁸ OSHA's mission is to assure safe and healthful workplaces by setting and enforcing standards, and by providing training, outreach, education and assistance. Under the OSH Act, employers are responsible for providing a safe and healthful workplace. Employers must comply with all applicable OSHA standards.³⁸

Additionally, in order to assist in protecting the professionals who produce sustainable supplies of high-quality drinking water, the American Water Works Association publishes detailed guidance on safety and safe working conditions for water plant personnel.³⁹

Furthermore, OSHA requires that Safety Data Sheets (SDS), previously known as Material Safety Data Sheets (MSDS), be readily available to all employees for potentially harmful substances handled in the workplace under the Hazard Communication regulation.⁴⁰ A SDS may include instructions for the safe use and potential hazards associated with a particular material and are typically made available in the area where the material is stored or used. Information contained in a SDS focuses on the potential hazards of working with the material in an occupational setting. Adherence to the SDS guidelines for handling fluoride additives helps to ensure the

recommended level of fluoride in drinking water flows through the water system while maintaining water operator safety. In the case of fluoride, the potential hazards faced by a water facility employee in dealing with concentrated fluoride additives before they enter the water system are not related to the level of fluoride in water as used by consumers. The information found in the SDS for fluoride additives is not applicable to water with fluoride at the recommended level. Therefore, SDS sheets should not be used by consumers to gauge potential hazards of community water fluoridation.

As part of safety procedures, water facility personnel receive training on the management of the additives in water plants. While the recommended fluoride level found in drinking water has been proven safe, water facility operators and engineers may be exposed to much higher fluoride levels when handling fluoride additives at the water treatment facility.⁴ Fluoride additives present risks comparable to other water additives in common use at water facilities, such as hypochlorite, quicklime, aluminum sulfate, sodium hydroxide and ferrous sulfate. In some cases, the fluoride additives are much less dangerous than many other additives, including chlorine gas commonly used in many water plants.³⁹

Today's equipment allows water facility personnel to easily monitor and maintain the desired fluoride concentration. Automatic monitoring technology is also available that can help to ensure that the fluoride concentration of the water remains within the recommended range.⁴

It is important that the water facility personnel responsible for monitoring the addition of fluoride to the water supply are appropriately trained and that the equipment used for this process is adequately maintained.⁴ With over 70 years of experience and thousands of water systems adding fluoride every day, water facility personnel have an excellent safety record related not only to their personal safety but in providing safe drinking water to their customers.

53. Does fluoridation present difficult engineering problems?

Answer.

No. Adding fluoride products to water is no different than adding other commonly used water treatment additive products using the same equipment and techniques.

Fact.

Fluoride additives used to adjust the fluoride level in drinking water are compatible with other water treatment processes often using the same type of equipment and other standard materials designed for the safe handling of other water treatment additive products in drinking water treatment facilities. Fluoride additives are introduced to the water supply as liquids. There are many control devices, some in use for decades and some newer equipment, that allow water facility personnel to easily monitor and maintain the desired fluoride level as well as levels of other water treatment additives and naturally occurring substances that may be in the water. Automatic monitoring technology is available that can help to ensure that the fluoride concentration of the water remains within the recommended range.⁴

When added to community water supplies, the concentrated fluoride additives become greatly diluted. For example, typically fluorosilicic acid is diluted approximately 315,000 times to reach the recommended target concentration of 0.7 mg/L. The exact dilution factor depends on the concentration of the fluoride additive and the amount of additive being used to reach the concentration of 0.7mg/L. At 0.7mg/L (or 0.7 parts per million), seven-tenths of one part of fluoride is diluted in 999,999.3 parts of water. To place this concentration in perspective, the following comparisons can be of assistance.

- 1 inch in approximately 23 miles
- 1 minute in approximately 1,000 days
- 1 cent in approximately \$14,000
- 1 seat in more than 34 Wrigley Field baseball parks (seating capacity 41,268)

With more than 70 years of experience with water fluoridation, there is considerable guidance on sound engineering practices to design, construct, operate and maintain water fluoridation systems. By design, and with proper maintenance and testing, water

systems can provide the recommended level of fluoride within a narrow control range of the target of 0.7mg/L.^{41,42} Additional design features such as the use of a day tank (that holds only one day's supply of fluoride) can limit the amount of fluoride that can be added to a water system in a 24-hour period and is the most reliable method to ensure overfeed protection.⁴ The State Office of Drinking Water, or similar state agency, will normally establish engineering requirements for safety. Additional standards and references on best engineering practice are available from the American Water Works Association and the Centers for Disease Control and Prevention.^{4,43}

54. Does fluoride at levels used in fluoridation corrode water pipes?

Answer.

No. Allegations that fluoridation causes corrosion of water pipes are not supported by the best available scientific evidence.

Fact.

The process of adding fluoride to water has minimal impact on the acidity or pH of drinking water and therefore will not corrode water pipes. Corrosion of drinking water pipes is related primarily to induced electrical current between dissimilar metals. Other contributing factors include the dissolved oxygen concentration, water temperature, acidity/alkalinity (pH), hardness, salt concentration, hydrogen sulfide content and the presence of certain bacteria. Under some water quality conditions, a small increase in the acidity of drinking water that is already slightly acidic may be observed after treatment with alum, chlorine, fluorosilicic acid or sodium fluorosilicate. In such cases, further water treatment to adjust the pH to neutralize the acid for corrosion control in water distribution systems is standard procedure in water plants.⁴⁴

The process of adding fluoride to water has minimal impact on the acidity or pH of drinking water and therefore will not corrode water pipes.

Note that the Water Quality Report or Consumer Confidence Report that all water systems must make available to customers on a yearly basis, may list the pH of the system's finished water.⁴⁵ Control of neutral pH (7.0) is essential as part of corrosion control requirements. Water facilities typically maintain a pH of between 7.0 and 8.0 as good practice indicating that the water leaving the plant is slightly alkaline and non-acidic.⁴⁶

55. Does fluoride at levels used in water fluoridation corrode glass, concrete or other surfaces in water plants?

Answer.

No. A correctly engineered and maintained system will not result in damage to the water plant.

Fact.

Fluorosilicic acid in a concentrated form can be corrosive if not correctly handled. The concentrated fluorosilicic acid is 75% water, and 25% fluorosilicic acid. Up to 1% of the fluorosilicic acid can be other acids including hydrogen fluoride. Hydrogen fluoride is volatile near room temperature so it will evaporate from the solution if the system is not properly engineered and maintained. The evaporation process occurs at an extremely slow rate. Less than 1% of fluorosilicic acid will be lost over a month from the evaporation of hydrogen fluoride. However, only a small release of hydrogen fluoride may be very corrosive to concrete, glass, and electrical components.³⁰

If a water system is reporting problems with corrosion from evaporating hydrogen fluoride in the storage room or fluoride handling room (i.e. the glass in the facility has become "frosted"), the system is being inadequately maintained. The storage tank and other locations in the fluorosilicic acid feed system may not be sealed or correctly vented and hydrogen fluoride gas can be released (leaked) at those points. All fluoride products storage, handling, and feed systems should be vented to the outside of the building and the system and piping should be pressure tested (low pressure is sufficient) to identify possible locations of leaks. Leaks should be promptly corrected.³⁰

With no system leaks and proper venting to outside the building, there will be no corrosion problems.³⁰

56. Does fluoridated water harm the environment?

Answer.

No. Scientific evidence supports the fluoridation of public water supplies as safe for the environment and beneficial for people.

Fact.

Fluoride is naturally occurring in the environment and is the 13th most abundant element in the earth's crust. It is found in naturally in all water sources as noted below.⁴⁷

Rain — between 0.1 to 0.2 mg/L

Streams and lakes — between 0.1 to 0.3 mg/L

Groundwaters — between 0.1 to 10 mg/L

Oceans and seawater — between 1.2 to 1.4 mg/L

A comprehensive literature review published in 2004 revealed no negative environmental impacts as a result of water fluoridation.⁴⁸ A 1990 study concluded that fluoridation has little or no impact on surrounding aquatic environment or soil.⁴⁹ Historically, issues surrounding problems with fluoride and the environment have involved incidents related to serious industrial pollution or accidents.⁴⁹

Under the Washington's State Environmental Protection Act (SEPA), a study was conducted in Tacoma-Pierce County to investigate the environmental consequences of adding optimal levels of fluoride to drinking water. Noting that the amount of fluoride in the water does not reach levels that are harmful to plants or animals, the SEPA study concluded that there are "no probable significant adverse environmental impacts."⁵⁰

There is no evidence that the recommended level of fluoride in drinking water has any adverse effect on gardens, lawns or plants.⁵⁰

Additional information regarding water fluoridation additives and engineering issues can be found on the CDC's fluoridation website, "Water Operators and Engineers" at <https://www.cdc.gov/fluoridation/engineering/index.htm>.

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Public Policy

57. What is public health?	85
58. Valuable measure?	86
59. Reduce disparities?	88
60. Support for fluoridation?	89
61. Courts of law?	91
62. Opposition?	92

63. Opposition tactics?	93
64. Internet?	96
65. Public votes?	97
66. International fluoridation?	101
67. Banned in Europe?	102

57. What is public health?

Answer.

Public health promotes and protects the health of people and the communities where they live, learn, work and play. Public health measures improve the quality of life for members of the community.

Fact.

Public health has numerous definitions and dimensions. It can encompass issues of research, education, regulation, policy and more. It focuses on the health of entire populations that can vary in size from as small as a local neighborhood to a small-sized community and a large-sized city. It also can focus on populations with a state, national or even global perspective. But how does public health affect our everyday lives? Individuals are touched by public health measures every day without giving them a second thought. For example, garbage pick-up and disposal prevent the spread of disease. The stoplight at a busy intersection protects motorists and pedestrians from injury. Building sidewalks in communities provides the option for people to walk to help control their weight and improve their heart health. Smoke-free laws help prevent lung cancer. All of these are public health in action.

Community water fluoridation is another example of a public health measure.

- Optimally fluoridated water is accessible to the entire community regardless of socioeconomic status, educational attainment or other social variables.¹
- Individuals do not need to take special action or otherwise change their behavior to obtain the benefits of fluoridation.

- Frequent exposure to small amounts of fluoride over time makes fluoridation effective through the life span in helping to prevent tooth decay.²
- Community water fluoridation is more cost-effective and cost-saving than other forms of fluoride treatments or applications.^{3, 4}

During the 20th century, the health and life expectancy of persons residing in the United States improved dramatically. Since 1900, the average life span of persons in the United States lengthened by greater than 30 years; 25 years of this gain are attributable to advances in public health. Many notable public health achievements occurred during the 1900s. In a series of reports during 1999, the *Morbidity and Mortality Weekly Report (MMWR)* profiled 10 public health achievements chosen to highlight the contributions of public health and to describe the impact of these contributions on the health and well being of persons in the United States.⁵

Ten Great Public Health Achievements — United States, 1900–1999⁵

- Vaccination
- Motor-vehicle safety
- Safer workplaces
- Control of infectious diseases
- Decline in deaths from coronary heart disease and stroke
- Safer and healthier foods
- Healthier mothers and babies
- Family planning
- Fluoridation of drinking water
- Recognition of tobacco use as a health hazard

In discussing the contribution of fluoridation, the October 22, 1999 MMWR⁶ noted fluoridation of community drinking water was a major factor responsible for the decline in tooth decay during the second half of the 20th century. Although other fluoride-containing products are available, water fluoridation remains the most equitable and cost-effective method of delivering fluoride to all members of communities, regardless of age, educational attainment, or income level.⁶

58. Is water fluoridation a valuable public health measure?

Answer.

Yes. Community water fluoridation is a public health measure that benefits people of all ages and is a public health program that saves money for families and the health care system. Because fluoridation reaches large numbers of people where they live, learn, work and play, it is more effective than other forms of fluoride delivery. Water fluoridation reaches everyone in the community regardless of age, race, education, income level or access to routine dental care. Because of the important role it has played in the reduction of tooth decay, the Centers for Disease Control and Prevention (CDC) has proclaimed community water fluoridation one of 10 great public health achievements of the 20th century.^{5,6}

Community water fluoridation is a public health measure that benefits people of all ages and is a public health program that saves money for families and the health care system.

Fact.

Throughout decades of research and more than 70 years of practical experience, fluoridation of public water supplies has been responsible for dramatically improving the public's oral health status.

It has been said that those who cannot remember the past are condemned to repeat it. As generations pass, details from life in the 1930s and 1940s fade.

The oral health of Americans suffered greatly during the time of the Great Depression and into the era of World War II. There were no public health programs in place that addressed tooth decay and the loss of teeth was viewed as an eventuality. In fact, as World War II approached, those joining the U.S. Army were required to have six back teeth (three on the top and three on the bottom) that opposed each other to serve the function of chewing food and six front teeth (three on the top and three on the bottom) that opposed each other for the purpose of biting into food. The number of men disqualified for dental reasons far exceeded all expectations as "dental disease" became the most common reason for military deferment. One out of eleven registrants examined was disqualified for military service due to dental issues.⁷ After Pearl Harbor it was apparent that the manpower needed to fight a global war could be obtained only if dental standards for induction were drastically relaxed. By March 1942, the standards had been revised so that a man who was "well nourished, of good musculature, and free from gross dental infections" but who was completely edentulous (without any teeth) could be inducted if his condition was corrected or could be corrected with dentures.⁷

Because fluoridation reaches large numbers of people where they live, learn, work and play, it is more effective than other forms of fluoride delivery.

In January 1945, a community water fluoridation trial began in Grand Rapids, Michigan followed within months by trials in Newburgh, NY (May 1945), Brantford, Ontario (June 1945) and Evanston, IL (February 1947). Reductions in tooth decay were dramatic leading to the rapid adoption of fluoridation in cities across the U.S. As a result, tooth decay declined sharply during the second half of the 20th century. Tooth loss was no longer considered inevitable.

Former U.S. Surgeon General, Dr. Luther Terry, called fluoridation as vital a public health measure as immunization against disease, pasteurization of milk and purification of water.⁸

Another former U.S. Surgeon General, Dr. C. Everett Koop, wrote:

...this preventive measure (fluoridation) is the single most important commitment that a community can make to the oral health of its children and to future generations. I urge all health officials and concerned citizens to join me in supporting this commitment and in the task of achieving water fluoridation for all community drinking water supplies which lack the fluoride content needed for the prevention of dental caries.⁹

In 1999, because of the dramatic role it played in the reduction of tooth decay, the Centers for Disease Control and Prevention (CDC) proclaimed community water fluoridation one of 10 great public health achievements of the 20th century.^{5,6}

In May 2000, U.S. Surgeon General Dr. David Satcher issued the first ever Surgeon General's report on oral health titled, *Oral Health in America: A Report of the Surgeon General*.¹⁰ In 2001, Dr. Satcher issued a statement on fluoridation in which he noted:

...community water fluoridation continues to be the most cost-effective, practical and safe means for reducing and controlling the occurrence of dental decay in a community...water fluoridation is a powerful strategy in efforts to eliminate health disparities among populations.¹¹

In the 2003 *National Call to Action to Promote Oral Health*,¹² U.S. Surgeon General Dr. Richard Carmona called on individuals and groups who are most concerned and in a position to act to apply strategies to enhance the adoption and maintenance of proven community-based interventions such as community water fluoridation.¹² In his 2004 *Statement on Community Water Fluoridation*,¹³ Dr. Carmona wrote:

While we can be pleased with what has already been accomplished, it is clear that there is much yet to be done. Policymakers, community leaders, private industry, health professionals, the media, and the public should affirm that oral health is essential to general health and well-being and take action to make ourselves, our families, and our communities healthier. I join previous Surgeons General in acknowledging the continuing public health role for community water fluoridation in enhancing the oral health of all Americans.¹³

In 2013, U.S. Surgeon General Dr. Regina M. Benjamin wrote:¹⁴

...As Surgeon General I have been working hard to encourage individuals and communities to make healthy choices because I believe it is better to prevent illness and disease rather than treat it after it occurs. Community water fluoridation is one of the most effective choices communities can make to prevent health problems while actually improving the oral health of their citizens... Fluoridation's effectiveness in preventing tooth decay is not limited to children, but extends throughout life, resulting in fewer and less severe cavities. In fact, each generation born since the implementation of water fluoridation has enjoyed better dental health than the generation that preceded it...¹⁴

U.S. Surgeon General Dr. Vivek H. Murthy issued a video statement supporting community water fluoridation in December 2015.¹⁵ In his video and written statement on fluoridation issued in 2016,^{15, 16} Surgeon General Murthy emphasized:

Our progress on this issue over the past 70 years has been undeniable. But we still have work to do. Because we know that so much of our health is determined by zip code rather than genetic code. That's why creating a culture of disease prevention through community efforts — and ensuring health equity for all — is one of my highest priorities. Community water fluoridation helps us meet these goals; as it is one of the most cost-effective, equitable, and safe measures communities can take to prevent tooth decay and improve oral health.^{15,16}

Today, the focus in achieving and maintaining health is on prevention. Established by the U.S. Department of Health and Human Services, Healthy People 2020¹⁷ provides a science-based, comprehensive set of ambitious, yet achievable, ten-year national objectives for improving the health of the public. Included under oral health is an objective to expand the fluoridation of public water supplies. Objective 13 states that at least 79.6% of the U.S. population served by community water systems should be receiving the benefits of optimally fluoridated water by the year 2020.¹⁸ Data from the CDC indicate that in 2014, 74.4% of the U.S. population on public water systems, or a total of 211.4 million people, had access to fluoridated water.¹⁹

Established by the U.S. Department of Health and Human Services in 1996, the Community Preventive Services Task Force develops and disseminates guidance on which community-based health promotion and disease prevention intervention approaches work, and which do not work, based on available scientific evidence. The Task Force issues findings based on systematic reviews of effectiveness and economic evidence. The Guide to Community Preventive Services ("The Community Guide") is a collection of evidence-based findings of the Community Preventive Services Task Force and is designed to assist decision makers in selecting interventions to improve health and prevent disease.²⁰

The Community Guide reviews are designed to answer three questions:

1. What has worked for others and how well?
2. What might this intervention approach cost, and what am I likely to achieve through my investment?
3. What are the evidence gaps?²⁰

The Community Preventive Services Task Force recommends community water fluoridation to reduce tooth decay.²¹

Reports have been released by the U.S. Department of Health and Human Services that encourage the use of preventive interventions to improve the overall and oral health of the nation.^{22,23} Specific to oral health, two reports issued in 2011 by the Institute of Medicine acknowledge water fluoridation is an effective intervention for the prevention of tooth decay. *Advancing Oral Health in America*²⁴ referred to water fluoridation as an effective prevention intervention, while *Improving Access to Oral Health Care for Vulnerable and Underserved Populations*²⁵ acknowledged that evidence regarding community water fluoridation programs continues to validate its effectiveness, safety and cost-saving benefits.

59. Does water fluoridation reduce disparities in dental health?

Answer.

Yes, evidence indicates water fluoridation helps to reduce the disparities in dental health at the community level. Populations with lower socioeconomic status (SES) who live in fluoridated communities have less tooth decay than their peers in nonfluoridated communities.

Fact.

In the first ever Surgeon's General Report on Oral Health issued in May 2000, U.S. Surgeon General David Satcher noted that community water fluoridation is safe and effective in preventing dental caries in both children and adults. Fluoridation benefits all residents served by community water supplies regardless of their social or economic status.¹⁰ In 2001, Dr. Satcher issued a statement on fluoridation in which he noted:

...community water fluoridation continues to be the most cost-effective, practical and safe means for reducing and controlling the occurrence of dental decay in a community...water fluoridation is a powerful strategy in efforts to eliminate health disparities among populations.¹¹

"...water fluoridation is a powerful strategy in efforts to eliminate health disparities among populations."

Established by the U.S. Department of Health and Human Services, Healthy People 2020 provides a science-based, comprehensive set of ambitious, yet achievable, ten-year national objectives for improving the health of the public and reducing health disparities.¹⁷ Starting with Healthy People 2000, one of the overarching goals of Healthy People has focused on disparities. With Healthy People 2020, that goal was expanded to achieve health equity, eliminate disparities, and improve the health of all groups.²⁵ Healthy People 2020 provides the following definitions.

Health disparity — a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic

group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.²⁵

Health equity — the attainment of the highest level of health for all people. Achieving health equity requires valuing everyone equally with focused and ongoing societal efforts to address avoidable inequalities, historical and contemporary injustices, and the elimination of health and health care disparities.²⁵

The association between social class and disparities in dental health has been established through extensive studies and reviews.^{26–28} Studies in communities both with and without fluoridated water consistently have shown higher levels of tooth decay in lower socioeconomic groups. Additional studies have evaluated the differences in children's tooth decay experience among socioeconomic groups and the effect that community water fluoridation has had on that experience.^{29–35} In areas with water fluoridation, children with low socioeconomic status (SES) had greater cavity experience than those with high SES. However, the tooth decay rates were higher for children with low SES who had no exposure to fluoridation compared to children with low SES who had exposure to fluoridated water.^{29–35} These studies demonstrate the positive effects that fluoridation has in reducing oral health disparities.

In 2011, a report by the Institute of Medicine, *Improving Access to Oral Health Care for Vulnerable and Underserved Populations*,³⁶ acknowledged that evidence regarding community water fluoridation programs continues to validate its effectiveness, safety and cost-saving benefits.

Under the topic "Oral Health," Healthy People 2020 includes an objective to expand the fluoridation of public water supplies. Objective 13 states that at least 79.6% of the U.S. population served by community water systems should be receiving the benefits of optimally fluoridated water by the year 2020.¹⁸ Data from the CDC indicate that in 2014, 74.4% of the U.S. population on public water systems, or a total of 211.4 million people, had access to fluoridated water.¹⁹ Conversely, approximately 25% or more than 72.7 million people on public water systems do not receive the decay preventing benefits of fluoridation — a powerful strategy communities can implement in efforts to eliminate health disparities.

60. Along with the American Dental Association, who supports community water fluoridation?

Answer.

Many organizations, such as the National Dental Association, Hispanic Dental Association, American Academy of Pediatrics, American Medical Association, American Public Health Association and the World Health Organization also have policies that support community water fluoridation.

Many organizations, such as the National Dental Association, Hispanic Dental Association, American Academy of Pediatrics, American Medical Association, American Public Health Association and the World Health Organization also have policies that support community water fluoridation.

Fact.

The American Dental Association (ADA) adopted its original resolution in support of fluoridation in 1950³⁷ and has repeatedly reaffirmed its position publicly and in its House of Delegates based on its continuing evaluation of the safety and effectiveness of fluoridation.²⁷

The National Dental Association (NDA) is the largest and oldest organization of minority oral health professionals in the world.³⁹ Representing more than 7,000 minority dentists, nationally and abroad,³⁹ the NDA seeks to provide continued advancement of the highest quality of oral health care and safety for the public.⁴⁰ In 2012, the NDA adopted the following position:⁴⁰

It is therefore, the position of the National Dental Association that Community Water Fluoridation is safe, beneficial and cost-effective and should be encouraged and supported under the following conditions:

- Community water supplies should contain the optimal fluoride levels as recommended by the U.S. Public Health Service (a range from 0.7 – 1.2 parts per million)
- Local communities and dental societies should be in agreement with and support the fluoridation project in their communities.

- Appropriate resources monitoring capabilities should be available to ensure that the appropriate water fluoride monitoring infrastructures are in place at all times in the impacted communities.⁴⁰

In a policy position released in 2012,⁴¹ the Hispanic Dental Association (HDA) noted that the HDA mission works toward the elimination of oral health disparities in the Hispanic community and that the benefits of fluoridation are critical to HDA's endorsement. The HDA position statement⁴¹ includes the following item:

Therefore, it is the position of the Hispanic Dental Association to:

1. Endorse community water fluoridation in all communities — especially the Hispanic and underserved communities — as a safe, beneficial and cost-effective public health measure based on science for preventing dental caries and to aid in the reduction of oral health disparities.⁴¹

As part of its core values⁴² the American Academy of Pediatrics (AAP) is dedicated to promoting optimal health and wellbeing for every child. With a strong emphasis on policy, advocacy and education,⁴² the AAP is a strong advocate for community water fluoridation. In support of water fluoridation⁴³ the AAP states:

Water fluoridation is a community-based intervention that optimizes the level of fluoride in drinking water, resulting in preeruptive and posteruptive protection of the teeth. Water fluoridation is a cost-effective means of preventing dental caries, with the lifetime cost per person equaling less than the cost of 1 dental restoration.⁴³

The American Medical Association's (AMA) mission is to promote the art and science of medicine and the betterment of public health.⁴⁴ Its House of Delegates first endorsed fluoridation in 1951⁴⁵ and the AMA reaffirmed its support for water fluoridation in 2011.⁴⁶

The American Public Health Association (APHA) champions the health of all people and all communities and speaks out for public health issues and policies backed by science.⁴⁷ It has supported community water fluoridation as a safe and effective public health measure for the prevention of tooth decay since 1950.⁴⁸ The APHA reaffirmed its support in 2008 by stating that it strongly endorses and recommends

"the fluoridation of all community water systems as a safe and effective public health measure for the prevention of tooth decay."⁴⁹

The goal⁵⁰ at the World Health Organization (WHO) is to build a better, healthier future for people all over the world. The WHO, which initially adopted policy recommending the practice of water fluoridation in 1969,⁵¹ reaffirmed its support for fluoridation in 1994⁵² stating:

Providing that a community has a piped water supply, water fluoridation is the most effective method of reaching the whole population, so that all social classes benefit without the need for active participation on the part of individuals.⁵²

In 2004, the WHO once again affirmed its support stating that "Water fluoridation, where technically feasible and culturally acceptable, has substantial public health benefits."⁵³ In 2007, the Sixtieth World Health Assembly adopted *WHA60.17-Oral health action plan for promotion and integrated disease prevention*⁵⁴ which urges member states to:

(4) for those countries without access to optimal levels of fluoride, and which have not yet established systematic fluoridation programmes, to consider the development and implementation of fluoridation programmes, giving priority to equitable strategies such as the automatic administration of fluoride, for example, in drinking-water, salt or milk, and to the provision of affordable fluoride toothpaste;⁵⁴

In 2016, WHO officials wrote:

The use of fluoride is a major breakthrough in public health. Controlled addition of fluoride to drinking water supplies in communities where fluoride concentration is below optimal levels to have a cariostatic effect began in the 1940s and since then extensive research has confirmed the successful reduction in dental caries in many countries.⁵⁵

Additionally a list of more than 35 organizations with positions/policies supporting community water fluoridation can be viewed on ADA's website at www.ADA.org/fluoride in the section marked "Fluoridation Links." Each organization is listed with a link to their specific fluoridation position/policy. Below are just a few of the organizations listed on the website.

- American Association of Dental Research
- American Association of Public Health Dentistry
- American Water Works Association
- Association of State and Territorial Dental Directors
- Centers for Disease Control and Prevention
- International Association of Dental Research
- National Institute of Dental and Craniofacial Research

Many organizations in the United States and around the world recognize the benefits of community water fluoridation. The ADA has developed a list of "National and International Organizations that Recognize the Public Health Benefits of Community Water Fluoridation for Preventing Dental Decay." Please see the ADA website at www.ADA.org/fluoride for the most current listing as well as information on reproduction and distribution of the list.

However, support for fluoridation doesn't end with a list of organizations. In many cases, local newspaper editorial boards support fluoridation. Perhaps the most notable of these efforts occurred when the 2013 Pulitzer Prize for Journalism — Editorial Writing⁵⁶ was awarded to Tim Nickens and Daniel Ruth of the *Tampa Bay Times*, St. Petersburg, Florida, for their diligent campaign that helped reverse a decision to end fluoridation of the water supply for the 700,000 residents of the newspaper's home (Pinellas) county. Copies of their 10 editorials from 2012 can be viewed at <http://www.pulitzer.org/winners/tim-nickens-and-daniel-ruth>.

61. Has the legality of water fluoridation been upheld by the courts?

Answer.

Yes. Fluoridation has been thoroughly tested in the United States' court system, and found to be a proper means of furthering public health and welfare. No court of last resort has ever determined fluoridation to be unlawful. Moreover, fluoridation clearly has been held not to be an unconstitutional invasion of religious freedom or other individual rights guaranteed by the First, Fifth or Fourteenth Amendments to the U.S. Constitution. And while cases decided primarily on procedural grounds have been won and lost by both pro- and anti-fluoridation interests, to ADA's knowledge, no final ruling in any of those cases has found fluoridation to be anything but safe and effective.

Fact.

The legality of fluoridation in the United States has been thoroughly tested in our court systems. Fluoridation is viewed by the courts as a proper means of furthering public health and welfare.⁵⁷ No court of last resort has ever determined fluoridation to be unlawful. The highest courts of more than a dozen states have confirmed the constitutionality of fluoridation.⁵⁸ In 1984, the Illinois Supreme Court upheld the constitutionality of the state's mandatory fluoridation law, resolving 16 years of court action at a variety of judicial levels.⁵⁹ Moreover, the U.S. Supreme Court has denied review of fluoridation cases thirteen times, citing that no substantial federal or constitutional questions were involved.⁵⁸

Fluoridation is viewed by the courts as a proper means of furthering public health and welfare. No court of last resort has ever determined fluoridation to be unlawful.

It has been the position of the American courts that a significant government interest in the health and welfare of the public generally overrides individual objections to public health regulation.⁵⁸ Consequently, the courts have rejected the contention that fluoridation ordinances are a deprivation of religious or individual freedoms guaranteed under the Constitution.^{58,60} In reviewing the legal aspects of fluoridation, the courts have dealt with this concern by ruling that: (1) fluoride is a nutrient, not a medication, and is present naturally in the environment; (2) no one is forced to drink fluoridated water as alternative sources are available; and (3) in cases where a person believes that fluoridation interferes with religious beliefs, there is a difference between the freedom to believe, which is absolute, and the freedom to practice beliefs, which may be restricted in the public's interest.^{61,62}

Fluoridation is the adjustment of the level of a naturally occurring mineral found in water in order to prevent tooth decay. Courts have consistently ruled that water fluoridation is not a form of compulsory mass medication or socialized medicine.^{58,61,63} In fact, water that has been fortified with fluoride is similar to fortifying salt with iodine, milk with vitamin D and orange juice with calcium — none of which are medications.

In recent years, challenges to fluoridation have been dismissed for a variety of reasons, including that plaintiffs admitted they could not establish injury by virtue of fluoridation and that state law supporting fluoridation prevailed over local attempts to oppose fluoridation.

Interestingly, pro- and anti- fluoridation interests have each won and lost legal challenges regarding which state or local agency has regulatory authority over fluoridation, which of course varies by state and locality.

State law variances have also led to different rulings on other issues, such as whether downstream end-users of fluoridation must be given an opportunity to vote on whether to fluoridate. While cases decided primarily on procedural grounds have been won and lost by both pro- and anti- fluoridation interests, to the ADA's knowledge no final ruling in any of those cases has found fluoridation to be anything but safe and effective.

For additional information regarding the legal status of community water fluoridation in the United States, refer to *The Fluoride Legislative User Information Database (FLUID)* which is a comprehensive database containing historical information on legal cases decided by U.S. courts. The database also contains current information on federal and state policies regarding community water fluoridation. The website can be accessed at: <http://fluidlaw.org>.

62. Why does opposition to community water fluoridation continue?

Answer.

Public health controversies sometimes exist regarding public health interventions. In public health there can be tension between "public good" and "individual freedoms." Because public health deals with populations it is all but impossible to resolve issues to achieve approval from 100 percent of the individuals within the population. When looking at fluoridation, some individuals opposed to fluoridation are sincere in their beliefs. Others ignore what constitutes reputable scientific evidence as defined by the vast majority of the scientific community and choose instead to base their beliefs on personal opinions and studies with flawed methodologies.

Fact.

Fluoridation is considered beneficial by the overwhelming majority of the health and scientific communities as well as the general public. A vast body of scientific literature endorses water fluoridation as a safe means of reducing the incidence of tooth decay. Support for fluoridation among scientists and health professionals, including physicians and dentists, is nearly universal. Recognition of the benefits of fluoridation by the American Dental Association, the American Medical Association, the American Academy of Pediatrics, governmental agencies and other national health and civic organizations continues as a result of published, peer-reviewed research.

Fluoridation has a long history of being a political issue, as well as a scientific one, with opposition including activists from both the right and the left of the political spectrum. In the late 40s, opposition to fluoridation began to appear nationwide. Reportedly, one of the first public votes on fluoridation occurred in 1950 in Stevens Point, Wisconsin,⁶⁴ when a local activist initiated a campaign to stop the introduction of what he called "poison" into the water system. The campaign quickly moved from being a discussion of the science to a political campaign that included the involvement of a large number of civic groups, unofficial public petitions, calls for a debate, campaign rallies and numerous letters to the editor that "kept typesetters busy preparing for print the thousands of words that poured into the editor's desk." After 1950 when the U.S. Public Health Service and ADA endorsed fluoridation, proponents became more organized in their efforts to promote fluoridation while the opposition capitalized on the political nature of the struggle and used lessons learned in Stevens Point.

Of the small faction that opposes water fluoridation for philosophical reasons, freedom of choice probably is one of the most frequently cited issues. People take the stance that society should not "force" individuals to act in ways that are beneficial to their own health or the health of others. They are opposed to "government interference" in their lives.⁶⁵ Some individuals are opposed to community action on any health issue, others are opposed due to environmental or economic concerns and some are opposed because they are simply misinformed.

Opposition to fluoridation has existed since the initiation of the first programs in 1945 and continues today despite over 70 years of practical experience

showing fluoridation to be safe and effective. An article⁵⁵ that appeared in the local newspaper shortly after the first fluoridation program was implemented in Grand Rapids, Michigan, noted that the fluoridation program was slated to commence January 1, but did not actually begin until January 25. Interestingly, health officials in Grand Rapids began receiving complaints of physical ailments, including "teeth falling out and enamel peeling off their teeth," attributed to fluoridation from citizens weeks before fluoride was actually added to the water.⁶⁶ In 1992 a community in Finland opted to stop their fluoridation program at the end of the year in December. However, it was discontinued at the end of November without the public being told. Public surveys conducted in November and December and again in March the following year revealed the occurrence and mean number of symptoms (the most common being itching and dryness of skin) were fairly similar during the periods of actual and supposed fluoridation indicating the symptoms were not caused by fluoride in the water. Interestingly, those who claimed to be able to taste the fluoride in the water made this claim equally often during actual and supposed fluoridation. A significant reduction in the symptoms occurred after those responding to the surveys became aware that fluoridation had stopped. The authors concluded that the prevalence rates of the symptoms were connected to the psychological rather than the physical effects of exposure to fluoride in water.⁶⁷

Over time, antifluoridation leaders and organizations have come and gone, but their basic beliefs have remained the same. These include: fluoride is toxic and causes numerous harmful health effects; fluoride does not prevent tooth decay; fluoridation is costly; and fluoridation interferes with freedom of choice and infringes on individual rights.

Opinions are seldom unanimous on any scientific subject. In fact, there really is no such thing as "final knowledge," since new information is continuously emerging and being disseminated. As such, the benefit evidence must be continually weighed against risk evidence. Health professionals, decision makers and the public should be cooperating partners in the quest for accountability where decisions are based on proven benefits measured against verified risks.⁶⁸ Dentists are a valuable source of accurate information regarding water fluoridation for both their patients and their communities.

63. What are the tactics fluoridation opponents use to provoke opposition to water fluoridation?

Answer.

Fluoridation opponents use numerous tactics to disseminate misinformation and raise the fears of the public about the safety of water fluoridation. Routinely, they use scare techniques,⁶⁹ present half-truths, downplay the significance of science-based evidence and use selective reporting of results and studies to support their false allegations.⁵⁹

Fact.

While many of the arguments against fluoridation have remained relatively constant over the years, antifluoridationists have used different approaches that play upon the popular concerns of the public at the time.⁶⁵ For example, in the 1950s fluoridation was said to be a Communist plot. With America's growing concern for environmental issues in the 1960s, fluoridation was called pollution. After the Vietnam War in the 1970s, the antifluoridationists capitalized on the popularity of conspiracy theories by portraying fluoridation as a conspiracy between the U.S. government, the dental-medical establishment and industry. As the population became more concerned about their health in the 1980s, antifluoridationists claimed fluoridation caused AIDS and Alzheimer's disease. In the 1990s, claims of hip fractures and cancer were designed to resonate with aging baby boomers. With the new millennium, overexposure and toxicity, in association with lead poisoning, surfaced as common themes. Since the economic crisis of 2008, discussions about the cost of fluoridation are more commonplace. In the 2010s, neurotoxicity became a constant theme with charges of lower IQ and autism. Over the years, none of these approaches have ever really disappeared, but instead are often recycled as antifluoridationists choose which approach will have the greatest effect on the intended audience.⁶⁵

The internet has breathed new life into the antifluoridation effort bringing the antifluoridation message into voters' homes.^{71,72} With just a click of the mouse, search engines can locate a large number of websites denouncing fluoridation, which can give the impression that this is a one-sided argument. Individuals who look to the internet as a source of valid and reliable information often fail to recognize that these sites frequently contain personal opinion rather than scientific fact. Newspaper stories,

press releases and letters to the editor are often posted as documentation of the “science” behind antifluoridationists’ claims. All too often, the public accepts this type of information as true simply because it is in print. Opposition videos are available from national antifluoridation organizations and are shared at no cost via vehicles such as YouTube making it possible for every campaign to bring an antifluoridationist to the community. Social media such as Facebook and Twitter are used to spread antifluoridation messaging to the public and to assist in organizing local efforts. These venues have allowed the small faction of antifluoridationists to be linked across the country and around the world and promote their message quickly, repeatedly and economically.

Spreading misinformation impacts public policy and costs society in immeasurable ways. The opponents’ claims and opinions can escalate to emotional arguments that, in the end, can delay, or prevent the introduction of a water fluoridation program or stop an existing program.⁷⁰ More people, especially those involved in policy decisions, need to be better informed about these tactics. In making decisions that affect the health of the community, it is important to distinguish between someone’s personal opinion disguised as science and information based on the best available scientific evidence. It is perfectly acceptable to have your own opinion but it is unacceptable to have your own “facts” derived from something less than reputable science.

In making decisions that affect the health of the community, it is important to distinguish between someone’s personal opinion disguised as science and information based on the best available scientific evidence.

In 1993 the U.S. Supreme Court issued a landmark decision that many view as likely to restrict the use of information inferred as science in the federal courts and in those state courts which adopt this reasoning. The Court determined that while “general acceptance” is not needed for scientific evidence to be admissible, federal trial judges have the task of ensuring that an expert’s testimony rests on a reasonable foundation and is relevant to the issue in question.⁷³ According to the Supreme Court, many considerations will bear on whether the expert’s underlying reasoning or methodology is scientifically valid and applicable in a given case. The Court set out four criteria that judges could use when evaluating scientific testimony:

1. whether the expert’s theory or technique can be (and has been) tested, using the scientific method,
2. whether it has been subject to peer review and publication (although failing this criteria alone is not necessarily grounds for disallowing the testimony),
3. its known or potential error rate and the existence and maintenance of standards in controlling its operation and
4. whether it has attracted widespread acceptance within a relevant scientific community, since a known technique that has been able to attract only minimal support may properly be viewed with skepticism.⁷³

The scientific validity and relevance of claims made by opponents of fluoridation might be best viewed when measured against these criteria.⁷³ The techniques used by antifluoridationists are well known and have been discussed at length in a number of published articles that review the tactics used by antifluoridationists.^{58,65,66-70,74-77} Examples of a few of the techniques can be viewed in Figure 5.

Figure 5. Opposition Tactics

Targeting Politicians and Community Leaders: Antifluoridation websites contain draft letters to be sent to newspaper publishers, water departments, and community public officials warning them of their “liability” should they support or endorse water fluoridation. Leaders are urged to remain “neutral” and allow fluoridation decisions to be put to a public vote, therefore, relieving the leaders of any and all responsibility in the matter. Antifluoridationists use the time gained to conduct a public referendum to bombard the public with misinformation designed to turn public opinion against fluoridation.

Unproven Claims: Antifluoridationists have repeatedly claimed fluoridation causes an entire laundry list of human illnesses, including AIDS, Alzheimer’s disease, cancer, Down Syndrome, genetic damage, heart disease, lower intelligence, kidney disease, osteoporosis and hip fractures. None of these claims has a basis in fact. These allegations are often repeated so frequently during campaigns that the public assumes they must be true. Their appearance in print, even if only in letters to the editor of the local newspaper, reinforces the allegation’s credibility. With just a small amount of doubt established, the opposition slogan, “If in doubt, vote it out,” often rings true with voters.

Innuendo: The statement, “Fifty years ago physicians and dentists posed for cigarette ads,” is an example of innuendo or, more specifically, guilt by association. Even though fluoridation is not mentioned, individuals are expected to make the connection that the medical community changed its position on smoking so it is possible health professionals are wrong about fluoridation, too.

Outdated Studies and Statements from “Experts” Antifluoridation websites often offer a list of “respected medical professionals and scientists” who have spoken out against fluoridation. One of those often quoted is Dr. Charles Gordon Heyd who is noted to be a Past President of the American Medical Association (AMA). What is not disclosed is the source of the quote or that Dr. Heyd was President of the AMA in 1936 – almost ten years before water fluoridation trials began. His decades-old quote certainly does not represent the current AMA position of support for water fluoridation and is characteristic of antifluoridationists’ use of items that are out of date. Additionally, antifluoridationists have claimed that fourteen Nobel Prize winners have “opposed or expressed reservations about fluoridation.” It should be noted that the vast majority of these individuals were awarded their prizes from 1929 through 1958.

Statements Out of Context: One of the most repeated antifluoridation statements is, “Fluoride is a toxic chemical. Don’t let them put it in our water.” This statement ignores the scientific principle that toxicity is related to dosage and not just to exposure to a substance. Examples of other substances that can be harmful in the wrong amounts, but beneficial in the correct amounts, are salt, vitamins A and D, iron, iodine, aspirin and even water itself.

Conspiracy Theories: Hardly a fluoridation campaign goes by without those opposed to fluoridation bringing up any number of conspiracy theories about fluoridation. Whether it is the claim that scientists from the original atomic bomb program secretly shaped and guided the early Newburgh, NY, fluoridation trial or that chemtrails are a government plot to spread fluoride, these claims have no basis in fact. Even the belief that fluoridation was a communist plot to destroy America was famously parodied in the 1964 movie *Dr. Strangelove*. Over the decades, those opposed to fluoridation have used propaganda schemes and conspiracy theories that reflected the social and political environment of the times. Today, “follow the money” is a common theme as the opposition claims that the beverage industry, the companies supplying fluoride additives and others are financially backing researchers, as well as dental and medical groups, who are promoting fluoridation. None of these claims has a basis in fact.

Treating Correlation as Causation. Many people have heard the phrase that “correlation does not imply causation.” In other words, just because two events seem to fluctuate in tandem does not prove that they are meaningfully related to one another. For example, statistics show that sales of ice cream increase in warm summer months. Statistics also show that crime goes up in large cities in the summer. However, it would be ludicrous to draw the conclusion that ice cream causes an increase in crime. Yet this is exactly the type of logic exercised in some arguments and studies promoted by those opposed to fluoridation. For example, the opposition often points to Kentucky as having a large portion of the population on public water supplies receiving fluoridated water. And that’s correct. In 2014, Kentucky was ranked the number one state in the U.S. as 99.9% of its public water systems were fluoridated. But the opposition also points to the fact that Kentucky suffers from a large number of people who have lost their teeth. They draw the conclusion that this proves fluoridation does not work — without looking at other factors that influence this outcome. For example, while there is a large number of public water systems that are fluoridated, Kentucky has a large rural population that does not have access to public water supplies. Additionally, and perhaps most importantly, Kentucky’s population has a high rate of tobacco use which is known to be a risk factor for periodontal (gum) disease which can lead to the loss of teeth.

64. Where can valid, evidence-based information about water fluoridation be found on the internet?

Answer.

There are many reputable sites on the internet that provide information on fluorides and fluoridation including the American Dental Association as well as other reputable health and science organizations and government agencies. These sites provide information that is consistent with the best available scientific evidence.

Fact.

One of the most widely respected sources for information regarding fluoridation and fluorides is the American Dental Association’s (ADA) Fluoride and Fluoridation website at www.ADA.org/fluoride. (See Figure 6.) From the ADA website individuals can link to other fluoridation websites such as:

- Centers for Disease Control and Prevention at www.cdc.gov/fluoridation
- The Community Guide at <https://www.thecommunityguide.org>
- Fluoride Science at <http://fluoridescience.org>

The internet contains numerous sources of information on fluoridation. However, not all

“science” posted on the internet is based on scientific fact. Searching the internet for “fluoride” or “water fluoridation” directs individuals to numerous websites. Some of the content found in the sites is scientifically sound. Other less scientific sites look highly technical, but contain information based on science that is unconfirmed or has not gained widespread acceptance. In many cases, the information is largely opinion. While everyone is entitled to their opinion, they are not entitled to make that opinion appear as scientific fact. Commercial interests, such as the sale of water filters, are often promoted.

Today’s technology can put the world at your fingertips but search engine technology can influence what is returned in searches. The first time the search for “fluoridation” is made, it is likely that the returns will include both pro- and anti- fluoridation websites. When you click to view a website, the search engine takes note and on subsequent searches for the same term, the search engine will return items similar to what you chose initially. For example, if you choose a pro-fluoridation website initially, the next time you search for “fluoridation,” the search engine will likely return a selection of other pro-fluoridation websites for your review. Of course the converse is also true. Clicking on anti-fluoridation websites will allow you to see a search laden with similar anti-fluoridation sites.

Figure 6. ADA Fluoride and Fluoridation Web Page



The graphic is a screenshot of the ADA Fluoride and Fluoridation web page. It features a dark background with a white water drop icon at the top. Below the icon, the text 'FLUORIDATION AT YOUR FINGERTIPS!' is displayed in large, bold, white capital letters. Underneath, the URL 'http://www.ADA.org/fluoride' is shown in a smaller white font. A bulleted list of resources follows: ADA Fluoridation Resources, ADA Fluoridation Videos, ADA Fluoridation News Stories, ADA Policy and Statements, and Links to Additional Fluoridation Websites. The ADA American Dental Association logo is present, along with the tagline 'America's leading advocate for oral health' and the website 'www.ADA.org'. A paragraph of text describes the resources available, and a call to action at the bottom encourages visitors to be resourceful and visit the website today.

FLUORIDATION AT YOUR FINGERTIPS!

<http://www.ADA.org/fluoride>

- ADA Fluoridation Resources
- ADA Fluoridation Videos
- ADA Fluoridation News Stories
- ADA Policy and Statements
- Links to Additional Fluoridation Websites

ADA American Dental Association®
America's leading advocate for oral health

www.ADA.org

Many ADA resources are at your fingertips 24/7/365. **Order** a library book or products online, **read** JADA articles, **discuss** important topics with colleagues, **find** helpful information on professional topics from accreditation to X-rays and **recommend** our dental education animations, stories and games to your patients.

**Be resourceful.
Visit ADA.org today!**

65. Why does community water fluoridation sometimes lose when it is put to a public vote?

Answer.

Voter apathy or low voter turnout due to the vote being held as a special election or in an "off" year, confusing ballot language (a "no" vote translates to support for fluoridation), blurring of scientific issues, the use of scare tactics by those opposed to fluoridation, long campaigns that lead to "fluoridation fatigue," lack of leadership by elected officials and a lack of political campaign skills among health professionals are some of the reasons fluoridation votes are sometimes unsuccessful.

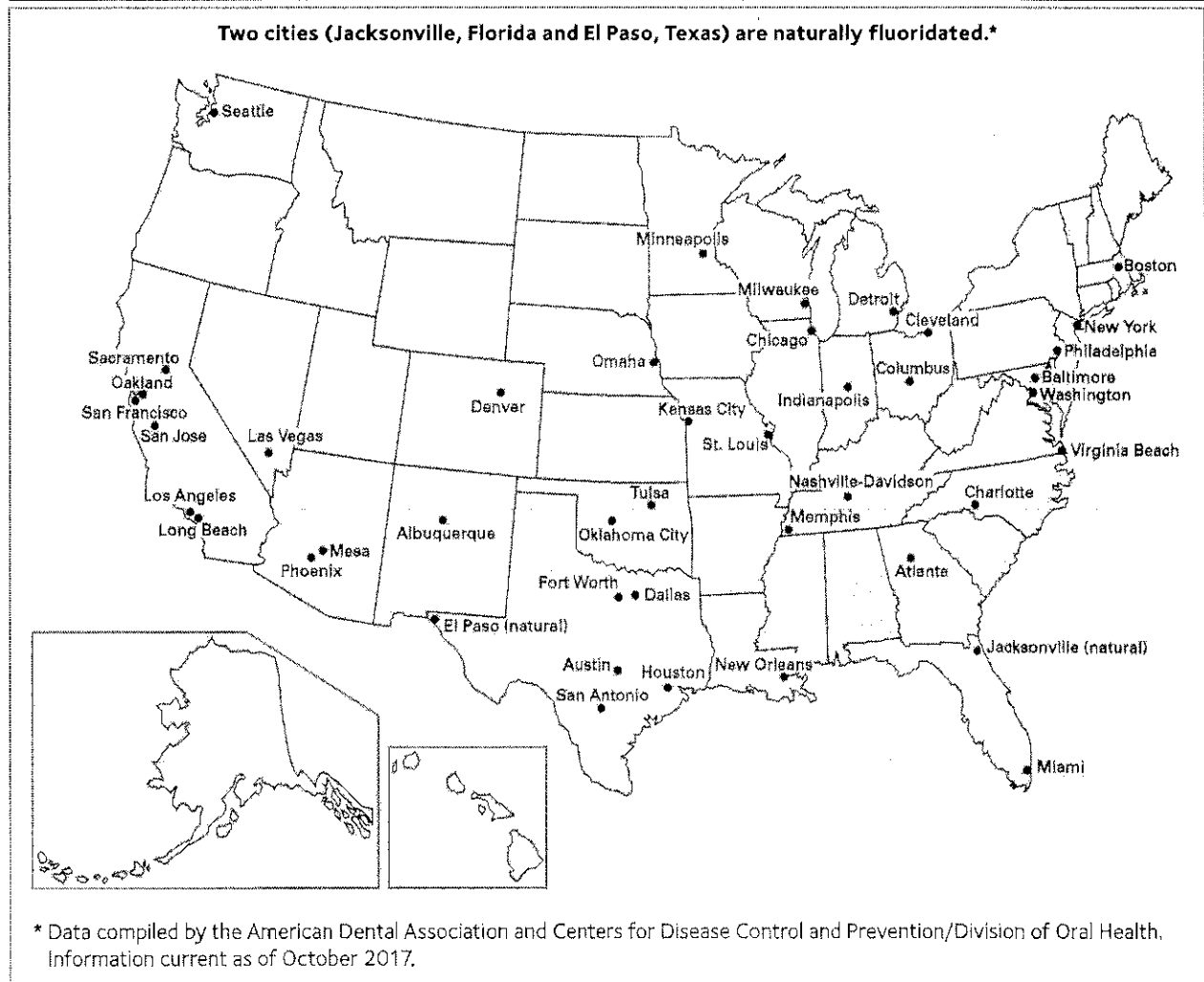
Fact.

The fact is that fluoridation votes in the U.S. are more often successful than not. In 2016, it was common to see those opposed to fluoridation make statements such as "450 communities had rejected fluoridation since 2000" or similar statements using different numbers. What is not made clear is that the number of communities in these statements is a global number. Many of these communities are outside the United States.⁷⁸ In fact from 2000 through 2016, more than 515 U.S. communities in 42 states voted to adopt or retain successful fluoridation programs.⁷⁹ In the five years from 2012 to 2016, U.S. communities voted in favor of fluoridation programs by a two to one margin.^{78,79}

The fact is that fluoridation votes in the U.S. are more often successful than not...In the five years from 2012 to 2016, U.S. communities voted in favor of fluoridation programs by a two to one margin.

Since 2000, nearly 50 million people have been added to the population on public water systems in the United States that enjoys the benefit of optimally fluoridated water.⁸⁰ In 2000, 65% of the public on public water systems received fluoridated water.⁸¹ In 2014, the percentage had increased nearly 10% to 74.4% of the population.¹⁹ But despite the continuing growth of fluoridation in this country over the past several decades, millions of people in the U.S. do not yet receive the protective benefit of fluoride in their drinking

Figure 7. Largest Fluoridated Cities

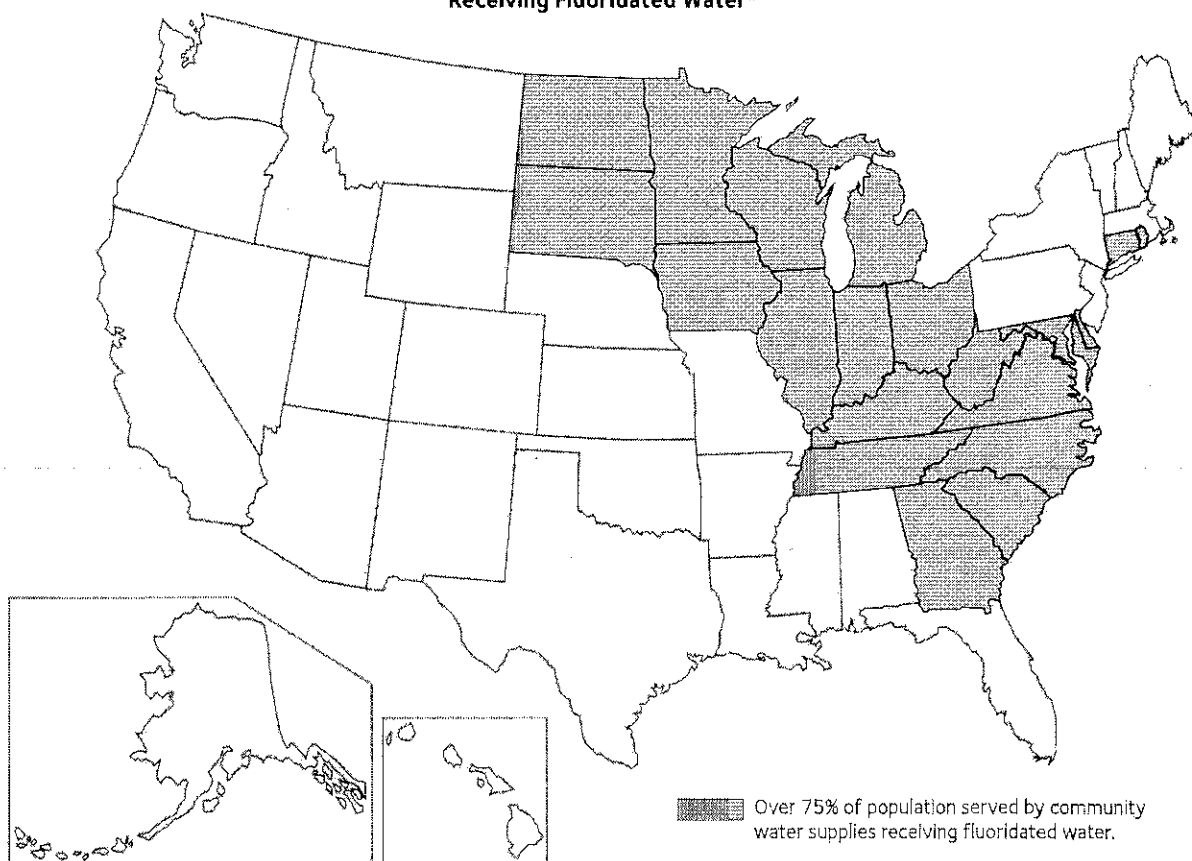


water. Centers for Disease Control and Prevention (CDC) data from 2014 indicated more than 25% of the population served by public water systems did not have access to fluoridated water.¹⁹ In 2017, 44 of the 50 largest cities were fluoridated.⁸² Of the 44 cities, 42 were fluoridated by adjustment and two had naturally occurring fluoride at the recommended levels (Figure 7). The remaining six largest nonfluoridated cities (in order of population largest to smallest) were: Portland, Oregon; Albuquerque, New Mexico; Tucson, Arizona; Fresno, California; Colorado Springs, Colorado; and Wichita, Kansas. In October 2017, the Albuquerque Bernalillo County Water Utility Authority authorized budget monies to restore fluoridation to their customers. It is estimated that fluoridated water will be available in six to eight months.

In 2010, recognizing the ongoing need to improve health and well-being, the U.S. Department of Health and Human Services revised national health objectives to be achieved by the year 2020.¹⁷ Included under oral health was an objective to significantly expand the fluoridation of public water supplies. Specifically, Objective 13 of Healthy People 2020 states that at least 79.6% of the U.S. population served by community water systems should be receiving the benefits of optimally fluoridated water by the year 2020.¹⁸ This replaced the Healthy People 2010 objective of 75%.⁸³ As of 2014, twenty states met or exceeded the 2020 objective.¹⁵ (See Figure 8.) Although water fluoridation reaches some residents in every state the coverage is uneven. Data from 2014 indicated that 26 states provided fluoridation benefits to 75% or more of their residents on community water systems while eight states were at or below 50%.¹⁹ (See Figure 9.)

Figure 8. States Meeting National Goal

States Meeting the Healthy People 2020 Goal Of 79.6% of the Population Served by Community Water Supplies Receiving Fluoridated Water*



* Data Source: Centers for Disease Control and Prevention/Division of Oral Health. "National Fluoridation Statistics" 2014. Available at <https://www.cdc.gov/fluoridation/statistics/2014stats.htm>

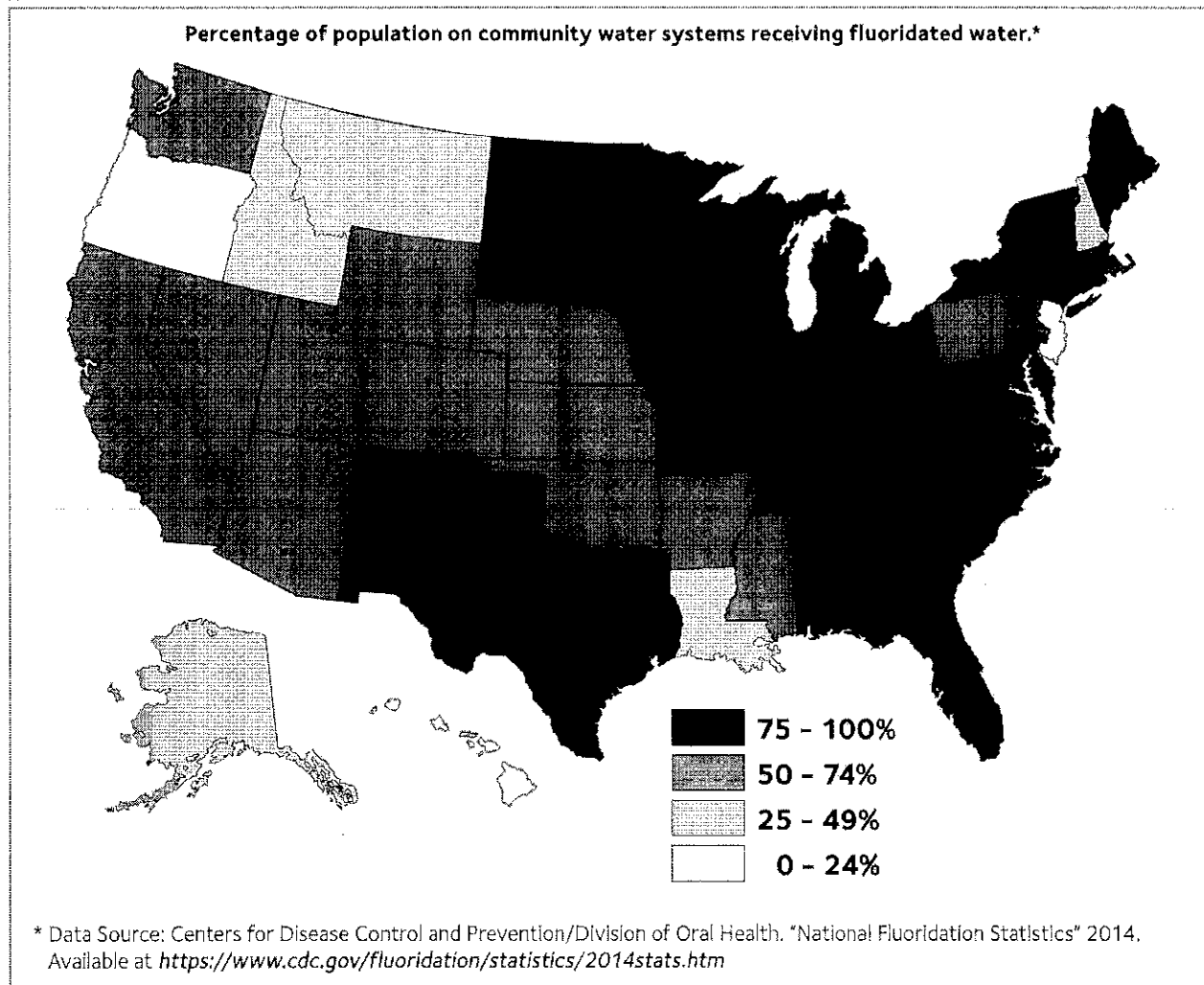
Fluoridation campaigns can vary greatly from community to community. To paraphrase an old saying, "If you've seen one fluoridation campaign, you've seen one fluoridation campaign." A number of factors commonly come into play when fluoridation is put to a public vote and does not succeed. Among those factors are a lack of funding, public and professional apathy, the failure of many legislators and community leaders to take a stand because of perceived controversy, low voter turnout and the difficulty faced by an electorate in evaluating scientific information in the midst of emotional charges by opponents. Voters are often unaware of the fluoride content of their water. Unfortunately, citizens sometimes mistakenly believe their water contains the recommended level of fluoride when, in fact, it does not. On the other hand, people sometimes say they have great teeth and don't need fluoridation

when in fact, the major reason they have such good teeth is because they've had the benefit of fluoride in the water their entire lives. And, in some cases, because fluoridation campaigns often become political campaigns, there are political factors that can sway a vote that have nothing at all to do with fluoridation.

Clever use of emotionally charged "scare" propaganda by fluoride opponents creates fear, confusion and doubt within a community when voters consider the use of fluoridation.^{84,85}

Defeats of referenda or the discontinuance of fluoridation have occurred most often when a small, vocal and well organized group has used a barrage of fear-inspiring allegations designed to confuse the electorate. In addition to attempts to influence voters, opponents have threatened community leaders with

Figure 9. State Fluoridation Status



personal litigation.⁸⁶ While no court of last resort has ever ruled against fluoridation, community leaders can be swayed by the threat of litigation due to the cost and time involved in defending even a groundless suit, not to mention threats of political fallout. The American Dental Association (ADA) knows of no cases in which community leaders have been found liable for their pro-fluoridation efforts. In no instance has fluoridation been discontinued because it was proven harmful in any way.⁸⁵⁻⁸⁷

Defeats of referenda or the discontinuance of fluoridation have occurred most often when a small, vocal and well organized group has used a barrage of fear-inspiring allegations designed to confuse the electorate.

Adoption of fluoridation is ultimately a decision of state or local decision makers, whether determined by elected officials, health officers or the voting public. Fluoridation can be enacted through state legislation, administrative regulation, ordinance or a public referendum. While fluoridation is not legislated at the federal level, it is legislated at the state and local level. As with any public health measure, a community has the right and obligation to protect the health and welfare of its citizens, even if it means overriding individual objections to implement fluoridation.

Those opposed to fluoridation sometimes comment that "the government is forcing fluoridation" on the community. But who is "the government?" The fact is that since fluoridation is implemented by state or local votes (by city councils or public vote), the people are "the government." Voters elect officials at the

state and local level to act on their behalf. Voters participate directly in public votes on fluoridation.

Each spring as part of the yearly ADA/ASTDD/CDC Community Water Fluoridation Awards program, the ADA, Association of State and Territorial Dental Directors and the CDC Division of Oral Health compile a list of water systems/communities in the United States that have adopted or retained community water fluoridation in the previous year.⁸⁸ This list is posted on the ADA website at <http://www.ADA.org/fluoride>. The ADA has also compiled a master list of U.S. communities voting to adopt or retain fluoridation programs dating from 1998 which is also available on the ADA website.⁷⁹ From 2000 through 2016, more than 515 U.S. communities in 42 states have voted to adopt or retain fluoridation. The size of these water systems/communities varies greatly — from those with a few thousand residents to the Metropolitan Water District of Southern California which provides fluoridated water to more than 18 million people.⁷⁹

The primary source for technical assistance with fluoridation efforts is the ADA's Council on Advocacy for Access and Prevention (CAAP) at the ADA. Additional support for fluoridation is available from the ADA's Division of Legal Affairs, Division of Communications and Department of State Government Affairs. Dental and health professionals seeking technical assistance can reach CAAP at 312.440.2500.

66. Is community water fluoridation accepted by other countries?

Answer.

According to the British Fluoridation Society,⁸⁹ as of November 2012, approximately 377.7 million people in 25 countries worldwide were supplied with water fluoridated by adjustment. Additionally, the number of people receiving naturally fluoridated water at the optimum level is approximately 57.4 million. Worldwide, the estimated number of people with access to optimally fluoridated water is 435.1 million and it continues to grow each year.⁸⁹ A second study estimates the number at 437.2 million.⁹⁰

According to the British Fluoridation Society, as of November 2012, approximately 377.7 million people in 25 countries worldwide were supplied with water fluoridated by adjustment.

Fact.

The value of water fluoridation is recognized internationally. Countries and geographic regions with water fluoridated by adjustment include the U.S., Argentina, Australia, Brazil, Brunei, Canada, Chile, China (Special Administrative Region of Hong Kong), Fiji, Guatemala, Guyana, the Irish Republic, Israel, Malaysia, New Zealand, Panama, Papua New Guinea, Peru, Republic of Korea (South Korea), Serbia, Singapore, Spain, the United Kingdom and Vietnam.⁸⁹ Major cities (outside the U.S.) with fluoridated water include Adelaide, Auckland, Bilbao, Birmingham, Brisbane, Buenos Aires, Cork, Dublin, Edmonton, Ho Chi Minh City (Saigon), Kuala Lumpur, Melbourne, Newcastle upon Tyne, Perth, Rio de Janeiro, San Paolo, Santiago, Seville, Sydney, Toronto, Wellington and Winnipeg.⁸⁹

Thorough investigations of fluoridation, conducted in a number of countries in addition to the U.S. including Australia, England, Ireland, New Zealand as well as by the European Commission and the World Health Organization, support the safety and effectiveness of water fluoridation.⁹⁰⁻⁹⁵

Considering the extent to which fluoridation has already been implemented throughout the world, the lack of documentation of adverse health effects is remarkable testimony to its safety.^{91-94, 96} The World Health Organization (WHO) has endorsed the practice of water fluoridation since 1969.⁵¹ In 1994, an expert committee of the WHO published a report which reaffirmed its support of fluoridation as being safe and effective in the prevention of tooth decay, and stated that "provided a community has a piped water supply, water fluoridation is the most effective method of reaching the whole population, so that all social classes benefit without the need for active participation on the part of individuals."⁵² In 2004, the WHO once again affirmed its support.⁵³ In 2007, the Sixtieth World Health Assembly recommended that countries without access to optimal levels of fluoride or systemic fluoridation programs should consider initiating fluoridation programs.⁵⁴

A scientific evaluation of fluoride was conducted by the Scientific Committee on Health and Environmental Risks (SCHER) upon request by the European Commission (EC).⁹⁵ The EC is the European Union's (EU) executive body with responsibility to manage EU policy. The Committee was asked to critically evaluate any new evidence on the hazard profile, health effects and human exposure to fluoride. The final report,

Critical review of any new evidence on the hazard profile, health effects, and human exposure to fluoride and the fluoridating agents of drinking water was released in 2011.⁹⁵ It stated that exposure to levels of fluoride used for fluoridation of drinking water is not expected to lead to unacceptable risks to the environment. Additionally, the report concluded there was insufficient evidence or no evidence that fluoridation was linked to endemic skeletal fluorosis, osteosarcoma, lower IQs in children, thyroid or reproductive problems.⁹⁵

There are parts of the world where water fluoridation is not common. In some of these instances water fluoridation is not feasible due to the lack of a central water supply, the existence of other more life-threatening health needs, the lack of trained technical personnel or sufficient funds for start-up and maintenance costs. In some cases where water fluoridation has not been implemented, countries have chosen to institute salt fluoridation programs.

67. Is community water fluoridation banned in Europe?

Answer.

No country in Europe bans community water fluoridation.

Fact.

Under European Union (EU) law and regulations, the individual Member States can decide whether to or not to fluoridate water. Members of the European Union (EU) construct their own water quality regulations within the framework of the Drinking Water Directive⁹⁷ adopted in 1998 which outlines the quality of water intended for human consumption. They can also decide whether to or not to add fluoride to milk or salt products. There is no EU-wide obligation to add fluoride to any product consumed by humans including water nor is there an EU-wide obligation not to add fluoride to any product including water.⁹⁷

The Directive provides maximum admissible concentrations for many substances, one of which is fluoride. The Directive does not require or prohibit fluoridation; it merely requires that the fluoride concentration in water does not exceed the maximum permissible concentration of 1.5 mg/L.⁹⁷

Many fluoridation systems that used to operate in Eastern and Central Europe did not function

properly and when the Iron Curtain fell in 1989–90, fluoridation stopped because of obsolete technical equipment and lack of knowledge as to the benefits of fluoridated water.⁹⁸

Water fluoridation is not practical in some European countries because of complex water systems with numerous water sources. As an alternative to water fluoridation, many European countries have opted for the use of dietary fluoride supplements or salt fluoridation.

Basel, Switzerland is one such example.⁹⁸ Those opposed to water fluoridation claimed a large victory when Basel voted to cease water fluoridation in 2003. The facts are that Basel was the lone city with fluoridated water surrounded by communities that used fluoridated salt. In the mid-1990s, trade barriers that had prevented fluoridated salt from being sold to those living in Basel fell and soon it was evident that residents were receiving fluoride from salt as well as through drinking water. The government voted to cease water fluoridation in 2003 in light of availability and use of fluoridated salt in the community. Basel, Switzerland did not stop providing fluoride. Officials simply chose another type of fluoridation — salt fluoridation.⁹⁸

Again, no European country bans fluoridation. It has simply not been implemented for a variety of technical, legal, financial or political reasons.

Those opposed to fluoridation sometimes comment that “97% of western Europe has rejected water fluoridation,” although frequently the line becomes “most of Europe has rejected water fluoridation.” But what is not mentioned is that there are a number of countries in Europe that have opted to use fluoridated salt or milk fluoridation. (Additional information on this topic can be found in Benefits Section, Question 14.) Letters have appeared on the internet reportedly from officials in foreign countries who comment negatively regarding their country’s position on fluoridation. However, from the letters it is apparent the writers are responding to a question that is not publically available and that was designed to illicit a negative response. Additionally the credentials of the respondents do not provide any insight as to what relationship, if any, they have with the governmental bodies who have jurisdiction over fluoridation practices in their respective countries. These letters should not be construed as any country’s official position on fluoridation.

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Cost

68. Cost-effective and cost-saving?	106
69. Practical?	109

68. Is water fluoridation a cost-effective and cost-saving method of preventing tooth decay?

Answer.

Yes. When compared to the cost of other prevention programs, water fluoridation is the most cost-effective means of preventing tooth decay for both children and adults in the United States. A number of studies over the past 15 years have attempted to place a specific dollar value on the benefit of fluoridation. These studies, conducted in different years (and therefore using different dollar values), encompassing different communities/populations and different methodologies have two conclusions in common: 1) for systems that serve more than 1,000 people, the economic benefit of fluoridation exceeds the cost and 2) the benefit-cost ratios increased as the size of the populations increase largely due to economies of scale.

Fact.

The cost of community water fluoridation varies for each community depending on the following factors.¹

1. Size of the community (population and water usage);
2. Number of fluoride injection points where fluoride additives will be added to the water system;
3. Amount and type of equipment used to add and monitor fluoride additives;
4. Amount and type of fluoride additive needed to reach the target fluoride level of 0.7 mg/L; its price, cost of transportation and storage; and
5. Expertise and preferences of personnel at the water plant.

In 2016, a study² led by researchers from the Colorado School of Public Health created a model of fluoridation program costs, savings, net savings and return on investment for the 2013 U.S. population with access to optimally fluoridated water systems that served 1,000 or more people. The researchers found that savings associated with individuals avoiding tooth decay in 2013 as a result of fluoridation were estimated at \$6.8 billion, or \$32.19 per person, for the more than 211 million people who had access to fluoridated water through community water systems serving more than 1,000 people that year. Based on the estimated cost of the systems to fluoridate (\$324 million), the net savings from fluoridation was estimated at \$6.5 billion and the estimated return on investment (ROI) averaged 20 to 1 across water systems of all sizes (from 1,000 to over 100,000 people with a ROI range of 15.5 to 26.2). However, it was noted that the cost per person to fluoridate can vary significantly among different sizes of communities based on a number of the factors outlined in the previous paragraph. Because of those variables, the researchers urged communities to inform their policy decisions by identifying their specific water system's annual cost and comparing that cost to the annual estimated per person savings (\$32.19) in averted treatment costs. The researchers noted that in 2013, while 211 million people had access to fluoridated water, more than 78 million people had access to a public water system that served 1,000 or more people that was not fluoridated. The study findings suggest that if those water systems had been fluoridated, an additional \$2.5 billion could have been saved as a result of reductions in tooth decay.²

The economic benefits of fluoridation were also reconfirmed in a systematic review³ conducted in 2013 by the Community Preventive Services Task Force which sought to update their prior review conducted in 2002⁴ which also found that fluoridation saved money. The 2013 review concluded that recent

evidence continues to indicate the economic benefit of fluoridation programs exceeds their cost. The review also noted that benefit-cost ratio increases with the population of the community.

Because of the decay reducing effects of fluoride, the need for restorative dental care is typically lower in fluoridated communities. Therefore, an individual residing in a fluoridated community will typically pay for fewer dental restorative services (such as fillings) during a lifetime. A study⁵ published in 2005, estimated the cost and treatment savings resulting from community water fluoridation programs in Colorado. The study also estimated the added savings if communities without water fluoridation initiated a fluoridation program. The study estimated a community fluoridation program generated treatment savings through prevented tooth decay of \$61 for every \$1 spent to fluoridate the community's water. On a state level, results indicated an annual savings of nearly \$150 million associated with the water fluoridation programs and projected a nearly \$50 million annual savings if the remaining 52 nonfluoridated water systems in Colorado were to implement water fluoridation programs.⁵

There are various types of dental restorations (fillings) commonly used for the initial treatment of tooth decay (cavities) including amalgam (silver) and composite resins (tooth-colored). In the 2016 study noted earlier², the most commonly used treatment was a two-surface composite resin restoration in posterior (back) permanent teeth. Considering the fact that in the United States the fee⁶ for a two-surface composite resin restoration in a permanent tooth placed by a general dentist typically ranges from \$165-\$305*, fluoridation clearly demonstrates significant cost savings. An individual can enjoy a lifetime of fluoridated water for less than the cost of one dental filling.

An individual can enjoy a lifetime of fluoridated water for less than the cost of one dental filling.

*The Survey data should not be interpreted as constituting a fee schedule in any way, and should not be used for that purpose. Dentists must establish their own fees based on their individual practice and market considerations. The American Dental Association discourages dentists from engaging in any unlawful concerted activity regarding fees or otherwise.

When it comes to the cost of treating dental disease, everyone pays. Not just those who need treatment, but the entire community — through higher health insurance premiums and higher taxes. Cutting dental care costs by reducing tooth decay is something a community can do to improve oral health and save money for everyone. With the escalating cost of health care, fluoridation remains a community public health measure that saves money and so benefits all members of the community.

When it comes to the cost of treating dental disease, everyone pays. Not just those who need treatment, but the entire community — through higher health insurance premiums and higher taxes. Cutting dental care costs by reducing tooth decay is something a community can do to improve oral health and save money for everyone.

The economic importance of fluoridation is underscored by the fact that the cost of treating dental disease frequently is paid not only by the affected individual, but also by the general public through services provided by health departments, community health clinics, health insurance premiums, the military and other publicly supported medical programs.⁷ For example, results from a New York State study published in 2010⁸ that compared the number of Medicaid claims in 2006 for cavity-related procedures in fluoridated and nonfluoridated counties showed a 33.4% higher level of claims for fillings, root canals and extractions in nonfluoridated counties as compared to such claims in fluoridated counties.⁸

Fluoridation contributes much more to overall health than simply reducing tooth decay. It prevents needless infection, pain, suffering and loss of teeth and saves vast sums of money in dental treatment cost — particularly in cases where dental care is received through surgical intervention in a hospital or through hospital emergency services.

In a study⁹ conducted in Louisiana, Medicaid-eligible children (ages 1-5) residing in communities without fluoridated water were three times more likely than Medicaid-eligible children residing in communities with fluoridated water to receive dental treatment in a hospital and the cost of dental treatment per eligible child was approximately twice as high. In addition

to community water fluoridation status, the study took into account per capita income, population and number of dentists per county.⁹

By preventing tooth decay, fluoridation also plays a role in reducing visits to hospital emergency rooms (ERs) for toothaches and other related dental problems where treatment costs are high. Most hospitals do not have the facilities or staff to provide comprehensive or even emergency dental care. Many patients receive only antibiotics or pain medication but the underlying dental problem is not addressed. In too many cases, the patient returns to the ER in a few days with the same problem or worse.

School-based dental disease prevention activities such as fluoride mouthrinse or tablet programs, professionally applied topical fluorides, dental health education and placement of dental sealants are beneficial but have not been found to be as cost-effective in preventing tooth decay as community water fluoridation.¹⁰ In 1985, the National Preventive Dentistry Demonstration Program¹⁰ analyzed various types and combinations of school-based preventive dental services to determine the cost and effectiveness of these types of prevention programs. Ten sites from across the nation were selected. Five of the sites had fluoridated water and five did not. Over 20,000 second and fifth graders participated in the study over a period of four years. Students were examined and assigned by site to one or a combination of the following groups:

- biweekly in class brushing and flossing plus a home supply of fluoride toothpaste and dental health lessons (ten per year);
- in-class daily fluoride tablets (in nonfluoridated areas);
- in-school weekly fluoride mouthrinsing;
- in-school professionally applied topical fluoride;
- in-school professionally applied dental sealants, and
- a control.¹⁰

After four years, approximately 50% of the original students were examined again. The study affirmed the value and effectiveness of community water fluoridation. At the sites where the community

water was fluoridated, students had fewer cavities, as compared to those sites without fluoridated water where the same preventive measures were implemented. In addition, while sealants were determined to be an effective prevention method, the cost of a sealant program was substantially more than the cost of fluoridating the community water demonstrating fluoridation as the most cost-effective preventive option.¹⁰

In an effort to balance budgets, decision makers sometimes make economic choices that amount to being “penny wise and pound foolish.” In other words, they cut an expense today that appears to be a sure money saver. But they fail to take a long-term view (or see the big picture) on the consequences of that action. They fail to see how money spent now can provide greater savings in the future. A decision to eliminate funding for a successful community water fluoridation program would be an example of that kind of action. Often decision makers are swayed by the promise of an alternative fluoride delivery system without considering who it will cover (and who it will not cover), how it will be administered and what it will cost. Examples of these alternative fluoride delivery programs include school-based fluoride mouthrinse programs, fluoride supplements, fluoride varnish and other professionally applied topical fluorides. Often dental health education programs including dispensing “free” toothbrushes and fluoridated toothpaste are mentioned as an alternative to fluoridation. All of these programs can be beneficial but are not as cost-effective as fluoridation programs because they typically require additional personnel to facilitate the programs, action on the part of the recipient and have much higher administrative and supply costs. Additionally, these programs typically target only children and so do not provide decay preventing benefits to adults. Fluoridation benefits all members of the community — children and adults — and is more cost-effective.

The CDC’s “Health Impact in 5 Years” (HI-5) initiative¹¹ launched in 2016 highlights community-wide approaches that have evidence reporting 1) positive health impacts, 2) results in five years and 3) cost-effectiveness or cost savings over the lifetime of the population or earlier. Fluoridation is one of the community approaches included in the HI-5 Initiative as it has great potential to help keep people healthy as it reaches all members of a community where they live, learn, work, and play. Documenting the impact

of fluoridation can be challenging partially because the beneficial effect is not immediately apparent.¹² Cost savings from fluoridation would be expected to increase over several years' time. The most notable decrease in tooth decay would be anticipated in young children who received the benefits of fluoridation over their lifetime in both their primary teeth and as their adult teeth begin to appear when the children are approximately six years old. More immediate savings could be realized in recently fluoridated communities as children who had once received fluoride supplements would no longer require these prescriptions which are typically recommended for children from six months to 16 years of age, whose primary drinking water source is not fluoridated and have been determined to be at high risk for tooth decay.

Benefits from the prevention of tooth decay can include:

- freedom from dental pain
- a more positive self-image
- fewer missing teeth
- fewer cases of poorly aligned tooth aggravated by tooth loss
- fewer teeth requiring root canal treatment
- reduced need for crown, bridges, dentures and implants
- less time lost from school or work because of dental pain or visits to the dentist

While some of these types of benefits are difficult to measure economically, they are extremely important.^{13,14}

Fluoridation remains the most cost-effective and practical form of preventing tooth decay in the United States and other countries with established municipal water systems. It is one of the very few public health measures that actually saves more money than it costs.^{13,15-17}

69. Why fluoridate an entire water system when the vast majority of the water is not used for drinking?

Answer.

It is more practical and less costly to fluoridate an entire water supply than to attempt to treat only the water that will be consumed.

Fact.

Water systems treat all the water supplied to communities to the same high standards, for disinfection, clarity or fluoridation, whether the water is to be used for washing dishes, washing a car, watering lawns, preparing food or drinking. Although not all that water needs to be disinfected, clarified or fluoridated, it is more practical and cost efficient to treat all the water delivered to the customer to the same standard.

Fluoride is only one of more than 40 different chemicals/additives that can be used to treat water in the United States. Many are added for aesthetic or convenience purposes such as to improve the odor or taste, prevent natural cloudiness or prevent staining of clothes or porcelain.¹⁸ The cost of additives for fluoridating a community's water supply is very low on a per capita basis; therefore, it is practical to fluoridate the entire water supply. It would be prohibitively expensive and impractical for a community to have two water systems — one that provided drinking water and another for all other water use (watering lawns, laundry, flushing toilets).

Many organizations that are concerned about water use, conservation and quality support the practice of water fluoridation. For example, the American Water Works Association, an international nonprofit scientific and educational association dedicated to the improvement of drinking water quality and supply, supports the practice of fluoridation of public water supplies.¹⁹

Cost References

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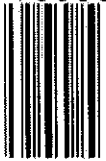
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c: 727.409.1770

Begin forwarded message:

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Date: September 30, 2020 at 9:18:28 PM EDT
To: Eric.Genrich@greenbaywi.gov, Barbara Dorff <district1@greenbaywi.gov>, Thomas De Wane <district2@greenbaywi.gov>, Andy Nicholson <district3@greenbaywi.gov>, Bill Galvin <district4@greenbaywi.gov>, David Nennig <district5@greenbaywi.gov>, Joe Moore <district6@greenbaywi.gov>, Randy Scannell <district7@greenbaywi.gov>, Christopher Wery <district8@greenbaywi.gov>, Guy Zima <district9@greenbaywi.gov>, Mark Steuer <district10@greenbaywi.gov>, "John S. Vander Leest" <district11@greenbaywi.gov>, Thomas Sladek <district12@greenbaywi.gov>
Cc: Celestine Jeffreys <Celestine.Jeffreys@greenbaywi.gov>, ClerkInquiries <ClerkInquiries@greenbaywi.gov>, Nancy Quirk <Nancy.Quirk@greenbaywi.gov>, "Dunkel, Russell D - DHS" <russell.dunkel@dhs.wisconsin.gov>, "Kuester, Robbyn L - DHS" <Robbyn.Kuester@dhs.wisconsin.gov>, Erika Valadez <evaladez@wda.org>, "Crespin, Matthew" <MCrespin@chw.org>, Johnny Johnson <drjohnnyjohnson@gmail.com>
Subject: Opponents claim fluoride is released from PFOS/PFAS compounds - False

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

I want to share with you a few of the claims that you are likely receiving so that we can dispatch them.

One has to do with claims of fluoride ions being released by PFOS/PFAS chemicals into the environment. As your water manager Nancy Quirk can tell you, this is not the case. However, opposition to community water fluoridation (CWF) will claim most anything that they think will sway or confuse you in making solid, science-based decisions on CWF.

AFS has consulted the world's top experts to develop a straightforward message about these manmade products. The bottom line is that the fluoride ion, like in water fluoridation, *is not* released from these chemicals. These chemicals are used as flame retardants (aircraft foams to fire extinguishing), Teflon production, and other industries. They persist in the ground and do not breakdown to release fluoride ions.



September 30, 2020

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

As you continue to receive volumes of emails and phone calls from opponents of community water fluoridation (CWF), the American Fluoridation Society (AFS) has chosen to send you information sparingly. We feel that inundating you with correspondence is not how to help you understand water fluoridation and the credible research that supports its 75 years of use in the U.S. The preponderance of scientific evidence continues to support CWF as effective in reducing cavities for all by at least 25%, and is safe for everyone to drink.

American Dental Association:

The American Dental Association has produced a booklet of common claims made by those that oppose CWF. The claims are constantly repeated in communities like Green Bay, Madison, and Spokane, WA most recently. Spokane's City Council, a city of almost 220,000, voted recently to start the process of CWF.

This booklet addresses each of those claims with the most current science and supplies voluminous references for their clarification of the opponents claims. The booklet is updated periodically and was last released in 2018. It was first published in 1956.

If you read anything that AFS sends you, please do me this favor of looking at the ADA Fluoridation Facts Table of Contents that I've attached. It is three pages. On those pages you will see nearly every single claim that you are hearing listed. The section in the booklet that covers those claims is given. Here is just a sample of what is covered:

<i>Topic:</i>	<i>Page #</i>
22. Total intake?	43
23. Daily intake?	44
24. Prenatal dietary fluoride supplements?	46
25. Body uptake?	47
26. Bone health?	47
27. Dental fluorosis?	49
28. Fluoridated water for infant formula?	52
29. Prevent fluorosis?	52
30. Warning Label?	54
31. Acute and chronic toxicity?	55
32. Cancer?	56
33. Osteosarcoma?	57
34. Enzyme effects?	58
35. Thyroid?	59

36. Pineal gland?	60
37. Allergies?	60
38. Genetic risk?	61
39. Fertility?	61
40. Down Syndrome?	62
41. Neurological impairment/IQ?	62
42. Lead poisoning?	64
43. Alzheimer's disease?	65
44. Heart disease?	66
45. Kidney disease?	67

AFS exists to help fill in the gaps between printings of this document with the current literature on CWF. The current literature includes studies which support CWF, call into doubt CWF, or are not able to show a correlation between CWF and any health claim. In other words, we, like every major health organization in the world, read all the research that is published in credibly recognized, peer reviewed scientific journals.

I appreciate your time in browsing the ADA Fluoridation Facts booklet's Table of Contents. I have also attached the full booklet as well to read any or all parts of it that you may have concerns with. It is also available [online](#).

Please do not hesitate to contact me personally with any questions or concerns that you may have.

Warm regards,

Johnny



Johnny Johnson, Jr., DMD, MS
 Pediatric Dentist
 Diplomate, American Board of Pediatric Dentistry
 Life Fellow, American Academy of Pediatric Dentistry
 President, American Fluoridation Society
 Web: <https://americanfluoridationsociety.org/>
 Cell: 727-409-1770
 Email: drjohnnyjohnson@gmail.com

About the American Fluoridation Society:

How we got started:

The American Fluoridation Society was founded in 2014 by a group of concerned professionals anxious to see all residents of the United States served by community water

systems enjoy the benefits of community water fluoridation (CWF). Equally important to this Society is to prevent rollback attempts by opponents of CWF, as well as to initiate CWF where it has not been previously available.

The Society's Aims:

- To promote improvement of dental health by securing the optimum fluoride content of community water systems in areas where it is sub-optimal.
- To promote and coordinate medical, dental, educational, and administrative efforts to achieve this remotely by means of electronic media and personal contacts.
- To distribute information about dental health and the benefits/risks of optimally fluoridated water to the fluoridation decision-makers in the communities.
- To provide direct support to communities across the United States that may need expert testimony from the American Fluoridation Society member(s).
- To provide the necessary information to debunk the opposition to fluoridation's pseudo-science.

**American Fluoridation Society's Board of Directors and
Advisory Committees**

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Johnny Johnson, Jr., DMD, MS
Pediatric Dentist

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Immediate past North Dakota State Dental
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Dentistry, former national lead for water
fluoridation with Public Health England and
regional consultant for the Midlands and
East of England

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School of Dentistry

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Metro North Oral Health Services, Former
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Dentistry, Chapel Hill, NC

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Assistant Professor of Health Sciences,
University of Alaska Anchorage, AK

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Immediate past CDC National Fluoridation Engineer

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AFS Communications Officer

Randy Johnson
Biology

I've attached the document which clearly goes through this information. While I do not wish to bombard you with information, it is time that you hear succinct, accurate scientific-based information.

Please don't hesitate to reach out to me with any concerns that you have. I have answers about CWF causing acne, allergies, racehorses dying (Cathy Justice), rat poison, and a host of other claims. But I won't take up your time chasing after these. Frankly, you want solid answers. That's what AFS is here to provide.

Please follow the lead of the Brown County Department of Health's recommendation to keep CWF in place.

I am always available. Just call or email me.

Warm regards,



August 19, 2020

Perfluorooctane Sulfonate (PFOS) Per- and Polyfluoroalkyl Substances (PFAS)

Concern is raised in water fluoridation areas by opponents of community water fluoridation because of the "fluoro" part of PFOS/PFAS. However, this component of these products is not related to fluoridation.

The PFAS/PFOS chemicals themselves are toxic. PFAS/PFOS are man-made chemicals used for industrial processes that contain the *fluorine atom, not the fluoride ion*. Fluoride ions are not released from these compounds. Fluoride is a naturally occurring mineral in lakes, rivers, groundwater and the oceans. PFAS/PFOS chemicals have nothing to do with the fluoride that is used in drinking water.

Part of the reason PFAS compounds do not release fluoride is that they resist biological and environmental degradation so they can potentially have a high persistence in the environment.

Recently, there has been an increased awareness of PFAS/PFOS and their presence in drinking water. They can be measured in some drinking water sources, and certain places have higher occurrence than others. Contamination has been a particular concern in rural areas in certain parts of the country as a result of fire-fighting foams.

One use for PFAS/PFOS that many consumers have heard of is Teflon for non-stick pans. The scientific world knows very little about their toxicological properties, and EPA has not established health-based criteria for them in drinking water. Part of the concern is that there are thousands of these compounds but virtually no toxicity data for any of them. It is suspected some of them may be carcinogenic but we actually don't have good data.

To summarize, PFOS/PFAS are not related to fluoride from water fluoridation. It is the compounds themselves that are the problem; fluoride is not released from them. People who try to connect PFOS/PFAS to water fluoridation are either ill-informed of the scientific nature of these compounds or they are deliberately seeking to mislead the public.

Resources:

EPA Technical Fact Sheet – Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA)

PFAS Chemistry:

- The PFAS group is made up of two subgroups: perfluoroalkyl substances and polyfluoroalkyl substances.
- PFOS and PFOA are perfluoroalkyl substances (compounds for which all hydrogens on all carbons (except for carbons associated with functional groups) have been replaced by fluorines).
- Polyfluoroalkyl substances are compounds for which some hydrogens (but not all) on the carbon atoms have been replaced by fluorines.
- PFASs are extremely persistent in the environment primarily because the chemical bond between the carbon and fluorine atoms is extremely strong and stable.

EPA

Per- and Polyfluoroalkyl Substances (PFAS)

Technical Fact Sheet

CDC

Per- and Polyfluorinated Substances (PFAS) Factsheet

Per- and Polyfluoroalkyl Substances (PFAS) and Your Health

American Water Works Association

PFAS: Contaminants of Emerging Concern

Association of State Drinking Water Associations

PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS)

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Immediate past CDC National Fluoridation Engineer

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Randy Johnson

Biology

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Sunday, October 4, 2020 9:17 PM
To: District Ten; District Eleven; District Six; District Five
Cc: Eric Genrich; District One; District Two; District Three; District Four; District Seven; District Eight; District Nine; District Twelve; Celestine Jeffreys; ClerkInquiries; Nancy Quirk; Johnny Johnson; Dunkel, Russell D - DHS; Kuester, Robbyn L - DHS; Crespín, Matthew; Erika Valadez; Jaime Fuge
Subject: It's time to separate Facts vs Opinions of water fluoridation
Attachments: Letter regarding attacks from opponents, concerns of PPC members, and science.pdf

Dear Chair Steuer, and Alderpersons VanderLeest, Lefebvre, and Stevens,

Please find attached a note from me regarding what's been disseminated to you by opponents at every level to water fluoridation. I've spoken with a couple of you, as well as other alderpersons, regarding the fluoridation information before you.

Quite honestly, I've been very respectful of the opponents up until this point. While you heard at the first PPC meeting that dentists were scared to speak up against fluoridation, Brenda Staudenmauer went out and filed claims against the dental license of WI State Dental Director Russ Dunkle for information that he provided you on the first meeting. That's been dismissed as Dr. Dunkle did nothing incorrect. Several other antics of intimidation have been implemented by the opponents since then including trying to get me and one of our group to have to register as "Lobbyists" in Madison, and sending emails to pro-fluoridation speakers to their workplace emails, although they registered to speak from their private emails. The lobbyist challenge failed as the American Fluoridation Society' Board of Directors are unpaid volunteers of our nonprofit. To meet the requirements of a lobbyist by Wisconsin law (as in most states), you have to be paid. The only one that got paid was our attorney who we had to have intervene to clarify this situation.

You will get answers to your thoughts, concerns, and questions that you have asked of me and others. Please read the attached note to you.

Thank you.

Warmly,

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770



October 4, 2020

To: Protection and Policy Committee (PPC)
From: Johnny Johnson, Jr, DMD, MS

RE: 1. Credibility of sources of your information
2. Attacks by Fluoridation Opponents of the public
3. Concerns of PPC members and other Alderpersons
4. The rest of the story on the new science

Dear Chair Steuer, and Alderperson's VanderLeest, Lefebvre, and Stevens,

Respectfully, the American Fluoridation Society and I have steered away from the mudslinging of the opponents of community water fluoridation who were present on the first PPC meeting. However, enough is enough. It is time that you know the group of people that flooded that Zoom meeting, how they are twisting credible science to fit their needs, including the researcher (Till) that wrote to you and me twice on her university's letterhead, and the intimidation techniques that they are using to silence the public. The opponents on that first call coordinated an all-out attack plan to challenge fluoridation. If the deck seemed stacked with 50+ opponents vs 6-8 proponents, that was because we had no earthly idea that that was going to happen. I just happened to be asked if I'd join in case any questions would come up that I could help with. I thank God for that request. You, and the proponents on that call, were blindsided with an orchestrated plan to lead you astray from the truth. Unfortunately, I'm afraid that some key misinformation has stuck. We will work to get the facts straight on this misinformation for you to be able to make your decisions based on the best available scientific evidence.

In phone and/or email conversations with several of you, I have heard of your concerns regarding several topics. AFS will work to address these concerns as I have asked other healthcare professionals and fluoridation experts from around the globe to write to you. They will succinctly address your stated concerns and questions.

In my following emails, I will address the three points listed above. I will be succinct and will pick salient points that are being presented to you in the presentations that are listed on the website. It is the same misinformation that was used recently in Madison to attempt to get them to cease fluoridation (which they have not), and in Spokane, WA whose city council voted to take the next step in implementing fluoridation. Spokane is a city of almost 220,000 people. They considered all the recent science. They listened to all of Spokane residents who called in on their Zoom call. They were not going to let the chosen opponents from outside of Spokane to flood their call with misinformation. They were tuned into what happened in Green Bay and Madison. Others have learned from how the opponents are seizing upon our horrible pandemic of COVID-19 to use virtual meetings to attack water fluoridation.

Please stay safe and healthy.

Warmest personal regards,



Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
Web: <https://americanfluoridationsociety.org/>
Cell: 727-409-1770
Email: drjohnnyjohnson@gmail.com

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- To provide the necessary information to debunk the opposition to fluoridation's pseudo-science.

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Randy Johnson
Biology

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Tuesday, October 6, 2020 7:46 PM
To: Okah, Abiye,
Cc: Jaime Fuge
Subject: Re: Letter of Support for Community Water Fluoridation

Hi Dr. Okah,

Thank you so very much for your letter of support for water fluoridation in Green Bay. You are on the front lines as a pediatrician, like one of my daughters, a pediatric endocrinologist, and have to deal with the fallout of cavities that have caused medical complications due to their advanced nature and invasion of adjacent tissues. Neck dissections, septicemia, and brain abscesses leading to death are an uncommon outcome. They are more common than people realize.

I have included Jaime Fuge from the Green Bay Clerk's office to forward your email to the Protection and Policy Committee. They are the ones that will be hearing it this Thursday. The full council and mayor will be hearing it in a few weeks. However, the meeting this Thursday is of vital importance for the families in Green Bay. I thank you from the bottom of my heart for writing to help these families.

Warmest personal regards,

Johnny

Johnny Johnson, Jr., DMD, MS
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Life Fellow, American Academy of Pediatric Dentistry
President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

On Tue, Oct 6, 2020 at 5:56 PM Okah, Abiye, <aokah@cmh.edu> wrote:

Dear Mayor and Common Council,

Please see the attached letter of support for community water fluoridation.

I hope you will consider this in your deliberations.

Please ignore my prior email sent with a draft attachment inadvertently.

Sincerely,

Abiye Okah MD

Electronic mail from Children's Mercy Kansas City. This communication is intended only for the use of the addressee. It may contain information that is privileged or confidential under applicable law. If you are not the intended recipient or the agent of the recipient, you are hereby notified that any dissemination, copy or disclosure of this communication is strictly prohibited. If you have received this communication in error, please immediately forward the message to the Children's Mercy Information Security Officer via return electronic mail at [informationsecurityofficer @cmh.edu](mailto:informationsecurityofficer@cmh.edu) and expunge this communication without making any copies. Thank you for your cooperation.

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Wednesday, October 7, 2020 8:28 AM
To: District Ten; District Eleven; District Five; District Six
Cc: Eric Genrich; District One; District Two; District Three; District Four; District Seven; District Eight; District Nine; District Twelve; Celestine Jeffreys; Nancy Quirk; Dunkel, Russell D - DHS; Robbyn Kuester; mcrespin@chw.org; Erika Valadez; ClerkInquiries; Johnny Johnson; Jaime Fuge
Subject: (For Agenda) Questions from Protection and Policy Committee on if I'm paid, doctors on both sides, and medical community not agreeing with fluoridation
Attachments: AAP CWF Letter Green Bay 10.05.20.pdf; Keep Community Water Fluoridation Green Bay 2020.pdf



October 7, 2020

Dear Chair Steuer, and Alderperson's VanderLeest, Lefebvre, and Stevens,

Recently in speaking with a couple of you, I have been asked three questions that I want to address with all of you.

1. Am I paid to speak at these meetings and/or promote water fluoridation (CWF)?

- Absolutely not.
- As the President of the American Fluoridation Society (AFS), I receive no income or perks for doing this. It is my honor to help our country's families, especially those most impoverished, to have the best oral and general overall health that they can have.

On the other hand, Paul Connett, the Executive Director of the Fluoride Action Network who has spoken before you and the Brown County Board of Health, *is* paid for the work that he does. Connett, and his wife Ellen, have openly said that they receive \$2,000 each/month for the work that they do.

You can decide if there is a motivation behind what I do and what British-American Chemist Connett does.

2. There are doctors and dentists on both sides of this debate. Who is right?

- There are doctors, dentists, PhDs, and others who oppose CWF. As in any field or subject matter, there are outliers in our fields. Who you've heard from at your first Protection and Policy Committee meeting was a one-sided cyberattack by those on that meeting. ~50 people

on that call were opposed to CWF. The proponents of CWF had no idea of that group being on the call in those numbers. That's why we had 6-7 people on the call.

- I pulled some numbers **just from the U.S.** on practicing physicians, nurses, dentists, and PhDs to compare with the numbers that FAN has on it's webpage that oppose CWF **worldwide**. That information is below.
- This information clearly shows that those who oppose CWF are an extremely small group, approximately 1:100,000. However, the internet has given FAN and others a worldwide stage to promote their anti-vaccination/anti-fluoridation opinions.
- In the U.S, there are over 960,000 physicians, over 3 million nurses, more than 180,000 dentists and about 4.5 million PhDs.
<https://bhw.hrsa.gov/sites/default/files/bhw/health-workforce-analysis/research/hrsa-us-health-workforce-chartbook-in-brief.pdf>
<https://www.census.gov/library/stories/2019/02/number-of-people-with-masters-and-phd-degrees-double-since-2000.html>
- According to FAN's website, fluoridalert.org, 4800 professionals had signed a statement calling for an end to fluoridation.
- However, only about 200 have signed the new statement issued in 2018.
- <http://fluoridalert.org/researchers/professionals-statement/the-new-statement-signers/>
- Of the 200, 27 are physicians (MD or MB degree), 19 are nurses, 25 are dentists (with a DDS, DMD or BDS), and 36 hold a PhD degree.
- That is a total of 107 physicians, nurses, dentists and PhDs opposing fluoridation, **which represents 0.001% of all physicians, nurses, dentists and PhD's or 1 in every 100,000 of those professionals in the USA.**
- Note that 54 of the 200 in the list of Professionals Opposed to fluoridation are from outside the US.

I hope that this information puts into perspective the people who have been calling, emailing, and who were on the first PPC meeting opposed to CWF. The overwhelming majority of professionals support CWF's safety and effectiveness.

3. The medical profession seems not to agree with CWF.

- The American Public Health Association (APHA) has sent you an emailed letter supporting the safety and effectiveness of CWF (attached). The APHA has over 25,000 members from every area of health represented.
- The American Academy of Pediatrics (AAP) has sent you an emailed letter supporting the safety and effectiveness of CWF (attached). The AAP had ~67,000 members. That number includes one of my daughters, a Pediatric Endocrinologist. If you have *any questions* about fluoridation and endocrine disorders, she will happily answer them. I will let you know that she, along with her mentor, Janet Silverstein (past president of the Endocrine Society in the

U.S. multiple times), will tell you that there are absolutely no interactions of CWF with any endocrine system, including the Thyroid gland.

Please consider the solid scientific evidence that has been published in credibly recognized scientific journals and vote to keep Green Bay's water fluoridated.

Thank you.

Warmly,



Johnny Johnson, Jr., DMD, MS
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American Academy of Pediatrics

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October 5, 2020

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Phone: 630/626-6000
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Joseph L. Wright, MD, FAAP

Dear Protection and Policy Committee,

On behalf of the American Academy of Pediatrics (AAP), a non-profit professional organization of 67,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults, I write to support the recommendations of the Centers for Disease Control and Prevention (CDC) and the American Dental Association (ADA) in stating that community water fluoridation is safe, effective, and prevents unnecessary dental disease, a costly and painful condition.

The AAP is particularly concerned with the high rates of early childhood caries (tooth decay) in the United States and the detrimental effects this disease can have on children. Dental caries, although largely preventable, is the most common chronic childhood disease, five times more common than asthma. Dental caries can lead to severe health problems, including serious infection, debilitating pain, dietary and speech problems, and in rare cases, even death.

The AAP supports community water fluoridation to help protect children's teeth. Regular and frequent exposure to small amounts of fluoride is the best way to protect the teeth against caries. This exposure can be readily accomplished through drinking water that has been optimally fluoridated and brushing with fluoride toothpaste twice daily.¹ The delivery of fluoride includes community-based, professionally applied, and self-administered modalities. Community-based water fluoridation intervention optimizes the level of fluoride in drinking water, resulting in pre-eruptive and post-eruptive protection of the teeth.

Water fluoridation is a cost-effective means of preventing dental caries, with the lifetime cost per person equaling less than the cost of one dental restoration. In short, fluoridated water is the cheapest and most effective way to deliver anti-caries benefits to communities.² Water fluoridation is seen as effective and inexpensive, does not require daily adherence, and promotes equity, because it benefits everyone regardless of socioeconomic status.³

The AAP continues its mission to ensure the health and well-being of all children, and, to this end, supports local and state efforts for children to have access to safe, optimally fluoridated water. If you require additional information, please contact Hollis Russinof, hrussinof@aap.org.

Sincerely,

Sara H. Goza, MD, FAAP
President

SHG/hr

¹ Bright Futures Guidelines for the Health Supervision of Infants, Children, and Adolescents, 4th Edition. 2017.

² Fluoride Use in Caries Prevention in the Primary Care Setting. *Pediatrics*. 2014; 134(3): 626-633.

³ Early Childhood Caries in Indigenous Communities. *Pediatrics*. 2011; 127(6): 1190-1198.



AMERICAN PUBLIC HEALTH ASSOCIATION
For science. For action. For health.

August 31, 2020

City of Green Bay
100 N Jefferson Street, Room 106
Green Bay, WI 54301

Dear Mayor Genrich, Common Council President Brunette, Vice President Dorff, and Alderpersons Corpus-Dax, Gerlach, Galvin, Stevens, LeFebvre, Scannell, Wery, Johnson, Steuer, and VanderLeest,

On behalf of the American Public Health Association, a diverse community of public health professionals who have championed the health of all people and communities around the world for more than 145 years, I write to urge you to maintain the fluoridation of community water supplies in Green Bay. APHA has supported community water fluoridation as a safe and effective means of preventing tooth decay for more than 60 years. APHA most recently reiterated its support for community water fluoridation by adopting the policy statement Community Water Fluoridation in the United States in 2008.

The overwhelming preponderance of scientific evidence supports community water fluoridation as a safe, effective and cost-saving public health measure for the prevention of dental caries that benefits all segments of the community. The Centers for Disease Control and Prevention recognized water fluoridation as one of ten great public health achievements of the twentieth century. The U.S. government's Healthy People initiative has included the expansion of community water fluoridation as a national health objective in each iteration since it began in 1990, including the new Healthy People 2030 health objectives for the nation.

Consistent with the recommendation of virtually every major public health, medical and dental organization in the United States, APHA urges you continue the important public health strategy of community water fluoridation.

Sincerely,

Georges C. Benjamin, MD
Executive Director
American Public Health Association

Josefine Ortiz Wolfe, PhD, RDH
Chair, Oral Health Section
American Public Health Association

Cc: Mayor's Chief of Staff, Celestine Jeffreys
City Clerk, Kris Teske
Nancy Quirk (General Manager, Green Bay Water Utility
Johnny Johnson, American Fluoridation Society

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Wednesday, October 7, 2020 8:22 AM
To: Jaime Fuge
Subject: (For Agenda) Fwd: American Academy of Pediatrics Support for Community Water Fluoridation
Attachments: AAP CWF Letter Green Bay 10.05.20.pdf

Forwarding to you in case it didn't get included. Thanks Jaime

----- Forwarded message -----

From: **Russinof, Hollis** <HRussinof@aap.org>
Date: Mon, Oct 5, 2020 at 12:54 PM
Subject: American Academy of Pediatrics Support for Community Water Fluoridation
To: district10@greenbaywi.gov <district10@greenbaywi.gov>, district11@greenbaywi.gov <district11@greenbaywi.gov>, district6@greenbaywi.gov <district6@greenbaywi.gov>, district5@greenbaywi.gov <district5@greenbaywi.gov>
Cc: Eric.Genrich@greenbaywi.gov <Eric.Genrich@greenbaywi.gov>, celestineje@greenbaywi.gov <celestineje@greenbaywi.gov>, clerkinquiries@greenbaywi.gov <clerkinquiries@greenbaywi.gov>, district1@greenbaywi.gov <district1@greenbaywi.gov>, district2@greenbaywi.gov <district2@greenbaywi.gov>, district3@greenbaywi.gov <district3@greenbaywi.gov>, district4@greenbaywi.gov <district4@greenbaywi.gov>, district7@greenbaywi.gov <district7@greenbaywi.gov>, district8@greenbaywi.gov <district8@greenbaywi.gov>, district9@greenbaywi.gov <district9@greenbaywi.gov>, district12@greenbaywi.gov <district12@greenbaywi.gov>, Nancy.Quirk@greenbaywi.gov <Nancy.Quirk@greenbaywi.gov>

Mayor Genrich and Members of the Green Bay City Council and Protection and Policy Committee-

I am contacting you at the request of local advocates.

The American Academy of Pediatrics supports community water fluoridation as a cost-effective means of preventing tooth decay throughout the lifespan and joins with other major medical and health organizations in advocating for this common sense public health policy.

Many people don't realize that tooth decay, although preventable, is the most common chronic childhood disease, 5 times more common than asthma. All too often, it leads to countless hours out of school and work, needless pain and suffering, and costly visits to the emergency room.

We support community water fluoridation because it is backed by a solid base of scientific evidence and over 70 years of practice and because it is safe and effective.

Attached you will find our letter of support. We invite you to visit our website, ILikeMyTeeth.org, for additional information.

Respectfully submitted,

Hollis Russinof, MUPP

American Academy of Pediatrics

Campaign for Dental Health

345 Park Boulevard

Itasca, Illinois 60143

630/626-6483

Pronouns: she/her/hers

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



90 Years of Caring for Children—1930–2020

October 5, 2020

345 Park Blvd
Itasca, IL 60143
Phone: 630/626-6000
Fax: 847/434-8000
www.aap.org

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Sincerely,

Sara Goza MD, FAAP

Sara H. Goza, MD, FAAP
President

SHG/hr

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³ Early Childhood Caries in Indigenous Communities. *Pediatrics*. 2011;127(6):1190-1198.

Jaime Fuge

From: Johnny Johnson <drjohnnyjohnson@gmail.com>
Sent: Wednesday, October 7, 2020 9:46 AM
To: District Ten; District Eleven; District Five; District Six
Cc: Eric Genrich; District One; District Two; District Three; District Four; District Seven; District Eight; District Nine; District Twelve; Celestine Jeffreys; Nancy Quirk; Dunkel, Russell D - DHS; Robbyn Kuester; mcrespin@chw.org; Erika Valadez; ClerkInquiries; Jaime Fuge
Subject: Re: (For Agenda) Questions from Protection and Policy Committee on if I'm paid, doctors on both sides, and medical community not agreeing with fluoridation

I do want to add that in addition to not being paid a single penny for what I do, I have been called a lobbyist by Brenda Staudenmaier.

In Madison, when I spoke there, along with another AFS Board member, we received an email after that meeting a couple of weeks ago that we had to register as lobbyists. We *are not* lobbyists and had to involve our attorney to help straighten this out. It was an underhanded move to intimidate us.

Further, after Madison's meeting, emails of people who registered to speak were accessed by "someone". Many of those who spoke are friends/colleagues of mine. They'd registered using their private emails. Soon after that meeting, they received emails from Brenda Staudenmaier and/or NYSCOF (New York State Coalition Opposed to Fluoridation) at their **workplace emails**. This is further evidence of attempts by the opposition to intimidate speakers, as Brenda Staudenmaier did by filing claims against the dental license of WI State Dental Director Dr. Russ Dunkel. Those claims were dismissed quickly as there was no basis for them. She's trying to intimidate him.....that's not going to work!

Please follow the credible science that you are receiving and not information that is based in conspiracy and misinformation. The following is just a sample of health and scientific organizations that endorse fluoridation as safe and effective:

1. American Academy of Pediatrics
2. American Dental Association
3. CDC
4. Mayo Clinic
5. U.S. Department of Defense
6. American Water Works Association
7. U.S. Public Health Service
8. World Health Organization

Thank you.

Johnny

Johnny Johnson, Jr., DMD, MS
Pediatric Dentist
Diplomate, American Board of Pediatric Dentistry
Life Fellow, American Academy of Pediatric Dentistry

President, American Fluoridation Society
www.AmericanFluoridationSociety.org
@AFS_Fluoride
c: 727.409.1770

On Wed, Oct 7, 2020 at 9:28 AM Johnny Johnson <drjohnnyjohnson@gmail.com> wrote:



October 7, 2020

Dear Chair Steuer, and Alderperson's VanderLeest, Lefebvre, and Stevens,

Recently in speaking with a couple of you, I have been asked three questions that I want to address with all of you.

1. Am I paid to speak at these meetings and/or promote water fluoridation (CWF)?

- Absolutely not.
- As the President of the American Fluoridation Society (AFS), I receive no income or perks for doing this. It is my honor to help our country's families, especially those most impoverished, to have the best oral and general overall health that they can have.

On the other hand, Paul Connett, the Executive Director of the Fluoride Action Network who has spoken before you and the Brown County Board of Health, *is* paid for the work that he does. Connett, and his wife Ellen, have openly said that they receive \$2,000 each/month for the work that they do.

You can decide if there is a motivation behind what I do and what British-American Chemist Connett does.

2. There are doctors and dentists on both sides of this debate. Who is right?

- There are doctors, dentists, PhDs, and others who oppose CWF. As in any field or subject matter, there are outliers in our fields. Who you've heard from at your first Protection and Policy Committee meeting was a one-sided cyberattack by those on that meeting. ~50 people on that call were opposed to CWF. The proponents of CWF had no idea of that group being on the call in those numbers. That's why we had 6-7 people on the call.
- I pulled some numbers **just from the U.S.** on practicing physicians, nurses, dentists, and PhDs to compare with the numbers that FAN has on it's webpage that oppose CWF **worldwide**. That information is below.
- This information clearly shows that those who oppose CWF are an extremely small group, approximately 1:100,000. However, the internet has given FAN and others a worldwide stage to promote their anti-vaccination/anti-fluoridation opinions.
- In the U.S. there are over 960,000 physicians, over 3 million nurses, more than 180,000 dentists and about 4.5 million PhDs.

<https://bhwhrsa.gov/sites/default/files/bhw/health-workforce-analysis/research/hrsa-us-health-workforce-chartbook-in-brief.pdf>

<https://www.census.gov/library/stories/2019/02/number-of-people-with-masters-and-phd-degrees-double-since-2000.html>

- According to FAN's website, fluoridealert.org, 4800 professionals had signed a statement calling for an end to fluoridation.
- However, only about 200 have signed the new statement issued in 2018.
- <http://fluoridealert.org/researchers/professionals-statement/the-new-statement-signers/>
- Of the 200, 27 are physicians (MD or MB degree), 19 are nurses, 25 are dentists (with a DDS, DMD or BDS), and 36 hold a PhD degree.

- That is a total of **107** physicians, nurses, dentists and PhDs opposing fluoridation, **which represents 0.001% of all physicians, nurses, dentists and PhD's or 1 in every 100,000 of those professionals in the USA.**
- Note that 54 of the 200 in the list of Professionals Opposed to fluoridation are from outside the US.

I hope that this information puts into perspective the people who have been calling, emailing, and who were on the first PPC meeting opposed to CWF. The overwhelming majority of professionals support CWF's safety and effectiveness.

3. The medical profession seems not to agree with CWF.

- The American Public Health Association (APHA) has sent you an emailed letter supporting the safety and effectiveness of CWF (attached). The APHA has over 25,000 members from every area of health represented.
- The American Academy of Pediatrics (AAP) has sent you an emailed letter supporting the safety and effectiveness of CWF (attached). The AAP had ~67,000 members. That number includes one of my daughters, a Pediatric Endocrinologist. If you have *any questions* about fluoridation and endocrine disorders, she will happily answer them. I will let you know that she, along with her mentor, Janet Silverstein (past president of the Endocrine Society in the U.S. multiple times), will tell you that there are absolutely no interactions of CWF with any endocrine system, including the Thyroid gland.

Please consider the solid scientific evidence that has been published in credibly recognized scientific journals and vote to keep Green Bay's water fluoridated.

Thank you.

Warmly,



Johnny Johnson, Jr., DMD, MS

Pediatric Dentist

Diplomate, American Board of Pediatric Dentistry

Life Fellow, American Academy of Pediatric Dentistry

President, American Fluoridation Society

Web: <https://americanfluoridationsociety.org/>

Cell: 727-409-1770

Email: drjohnnyjohnson@gmail.com

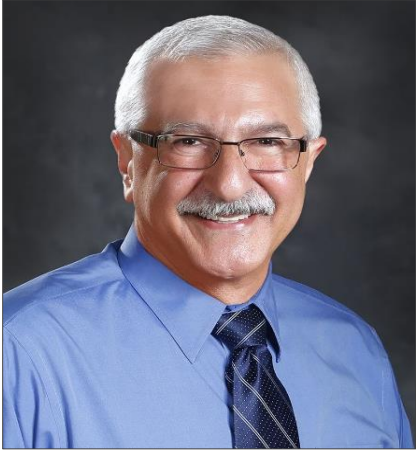
The Risks vs Benefits of Community Water Fluoridation



**Green Bay Protection and Policy Committee Meeting
on Water Fluoridation**

Green Bay, WI
October 8, 2020

Disclosures



Johnny Johnson, MS, DMD, is president of the American Fluoridation Society. He has no financial or other conflicts to disclose related to the information cited in this presentation.

He is a non-paid volunteer of the American Fluoridation Society

1. How did we discover fluoride's benefits?

Fluoride: A naturally occurring mineral



- 13th most abundant mineral in the earth's crust
- **Surface water** (rivers) — typically low concentrations, 0.2 mg/L (ppm) or less
- **Groundwater** (wells) — higher concentrations, 0.1 mg/L to over 5.0 mg/L
- **Ocean** is typically 0.8 to 1.4 mg/L

The early years of fluoride research

Dr. Frederick S. McKay

- **1901:** He established his dental practice in Colorado Springs, CO
- “Colorado Brown Stain” — Only life-long residents (or those who had moved there as infants) had it
- **1908** — He began to investigate the extent of fluorosis in surrounding areas



Key Observation: *Very few cavities in this population*

Intensive research begins

Objective: Explore the link between fluoride & cavity reduction

1.0 mg/L
fluoride led to
optimal cavity
reductions
without brown
staining

H. Trendley Dean

- 1931 begins to study epid. of F-
 - Improves technology of assay
 - Creates and index
- 1933 - Compares "High" and "Low" F- communities.
- 1939 - Compares "high" and "low" F- communities.
- 1941- Launches field investigation – "21 Cities" study.

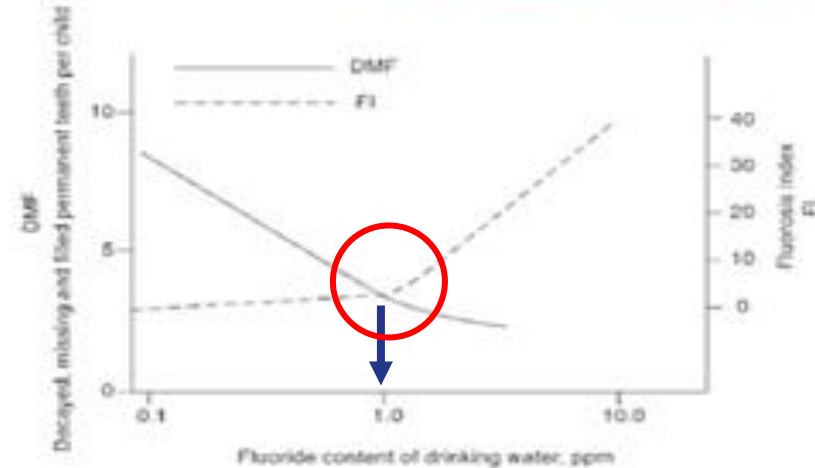


FIGURE 5.3 Relationship between the fluoride content of drinking water, caries occurrence, and dental fluorosis. (Source: H. C. Hodge, The concentration of fluorides in drinking water to give the point of minimum caries with maximum safety. *J. Am. Dent. Assoc.*, 40, 436–439, 1950. Copyright © 1950 American Dental Association. All rights reserved. Adapted 2008 with permission of the American Dental Association.)

Studies to replicate Mother Nature

- 4 pairs of cities in the U.S. and Canada were identified to study the effect of water fluoridation
 - *4 cities adjusted to 1.0 mg/L of F, and 4 remained non-fluoridated*
- Grand Rapids, Mich. was the first city to adjust fluoride levels in public drinking water (1945)
 - *Muskegon, MI was the control city*
- Cavity rates dropped dramatically: **60-70%**



Mother Nature was replicated!

The paired city studies showed that Mother Nature had been replicated

Centers for Disease Control and Prevention (CDC) named water fluoridation "one of ten great public health achievements of the 20th century". Others included:

- Vaccination
- Motor-vehicle safety
- Safer workplaces
- Control of infectious diseases
- Decline in deaths from coronary heart disease and stroke
- Healthier mothers and babies
- Recognition of tobacco use as a health hazard

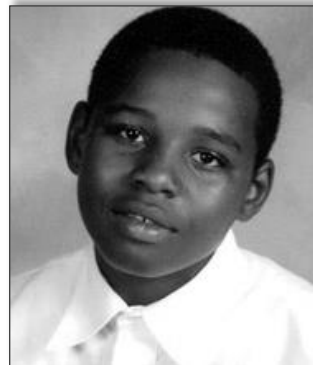


2. What are the health benefits of Fluoridation?

Why oral health matters

Dental cavities are the **most common chronic disease** for children and teens. It's significantly more common than *asthma, obesity, and diabetes*. **Infectious and Transmissible**

- Severe pain (toothaches)
- Difficulty in chewing
- Poor weight gain
- Difficulty concentrating
- Predictor of cavities later in life
- Costly to treat
- Deaths



Cavities are unevenly distributed



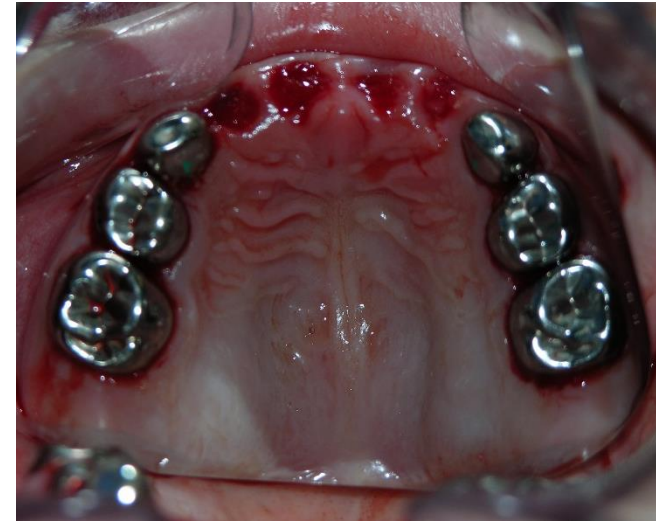
- Low-income kids are more than twice as likely to experience tooth decay.
- The disadvantaged bear a disproportionate burden of cavities
- **In Green Bay, 1 in 6 people live in poverty, nearly 17,000 people**

Avoiding the need for hospital treatment

- The average cost of treating early childhood decay in hospital operating rooms in Colorado ranged from **\$10,000 to \$15,000** per child
- A study in Israel study estimated that water fluoridation may be preventing approximately **300 hospitalizations** each year from dental infections



Reducing OR/General Anesthesia full-mouth restorations by 2/3



Everyone feels the financial impact

Treating a preventable disease financially punishes families and taxpayers

- CWF (or the lack of it) impacts the health and wealth of families and the community
- Average cost of a filling = **\$204**
- The lifetime cost of a single decayed molar can reach as high as **\$6,105**
- CWF saved Texas' Medicaid program **\$24 per child, per year** in dental treatment costs



A form of prevention that reaches everyone

Impact of CWF:

1. 25% cavity reductions for all, regardless of age, income level, race, ethnicity, education level, or access to dental care
2. Saves \$32/person/year in averted dental treatment*
3. For Green Bay, ~\$3.4 million saved b/c of CWF**



A window to overall health



The Mayo Clinic calls oral health a “window to your overall health”

A (big) ounce of prevention

- The CDC called water fluoridation one of “*10 great public health achievements of the 20th century.*”
- Fluoridation reduces tooth decay by **25%** over a lifetime — protection **beyond** what is offered by **fluoride toothpaste** and other methods.
- Over 207 million U.S. residents have access to fluoridated water.



How fluoride works

Topical Effect

- From the outside of the tooth
- Saliva, fluoridated toothpaste and other topical products

Systemic Effect

- From the *inside* and *outside* of the tooth
- Saliva bathes the teeth enamel 24/7 every day*



Adults also benefit, rather than only children (as was once assumed)

A strong consensus of support

- **American Water Works Association**
- **Department of Defense**
- American Academy of Family Physicians
- **American Academy of Pediatrics**
- American Academy of Pediatric Dentistry
- **American Dental Association**
- American Dental Hygienists' Association
- **American Medical Association**
- American Osteopathic Association
- American Nurses Association
- American Public Health Association
- Assoc. of Maternal & Child Health Programs
- **CDC**



- National Academy of Medicine (*formerly known as the Institute of Medicine*)
- **Mayo Clinic**
- U.S. Surgeon General
- **World Health Organization**

3. What happens when Fluoridation is stopped?

What happens when CWF ends



Major cavity increases after cessation:

- **Juneau, Alaska** – Dental disease among preschool-age kids increased, requiring an average of 1 additional dental procedure *per child, per year*
- **Calgary (Canada)** – Cavity rates among children skyrocketed 146% in 3 years
- **Windsor (Canada)** – Cavity rates increased 51% in a 5-year period

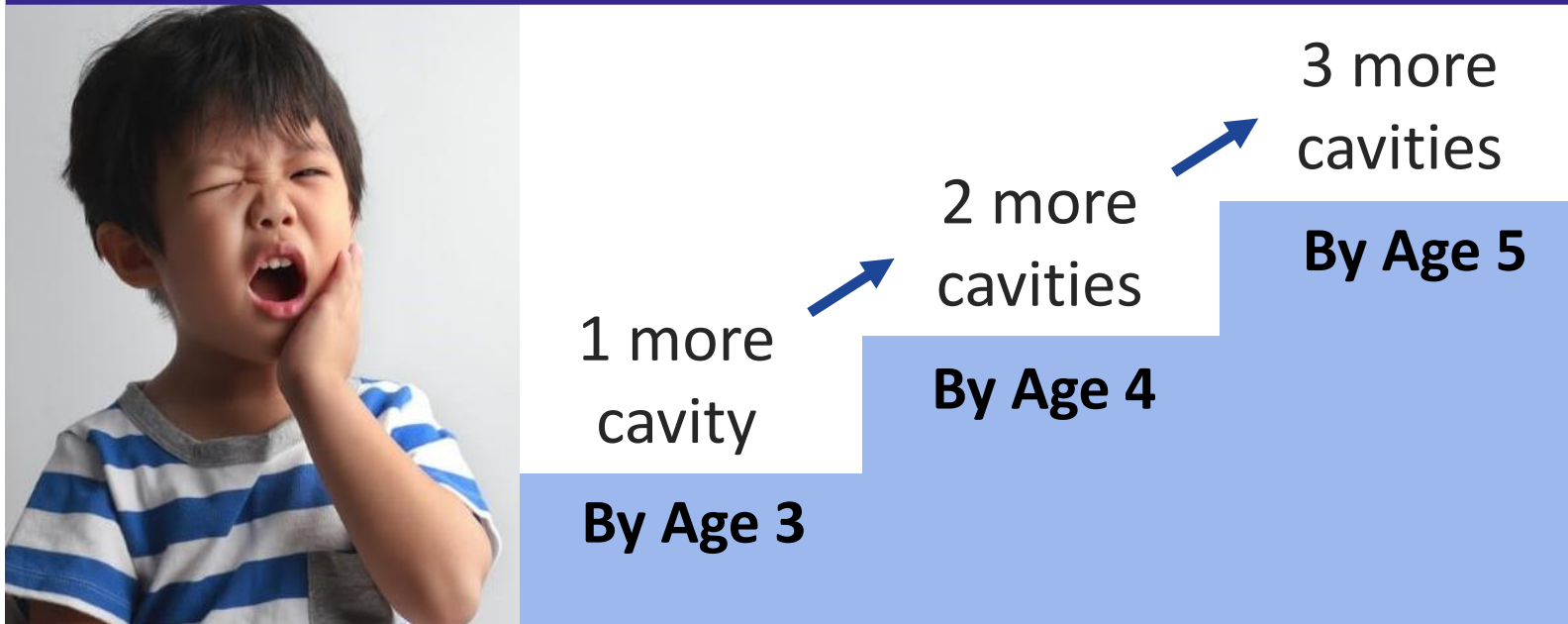
What happens when CWF ends

- Alaska's capital city **Juneau** stopped adding fluoride to its drinking water in 2007.
- Researchers carried out a study to examine Medicaid dental claims to explore the impact of cessation.



What happens when CWF ends

After fluoridation ended in Alaska's capital city, the average low-income child needed **1 additional procedure each year** to treat tooth decay



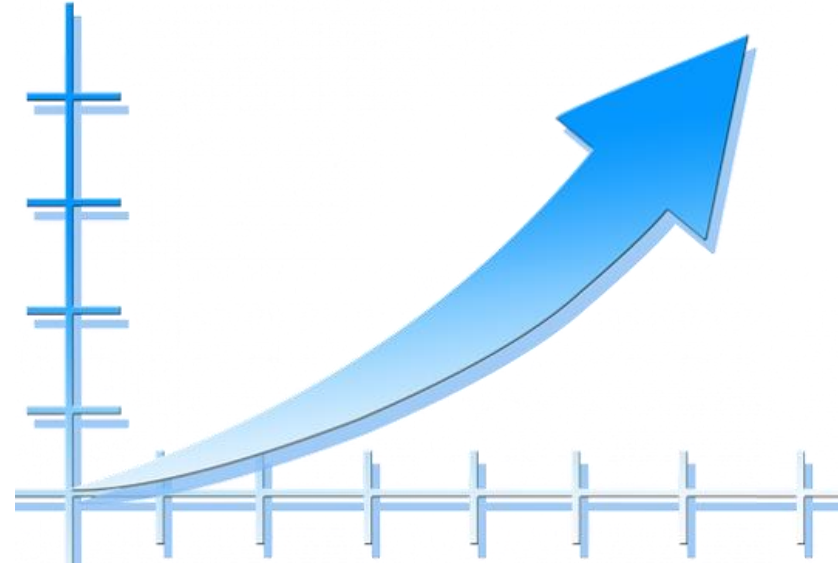
What happens when CWF ends

- In 2016, a study was published examining tooth decay trends among 2nd grade children in two Canadian cities: **Calgary** and **Edmonton**.
- Calgary had ceased fluoridation in 2011. Edmonton remained fluoridated throughout the period that was studied.



What happens when CWF ends

- In order to compare apples to apples, the study examined tooth decay rates in both cities at the same two points.
- The cavity rate for Calgary children jumped **146%** after fluoridation ceased.
- Although decay also rose in Edmonton during this period, cavities in Calgary rose at **3 times the rate** of Edmonton.



What happens when CWF ends

In Canada, the city of **Windsor** voted to resume CWF after their public health unit released data showing a **51% increase** in cavities and emergency dental needs.



4. Why do we know that fluoridation is safe?

Numerous reviews and studies support CWF's safety

- **Archives of Toxicology (2020)**
- National Toxicology Program (2018)
- Food Safety Authority of Ireland (2018)
- Environmental Protection Agency (2017)
- National Health & Medical Research Council of Australia (2016)
- Water Research Foundation (2015)
- Public Health England (2014, 2018)
- Royal Society of New Zealand (2014)
- Community Preventive Services Task Force (2013)
- Calif. Office of Environmental Health Hazard Assessment (2011)
- **National Research Council** (2006, 1993, 1977 & 1951)
- Irish Forum on Fluoridation (2002)
- U.S. Public Health Service (1991)
- Britain's Royal College of Physicians (1976)
- Univ. of Michigan School of Public Health (1960)

Research confirms fluoridation's safety

Opponents: *"The EPA should review our petition."*

In 2017, the EPA carefully reviewed their petition — and rejected it.



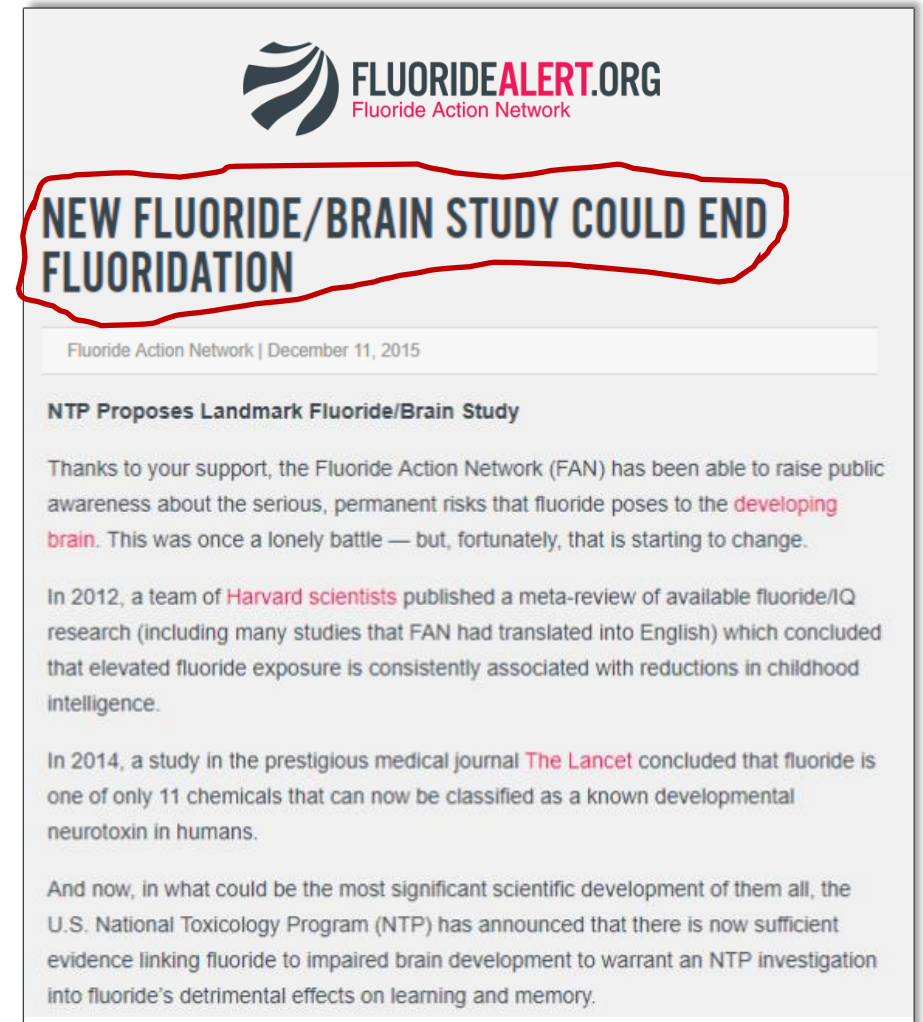
The petition “has **not** set forth a scientifically defensible basis to conclude that any persons have suffered neurotoxic harm” from water fluoridation.

Research confirms fluoridation's safety

Opponents: “The NTP should conduct a study.”

(Source: C.A. McPherson et al., “An Evaluation of Neurotoxicity Following Fluoride Exposure from Gestational Through Adult Ages in Long-Evans Hooded Rats,” Neurotoxicity Research, 2018; Article from FAN’s website was written by Michael Connett, Dec. 11, 2015; Note: The statement in quotations is intended to paraphrase the kinds of assertions that opponents have made; it is not a verbatim quotation by a specific individual.)

- The National Toxicology Program (NTP) conducted a study
- The NTP “observed no exposure-related differences in motor, sensory, or learning and memory performance” for any of the 9 tests they conducted
 - Thyroid hormone levels were **not** affected — even at levels of 0, 10 or 20 parts per million of fluoride



 **FLUORIDEALERT.ORG**
Fluoride Action Network

NEW FLUORIDE/BRAIN STUDY COULD END FLUORIDATION

Fluoride Action Network | December 11, 2015

NTP Proposes Landmark Fluoride/Brain Study

Thanks to your support, the Fluoride Action Network (FAN) has been able to raise public awareness about the serious, permanent risks that fluoride poses to the **developing brain**. This was once a lonely battle — but, fortunately, that is starting to change.

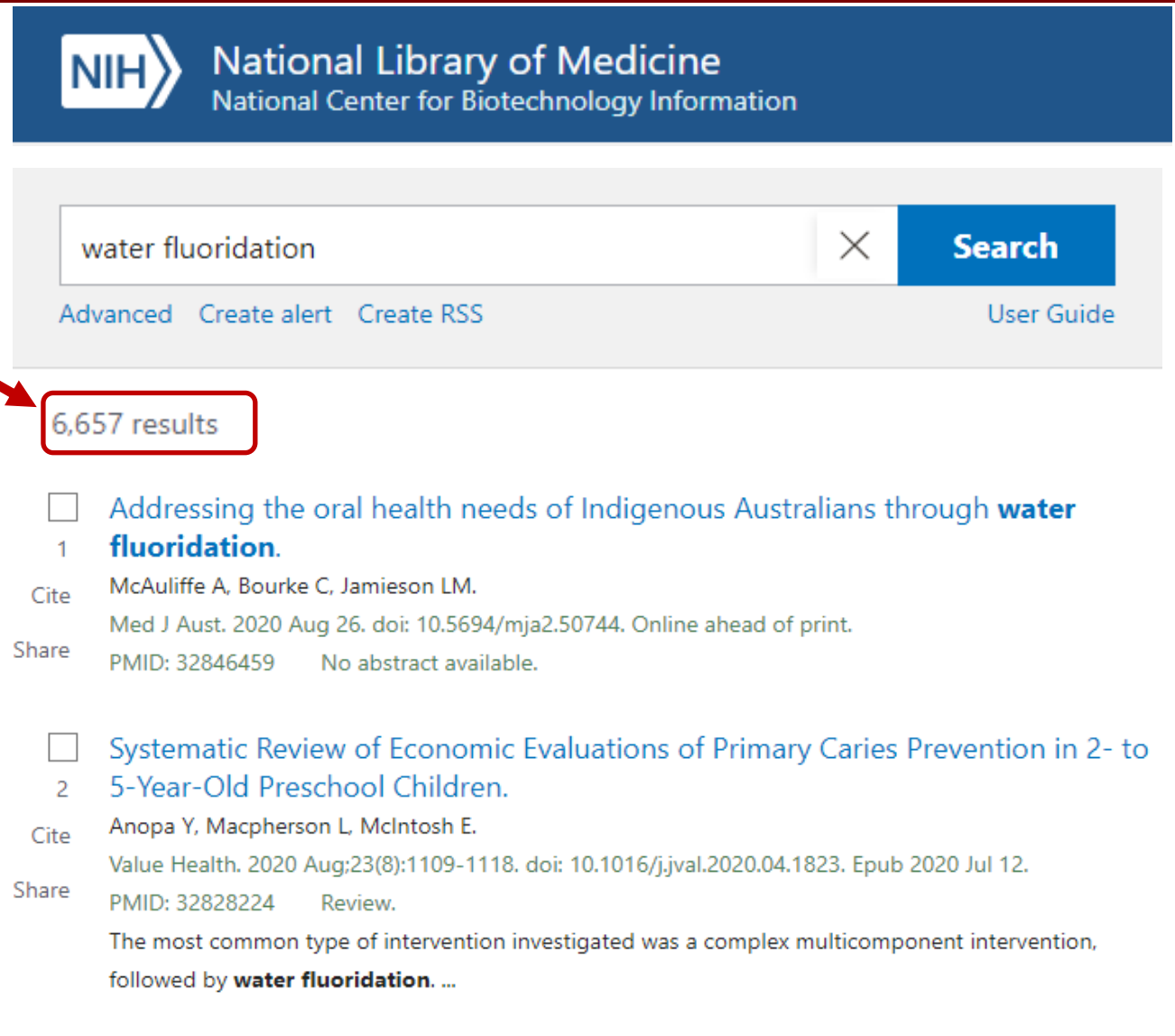
In 2012, a team of **Harvard scientists** published a meta-review of available fluoride/IQ research (including many studies that FAN had translated into English) which concluded that elevated fluoride exposure is consistently associated with reductions in childhood intelligence.

In 2014, a study in the prestigious medical journal **The Lancet** concluded that fluoride is one of only 11 chemicals that can now be classified as a known developmental neurotoxin in humans.

And now, in what could be the most significant scientific development of them all, the U.S. National Toxicology Program (NTP) has announced that there is now sufficient evidence linking fluoride to impaired brain development to warrant an NTP investigation into fluoride's detrimental effects on learning and memory.

Consensus of literature = Public Health Policy

Thousands of studies have been conducted about water fluoridation



NIH National Library of Medicine
National Center for Biotechnology Information

water fluoridation X Search

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6,657 results

☐ 1 Addressing the oral health needs of Indigenous Australians through **water fluoridation**.

Cite McAuliffe A, Bourke C, Jamieson LM.
Med J Aust. 2020 Aug 26. doi: 10.5694/mja2.50744. Online ahead of print.

Share PMID: 32846459 No abstract available.

☐ 2 Systematic Review of Economic Evaluations of Primary Caries Prevention in 2- to 5-Year-Old Preschool Children.

Cite Anopa Y, Macpherson L, McIntosh E.
Value Health. 2020 Aug;23(8):1109-1118. doi: 10.1016/j.jval.2020.04.1823. Epub 2020 Jul 12.

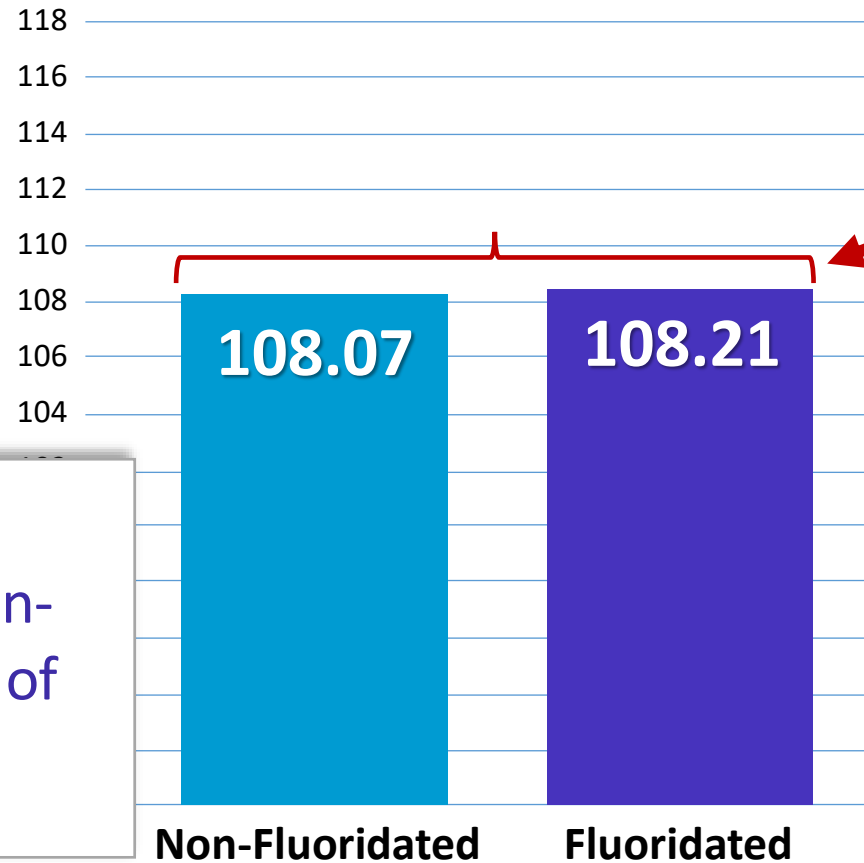
Share PMID: 32828224 Review.

The most common type of intervention investigated was a complex multicomponent intervention, followed by **water fluoridation**. ...

What did the Green, Till et al study reveal?

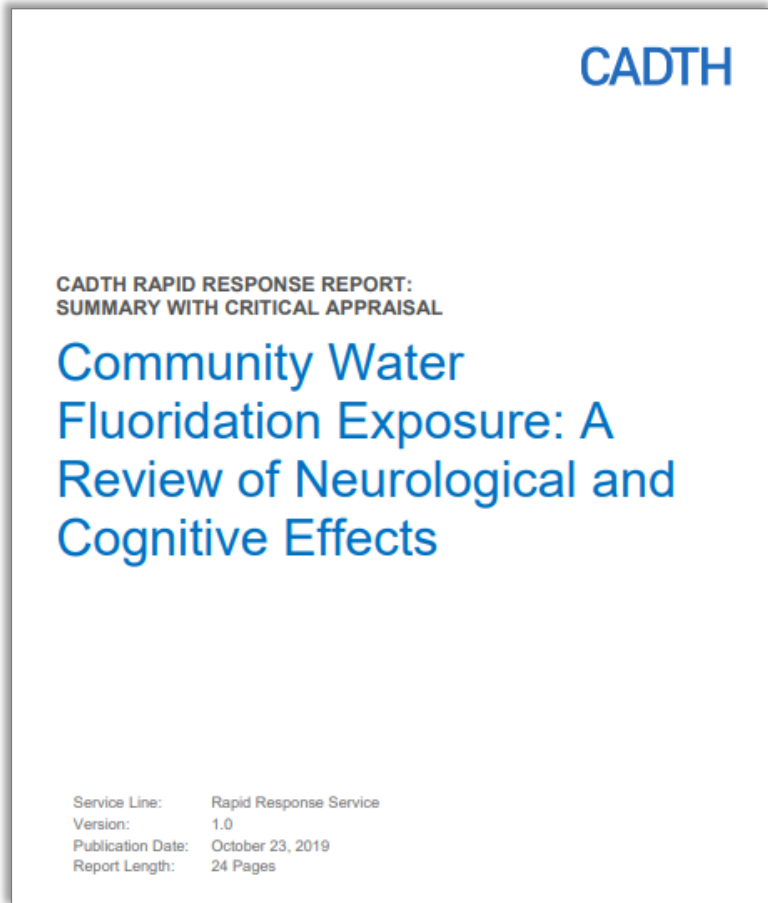
The average IQ score of 3 and 4 year-old children in Canada by the fluoridation status of their tap water

A subgroup analysis revealed a significant IQ deficit in boys but a non-statistically significant increase in IQ of girls



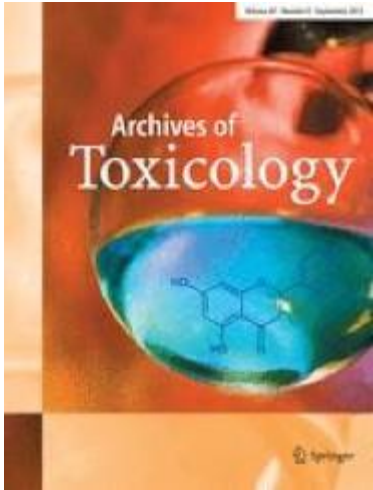
The difference in the average IQ score was only **0.14 pts.**

The Canadian fluoride-IQ study (Green et al.)



- An August 2019 Canadian study linked fluoride and IQ scores.
- The study lacked access to key data, including mothers' IQ scores and post-natal lead exposures.
- “The study by Green et al., 2019¹³ concluded that “maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years.” **This conclusion was not supported by the data.**”

Review article calls statistical analysis “Problematic”



Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses

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Research on fluoride's safety - Ignored by opponents!

- A Swedish study found “**zero effects on cognitive ability**” from drinking water with optimal fluoride levels. ~81,000 subjects



- A New Zealand study collected IQ scores over a 30-year period and found **no link** between fluoridation and IQ scores. >1,000 subjects retained over the 30-year period

Evaluating the 1st NTP DRAFT Monograph

- The National Academies committee voiced “**substantive concerns**” with how NTP evaluated the evidence for its monograph about fluoride.
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(Source: The National Academies of Sciences, Engineering and Medicine, "revised 3Draft NTP Monograph Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects," September 16,, 2020)

The revised NTP DRAFT monograph – Sept 16, 2020

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Research confirms fluoridation's safety

Opponents: *“Mother nature protects babies from fluoride.”*

- Breast feeding is encouraged by leading scientific groups (nutrition, antibodies, etc.).
- **However** . . . breast milk is not perfect. For example, it lacks sufficient:
 - Vitamin D (soft bones)
 - Vitamin K (clotting)
 - Iron (anemia)
 - *Infants are given injections of these shortly after birth to prevent these problems*



Research confirms fluoridation's safety

Opponents: *"Fluoride harms the thyroid gland."*

This 2017 Canadian study showed **no link** between fluoridated water and thyroid problems.

"There was no evidence of a relationship between fluoride exposure (from urine and tap water) and the diagnosis of a thyroid condition."

Research confirms fluoridation's safety

Opponents: *"Fluoride additives are not pharmaceutical grade."*



What the CDC says:

"Some have suggested that pharmaceutical grade fluoride additives should be used for water fluoridation. **Pharmaceutical grading standards used in formulating prescription drugs are not appropriate for water fluoridation additives.** If applied, those standards could actually exceed the amount of impurities allowed by AWWA and NSF/ANSI in drinking water."

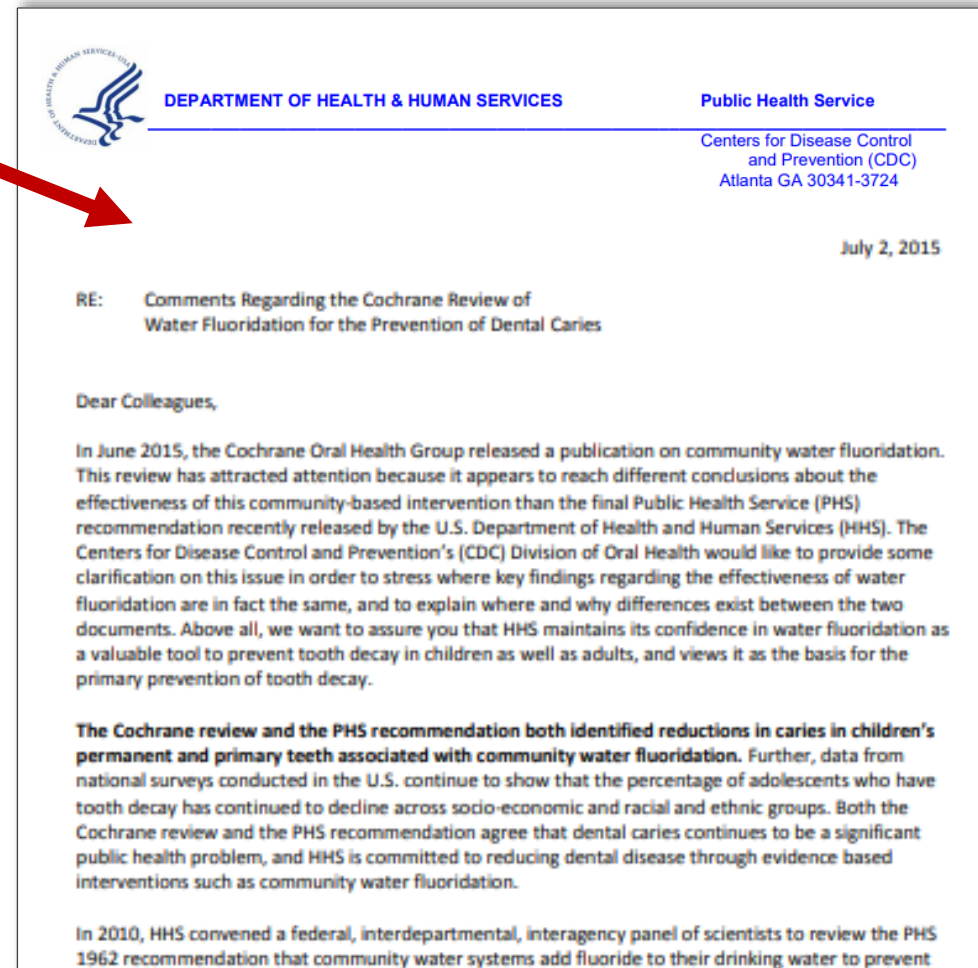
Research confirms fluoridation's safety

Opponents: *"RCTs have never been done on fluoridation."*

- RCTs are a form of research that "is often not feasible for interventions that occur on a community level, like community water fluoridation."
- Observational studies are commonly used for CWF and have been used for:

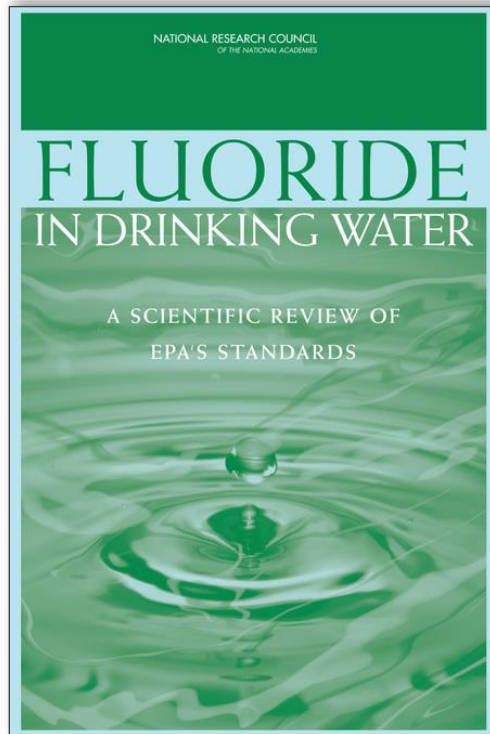
- ✓ Smoking & lung disease
- ✓ Sexually Transmitted Diseases
- ✓ Chronic Alcohol Use

(Source: K. Weno, CDC, "Comments Regarding the Cochrane Review of Water Fluoridation for the Prevention of Dental Caries, July 2, 2015.)



Research confirms fluoridation's safety

Opponents: *“NRC’s 2006 report shows CWF is harmful.”*

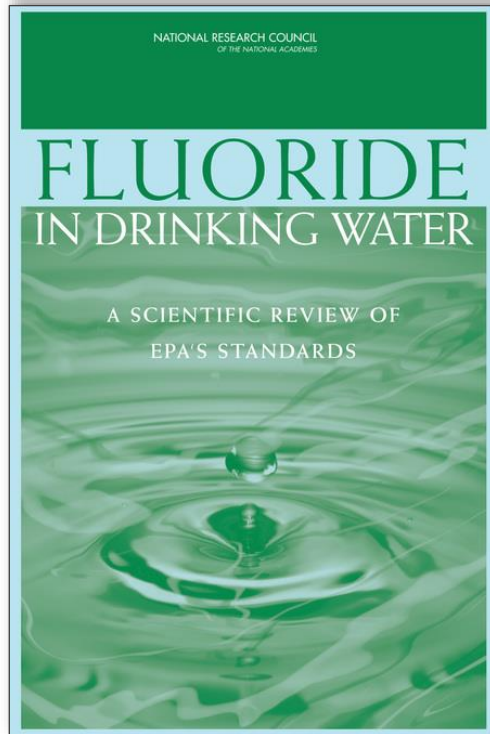


BACKGROUND:

- In 2006, NRC evaluated the appropriate limit on naturally occurring fluoride level* in water to confirm that current limit (4 mg/L) is still protective of health.
- 200,000+ Americans live in areas where the natural fluoride level exceeds 4 mg/L.

Research confirms fluoridation's safety

Opponents: *"NRC's 2006 report shows CWF is harmful."*



FACTS:

As the report explained, the EPA's maximum limit on fluoride is "set at a concentration at which **no adverse health effects** are expected to occur and the margins of safety are judged 'adequate'."

Research confirms fluoridation's safety

Opponents: “NRC’s 2006 report shows CWF is harmful.”

Was there definitive evidence at 4.0 ppm showing that fluoride had an effect on...?

- Tooth enamel ✓
- Liver ✗
- Kidneys ✗
- Endocrine system ✗
- Gastrointestinal system ✗
- Immune system ✗
- Cancer ✗
- Musculoskeletal system ✗
- Reproduction and development ✗
- Neurotoxicity and neurobehavioral ✗
- Genetic damage ✗

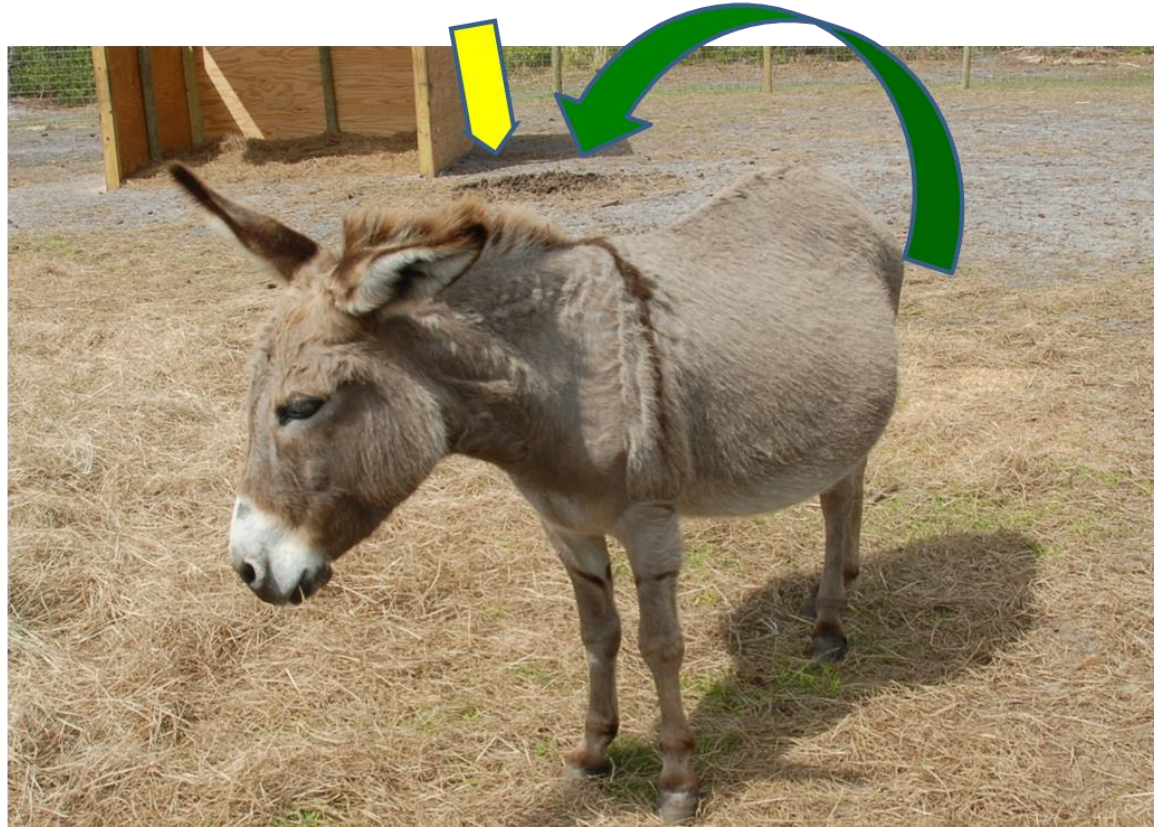
5. Why do a small group of people oppose fluoridation?

A long list of false claims by fluoridation opponents

- No toxicological testing has been conducted on fluoride
- The ADA says it shouldn't be used in infant formula
- Fluorosis is a sign of toxic effects
- It causes ADHD
- It causes Alzheimer's
- It harms the kidney, the immune system and other systems
- It's a conspiracy — the phosphate fertilizer industry is disposing of its "hazardous waste"
- Cavities have fallen in all nations, so fluoridation must not matter
- Some people are allergic to fluoridated water
- It causes thyroid problems
- The only way fluoride works is by topical application
- This is "forced medication"
- The Cochrane Group says there's no evidence behind fluoridation
- Water systems should use a pharmaceutical grade of fluoride

Opponents to CWF: Strategies

Throw it at the wall often and hope something sticks



6. Credibility of the leaders of the opposition

Who is Paul Connett?

- The Executive Director of the Fluoride Action Network, FAN
- British-American PhD Chemist
- He opposes community water fluoridation
- Connett spends much of his time on the road, giving speeches about fluoride to a variety of audiences



Royal Society of Chemistry



Royal Society of Chemistry

We promote, support and
celebrate chemistry

The world's leading chemistry community, advancing
excellence in the chemical sciences



Royal Society of Chemistry: Pro evidence-based science



The Royal Society of Chemistry is *neither* pro *nor* anti water fluoridation but ***they are pro the accurate interpretation of scientific research.***

RSC Spokesperson Dr. Susan Vickers: “On the basis of published **robust** evidence water fluoridation **was both safe and effective in reducing dental decay**”



Source: Hull Science Festival, April 7, 2017, Barry Cockcroft, CBE, BDS, FDS (RCS Eng), FFGDP (UK), DDSc., Chief Dental Officer England 2005-2015

Connett is out of step



**Connett is out of step with Royal
Society of CHEMISTRY organization's
>49,000 members**



Critics call it “mass medication”

- America has a tradition of fortifying foods and drinks to improve human health:

✓ Folic acid	✓ Calcium
✓ Vitamin D	✓ Iodine



- U.S. courts have consistently **rejected** this argument against fluoridation.
- Fluoridation (like chlorination) is about **prevention**.

Critics distort oral health data-Fluoride toothpaste = decline

Figure 1: Data from WHO Database

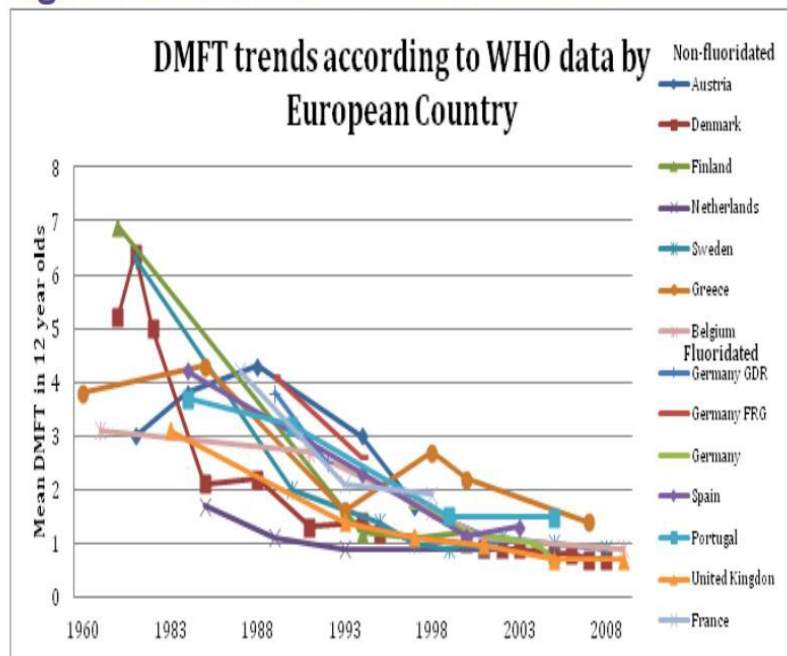


Figure 2: Data manipulated to show linear trend

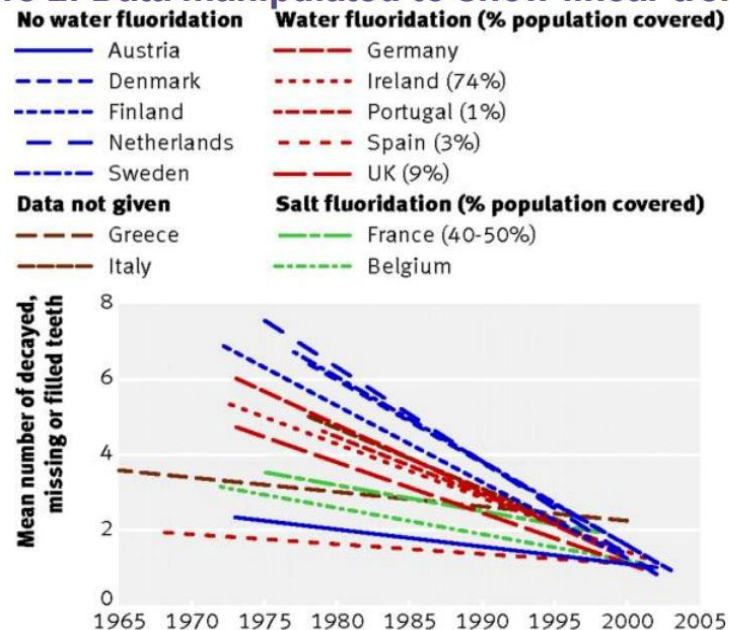
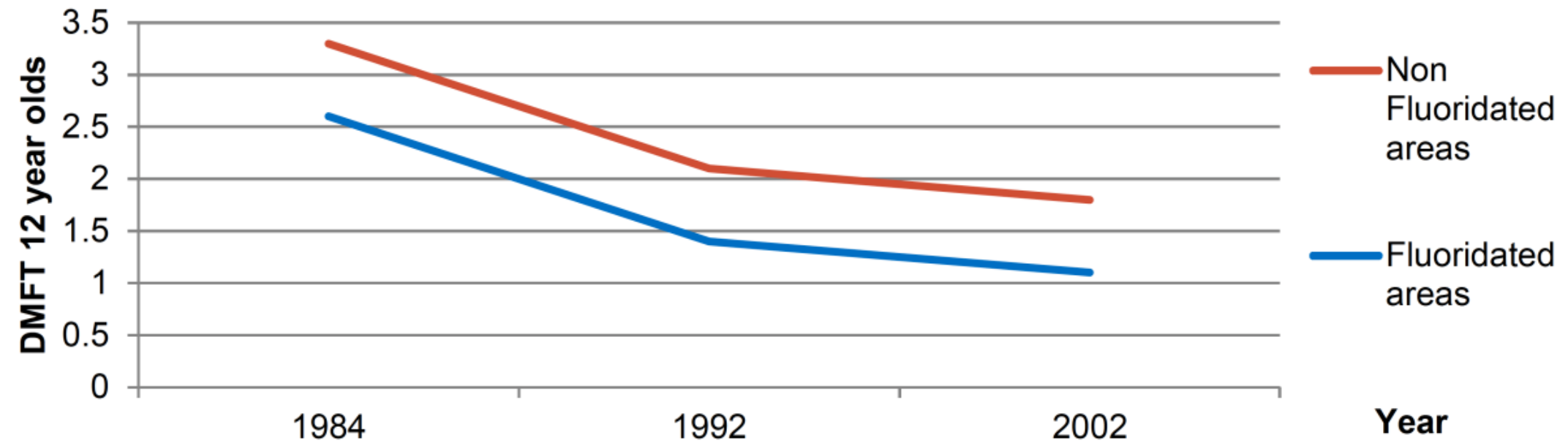


Figure 1 scatter-plot is drawn from data collected by the World Health Organization. Figure 2 is attributed to Cheng et al., "Adding fluoride to water supplies," BMJ, 2007, 335:7622.

- The chart on the left is data from the World Health Organization
- The chart on the right is by opponents of water fluoridation. Straightened out true data points

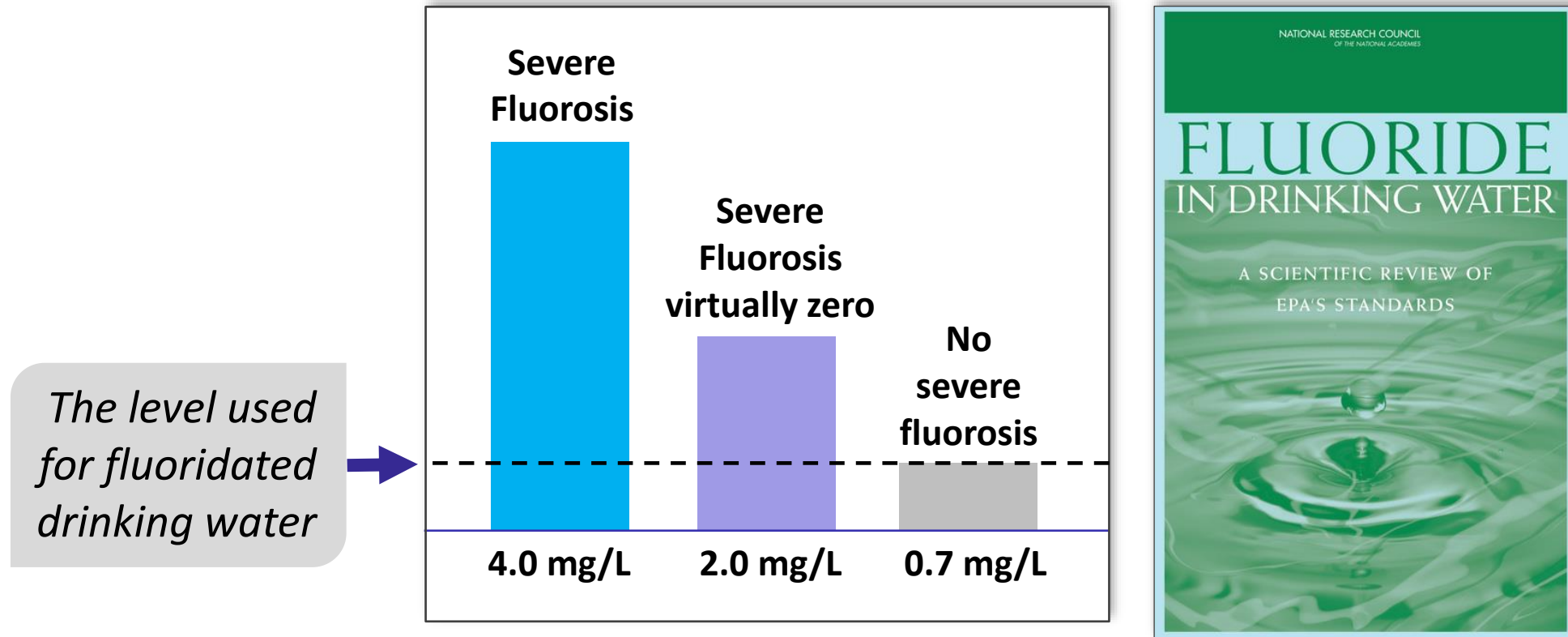
A clear benefit from fluoridation-cavities reduced 25% more by fluoridation

A chart like this compares apples to apples. Children in Ireland who live in fluoridated areas have lower rates of decay



7. What do we know about dental fluorosis?

Critics distort the facts about dental fluorosis



Dental fluorosis

What is dental fluorosis?

- Dental fluorosis is a change in the appearance of tooth enamel caused by high intakes of fluoride during the tooth-forming years.

Dental fluorosis

**What effect
does it have?**

- Dental fluorosis is a change in the appearance of tooth enamel caused by high intakes of fluoride during the tooth-forming years.
- Dental fluorosis is typically a mild cosmetic effect:
 - It does not cause pain
 - It does not affect the health or function of teeth
 - It is so subtle most people don't even notice it

Dental fluorosis

When can
it occur?

- Dental fluorosis is a change in the appearance of tooth enamel caused by high intakes of fluoride during the tooth-forming years.
- Dental fluorosis is typically a mild cosmetic effect:
 - It does not cause pain
 - It does not affect the health or function of teeth
 - It is so subtle most people don't even notice it
- Dental fluorosis can only occur **up to 8 years of age** while permanent teeth are developing.

Critics distort the facts about dental fluorosis

Variations in tooth enamel (fluorosis)



Normal



Very Mild



Moderate

Improper
use of
fluoride
products



Questionable



Mild



Severe

Not
caused
by CWF

Critics distort the facts about dental fluorosis

Opponents
distort the
facts about
fluorosis

Which would you rather have?

Cavities



OR

Mild fluorosis

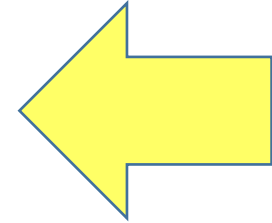


7. Final thoughts about fluoridation

The clear weight of the science



No widely respected
medical and health
organizations
opposes fluoridation



Summary . . .

- ☑ **Effective** at reducing cavities
- ☑ **Safe** — no adverse health effects
- ☑ **Saves money** — in fact, the average person saves \$32.19 per year in dental costs.
- ☑ Prevention that **benefits everyone** in the community (just by turning on the tap)
- ☑ **Recommended by the most respected health/medical organizations:** CDC, American Academy of Pediatrics and the ADA

Resources: Credible scientific resources on Fluoridation

CDC: [Water Fluoridation Information](#): General and specific information on CWF

American Fluoridation Society:

- For the latest information on studies, explaining them, refutations, and scientific hyperlinks

American Dental Association:

- [Fluoridation Facts](#): Detailed information on common claims and charges made against CWF with answers and fully referenced
- [Frequently asked questions](#)
- [Mouth Healthy](#): More information on Fluoridation from ADA

American Academy of Pediatrics:

- [Campaign for Dental Health](#) Fluoridation Information and resources

What Q's do you have?



Johnny Johnson, Jr., DMD, MS

Pediatric Dentist

President

American Fluoridation Society

Johnny@americanfluoridationsociety.com

C: 727-409-1770



The Risks vs Benefits of Community Water Fluoridation



**Green Bay Protection and Policy Committee Meeting
on Water Fluoridation**

Green Bay, WI
October 8, 2020

Fluoride: A naturally occurring mineral



- 13th most abundant mineral in the earth's crust
- **Surface water** (rivers) — typically low concentrations, 0.2 mg/L (ppm) or less
- **Groundwater** (wells) — higher concentrations, 0.1 mg/L to over 5.0 mg/L
- **Ocean** is typically 0.8 to 1.4 mg/L

The early years of fluoride research

Dr. Frederick S. McKay

- **1901:** He established his dental practice in Colorado Springs, CO
- “Colorado Brown Stain” — Only life-long residents (or those who had moved there as infants) had it
- **1908** — He began to investigate the extent of fluorosis in surrounding areas

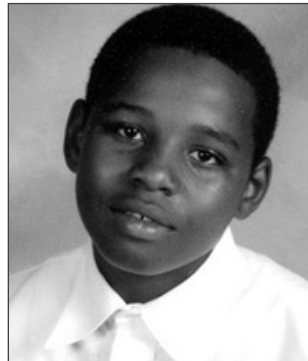


Key Observation: *Very few cavities in this population*

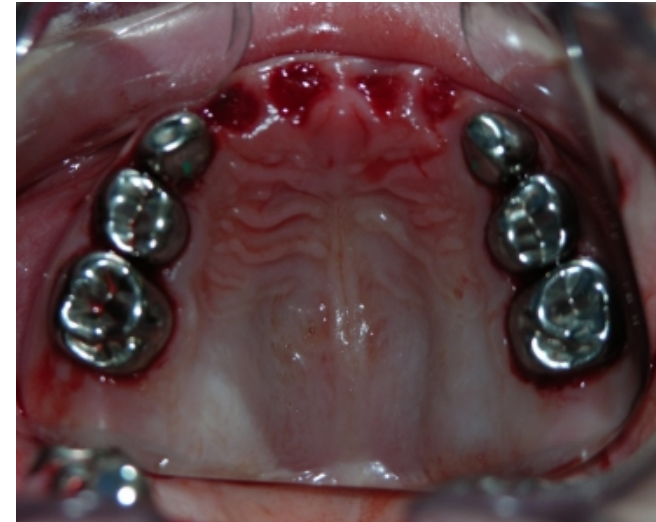
Why oral health matters

Dental cavities are the **most common chronic disease** for children and teens. It's significantly more common than *asthma, obesity, and diabetes*. **Infectious and Transmissible**

- Severe pain (toothaches)
- Difficulty in chewing
- Poor weight gain
- Difficulty concentrating
- Predictor of cavities later in life
- Costly to treat
- Deaths



Reducing OR/General Anesthesia full-mouth restorations by 2/3



What happens when CWF ends



Major cavity increases after cessation:

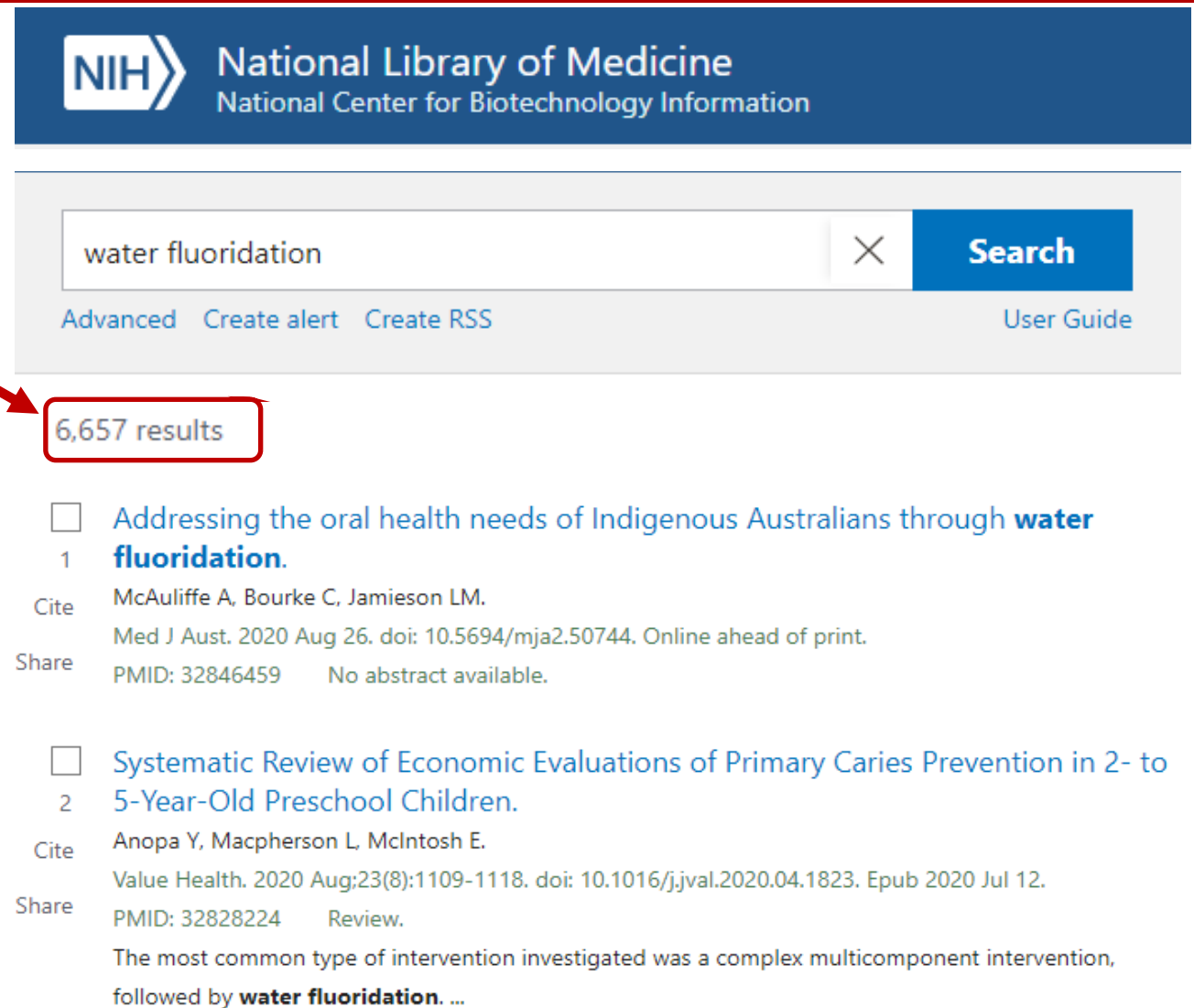
- **Juneau, Alaska** – Dental disease among preschool-age kids increased, requiring an average of 1 additional dental procedure *per child, per year*
- **Calgary (Canada)** – Cavity rates among children skyrocketed 146% in 3 years
- **Windsor (Canada)** – Cavity rates increased 51% in a 5-year period

Numerous reviews and studies support CWF's safety

- **Archives of Toxicology (2020)**
- National Toxicology Program (2018)
- Food Safety Authority of Ireland (2018)
- Environmental Protection Agency (2017)
- National Health & Medical Research Council of Australia (2016)
- Water Research Foundation (2015)
- Public Health England (2014, 2018)
- Royal Society of New Zealand (2014)
- Community Preventive Services Task Force (2013)
- Calif. Office of Environmental Health Hazard Assessment (2011)
- **National Research Council** (2006, 1993, 1977 & 1951)
- Irish Forum on Fluoridation (2002)
- U.S. Public Health Service (1991)
- Britain's Royal College of Physicians (1976)
- Univ. of Michigan School of Public Health (1960)

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water fluoridation

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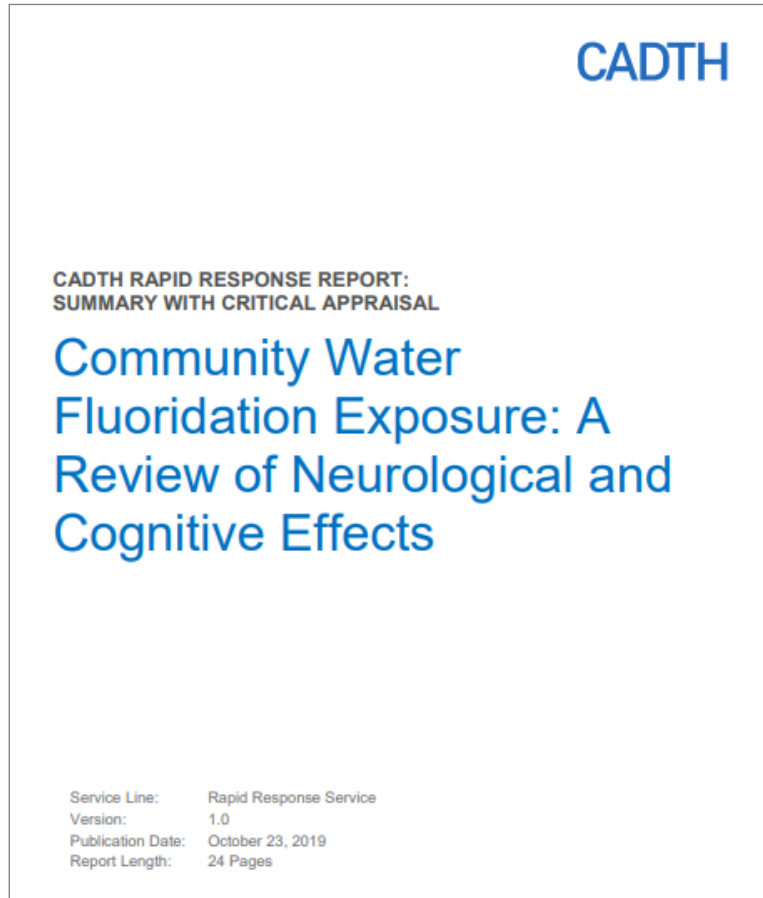
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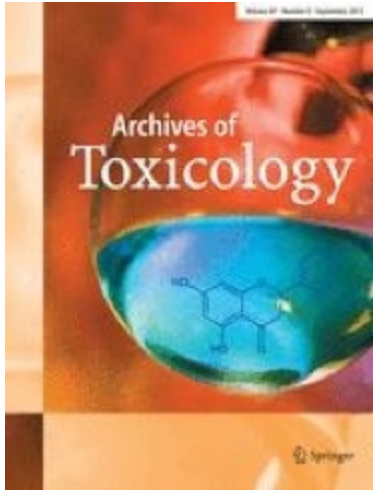
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Critics distort the facts about dental fluorosis

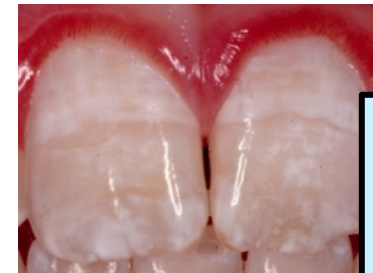
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Johnny Johnson, Jr., DMD, MS

Pediatric Dentist

President

American Fluoridation Society

Johnny@americanfluoridationsociety.com

C: 727-409-1770





Report to the
Protection and Policy Committee
of the City of Green Bay

MEETING DATE

July 13, 2020

PREPARED BY

AGENDA ITEM # E.14

Consideration with possible action on a request with Ald. Galvin that the city consider taking fluoride out of the treatment process for the city water.

BACKGROUND

RECOMMENDATION

FISCAL IMPACT

ATTACHMENTS

1. GALVIN COMMUNICATION
2. tsca-trial.closing.june2020
3. EPA-trial-Grandjean-Declaration
4. EPA-trial-Thiessen-Declaration
5. EPA-trial-Lanphear-declaration
6. Till_Green_EvolvingScience
7. EPA-trial-Hu-Declaration
8. neurath-ppt.w-notes
9. brendafluoride
10. 01.30.2017minutes
11. 02.27.2017minutes

Jaime Fuge

From: Kris Teske
Sent: Thursday, July 2, 2020 11:32 AM
To: Jaime Fuge
Subject: FW: communication for protection and policy

Kris Teske, WCMC
Green Bay City Clerk
100 N. Jefferson St., Rm 106
Green Bay, WI 54301
920-448-3014



From: District Four
Sent: Thursday, July 2, 2020 9:14 AM
To: Kris Teske <Kris.Teske@greenbaywi.gov>
Subject: communication for protection and policy

Kris, I apologize for the lateness of this communication. unfortunately, yesterday on my way home I was caught up in a traffic jam for a considerable time due to the multi vehicle accident with injuries near the Sturgeon Bay bridge.

For the Protection and Policy committee. That the city consider taking fluoride out of the treatment process for the city water.

Kris, if it can't be on the agenda for the upcoming meeting, would you let me know.

Thanks,

Bill Galvin

ALDERMAN DISTRICT FOUR

1244 Emilie St.

Green Bay, WI 54301

920-639-4640

Tada Gan Iarracht

district4@greenbaywi.gov

www.greenbaywi.gov



Think Green. Please don't print this message unless it's really necessary. Thank you.

PLAINTIFFS' CLOSING ARGUMENT (Wed June 17,2020)



MR. CONNETT: Thank you, Your Honor.

May it please the Court. On behalf of the plaintiffs I wish to begin today by expressing our immense gratitude for having had an opportunity to present our case in court, and in so doing to give voice to those who have too often been voiceless, and to hold accountable an agency that, at least on this particular issue, has failed to responsibly carry out its duties to protect this nation from harm.

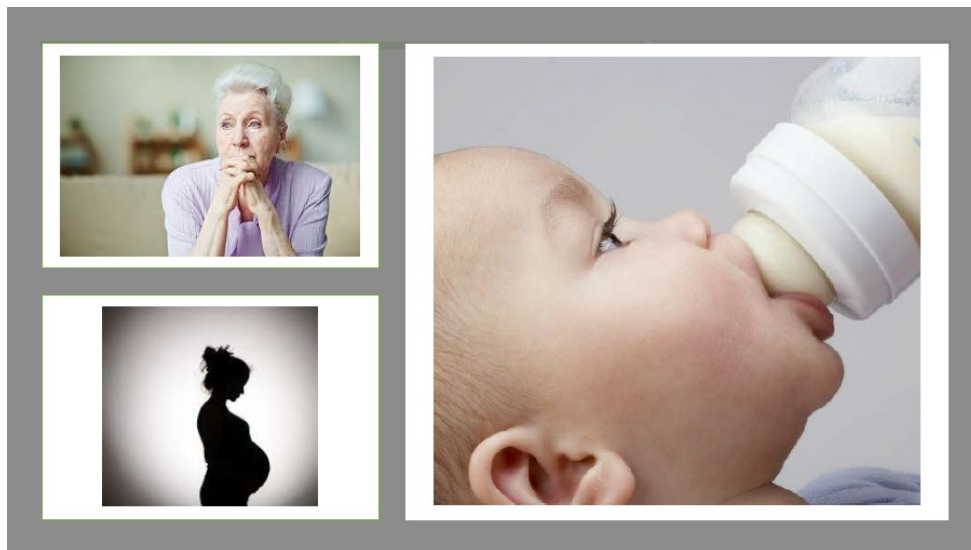
In most cases closings are about argument, but today, Your Honor, I'm not going to argue that much. Because the undisputed facts in this case speak for themselves.

THE STANDARD



So I begin, Your Honor, by addressing a simple fundamental question to this case. What is a risk? What is the standard that EPA uses to determine when a risk exists?

First off, we know that TSCA commands that the EPA protect not just the general public, but susceptible subpopulations as well, including pregnant mothers and bottle-fed infants.



The statute makes clear that if there is one unreasonable risk to one susceptible subpopulation, EPA must take regulatory action to protect from harm.

What is a risk?

So what is a risk? As Dr. Thiessen explained to Your Honor, a risk exists if the human exposure level is unacceptably close to the estimated hazard level. EPA has not and does not require data demonstrating that human exposures under the condition of use cause the hazard.



A risk exists if:
The dose is *unacceptably close* to
the *estimated hazard level*

Now, Your Honor, this standard is not in dispute. Indeed, it is an undisputed fact in this case, undisputed fact No. 16, that EPA does not require that human exposure levels exceed a known adverse effect level to make a finding of risk.



8 | 16. EPA does not require that human exposure levels exceed a known
9 | adverse effect level to make an unreasonable risk determination under TSCA. For

Undisputed Fact

Food & Water v. EPA
3:17-cv-02162-EMC

But despite this, Dr. Tala Henry admitted yesterday in no uncertain terms that EPA has from day one of this litigation used the wrong standard. They used the wrong standard of risk to assess the plaintiff's evidence.

As Dr. Tala Henry talked about yesterday, each and every one of EPA's experts in this case used a *causation* standard to assess the evidence, not a *risk* standard.



EPA Used the Wrong Standard:

16 | Q. You held the plaintiffs to a burden of proof that EPA has
17 | not held a single chemical under Section 6 before; correct?
18 | A. By the words on the page, I guess that's -- that's true,

Now, causation is relevant, your Honor, to a risk finding, but it is not and never has been a pre-requisite to a finding of risk.

THE EXPERTS



So now I'll talk about the experts that your Honor has heard from in this case. The three experts that EPA called to the stand to discuss fluoride were not actually experts on fluoride prior to this litigation. But as you heard, Your Honor, EPA does have experts on fluoride at the agency, including Dr. Kristina Thayer.

Now, EPA did call Dr. Thayer as a fact witness to discuss the process of systematic review, but EPA avoided asking Dr. Thayer the obvious. They avoided asking Dr. Thayer for her assessment of the fluoride literature.

It was the plaintiffs, Your Honor, not the EPA, who asked this question. And Dr. Thayer agreed that fluoride damages the brain and that the animal data supports the biological plausibility of fluoride causing neurotoxic effects in animals.

EPA's In-House Expert

- Dr. Thayer agrees that fluoride **damages the brain** in animals
- Dr. Thayer agrees that the animal data supports **biologic plausibility** of fluoride causing neurological effects in **humans**



Dr. Kristina Thayer

So why did EPA go outside the agency and hire experts from Exponent? I submit, Your Honor that the answer to this question is obvious and needs no further comment from me.

Although plaintiffs are citizen groups and without the resources of the EPA, we brought before your Honor world-class experts of the highest caliber. Experts who have devoted their professional lives to understanding the impact of environmental chemicals on human health. Experts who EPA has consistently relied upon for protecting this nation from harm. This includes Dr. Howard Hu. This includes Dr. Bruce Lanphear. And Phillipe Grandjean. And Dr. Kathleen Thiessen.





And as you heard, Your Honor, there is no substitute for expert judgment. No matter how many thousands of pages a systematic review may be, at the end of the day the determination of risk will always come down to expert judgment.

And as you have heard throughout this trial, EPA's own actions show that the agency trusts the expert judgment of plaintiff's experts.

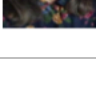


EPA's Actions Outside of Litigation









EPA Regulations

- EPA based its national air standard for lead on **Dr. Lanphear's** and **Dr. Hu's** research
- EPA based its reference dose for mercury on **Dr. Grandjean's** research

EPA Research Funding

- EPA has awarded tens of millions of dollars in research funding to **Dr. Hu, Dr. Lanphear,** and **Dr. Grandjean** to investigate the impact of environmental chemicals on human health

EPA Reviews on Fluoride

- EPA contracted with **Dr. Thiessen** to write a health assessment on fluoride compounds

EPA Science Advisory Boards

- EPA has repeatedly invited **Dr. Hu, Dr. Lanphear,** and **Dr. Grandjean** to serve on their Science Advisory Boards to advise EPA on how to best protect public health

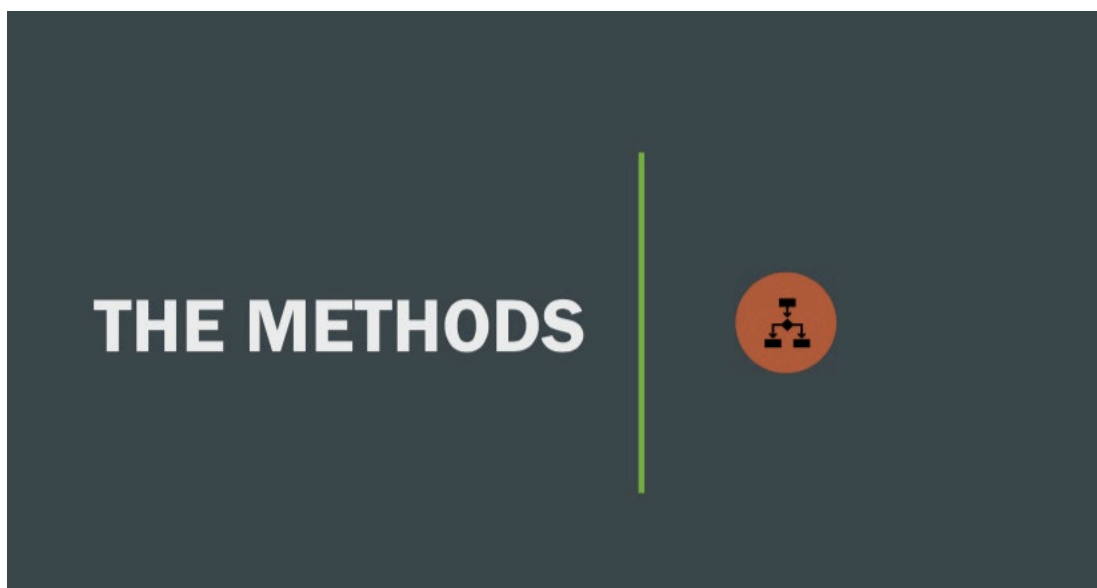
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EPA has based its regulations on the major neurotoxicants, lead and mercury, on the research of plaintiffs' experts. EPA has awarded plaintiffs' experts tens of millions of dollars in research funding.

EPA contracted with Dr. Thiessen to write the agency's health assessment on fluorides.

And EPA has repeatedly invited plaintiffs' experts to serve on its science advisory boards, including as recently as two weeks ago.

By contrast, Your Honor, the record in this case is devoid of any evidence showing EPA has ever once relied on the expert judgment of the Exponent scientists it retained. Not a single solitary example.



So I'll talk now about the methods, the methods that plaintiffs' experts used to assess the evidence in this case. The TSCA statute commands that EPA base its decisions on the best available science, and we brought that science before your Honor. Dr. Hu and Dr. Lanphear explained how their NIH funded cohort studies easily satisfied EPA's definition of best available science. This is not even in dispute.



Dr. Chang has admitted that these studies are the best, most rigorous studies ever done on fluoride and neurodevelopment.

A presentation slide with a white background and a thin green horizontal line at the top. It features the NIH logo on the left and right sides. In the center, the title 'The NIH-Funded Studies' is displayed in bold black text. Below the title, there is a list of five bullet points, with the first one in green and the others in grey.

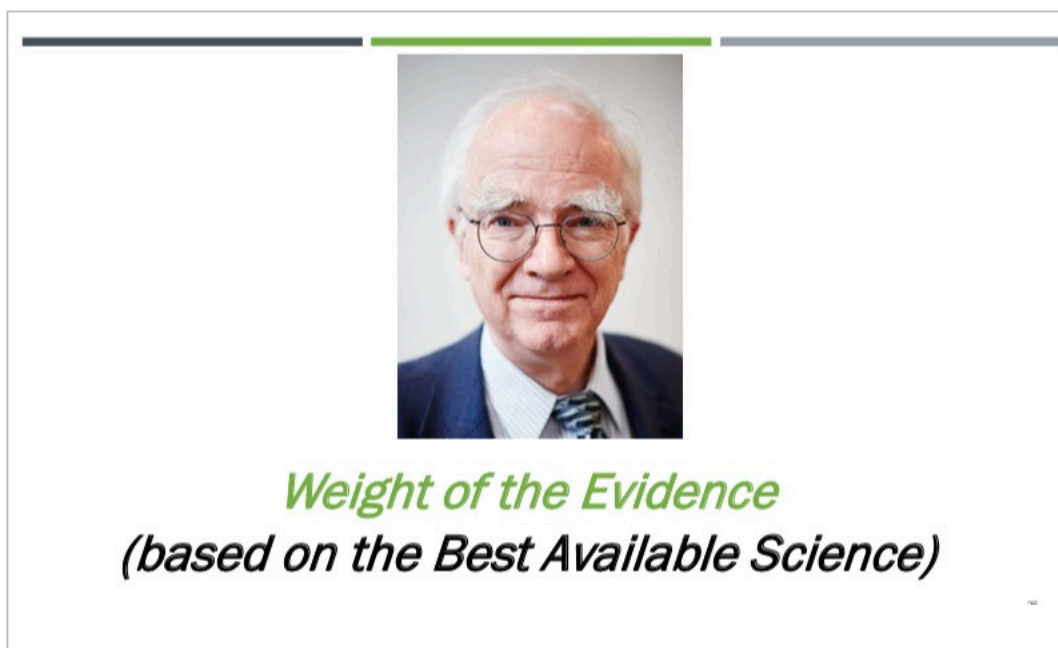
- **Extensive vetting from NIH**
 - Extensive peer review
- Extensive control for potential confounders
 - Individual Measurements of Fluoride
 - Blinded Examinations
- "Low" Levels of Fluoride Exposure

The methodology used by Drs. Hu and Lanphear underwent extensive vetting. Before they even did the studies, they underwent extensive vetting by the NIH specialist committees. And then after they did the studies and got the results, you heard testimony that they

submitted these studies to world-class leading scientific journals, who then did another round of extensive peer review.

And as you heard, Your Honor, the MIREC and ELEMENT studies had extensive control for potential confounders. And unlike the much cruder studies from New Zealand, the NIH studies had individual measurements of fluoride during the critical window of development, the prenatal period, just as recommended by the Faroes statement back in 2007.

In addition, the examinations were fully blinded, eliminating the potential for examiner bias, and the studies investigated so-called optimal levels of fluoride exposure that are added to drinking water here in the United States.



In addition to providing the best available science, Dr. Grandjean conducted an extensive weight of the evidence analysis in which he focused and he gave greatest weight to the best available science. And as Dr. Thayer explained on Friday, this is the approach that EPA has used since its inception to assess the risk of environmental chemicals, a weight of the evidence analysis that focuses on the best available science.

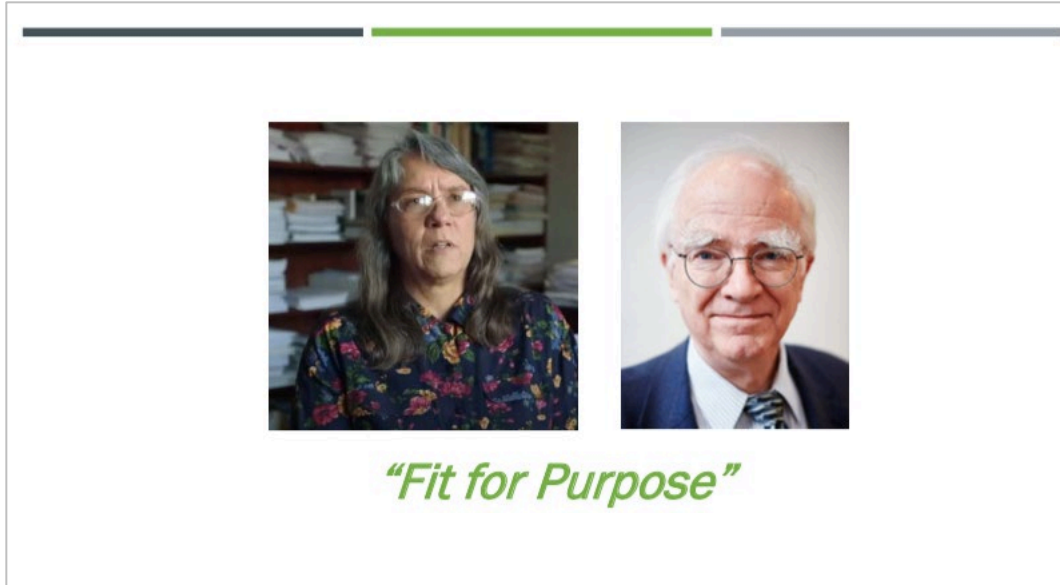


Systematic Review
(building on previous systematic reviews)

Additionally, both Dr. Grandjean and Dr. Thiessen conducted the functional equivalent of a systematic review. For Dr. Grandjean, he built upon the systematic review that he had published in 2012. In addition, he fully considered the systematic review conducted by Dr. Chang in this case.

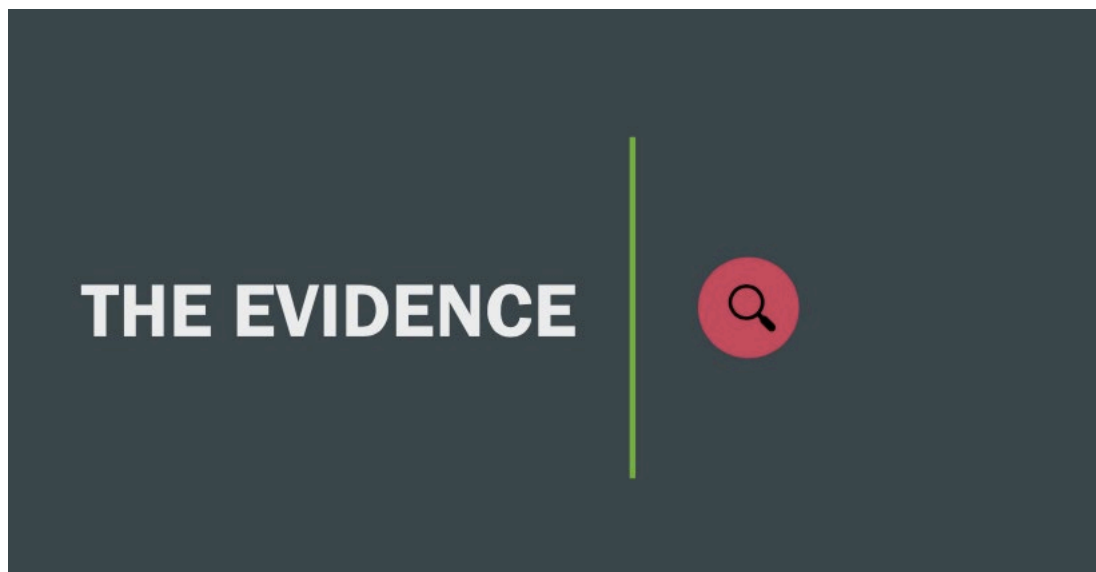
And as Dr. Thayer explained on Friday, it is now a recommended practice that even EPA agrees with that when you are doing a systematic review, you can and should build upon existing systematic reviews.

Dr. Thiessen, meanwhile, conducted a risk assessment under the Guidelines for Neurotoxicity Risk Assessment, which Dr. Henry explained yesterday is the effective equivalent of a systematic review.



Your Honor, you've heard this concept at points throughout this case of "fit for purpose." This is a concept that EPA specifically discusses in the risk evaluation rule. It's a concept that recognizes that a risk evaluation under TSCA is not a straightjacket. EPA recognizes that there is room for practicality. There is room for flexibility. There is room for common sense.

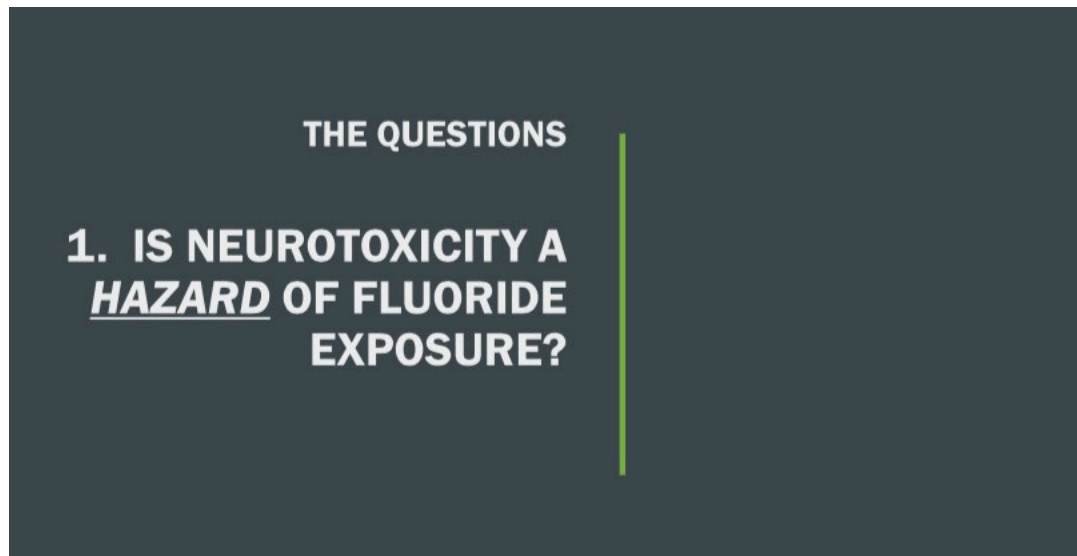
This recognition is embodied in this concept of fit for purpose. And both Dr. Grandjean and Dr. Thiessen conducted fit for purpose assessments in this case, and there has been no demonstration to the contrary.



So now, Your Honor, I will turn to the evidence.

At the beginning of this case I said that there were three key questions that need to be answered: is there a hazard? Is there a risk? And is the risk unreasonable?

The undisputed evidence in this case, we submit, demonstrates that the answer to all three of these questions is yes.



First, it is undisputed that fluoride passes through the placenta and gets into the fetal brain. This means that when a pregnant mother drinks a glass of fluoridated water, the fluoride in the water will have access to the child, including the brain.



30. Fluoride passes through the placenta and gets into the fetal brain.

Undisputed Fact

Food & Water v. EPA
3:17-cv-02162-EMC

30

It is also undisputed that, unlike older children and healthy adults, a young child does not have the protection of the blood-brain barrier in utero and in early infancy. In fact, as you can see in this undisputed fact in the case, the blood-brain barrier is not fully developed

until six months after birth. And because of this, Dr. Thayer explained on Wednesday that the EPA recognizes we need to pay special attention to chemical exposures that occur during the first six months of life.




29. The developing brain is distinguished by the absence of a blood-brain barrier. The development of this barrier is a gradual process, beginning in utero and complete at approximately 6 months of age.

Undisputed Fact

Food & Water v. EPA
3:17-cv-02162-EMC

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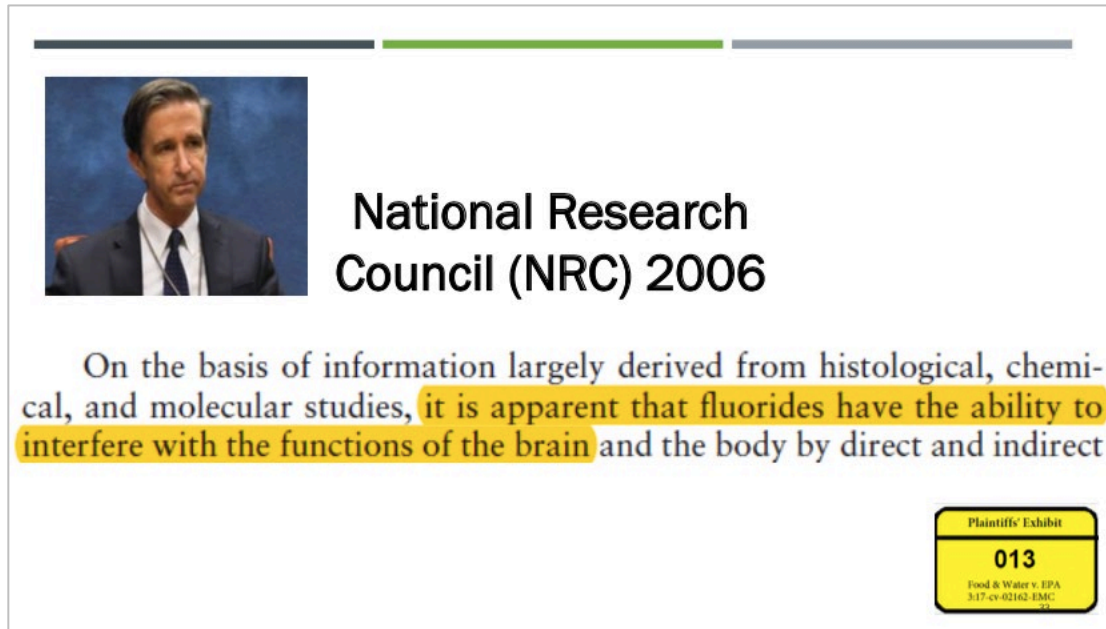
Yet, Your Honor, that is precisely what happens when we add fluoridation chemicals to drinking water. It is undisputed – undisputed -- that babies who are bottle fed with fluoridated water receive the highest doses by far of any age group in the population. At the moment of their greatest vulnerability, we are exposing infants, often from the poorest and most disadvantaged communities, to a very high burden of fluoride.



Now, there is no dispute in this case, Your Honor, that fluoride damages the brain. The NRC made this finding as far back as 2006. And the CDC representative in this case, Casey Hannan, who you heard from, testified that the CDC agrees with the NRC's summary of the hazard, including the NRC's summary of the neurotoxic hazard.

And here you can see, Your Honor, the finding of the NRC, that:

"It is apparent that fluorides have the ability to interfere with the functions of the brain."



Now, at that point, Your Honor, they were focusing on the neurochemical and neuroanatomical effects because there was not many learning and memory studies then available, but many such studies have since become available.

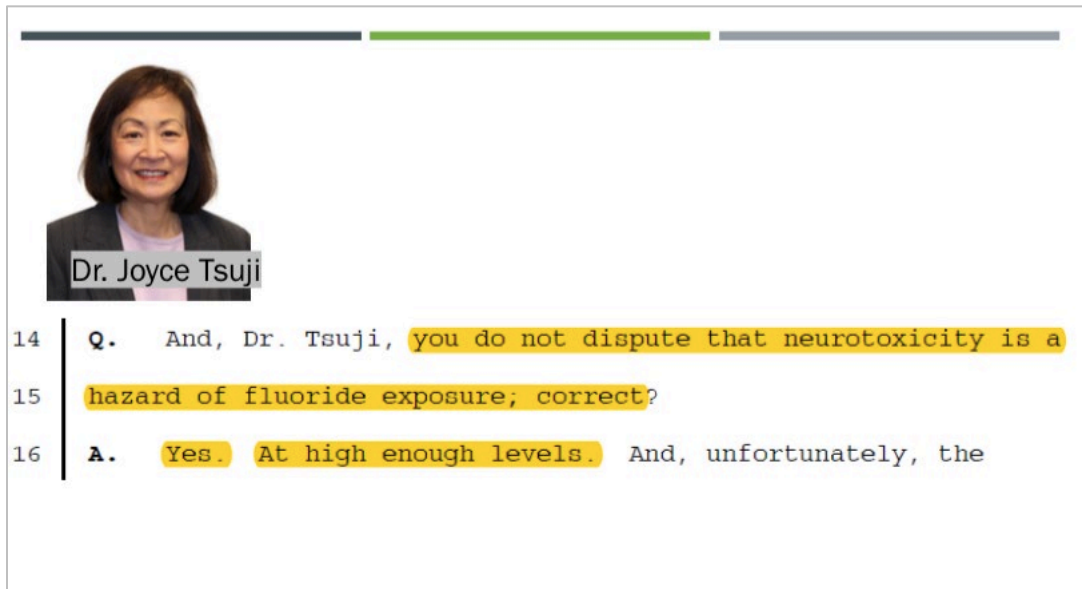
Now, while EPA's experts in this case have criticized the methods of many of the studies, it is important to keep in mind what they do *not* dispute. No one came before your Honor to say that fluoride is not a neurotoxicant. So the question of hazard really is not in dispute in this case.

Here you can see testimony from Dr. Joyce Tsuji. I asked her:

"QUESTION: You do not dispute that neurotoxicity is a hazard of fluoride exposure; correct?"

And her answer was:

"ANSWER: Yes, at high enough levels."



But what EPA didn't do is they never even attempted, never once attempted to determine, but what are those levels? They never attempted to provide to Your Honor an estimate as to what the levels are that are causing these neurotoxic effects.

The record is devoid of any EPA expert in this case making any attempt to do that. But importantly, they do not dispute that fluoride will damage the brain at a certain dose.

THE COURT: And my understanding is that they didn't do so because the levels that -- that all of these studies that you're talking about show involve levels well above the exposure levels of humans in the United States. I think that's the EPA's position; right?

MR. CONNETT: Well, the problem with that position, Your Honor, is even -- Dr. Joyce Tsuji testified on Monday that she accepts that 20 parts per million in the water of rats is effectively the equivalent of 1.3 parts per million in the water of humans.

And Your Honor, as Dr. Thiessen explains in her declaration, it's absolutely standard practice for EPA, when interpreting animal data, to do an analysis for calculating the human equivalent dose.

And for fluoride, specifically, we know that rats need more fluoride in their water to obtain the same level of fluoride in their blood. That's a toxicokinetic difference.

THE COURT: I understand that, but 1.3 is still well above -- isn't that well above the exposure levels in the United States?

MR. CONNETT: Not at all, your Honor. And that is only -- just to put this in context. That 1.3 figure, Your Honor, that's just providing for interspecies differences. Under EPA risk assessment you still need to provide a factor to assess, to account for human-to-human differences.

So going from 20 to 1.3, Your Honor, all that is doing is adjusting for interspecies differences.

Then you also need to do an adjustment for human-to-human differences. And as we've talked about throughout this case, EPA almost always uses an adjustment of 10. So if you put the adjustment of 10 to that 1.3 figure, you're down to .13.

So it's important when looking at animal data, we can't treat the water fluoride level in rats as equivalent to the water fluoride levels in humans. You need to dose the animals at substantially higher levels.

And, also, you need to account for the fact that you have much fewer rats, much fewer animals. You know, with fluoridated water you have 200 million people drinking it.

So, Your Honor, it is standard practice for the EPA to make adjustments to the animal data to account for the differences in susceptibility between rodents and humans.



And so in terms of this hazard assessment, Your Honor, we have, as you've heard throughout this case, four high quality prospective cohort studies. Each of them have found significant associations between early life fluoride exposures and large reductions in IQ on the magnitude of up to five points, when you go from zero to one milligram per liter of fluoride in the urine. That's a very large effect size that rivals the effect of lead.

And under EPA's Guidelines for Neurotoxicity Risk Assessment, the NIH studies are actually sufficient, Your Honor, by themselves. And, clearly, we have a lot of other data besides the NIH studies, but the EPA's guidelines recognize that sufficient evidence of a neurotoxic hazard can be demonstrated by cohort studies which associate the chemical with a neurotoxic effect. And we certainly have that here in the fluoride database.



Guidelines for Neurotoxicity Risk Assessment

(Published on May 14, 1998, Federal Register 63(93):26926-26954)



**Sufficient human
evidence**

This category includes agents for which there is sufficient evidence from epidemiologic studies, e.g., case control and cohort studies, to judge that some neurotoxic effect is associated with exposure. A case series in conjunction

Plaintiff's Exhibit
017
Food & Water - EPA
3:17-cv-00142-RBC

And you heard from EPA staff scientist Dr. Joyce Donohue from the Office of Water. She confirmed the obvious, that these are well-conducted studies, but she also said that these studies warrant a reassessment of all existing fluoride standards.



EPA Staff Scientist on NIH Studies:

- “Well Conducted”
- NIH studies warrant a reassessment of *all* existing fluoride standards

Dr. Joyce Donohue

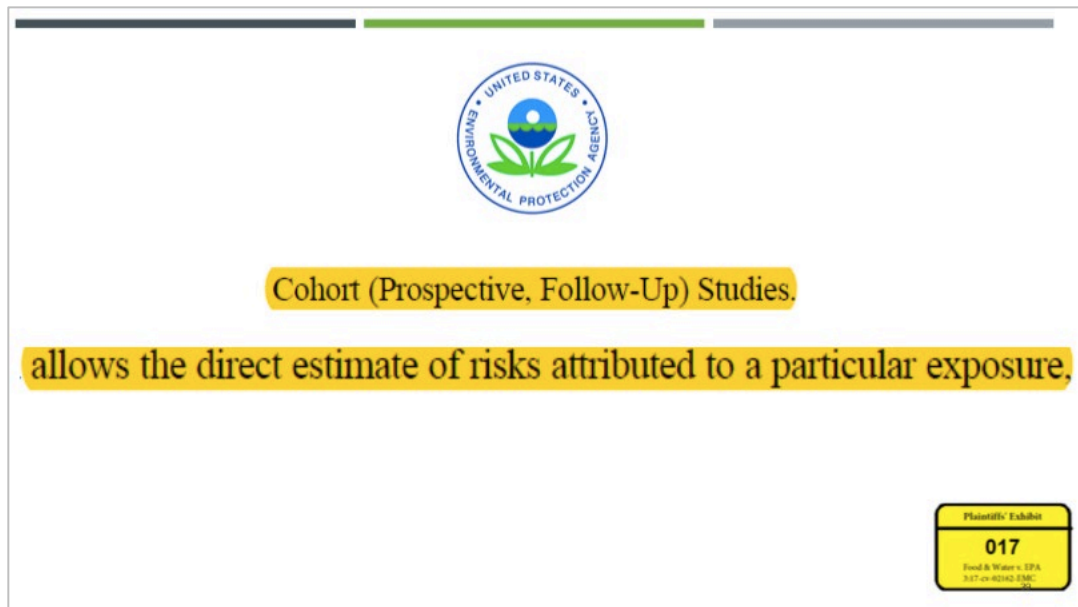
And, you know, Dr. Donohue has focused her work at EPA on the dental and skeletal effects. So the neurotoxicity subject is a bit beyond what she has focused on, but she recognizes that these are high quality studies that warrant a reassessment of the current framework for regulating fluoride.

So that brings us to the second question, Your Honor, is the risk question. Do fluoridation chemicals in water present a risk of this hazard?

THE QUESTIONS

2. DO FLUORIDATION CHEMICALS IN WATER PRESENT A RISK OF THE HAZARD?

And to answer this, I think we again should look for guidance from EPA's Guidelines for Neurotoxicity Risk Assessment. And these guidelines specifically state that:



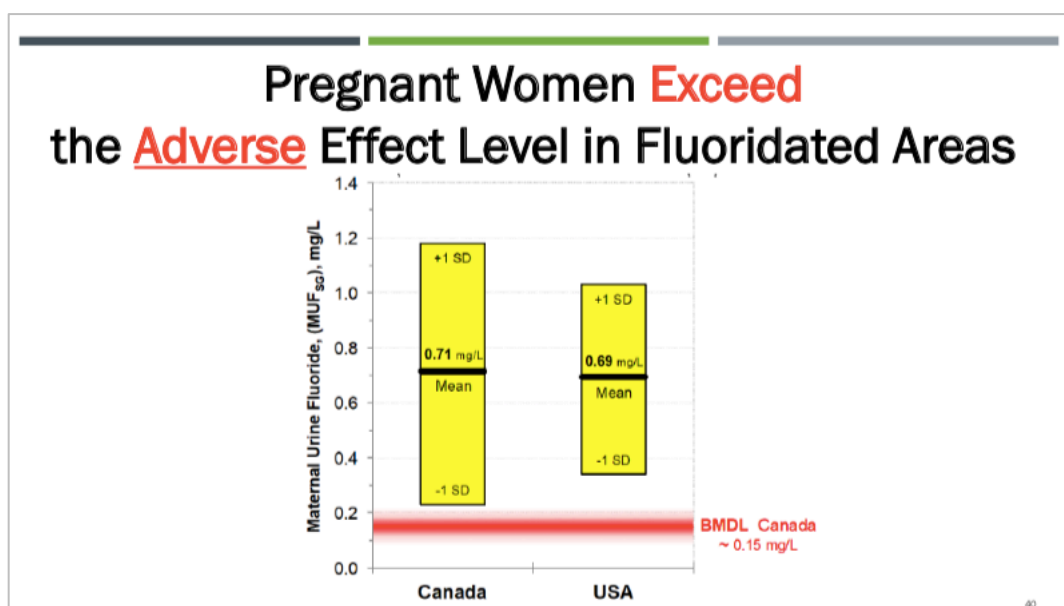
"Prospective cohort studies allow the direct estimate of risks attributed to a particular exposure."

Again: "Allows the direct estimate of risks attributed to a particular exposure."

So we have the proper studies, Your Honor, to make a finding of risk according to EPA's own guidelines.

And Dr. Grandjean, as you've heard, he did a BMD analysis to take those prospective cohort studies and to assess the risk from those studies.

And this figure, which was discussed during Dr. Grandjean's testimony, shows that pregnant women living in fluoridated areas of both the United States and Canada substantially exceed -- if you just look at the mean levels, Your Honor, the average levels, these average levels substantially exceed the BMDL for a one-point loss of IQ.



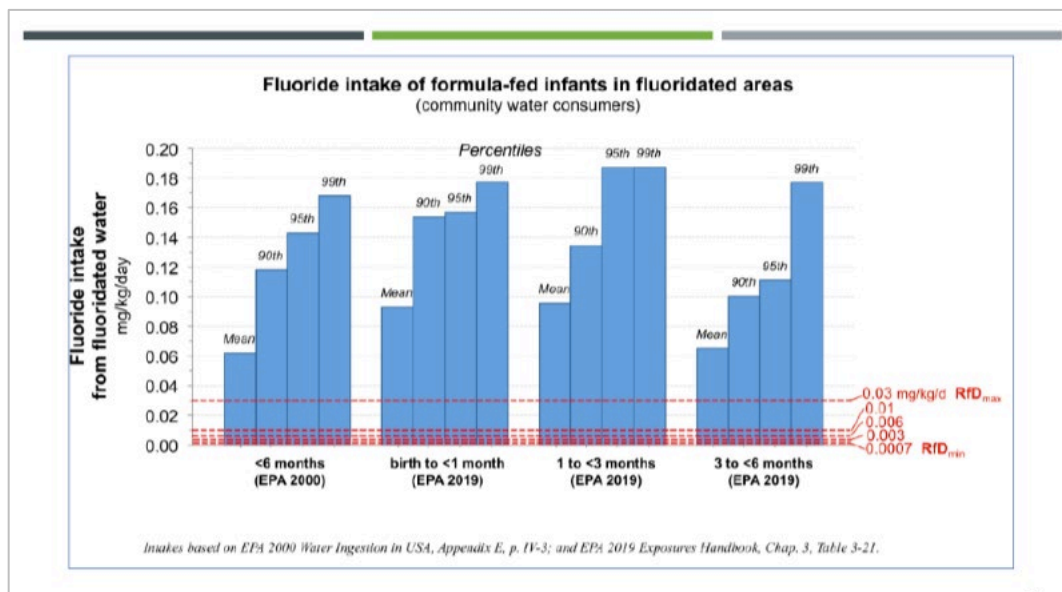
And when you start to consider the upper range of exposures, which TSCA commands that we do -- TSCA commands that we don't just look at the average. TSCA commands that we look at highly exposed people. If you look at the highly exposed people in fluoridated areas, you are going to see a very large differential there.

There is no dispute in this case, Your Honor, that the human data is the appropriate data to derive the point of departure. To derive the reference dose. To derive your risk calculations. But that does not mean that the animal data is irrelevant.

EPA has recognized that even where you have high quality human studies, it's still relevant to consider the animal data, to derive reference doses from the animal data because if it's consistent with what the human data shows, it adds robustness and confidence to the conclusions.



And as Dr. Thiessen explains, Your Honor, the animal data, when you calculate the full range of RfDs that can be justified from the data, human exposures from fluoridated water exceed the entire range. Even the least protective reference dose.



Dr. Thiessen, as one of her points of departure, used the McPherson study. And when you use the McPherson study as the point of departure and apply standard EPA adjustments, you get a reference dose that is well exceeded by the exposures to fluoridated water.

So the animal data and the human data are consistent in indicating and showing a risk.

And that brings us lastly, Your Honor, to the question of whether this risk is unreasonable. And as I noted at the beginning of this case --

THE COURT: Before you get to that, let me ask you about the McPherson study, because a lot was made by the EPA that the negative findings of the McPherson study post the -- you know, the systematic review.

Why shouldn't -- why isn't that significant? That is -- you would agree, just as they would agree, that the best studies are the MIREC and the ELEMENT studies on the human side.

Wouldn't you agree that the McPherson study is the best available evidence on the animal side?

MR. CONNETT: I think it is a -- it is a well-done study. It has significant limitations.

But I think, Your Honor, a key point here is this. They max their dose at 20 parts per million. And I asked Dr. Tsuji: Shouldn't they have dosed the animals at 40 parts per million or 45 parts per million?

And Dr. Tsuji said it wasn't necessary because we know you see effects up in that range.

And so I think that's an important context to put it in. It had a lower dose. And in this case there is no dispute: If you start going beyond 20 parts per million, you're seeing effects.

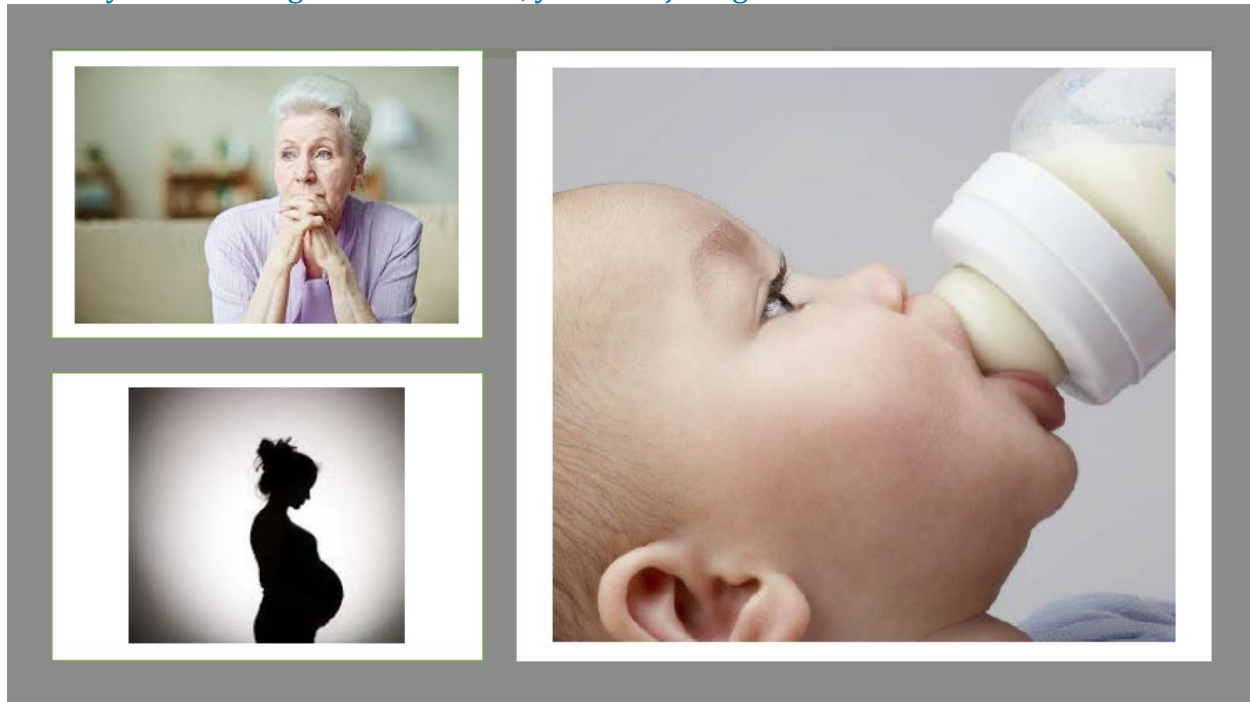
So McPherson doesn't do anything to contradict that. And, also --

THE COURT: I thought McPherson found at the maximum they tested, which was 20 parts per million, there were no associations except for pain sensitivity.

MR. CONNETT: Yes, Your Honor. At 20 parts per million in the McPherson study there was an increase in pain sensitivity, which is a neurotoxic effect. So 20 ppm would be a LOAEL for pain sensitivity.

They also found that the rats swam faster. And while it's not dispositive of hyperactivity, it's certainly not a clean result. It's not a -- this is not a clean bill of health study. You have increase in pain sensitivity. You have rats swimming faster. So it's not a clean bill of health from the McPherson study.

THE COURT: Well, but no association with respect to the critical endpoints of learning and memory. Isn't that significant? I mean, you can't just ignore that.



I know it's not a clean bill of health, but you're looking at an indicator that may not have much association or effect with respect to learning and memory, which is the key here.

MR. CONNETT: Well, a few things, Your Honor, about this.

First is, the McPherson study, as with all animal studies to date, did not expose the neonates to fluoride. Okay? So there is not a single animal study, as we sit here today, that has ever attempted to assess the neurological effects of a critical window of development.

In humans we have -- we have many -- we have many infants who are drinking fluoridated water from day one all the way through infancy. That is a critical window of development. EPA recognizes that. But we have no animal data to assess the neurological effects of that, including McPherson.

Secondly, the McPherson study did not have any exposure during the first six days of gestation. Your Honor, that's about one-third of the gestational period.

And the OECD guidelines say, if you can expose the rats from day zero, do it if you can. They are not saying don't. They are saying if you don't have pre-implantation loss at day zero, dose them at day zero. But McPherson did not do that.

THE COURT: But exposure at day six is also an accepted protocol; is it not?

MR. CONNETT: It is an accepted protocol, Your Honor. It's not as sensitive a protocol as you could have.

So what's important here, Your Honor, is that the study is ultimately not reflecting the full range of susceptibility.

So you can't take from McPherson, you can't have any confident conclusion that the study is capturing what we see in humans, which is full pregnancy exposure, full infancy exposures. It's not there in McPherson.

And, Your Honor in Dr. Thiessen's risk calculations, she treated the 45 part per million concentration, which Dr. Tsuji accepts is a neurotoxic level. She treated that concentration as a lowest observed adverse effect level.

And even if you treat 45 parts per million as a lowest observed adverse effect level, your reference dose is still well below human exposures.

THE COURT: When you apply the uncertainty factors, et cetera, et cetera?

MR. CONNETT: Correct.

THE COURT: But you would agree that you start with the NTP -- was it the NTP study that gave only low level of -- I forget the term, confidence about effect with respect to infant animals, young animals? And then you add to that McPherson, at least when you look at it on that basis, it appears to me that the animal studies are not very helpful.

MR. CONNETT: Your Honor, I think what's -- as Dr. Thayer testified last week, she said: It's a reasonable hypothesis if you're seeing learning impairments in the adult treated rats, it's a reasonable hypothesis that you would also see the learning impairments in the developmental studies.

So we can take from the moderate confidence finding that the NTP had in the adult studies, you can impute from that into the developmental studies that if you had the well-conducted studies, you're going to find an effect as well.

THE COURT: Well, that's what I found sort of curious. Why did they have different confidence levels? I mean, based on the -- their review of the literature, you have kind of an inverse relationship.

MR. CONNETT: Right. And I think the reason that Dr. Thayer has provided is that at the time that the NTP did its review in 2016, there were very few developmental studies available. Certainly, few at the -- in the dose range of greatest interest.

So in part, Your Honor, that was why the NTP had lower confidence in the developmental studies, as well as the issue of not controlling for litter effects, which is, as you have noted, a methodological limitation.

But I don't think we can or should divorce the moderate confidence in the adult studies from our assessment of the developmental studies. It makes no biological sense that you would find learning impairments in adult animals, but not find it in the developmental studies.

THE COURT: So the low level of confidence is due to the nature of the number of studies and the quality of studies and the limitations, not necessarily reflective of the real world.

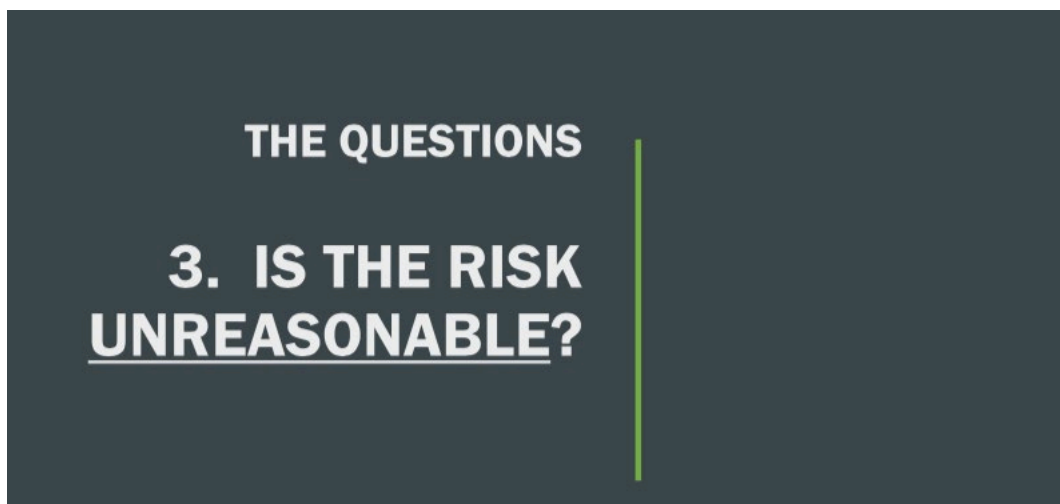
MR. CONNETT: I believe so, Your Honor. I believe that's what the evidence suggests.

Again, Dr. Thayer said on Wednesday that it's a reasonable hypothesis that if you're seeing the effects in the adults, you're going to see it in the fetal and neonatal exposures.

And there is no dispute in this case that the developing brain is the most susceptible to environmental toxicants. It would be the a priori expectation that an animal exposed in early life will suffer greater effects than animals exposed during adulthood.

THE COURT: Okay.

MR. CONNETT: So now to this question of unreasonable risk.



And I believe the evidence, Your Honor, in this case -- and you've heard from Dr. Hu, you've heard from Dr. Lanphear and Dr. Grandjean -- is that the situation with fluoridated water today is analogous to the situation this nation once faced with leaded gasoline. There, as here, we have a widespread dispersal of a neurotoxicant, which results in exposure to an enormous amount of people, including the most vulnerable.

It's an undisputed fact in this case that approximately 200 million people live in communities where fluoridation chemicals are added to water, and many more drink processed beverages that have been contaminated with fluoridation chemicals.



To put this number in context, Your Honor, the EPA has found unreasonable risks under Section 6 where the conditions of use impact less than 2,000 people.

Because of the widespread reach of fluoridation, you have millions of susceptible people being exposed on a daily basis, including 2 million pregnant mothers and over 400,000 exclusively formula-fed babies.



**Over 2 million pregnant women
in fluoridated communities**

A graphic element consisting of a horizontal bar at the top with three segments: a dark grey segment on the left, a green segment in the middle, and a light grey segment on the right. Below this bar is a square image showing the silhouette of a pregnant woman from the side, standing against a light background. Below the image is the text "Over 2 million pregnant women in fluoridated communities" in bold, black, sans-serif font.



Over 400,000 exclusively formula-fed babies in fluoridated areas

Your Honor, these are children -- and most of them are in lower income, more disadvantaged communities -- who from day one of their life, their only sustenance is infant formula, and that infant formula is reconstituted with the tap water. These are children who are being placed at a much higher risk of harm, and their interests should be considered by the EPA.

Now, plaintiffs do not need to prove causation at .7 parts per million to prevail in this case. That's not the standard that EPA has ever used, as Dr. Tala Henry admitted yesterday. But what makes this case so compelling, Your Honor, is that the evidence actually supports this conclusion.

Dr. Grandjean explained this in his testimony. The Bradford Hill factors support a finding of causation, rather than detract from it.



Bradford Hill:

- 1) Strength of Association
- 2) Consistency
- 3) Biological Gradient (Dose Response)
- 4) Temporality
- 5) Biological Plausibility

And all risk assessments, Your Honor, have uncertainties. Every single one. I don't think there is a single risk assessment in the history of this world where you don't have some uncertainties.

These are not the exception. They are the rule. Uncertainties do not preclude a finding of risk. If they did, I don't think the EPA would have made many risk determinations with the chemicals it has assessed so far under Section 6.

Exponent scientists in this litigation have identified for Your Honor a long list of possible reasons to possibly explain the findings.

But I think Your Honor's exchange with Dr. Ellen Chang yesterday was notable and important. Dr. Chang was unable to identify for this Court any reason why the MIREC or ELEMENT studies would have been biased towards showing an effect.



The EPA, Your Honor, has not identified for you any cogent explanation that can explain the consistent results that we see across the human studies, across multiple populations, multiple study designs, both strong and weak.

What is the *Most Likely* Explanation for the Observed Adverse Effects?

Your Honor, we would submit what we submitted at the beginning of this case. The most likely explanation for the consistent results in both animal and human studies is that fluoride is a neurotoxicant that reduces IQ, including at the levels added to community water supplies in the United States. And this effect is strong enough to be detected, even in studies with weak study designs.

So, Your Honor, I believe the preponderance of evidence in this case has demonstrated that fluoridation chemicals present an unreasonable risk of harm.

And we thank you again for giving us an opportunity to present the evidence in this case.



THE COURT: Thank you Mr. Connett. If I can hear from the government please.

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4 **U.S. FEDERAL COURT**

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6 **ACTION NO. 17-CV-02162**

7 **FOOD AND WATER WATCH, *et al.* v. U.S. EPA**
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12 **EXPERT DECLARATION OF**
13 **PHILIPPE GRANDJEAN, MD, DMSc**

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17 **PREPARED ON BEHALF OF**
18 **PLAINTIFFS**

19 **20 May 2020**
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TABLE OF CONTENTS

I.	SUMMARY OF QUALIFICATIONS.....	1
II.	SUMMARY OF OPINIONS	4
III.	SUMMARY OF METHODOLOGY	4
A.	Weight of the Evidence.....	4
B.	Factors Considered When Assessing Epidemiological Literature.....	5
C.	Benchmark Dose Methodology	7
D.	Materials Relied Upon	7
IV.	GENERAL CONSIDERATIONS	7
A.	Emergence of Brain Development as Vulnerable Target	7
B.	Toxicokinetics During the Fetal Period	10
C.	Toxicological Findings	11
V.	EPIDEMIOLOGICAL STUDIES (CROSS-SECTIONAL).....	12
A.	Neurotoxicity from Occupational Fluoride Exposure.....	12
B.	Neurotoxicity in Endemic Fluorosis Areas.....	13
1.	Neurotoxic Endpoints in Fetuses and Neonates.....	15
2.	Neurotoxic Endpoints in Adults.....	16
3.	Childhood IQ.....	16
C.	Studies of Fluoride and ADHD in North America.....	20
VI.	EPIDEMIOLOGICAL STUDIES (PROSPECTIVE)	21
A.	Prospective Cohort Studies with Individual Assessment of Prenatal Exposure.....	21
B.	Prospective Cohort Studies without Prenatal Exposure Assessment.....	23
VII.	SYSTEMATIC REVIEW	24
A.	Dr. Chang's Systematic Review Confirms that I Considered All Significant Data.....	25
B.	Dr. Chang's Review Fails to Identify Any Systematic Biases that Explain Fluoride's Consistent Association with Neurodevelopmental Harm.....	27

C.	Bradford Hill Aspects Support, Rather than Detract from, the Causal Nature of Fluoride’s Association with Neurodevelopmental Harm.....	30
VIII.	BENCHMARK DOSE (BMD) ANALYSIS	35
A.	Selection of Source Data.....	35
B.	Selection of Benchmark Response (BMR)	37
C.	Analyses of ELEMENT and MIREC Data	38
IX.	ASSESSMENT OF RISK.....	41
A.	Comparing BMDLs with Current Exposures in Fluoridated Areas.....	41
B.	Comparing Fluoride’s Population-Level Effects with Other Causes of IQ Loss.....	46
X.	CONCLUSIONS.....	48

1 I, Philippe Grandjean, MD, DMSc, declare that:

2 1. I am a physician and environmental epidemiologist and serve as both an Adjunct Professor
3 at the Harvard T.H. Chan School of Public Health, and Professor and Chair of Environmental Medicine
4 at the University of Southern Denmark.

5 2. I was asked by Plaintiffs' counsel to provide an evaluation of the neurological health risks
6 associated with the exposure to fluoride in drinking water.

7
8 **I. SUMMARY OF QUALIFICATIONS**

9 3. A complete summary of my qualifications and publications can be found in my
10 Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 3 and attached herein.

11 4. Over the past 25 years, my research has focused on developmental exposures to
12 environmental chemicals and the association with adverse health effects in children, as described in my
13 book "Only One Chance" (2013) published by Oxford University Press.

14 5. My research has been entirely funded by public sources, mainly the National Institutes of
15 Health (NIH). In 2003-2007, my study of children's vulnerability to environmental immunotoxicants
16 was supported by the U.S. Environmental Protection Agency (EPA). My current funding as principal
17 investigator includes grants from the Superfund Research Program at the National Institute of
18 Environmental Health Sciences and the U.S. Agency for Toxic Substances and Disease Registry
19 (ATSDR).

20 6. I have published about 500 scientific papers, of which most are research articles in
21 international scientific journals with peer review. My h-index in the Web of Science data base is 70, and
22 my work is cited in scientific journals well over a thousand times every year. Seven of my articles
23 published in the last 10 years have earned the attribute "Highly Cited Paper," i.e., they received enough
24 citations to place them in the top 1% of published papers in the field.

25 7. My study on the neurodevelopmental effects of prenatal mercury exposure in a birth cohort
26 from Faroe Islands was relied upon by the EPA as the critical study for the Agency's derivation of a
27

1 Reference Dose for methylmercury (EPA 2001).

2 8. I have served as a technical advisor to the World Health Organization on environmental
3 health issues, including five occasions where I was elected Rapporteur. I have also served on, sometimes
4 chaired, or acted as rapporteur for, expert committees under the auspices of the EPA, ATSDR, Food &
5 Drug Administration (FDA); NIH; White House Office of Science and Technology Policy; International
6 Agency for Research on Cancer (IARC), European Commission, European Environmental Agency,
7 European Food Safety Authority, and other organizations. I have also served for over 30 years as
8 Consultant in Toxicology for the Danish Ministry of Health.

9 9. I am (Founding) Editor-in-Chief of the journal *Environmental Health* (since 2002), which
10 ranks among the most frequently cited journals in the field. I also serve or have served on editorial
11 boards of about a dozen journals within medicine, environmental science, and toxicology. As editor and
12 as reviewer for other major journals, I frequently evaluate manuscripts on environmental epidemiology
13 and toxicology.

14 10. I have received various awards and honors for my scientific work, including the John R.
15 Goldsmith Award from the International Society for Environmental Epidemiology, which is given to
16 investigators for “sustained and outstanding contributions to the knowledge and practice of
17 environmental epidemiology.”

18 11. I have been retained as an expert on the impact of environmental chemicals on human
19 health by government bodies, including the U.S. Department of Justice (on behalf of the EPA) and the
20 State of Minnesota.

21 12. I first began studying fluoride in 1980 at the suggestion of Dr. Irving J. Selikoff, who was
22 my mentor at the Mt. Sinai School of Medicine during my two-year Senior Fulbright Scholarship. Upon
23 returning to Denmark, I initiated a series of studies on a cohort of workers who had been occupationally
24 exposed to fluoride. I have remained involved in fluoride research since that time and have published 16
25 peer-reviewed reports on fluoride exposure and toxicity in humans.

26 13. In 1984, I drafted the Environmental Criteria Document on fluoride for the World Health
27

1 Organization (WHO). Ten years later, I drafted the Criteria Document for an occupational exposure
2 limit value for fluorine for the European Commission. In 2006, I served as a reviewer of the National
3 Research Council's report *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*.

4 14. During the past 10 years, my research work on fluoride has focused on its developmental
5 effects on the brain. In 2012, I published a meta-analysis of the epidemiological studies on fluoride and
6 IQ (Choi et al. 2012); in 2015, I published an epidemiological study of fluoride and IQ in China (Choi et
7 al. 2015); and, in December of 2019, I published an updated review of fluoride neurotoxicity, which
8 relied in part on the work that I have performed in this case (Grandjean 2019).

9 15. In addition to my work on fluoride, I also have expertise in Benchmark Dose (BMD)
10 analysis. My experience doing BMD analysis started about 20 years ago in connection with my research
11 on the neurodevelopmental effects of methylmercury in the Faroe Islands that was selected as the critical
12 study for risk assessment by the EPA. Based on this research, the EPA provided me with a contract to
13 produce a BMD analysis of the data, which I carried out in collaboration with my biostatistician
14 colleagues, Dr. Esben Budtz-Jorgensen and Professor Niels Keiding. The EPA relied on this BMD
15 analysis to establish the safe level for methylmercury exposure in the U.S. (U.S. EPA 2001).

16 16. In 2009, I served on an expert panel that assisted the European Food Safety Authority
17 (EFSA) in developing a guidance document on BMD analysis titled "Use of the Benchmark Dose
18 (BMD) Approach in Risk Assessment."

19 17. In 2013, Dr. Budtz-Jorgensen and I extended our BMD methodology in collaboration with
20 the International Pooled Lead Study Investigators, which was peer-reviewed and published in the journal
21 *Risk Analysis* (Budtz-Jorgensen et al. 2013). As part of this analysis, we developed a BMD for lead and
22 IQ by analyzing pooled data from multiple different cohort studies. The paper was co-authored by
23 leading scholars on lead neurotoxicity, including Drs. David Bellinger and Bruce Lanphear.

24 18. More recently, Dr. Budtz-Jorgensen and I conducted an advanced BMD analysis on
25 perfluorinated chemicals, which was published in 2018 in the peer-reviewed journal *PLOS One* (Budtz-
26 Jorgensen and Grandjean 2018). In total, our achievements on BMD approaches and applications have
27

1 been published in seven articles so far in international biostatistical and biomedical journals.

2 19. In addition to my scientific training, I remain mindful, of the importance of translating the
3 results of epidemiological studies in a way that can facilitate public participation in making informed
4 decisions to protect their health, even prior to a “final proof” of causation being available; a final proof
5 that, all too often, has come too late to protect the public from harm, as reviewed most recently in the
6 monograph on *Late Lessons of Early Warnings*, published by the European Environment Agency (EEA
7 Report No 1/2013), for which I served as an editor. As Dr. Selikoff once impressed upon me, “Never
8 forget that the numbers in your tables are human destinies, although the tears have been wiped away.”

9 **II. SUMMARY OF OPINIONS**

10 20. The weight of epidemiological evidence leaves no reasonable doubt that developmental
11 neurotoxicity is a serious human health risk associated with elevated fluoride exposure, including those
12 occurring at the levels added to drinking water in fluoridated areas. The IQ losses associated with
13 community water fluoridation are substantial and of significant public health concern.

14 21. Application of the Benchmark Dose (BMD) methodology to the recent prospective birth
15 cohort data shows that the level of fluoride added to water in fluoridation programs greatly exceeds the
16 science-based limit needed to protect against developmental neurotoxicity.

17 22. The systematic review conducted by Dr. Ellen Chang, when corrected for its biases and
18 errors in judgment, further supports my opinions on the neurotoxic risks posed by elevated fluoride
19 exposure.

20 **III. SUMMARY OF METHODOLOGY**

21 **A. Weight of the Evidence**

22 23. I conducted a weight of the evidence assessment of available research on fluoride
23 neurotoxicity, with an emphasis on the epidemiology. While I place the greatest weight on the strong
24 epidemiological evidence, I also consider toxicokinetics, experimental toxicology data, and background
25
26
27

principles of brain development as part of my comprehensive analysis.

24. My review focuses on the evidence that carries the greatest weight which, as generally accepted, emphasizes the recent prospective cohort studies.

25. My methodology follows the general approach applied by the EPA, in the sense that I did a weight of the evidence analysis that focuses on the best available science (e.g., EPA 2017).

26. In light of my familiarity with the scientific literature on fluoride neurotoxicity, I did not conduct a formal systematic review on this occasion. Instead, my conclusions rely on a comprehensive and thorough review supplemented by a Benchmark Dose analysis of the recent prospective data.

27. I have read and considered the systematic review conducted by Dr. Ellen Chang, which mostly relies on the same evidence and which further confirms and supports my assessment of the literature. My opinions are thus fully informed by the insights offered by a formal systematic search of the literature.

B. Factors Considered When Assessing Epidemiological Literature

28. In evaluating the weight of the evidence, the question must be asked what each study could potentially reveal, given the design and choice of study parameters, including such factors as the precision of the exposure assessment. In the field of epidemiology, there is a well-known bias toward the null, e.g., from imprecise assessment of the exposure, of which epidemiologists (and readers of epidemiology reports) need to be careful, especially when human health is at stake (EPA 2005).

29. The following Table highlights common causes of bias toward the null in epidemiological studies, i.e., reasons that a study might not show the existence of a risk that indeed is present, though hidden due to the bias. While biases in the opposite direction also exist, they are usually of much less significance (Grandjean 2013).

*Table 1. Causes of bias toward the null in epidemiology studies
(Grandjean 2013a).*

Inadequate statistical power in small studies
Lost cases and inadequate follow-up for long-term effects
Exposed or otherwise inappropriate comparison (control) group
Exposure misclassification
Insensitive or imprecise outcome measures
Failure to adjust for confounders with effects in the opposite direction
Disregarding vulnerable subgroups
5% probability level to minimize risk of false positives (Type I error)
20% probability level to minimize risk of false negatives (Type II error)
Pressure to avoid false alarm

30. Studies that do not show a statistical significance are sometimes called “negative,” although this term is misleading. Joint analyses of several such studies may well show a significant difference or trend.

31. Observational studies will rarely if ever provide definitive proof of causation, and it is always possible for someone to raise doubts and uncertainties that require additional or improved data to resolve (Michaels 2008). It is important to recognize, however, that the presence of uncertainties often tends to cause underestimations of actual risks, not the opposite. This issue is of importance especially regarding substances that have not yet been studied in the detail desired or cannot be examined in randomized clinical trials. Many unfortunate past errors in regard to industrial chemicals have shown that initial assessments were often erroneous and led to an underestimation of the true risks (European Environment Agency 2001 & 2013).

32. In the context of developmental neurotoxicity, I place greatest weight on prospective studies of population-based birth cohorts followed over time (Grandjean et al. 2008; Grandjean & Landrigan 2014). Birth cohorts are crucial because it is not just the dose that can matter but also the timing of the dosing in regard to the developmental stage of the subjects (Grandjean et al. 2008; Grandjean et al. 2019). Follow-up studies of birth cohorts can thus reveal with greater certainty the

impacts of exposures incurred during early life stages.

C. Benchmark Dose Methodology

33. As part of my assessment in this case, I worked with my biostatistician colleague Dr. Budtz-Jørgensen on a BMD analysis of the prospective cohort data on fluoride and IQ using the same peer-reviewed method that we used for lead (Budtz-Jorgensen et al. 2013).

34. The statistical uncertainty in the BMD estimation is taken into account by calculating its lower one-sided 95% confidence limit, which is called the benchmark dose level (BMDL). The BMDL is then used as the point of departure for calculation of the exposure limit, by dividing the BMDL by an uncertainty factor (usually fixed at 10) to obtain a protective Reference Dose (RfD) or tolerable exposure (EFSA 2009; EPA 2012).

D. Materials Relied Upon

35. In my assessment, I relied upon my existing knowledge of the scientific literature (with citations to specific studies noted in my reports), my own meta-analysis of the epidemiological studies of fluoride and IQ (Choi et al. 2012), the more recent meta-analysis by Duan (2018), all available prospective studies, as well as the reviews by NRC (2006) and NTP (2016).

36. I also considered studies provided by counsel,¹ many of which I was already familiar with, and conducted supplemental searches on PubMed, including searches to see if there were any significant epidemiological studies published that I might have overlooked.

37. A complete list of the studies I relied upon is provided in my expert reports.

IV. GENERAL CONSIDERATIONS

A. Emergence of Brain Development as Vulnerable Target

38. Evidence has been accumulating over several decades that industrial chemicals can cause

¹ I understand that these studies were provided to EPA's experts as well, including Dr. Chang.

1 neurodevelopmental disorders that include learning disabilities, sensory deficits, developmental delays,
2 and cerebral palsy (NRC 2000), and current evidence also relates to other neurodevelopmental deficits,
3 such as attention deficit hyperactivity disorder (ADHD) (Bennett et al. 2016). Subclinical stages of these
4 conditions also appear to be common, and the suspicion of a link between neurotoxic chemical
5 exposures and widespread neurobehavioral damage has increased since it was first raised by research
6 demonstrating that lead is particularly toxic to the developing brain across a wide range of exposures
7 (Baghurst et al. 1987; Dietrich et al. 1987; Landrigan et al. 1975; Needleman et al. 1979).

8
9 39. The developing human brain is inherently much more susceptible to injury caused by toxic
10 agents than the brain of an adult. This susceptibility reflects the fact that in the nine months of prenatal
11 life the human brain must evolve from a strip of cells along the dorsal ectoderm into a complex organ
12 comprised of billions of precisely located, highly interconnected and specialized cells. Optimal brain
13 development requires that neurons move along precise pathways from their points of origin to their
14 assigned locations, that they establish connections with other cells near and distant, and that they
15 generate intercommunications in meaningful ways (Dobbing 1968; Rice and Barone 2000; Rodier
16 1995).

17
18 40. All of these processes must take place within a tightly controlled time frame, in which each
19 developmental stage must be reached on schedule and in the correct sequence. Due to the extraordinary
20 complexity of human brain development, windows of unique susceptibility to toxic interference occur
21 that have no counterpart in the mature brain, or in any other organ. Because of the unique structure of
22 the human brain and its advanced function, no other species shows similar degree of developmental
23 vulnerability. Thus, if a developmental process in the brain is halted or inhibited, there is little potential
24 for later repair, although plasticity will allow some compensation, and the consequences are therefore
25 likely to be permanent (Dobbing 1968; Rice and Barone 2000).

1 41. To test chemicals for developmental neurotoxicity, standardized protocols have been
2 developed using rodent models (OECD 2007). However, they may not necessarily be sufficiently
3 sensitive, as rodent brains are far less complex than human brains, and intrauterine brain development is
4 completed at a stage where the human fetal brain is still rapidly developing *in utero* for several more
5 weeks with possible continued impact from maternal transfer of neurotoxicants (Bal-Price et al. 2018).

6 42. During fetal development, the placenta can offer some protection against unwanted
7 chemical exposures, but it is not an effective barrier against most environmental neurotoxicants
8 (Andersen et al. 2000), including fluoride (NRC 2006). In addition, the blood-brain barrier, which
9 protects the adult brain from many toxic agents, is not completely formed until about 6 months after
10 birth (Adinolfi 1985).

12 43. Postnatally, the human brain continues to develop, and the period of heightened
13 vulnerability therefore extends over many months through infancy and into early childhood. While most
14 neurons have been formed by the time of birth, growth of glial cells and myelination of axons continue
15 for several years and is not complete until late teenage years (Rice and Barone 2000; Rodier 1995).

16 44. The susceptibility of infants and children to industrial chemicals is further amplified by
17 their relatively increased exposures in regard to body weight, their augmented absorption rates, and
18 diminished ability to detoxify many exogenous compounds as compared to adults (Ginsberg et al. 2004;
19 NRC 1993).

21 45. In 2005, when I evaluated the evidence of industrial chemicals regarding developmental
22 neurotoxicity, only five substances (arsenic, lead, methylmercury, polychlorinated biphenyls, and
23 toluene) fulfilled our criteria for causal relationship in humans (Grandjean and Landrigan 2006). Eight
24 years later, when we reassessed the evidence, we added six more substances, including fluoride
25 (Grandjean and Landrigan 2014), based on new evidence that had emerged.
26

1 46. Our 2014 assessment was focused on *hazard* (i.e., whether fluoride causes developmental
2 neurotoxicity in humans), not on *risk* (i.e., the exposure level at which this hazard may occur).
3 Substantial new evidence published since that time, particularly the prospective birth cohort studies,
4 now permit an assessment of risk.

5 **B. Toxicokinetics During the Fetal Period**

6 47. In my assessment, I considered the toxicokinetics of fluoride, with a particular focus on the
7 uptake, distribution and retention during the fetal period.

8 48. It is well accepted that fluoride crosses the placenta and reaches the fetus from the
9 mother's blood stream (NRC 2006; WHO 2006).

10 49. The first documentation of placental transfer in humans was the observation in 1974 (Shen
11 and Taves 1974) that fluoride concentrations in maternal and cord serum correlated well, with the cord
12 blood showing slightly lower concentrations. These findings were replicated in 1986 (Ron et al. 1986),
13 with results suggesting minor deviations depending on gestational age. A more recent study from an area
14 with water-fluoride levels of 0.4-0.8 mg/L showed that cord serum contained about 80% of the
15 concentrations occurring in maternal serum (Opydo-Szymaczek and Borysewicz-Lewicka 2007).
16 Consistent with this, French researchers measured fetal blood concentrations of fluoride after the
17 mothers were administered a small dose of sodium fluoride, and the elevations were statistically
18 significantly higher (2.6 $\mu\text{mol/l}$) than in a control group (less than 1 $\mu\text{mol/l}$) (Forestier et al. 1990).
19

20 50. A recent study from scientists at the University of California San Francisco (UCSF) further
21 confirms the placental transfer of fluoride (Uyghurturk et al. 2020). In this study, fluoride concentrations
22 were measured in the urine, blood, and amniotic fluid among pregnant women in fluoridated and non-
23 fluoridated areas of Northern California. Each additional 0.1 mg/L of fluoride in water was associated
24 with a significant increase in the fluoride levels in the amniotic fluid ($p < 0.001$), thus confirming the
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27

transplacental passage of fluoride.

51. As would be expected, given the undeveloped nature of the blood-brain barrier during the fetal period, laboratory studies of animals exposed to prenatal fluoride have found significant elevations of fluoride in the brain (McPherson et al. 2018; Mullenix et al. 1995). Similarly, in aborted human fetuses, fluoride concentrations in the brain have been shown to be higher in geographic areas with endemic fluorosis as compared to controls at lower exposures (Du et al. 2008; He et al. 2008).

C. Toxicological Findings

52. Neurotoxicity is a documented hazard of fluoride exposure in laboratory animals (NRC 2006), which supports the plausibility of fluoride causing neurotoxic effects in humans.

53. One of the first U.S. reports on experimental fluoride neurotoxicity emerged when a new method was developed for computerized surveillance of rat behavior. Fluoride was selected for a test of the new methodology and showed clear neurotoxicity (Mullenix et al. 1995). The authors noted that the behavioral effects they observed in the rats are indicative of fluoride's potential ability to cause IQ deficits in humans. This assessment, which was made prior to the publication of any studies of fluoride and IQ in western journals, proved prescient.

54. Since the Mullenix study was published in 1995, many additional animal studies have documented neurochemical and anatomic changes in the brains of fluoride-treated animals. By 2006, the NRC concluded that there was enough neurochemical and anatomic data to conclude that fluoride interferes with brain functions by both direct and indirect means.

55. Among prominent adverse outcome pathways, the NRC concluded that fluoride is an endocrine disrupter that can affect thyroid function at intake levels as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency (NRC 2006).² Thyroid toxicity supports the plausibility of fluoride

² Large epidemiological studies published since the NRC report suggest that thyroid dysfunction is a relevant risk at elevated fluoride exposures in fluoridated communities, especially in

1 neurotoxicity because availability of thyroid hormone is crucial for optimal brain development (Rovet
2 2014).

3 56. At the time of the NRC's review, there was little data yet available on fluoride's impact on
4 behavior and cognition in animals, but considerable data has since been published. In 2016, the National
5 Toxicology Program (NTP) conducted a systematic review of these behavioral/cognitive studies (NTP
6 2016). Although NTP did not consider any of the neurochemical/anatomical effects, it still concluded
7 that the evidence is "suggestive of an effect on learning and memory" (NTP 2016, p. vii). The NTP
8 characterized its confidence in the evidence as "moderate" for adult studies, and "low" for the few
9 available developmental studies.
10

11 57. Additional animal research on learning/memory has been published subsequent to the NTP
12 review, and most of it has reported adverse effects. As is often the case, the animal studies on
13 learning/memory have limitations or discrepancies but given the general consistency in their findings
14 they continue to be *at least* "suggestive" of fluoride being a neurocognitive hazard.
15

16 **V. EPIDEMIOLOGICAL STUDIES (CROSS-SECTIONAL)**

17 **A. Neurotoxicity from Occupational Fluoride Exposure**

18 58. The neurotoxicity of chemicals is often first discovered from workplace exposures
19 (Grandjean and Landrigan 2006), which are later followed by case reports that involve children or
20 pregnant women from the general population (Grandjean 2013). The same is true of fluoride.
21

22 59. Although largely overlooked or ignored, Roholm first reported evidence of nervous system
23 effects in his seminal study of cryolite workers in Copenhagen (Roholm 1937): "The marked frequency
24 of nervous disorders after employment has ceased might indicate that cryolite has a particularly harmful
25 effect on the central nervous system" (p. 178). The nervous system effects reported by Roholm included
26 tiredness, sleepiness, indisposition, headaches, and giddiness (p. 138).

27 adults with iodine deficiency (Malin et al. 2018; Peckham et al. 2015).

60. My own mortality study of the cryolite workers studied by Roholm showed an excess of violent deaths (Grandjean et al. 1985), but information on the causes of death did not allow any conclusions on deaths from nervous system disease.

61. One of the challenges with occupational studies of fluoride-exposed workers is that the fluoride exposure usually occurs as part of a mixture. In the 1940s, scientists at the Manhattan Project recorded CNS effects in workers exposed to uranium hexafluoride gas (UF₆). They observed a “rather marked central nervous system effect with mental confusion, drowsiness and lassitude as the conspicuous features” and attributed it to the fluoride rather than uranium (Ferry 1944; Mullenix 2005).

62. Consistent with the observations of the Manhattan Project scientists, published case reports have highlighted difficulties with concentration and memory accompanied by general malaise and fatigue following occupational fluoride exposures (Spittle 1994).

63. More recently, skeletal fluorosis in workers was found to be associated with gradually progressive effects on the normal function and metabolism of the brain and other aspects of the nervous system (Duan et al. 1995), and application of neuropsychological tests (i.e., WHO’s Neurobehavioural Core Test Battery) have reported significant associations between workplace fluoride exposures and cognitive problems (Guo et al. 2008; Yazdi et al. 2011).

64. The available evidence from occupationally exposed workers supports the neurotoxicity of fluoride but does not allow any detailed consideration of its dependence on dose, timing, and duration.

B. Neurotoxicity in Endemic Fluorosis Areas

65. Fluoride toxicity has received particular attention in China, where widespread dental fluorosis indicates pervasive high exposures (Wang et al. 2012). Areas with high prevalences of dental (and skeletal) fluorosis are known as “endemic fluorosis” areas.

66. Although microbiologically safe, water supplies from wells, small springs or mountain

1 sources have created pockets of increased fluoride exposures near or within areas of low exposures, thus
2 representing optimal settings for epidemiological research because only the fluoride exposure would
3 likely differ between nearby neighborhoods. In addition, rural families in China move much less
4 frequently than U.S. families, thus facilitating assessment of impacts from long-term exposures. Chinese
5 researchers took advantage of this fact and published their findings, though mainly in Chinese journals,
6 and according to the standards of science at the time. The early research dates to the 1980s but has not
7 been widely cited, in part because of limited access to Chinese journals, in part because the notion of
8 adverse effects from fluoride intake has often been considered unwelcome.
9

10 67. Most of the studies on fluoride neurotoxicity from China, and other countries (i.e., India,
11 Iran, and Mexico), have focused on IQ measures as the endpoint of concern, with the clear majority of
12 these studies reporting inverse associations (i.e., higher levels of fluoride exposure are associated with
13 lower IQ).

14 68. Many of the studies from China have significant limitations, including lack of information
15 on covariates, missing information on study details, assessment of exposures on a community basis, and
16 use of cross-sectional study designs. The reports have also tended to be relatively brief and simple in
17 design. These deficiencies, which in some cases are rather severe, limit the conclusions that can be
18 drawn, but are unlikely to explain the almost uniformly consistent inverse associations that have been
19 reported.
20

21 69. While most of the endemic fluorosis studies have rather simple designs and may have
22 failed to control for confounding factors of possible importance, they also have important strengths,
23 including: 1) Stable populations with stable water-fluoride concentrations; many of the studies
24 specifically limited the populations to those who had lived in the community their entire life. 2) Unlike
25 in the U.S., children in rural China have very little exposure to fluoridated dental products (Zhu et al.
26
27
28

2003), thus making water a more important and reliable metric of fluoride exposure. 3) The studies in endemic fluorosis areas that have controlled for or excluded key confounding factors (arsenic exposure, iodine deficiency, parental education) were still capable of identifying clear associations between elevated fluoride exposure and cognitive deficits (Choi et al. 2012).

70. I will discuss the Chinese research on IQ in fluoride-exposed communities in more detail, but I begin first with studies that have examined other neurotoxicity endpoints, including neuropathological outcomes in aborted fetuses, neurobehavioral effects during infancy, and cognitive deficits and other neurological problems in adults.

1. Neurotoxic Endpoints in Fetuses and Neonates

71. In brain tissue obtained from aborted fetuses in endemic fluorosis areas, electron microscopy showed retarded cell growth in the cerebral cortex, with substantial cytology changes (He et al. 2008). A similar study used stereology to examine nerve cell numbers and volumes in fetal brain tissue and found lower densities (Du et al. 2008). A third study focused on neurotransmitters and receptors and found deviations that suggested neural dysplasia (Yu et al. 2008). Another study of aborted fetal brain tissue showed similar neurotransmitter results (Dong et al. 1993). These studies are consistent with prenatal fluoride exposure causing anatomic and biochemical changes in the fetal brain, as concluded by the NRC. A limiting factor, however, is that the elevated fluoride exposure in these studies came primarily from coal burning, which may have contributed other contaminants besides fluoride that were not assessed.

72. The impact of elevated fluoride in drinking water on neurological behavior in 91 neonates was assessed by Li et al. (2008). The study found that neonates born in an endemic fluorosis area (water-fluoride concentrations of 1.7 - 6.0 mg/L) scored more poorly on the standard Neonatal Behavioral Assessment, and that visual and auditory responses were also deficient, as compared to controls from

1 areas with less than 1 mg/L (Li et al. 2008). These findings are again consistent with the notion that
2 fluoride can affect the brain during the prenatal period, although neonatal neurological assessments can
3 be somewhat imprecise and may be only weakly predictive of subsequent brain development.

4 73. In a separate study, infants from an endemic area were examined at ages 3, 6, 9 and 12
5 months and scored significantly lower in mental and psychomotor development indices than those of the
6 control group (Chang et al. 2017). The exposed group also showed lower birth weight, and it is unclear
7 whether this difference can lead to confounding or if a lower birth weight is a concomitant effect of the
8 fluoride exposure. As with the fetal neuropathology studies, the source of fluoride exposure in this study
9 was coal, not water, which limits the conclusions that can be drawn due to the potential for confounding.
10

11 2. Neurotoxic Endpoints in Adults

12 74. Studies in China using cross-sectional designs have also found cognitive problems and
13 neurological symptoms in adults with skeletal fluorosis living in endemic fluorosis areas. Using
14 neuropsychological tests, including the Wechsler scale, 49 adult fluorosis patients (it is not clear whether
15 the patients were from a coal- or waterborne fluorosis area) were compared with controls and showed
16 deficits in language fluency, recognition, similarities, associative learning, and working memory (Shao
17 et al. 2003). Likewise, cognitive impairment in elderly subjects was clearly elevated in a waterborne
18 fluorosis area, although within-group assessment of urine-fluoride concentrations failed to show a clear
19 gradient of effect (Li et al. 2016). Excess occurrence of neurological symptoms has also been recorded
20 in both adults and children from waterborne fluorosis areas, with headaches being the primary
21 manifestation (Sharma et al. 2009).
22

23 3. Childhood IQ

24 75. As noted above, most of the epidemiological studies on fluoride neurotoxicity have
25 focused on IQ scores in childhood. In 2012, my colleagues and I published a meta-analysis of the
26
27
28

1 available 27 studies, most of which were published in China³ (Choi et al. 2012). Because these
2 published studies were conducted independently, we used meta-analysis—a quantitative, formal,
3 statistical technique—to systematically review and assess these published research studies to derive
4 conclusions about the neurotoxicity of fluoride. The outcome of the meta-analysis includes a more
5 precise estimate of the association than any individual study that contributes to the pooled analysis. The
6 variability or heterogeneity in study results was also examined. We did not attempt to generate any
7 dose-response relationship, and the fluoride concentrations were used only for definitions of high and
8 low (reference) groups in each study.
9

10 76. Among the 27 studies we reviewed, two involved populations exposed to fluoride from
11 coal burning (Guo et al. 1991; Li et al. 2010); the rest of the studies involved exposure to fluoride
12 through drinking water containing fluoride from soil minerals. The Combined Raven's Test – The Rural
13 Edition in China (CRT-RC) was used to measure the children's intelligence in 16 studies. Other
14 intelligence measures included the Wechsler Intelligence scale (3 studies), Binet IQ test (2 studies),
15 Raven's test (2 studies), Japan IQ test (2 studies), Chinese comparative intelligence test (1 study), and
16 the mental work capacity index (1 study). As each of the intelligence tests used is designed to measure
17 general intelligence, we used data from all eligible studies to estimate the possible effects of fluoride
18 exposure on the children's intelligence. We conducted a sensitivity analysis restricted to studies that
19 used similar tests to measure the outcome (specifically, the CRT-RC, Wechsler Intelligence test, Binet
20 IQ test, or Raven's test), and an analysis restricted to studies that used the CRT-RC. We also performed
21 an analysis that excluded studies with possible concerns about co-exposures, such as iodine status and
22 arsenic exposure, or with non-drinking water fluoride exposure from coal burning, without finding
23 appreciable differences, as described below.
24
25

26
27 ³ Two of the 27 studies included in the analysis were conducted in Iran (Poureslami et al.
2011; Seraj et al. 2006), otherwise the study cohorts were populations from China.

77. The levels of fluoride exposure in the studies we examined, while higher than those associated with fluoridation programs (0.7 mg/L), are not as high as some have claimed. A surprising number of commentators, including the EPA, have only mentioned the *highest* concentration examined in the studies (11.5 mg/L) (Allukian et al. 2018; EPA 2018), although this high concentration occurred in only one of the 27 studies. The majority of studies that reported the water-fluoride level in the exposed group had between 1.5 and 4 mg/L, which is elevated, but only modestly.⁴ Similarly, Duan's more recent meta-analysis of waterborne fluoride exposures reported that 18 of 27 studies addressed water-fluoride concentrations below 4 mg/L, and IQ reductions were observed at elevated concentrations of 1 to 2 mg/L (Duan et al. 2018 Table 2).

78. Among the 27 studies, all but one showed random-effect standardized mean difference (SMD) estimates that indicated an inverse association, ranging from -0.95 to -0.10 (one study showed a slight, non-significant effect in the opposite direction). The overall random-effects SMD estimate (and the 95% confidence interval, CI) were -0.45 (-0.56, -0.34). Given that the standard deviation (SD) for the IQ scale is 15, an SMD of -0.45 corresponds to a loss of **6.75 IQ points**.⁵ I shall return to this result later. Among the restricted sets of intelligence tests, the SMD for the model with only CRT-RC tests and drinking-water exposure was lower than that for all studies combined, but the difference was not significant, and heterogeneity remained at a similar magnitude in the restricted analyses.

79. Several studies (Hong et al. 2001; Lin et al. 1991; Wang et al. 2001; Wang et al. 2007; Xiang et al. 2003; Zhao et al. 1996) reported other risk factors, such as iodine status, and exposure to arsenic or lead, both neurotoxicants, and our sensitivity analyses showed similar associations between

⁴ The fluoride levels in the control groups in the studies often approximated the concentrations (~0.7 mg/L) used in fluoridation programs. Some ill-informed commentators have mistakenly interpreted this to mean that these control levels are thereby safe. This is false. The control groups are not being compared to *lower* or zero fluoride groups, and, as such, provide no information about the safety, or lack thereof, of the control values.

⁵ The effect size we found is consistent with the prior meta-analysis of Tang (2008), who reported a mean difference of 5.03 IQ points between the high- and low-fluoride areas.

1 high fluoride exposure and the outcomes even after exclusion of these studies. Although large tracts of
2 China have superficial fluoride-rich minerals, there is little, if any, likelihood of contamination by other
3 neurotoxicants that would be consistently associated with fluoride concentrations in drinking water and
4 thereby systemically confound the results. For example, follow-up testing documented lower levels of
5 blood-lead concentrations and waterborne arsenic in the high-fluoride community than the control
6 (Xiang et al. 2003; Xiang et al. 2003; Xiang et al. 2013). In some instances, therefore, potential co-
7 exposure to other neurotoxicants may cause reverse confounding (i.e., may attenuate the real
8 relationship between fluoride and IQ), as we have documented for methylmercury exposure from
9 seafood (Choi et al. 2008).
10

11 80. Additional IQ studies in endemic fluorosis areas have been published since our 2012
12 review. As with the previous studies, these newer studies continue to replicate the consistent inverse
13 association between fluoride exposure and IQ, although many—but not all—suffer from similar
14 limitations. Two of the studies reported linear relationships between urinary fluoride excretion and IQ
15 (one study also included plasma-fluoride) among children living in areas with mean water-fluoride
16 contents of 1.4 mg/L and 1.5-2.5 mg/L (Cui et al. 2018; Zhang and Cheng 2015).⁶ Another study
17 published since our meta-analysis is the one I conducted with colleagues in China, which I will now
18 discuss.
19

20 81. To ascertain the validity of the Chinese reports on fluoride neurotoxicity, we carried out a
21 pilot study in Sichuan using methods commonly applied in neurobehavioral epidemiology (Choi et al.
22 2015). The children examined had lived in their respective communities since conception. Although we
23 examined only 51 children, our results are consistent with elevated fluoride exposure being a cause of
24 cognitive deficits. Interestingly, negative associations were found for cognitive function tests regarding
25

26 ⁶ These results are consistent with the findings of Ding et al. (2011), who reported a dose-
27 response relationship between urine-fluoride concentrations (range = 0.24-2.84 mg/L) and reduced IQ in
a population without any severe dental fluorosis (Ding et al. 2011).

all three measures of fluoride exposure. One was the known water-fluoride concentration at the residence where the child was born and had grown up, another was the child's morning urine-fluoride after having ingested fluoride-free water the night before (neither measure reached formal statistical significance as a predictor of cognitive deficits). The strongest and statistically significant association was seen with the degree of dental fluorosis that served as a marker of early-life fluoride exposure. While the milder forms of dental fluorosis have been considered a cosmetic effect (Aoba and Fejerskov 2002; WHO 2006), our study suggested that fluorosis can serve as a useful marker of early fluoride exposure in studies of neurodevelopmental toxicity.⁷

C. Studies of Fluoride and ADHD in North America

82. Four epidemiological studies have investigated the relationship between fluoride and ADHD behaviors in North America, the most important of which is the prospective cohort study by Bashash (2018). Two of the other three studies examined ADHD-related outcomes in the Canadian Health Measures Survey (CHMS) (Barberio et al. 2017; Riddell et al. 2019).⁸

83. In 2017, Barberio et al. examined two cycles of the CHMS to investigate the relationship between randomly measured urine-fluoride levels (in 3-to-12-year-old children) and parental reports or self-reported learning disabilities. When the two cycles of the CHMS were combined (both including at least 1,100 subjects), unadjusted urine-fluoride was significantly correlated with an increased incidence of learning disabilities. However, this effect lost its statistical significance after controlling for urine dilution by creatinine and specific gravity. The authors concluded that there was no robust association

⁷ A prior study that was co-authored by my colleague David Bellinger failed to observe a relationship between dental fluorosis and behavior, as determined from parental questionnaires (Morgan et al. 1998). Due to several weaknesses, the conclusions were cautious and, in the authors' wording, "cannot lay this issue to rest." The relationship between dental fluorosis and neurobehavioral deficits is an issue that thus requires further study, including the possibility that the relationship is only apparent for fluorosis of certain teeth that share windows of susceptibility that overlap the windows of susceptibility for developmental neurotoxicity.

⁸ The third study (Malin and Till 2015) was an ecological study that found an association between ADHD and water fluoridation in the U.S. This association was not robust, however, as it lost its significance after adjustment for altitude, although this adjustment is questionable.

between fluoride exposure and reported learning disability among Canadian children at the ages studied.

84. A more sophisticated study using the same CHMS data has now been completed and shows a significant association between fluoridated water and ADHD diagnoses/symptoms (Riddell et al. 2019). The latter study controlled for more potential covariates than Barberio and focused on an older subset of children (6 to 17 years old). Riddell's focus on an older group of children is an improvement because 90% of children with ADHD are diagnosed after age 6 (Riddell et al. 2019). Riddell also focused specifically on ADHD symptoms and diagnoses, rather than the broader category of "learning disabilities." The Riddell team also analyzed fluoride in water as well as in urine and conducted regression analyses to test the association with specific ADHD parameters: i.e., ADHD diagnosis and the hyperactivity/inattention score on the Strengths and Difficulties Questionnaire (SDQ).

85. After adjustment for covariates, including lead exposure, Riddell and colleagues found that fluoridation of the home water supply significantly increased the risk of an ADHD diagnosis. An increase in water-fluoride by 1 mg/L was associated with a (statistically significant) 6-fold higher odds of an ADHD diagnosis in the 710 children known to rely on community water, although this association was not replicated using urine concentrations that may have been more variable. Similar tendencies were seen for the SDQ scores of hyperactivity/inattention, especially among the older youth (not covered by the Barberio study).

86. With its individual exposure data, more specific ADHD outcomes in adolescents, and large effect size, the Riddell study, along with Bashash et al. (2018) that I will discuss below, provide additional weight to the evidence of fluoride being a neurotoxicant at current levels of exposure in fluoridated areas.

VI. EPIDEMIOLOGICAL STUDIES (PROSPECTIVE)

A. Prospective Cohort Studies with Individual Assessment of Prenatal Exposure

1 87. The most reliable evidence of developmental neurotoxicity is obtained through prospective
2 studies that include real-time recording of information about exposure in early life followed by
3 subsequent clinical assessments of the child. (Grandjean & Landrigan 2014; Grandjean 2008). In our
4 meta-analysis we recommended that prospective studies be conducted to formally evaluate dose-
5 response relations based on individual-level measures over time, including more precise prenatal
6 measurements (Choi et al. 2012). Five such studies have now been conducted, and they have each found
7 significant adverse associations between prenatal fluoride exposure and neurodevelopmental harm
8 (Bashash 2017; Bashash 2018; Green 2019; Valdez-Jiminez 2017), with an additional study finding an
9 association between fluoride exposure during early infancy and IQ loss (Till 2020). The quality of these
10 studies, coupled with the consistency of their findings, also in regard to the cross-sectional studies, add
11 *substantial* weight to the evidence for developmental neurotoxicity from fluoride exposure.
12

13 88. I understand that Dr. Hu and Dr. Lanphear will be discussing the ELEMENT and MIREC
14 cohort studies in detail, so I will forego doing so here. As I explained in my initial expert report, these
15 are high-quality studies given their prospective birth cohort design, individual measurements of fluoride
16 exposure, and extensive control for potential confounders.
17

18 89. In addition to the ELEMENT and MIREC studies, a prospective birth cohort study has also
19 been published from a separate area of Mexico where there are elevated levels of fluoride in drinking
20 water (Valdez Jiminez 2017). In this study, maternal urine-fluoride (corrected for specific gravity) was
21 examined for its association with scores on the Bayley Scales among 65 children evaluated at age 3-15
22 months. The mothers in the study had average urine-fluoride concentrations at each of the three
23 trimesters of pregnancy of 1.9, 2.0, and 2.7 mg/L. These fluoride exposure indicators during the first and
24 second trimesters were associated with large and significant reductions in the Bayley Mental
25 Development Index (MDI) (cognitive) score after adjusting for covariates, including gestational age.
26
27

1 While this study is not as robust as the ELEMENT and MIREC studies due to the limited size, its
2 findings are consistent with and reinforce their findings, and add further weight to the neurotoxicity
3 assessment given its prospective cohort design.

4 **B. Prospective Cohort Studies without Prenatal Exposure Assessment**

5 90. Two additional prospective studies have been previously published on fluoride and
6 neurodevelopment (Shannon et al. 1986; Broadbent et al. 2015), both from New Zealand. They have
7 substantial limitations that make them much less informative than the North American studies, including
8 a failure to obtain individual measurements of fluoride exposure, and a failure to ascertain prenatal
9 fluoride exposure.
10

11 91. The first of the New Zealand studies was published in 1986 by Shannon. It found no
12 association between childhood behavior (as scored by mothers and teachers) and the duration of time the
13 child had lived in a fluoridated area during the first 7 years of life. The authors, however, made no
14 attempt to ascertain prenatal and early postnatal exposures. Postnatal exposures were measured by
15 simply tallying the number of years a child resided in a fluoridated area, with no distinctions made for
16 the *timing* of postnatal exposure. Under this exposure metric, a child who lived her first year of life in a
17 fluoridated area (a period of increased vulnerability) would be treated the same as a child who lived her
18 seventh year of life in a fluoridated area.
19

20 92. A second prospective study from New Zealand was based on a birth cohort established
21 from births in 1972-1973 (Broadbent et al. 2015). The 1,037 children were recruited at age 3 years, and
22 IQ tests were administered at ages 7, 9, 11 and 13 years, and again at age 38. Urine samples were again
23 not available for analysis, and the authors had no individual data on water intake. Instead, the authors
24 compared individuals who had lived for an undefined period of time in a fluoridated area during their
25 first five years of life, with individuals who had not lived in a fluoridated area during their first five
26 years of life.
27

years. No significant differences in IQ were noted using this exposure metric, and this finding was independent of potential confounding variables, including sex, socioeconomic status, breastfeeding, and birth weight.⁹

93. The Broadbent study also made no attempt to ascertain prenatal exposures, including maternal tea consumption, which is an important limitation given the high rate of tea consumption in New Zealand. Tea contains elevated levels of fluoride, and tea consumption can be a major source of fluoride intake among adults (Waugh 2017). During the time that the children in this study were born (1972-1973), New Zealanders consumed as much as 2.6 kg of tea per capita per year (corresponding to 3-4 teabags per day), as compared to the consumption of 0.5 kg in Canada in the approximate time the MIREC cohort was recruited (Grigg 2002). The failure of both New Zealand studies to consider maternal tea consumption may have introduced substantial imprecision into the exposure classification.

94. An additional concern is that the 10% of cohort subjects who had not lived in fluoridated areas very likely received fluoride supplements, which would eliminate much of the (postnatal) difference in exposure between the fluoridated and non-fluoridated areas. In a letter published subsequent to the study, the authors estimated that the average difference in exposure between children in fluoridated vs. non-fluoridated areas was only 0.3 mg/day (Broadbent et al. 2016).

95. Based on the absence of individual measurements of exposure; failure to control for the timing of exposure, including prenatal exposures; and the relatively small difference in postnatal exposures in the Broadbent study, the New Zealand studies provide virtually no information about the neurotoxic impact of early-life fluoride exposures. They carry little weight in my assessment.

VII. SYSTEMATIC REVIEW

96. Although I decided not to conduct a formal systematic review for my weight-of-the-

⁹ Despite the fact that lead exposure in this cohort was later reported to cause IQ deficits (Reuben et al. 2017), the authors of the fluoride study chose not to control for exposure to lead or other chemicals that can affect neurodevelopment.

evidence analysis, I had the opportunity to consider and analyze the review conducted by Dr. Ellen Chang of Exponent. As I described in my expert rebuttal report, Dr. Chang's systematic review provides no credible grounds for questioning my assessment of the literature; in fact, it further supports it.

A. Dr. Chang's Systematic Review Confirms that I Considered All Significant Data

97. Dr. Chang stated that her systematic review identified numerous studies that I did not address, with the apparent implication that these studies are somehow at odds with my opinion (p. 8). What Dr. Chang failed to reveal, however, is that the great majority of these studies reported significant associations between fluoride exposure and neurotoxic outcomes, further confirming my own assessment.

98. Of the 31 studies that Dr. Chang has identified and which I did not specifically address, 27 found associations of elevated fluoride exposure with adverse effects.¹⁰ These studies, which provide further *support* for my opinions, were not cited in my report because most are repetitions of the cross-sectional study design in endemic fluorosis areas that I have already discussed at length; some are only available in abstract form;¹¹ some are secondary analyses of primary studies that I already addressed;¹² and one was not available to me at the time of submitting my report (Till et al. 2020). As explained in my report, I do not consider it necessary to address and discuss each and every paper that reports on fluoride effects, especially when peer-reviewed systematic reviews are available, including our own (Choi et al. 2012). I consider it more informative to examine the various *types* of studies, including toxicokinetics (e.g., distribution of fluoride throughout the body, including transfer through the placenta and blood-brain barrier); toxicological findings from animals; and different endpoints relevant to

¹⁰ Aravind (2016); Asawa (2014), Calderon (2000), Das (2016), Khan (2015), Kundu (2015), Liu (2000); Lu (2019), Manju (2017), Mustafa (2018), Nagarajappa (2013); Qin (1990), Razdan (2017), Rocha-Amador (2007), Rocha-Amador (2008), Rocha-Amador (2009), Saxena (2012), Shivaprakash (2011), Singh (2013), Sudhir (2009), Thomas (2018), Till (2019), Trivedi (2007), Wang (2005), Xiang (2015), and Yu (2018).

¹¹ Calderon (2000); Thomas (2018).

¹² Xiang (2015); Wang (2012).

neurotoxicity (e.g., cognitive tests, thyroid function, histological assessments of fetal brain).

99. Conversely, many of the studies that I addressed in my report¹³ were not considered by Dr. Chang for unexplained or spurious reasons. Dr. Chang's review, for example, never addressed or considered fluoride's (i) passage through the placenta, (ii) uptake into fetal brain, and (iii) neurochemical and anatomical effects, and she spuriously dismisses the evidence of neurotoxicity in adults as irrelevant to developmental effects in humans (p. 31). In several important ways, therefore, Dr. Chang's review is not as systematic as my own.

100. Dr. Chang's systematic search of the literature identified four papers that reported no significant associations with neurodevelopmental effects and that I did not rely on, but upon inspection, they have no material effect on the conclusions that can be drawn, as I will now discuss.

101. One study highlighted by Dr. Chang is a publication by Spittle and colleagues (Spittle 1998) that Dr. Chang refers to repeatedly throughout her review. Although noted in a lengthy table at the end, Dr. Chang fails to acknowledge in the body of her review that this report is in the form of an abstract and relates to a previous (full) publication (Shannon et al. 1986) that I addressed in my report (and above). I did not cite the Spittle abstract in my report, just as I did not cite abstracts of studies reporting harm.¹⁴ It is standard practice for systematic reviews to omit abstracts, as practiced in systematic reviews conducted by the authoritative Cochrane group (Iheozor-Ejiofor et al. 2015). Dr. Chang provides no justification for including abstracts in her review, such as the one by Spittle (Spittle 1998). Dr. Chang's prominent references to the Spittle abstract is particularly surprising given that it does not describe *any* confounder adjustment,¹⁵ and uses an ecological metric for exposure (group water

¹³ *E.g.*, Dong (1993); Duan (1995); Ekstrand (1981); Li (2016); Spittle (1994); Guo (2001); Malin (2018); Opydo-Szymaczek (2005, 2007); Peckham (2015); Ron (1986); Salgarello (2016); Shao (2003); Shen & Taves (1974); Yazdi (2011); Yu (2008).

¹⁴ Calderon (2000); Thomas (2018).

¹⁵ On p. 132 of her Table, Dr. Chang "assume[s]" that the Spittle analysis controlled for the same confounders as the Shannon analysis. I understand that neither Dr. Chang, nor anyone else in her

1 F level) – features which Dr. Chang has used to dismiss many papers that support the neurotoxicity of
2 fluoride.

3 102. The other three “no-effect” studies that Dr. Chang cites and that I did not address are
4 similarly unavailing. Two are cross-sectional studies from China which fail to show statistically
5 significant associations between fluoride exposure and IQ,¹⁶ and one is an ecological analysis (Perrott
6 2018) of the Malin & Till (2015) study on ADHD which I addressed but placed little weight on. As I
7 explained in my report, there are many reasons why an ecological/cross-sectional study can fail to detect
8 an effect even when one is present. The failure of these three studies to find statistically significant
9 effects does nothing to contradict the robust literature that I rely upon, including the prospective birth
10 cohort studies that I placed the greatest weight on. Even Dr. Chang appears to recognize this, as she does
11 not include any of these three studies in her causal analysis, and correctly notes that the analysis by
12 Perrott (Perrott 2018) is a “relatively low quality” ecological study (p. 66).
13

14 103. In summary, despite asserting that my review failed to consider “numerous” papers, Dr.
15 Chang’s own review confirms that I addressed and considered the most relevant epidemiological studies
16 on cognitive outcomes. Dr. Chang’s literature search also confirms that the majority of studies that I did
17 not specifically address are consistent with and further support the association between fluoride and
18 cognitive impairment, in accordance with my conclusions.
19

20 **B. Dr. Chang’s Review Fails to Identify Any Systematic Biases that Explain Fluoride’s**
21 **Consistent Association with Neurodevelopmental Harm**

22 104. Dr. Chang’s systematic assessment of study quality provides a lengthy discussion of real or
23 perceived methodological limitations in the available studies. Importantly, however, Dr. Chang failed to
24 identify a likely explanation for how these limitations can explain the consistent adverse associations
25

26 office has contacted Dr. Spittle to confirm this statement (Personal email communication with Bruce
27 Spittle, August 13, 2019). According to Dr. Spittle, the abstract provided all important methodological
28 details.

¹⁶ He (2010); Kang (2011).

1 between fluoride and IQ across both cross-sectional and prospective studies. For example, Dr. Chang
2 referred to “high potential for selection bias” but did not consider how unlikely it is that dozens of
3 studies should all suffer from some particular exposure misclassification or selectivity that would all
4 cause bias *away* from the null, e.g., selection bias that would result in participation of intellectually
5 disabled children only in the high-fluoride group, or residual confounding resulting in bias only away
6 from the null in the many different study settings.

7
8 105. Dr. Chang claimed that “methodological uncertainties remain about the assessment of
9 fluoride exposure and neurodevelopmental outcomes; and the reported findings are plausibly explained
10 by confounding, bias, and chance” (p. 9). However, she did not provide any convincing evidence that
11 such issues could have resulted in erroneous conclusions, especially in the high-quality prospective
12 studies.

13
14 106. Throughout her analysis, Dr. Chang failed to grapple with the fact that random (i.e., non-
15 differential) error is unlikely to cause a bias away from the null, as is well-known in epidemiology, as I
16 have also discussed in past publications (Grandjean and Budtz-Jorgensen 2007, 2010). Dr. Chang thus
17 did not articulate a plausible basis for why the limitations she claimed to have identified can
18 *systematically* bias the results across the many study settings, including the North American birth
19 cohorts.

20
21 107. Dr. Chang described cross-sectional studies as if they are all equal and as if the exposure
22 parameter always represents a current and short-lasting exposure only. In so doing, Dr. Chang failed to
23 acknowledge in her causal analysis that exposure measures in many studies represent long-term
24 community conditions, in some studies also likely covering prenatal exposures, a critical detail.

25
26 108. Dr. Chang referred to exaggerated associations that can result from lack of blinding (p.
27 59), but failed to acknowledge that at least 11 of the studies reporting adverse neurocognitive effects

1 have clearly been blinded, including the recent birth cohort studies, where the exposure was determined
 2 *after* the cognitive tests had been completed. Thus, while lack of blinding can create observation bias, it
 3 cannot explain the inverse association between fluoride and IQ because similar associations have been
 4 consistently found in studies known to be blinded. Despite producing a 56-page table to address “key
 5 characteristics” of the studies, Dr. Chang failed to mention this methodological strength in her summary
 6 of the studies (pp. 90-146).

7 109. Dr. Chang repeatedly highlighted the risk of publication bias, e.g., in the biomedical
 8 journal *Fluoride*, which is not indexed by PubMed. However, she does not mention the bias *against*
 9 publication, i.e., a bias that acts in the opposite direction. The examples that I mentioned in my report
 10 illustrate that such bias exists.¹⁷ Further, Dr. Chang speculated that Chinese-language studies that did
 11 not find adverse effects may not have been translated into English (p. 37). Instead of speculating about
 12 this, Dr. Chang’s systematic review could have included a search of online databases of Chinese-
 13 language research (e.g., CNKI) but, for unexplained reasons, did not do so.¹⁸

14 110. In summary, although Dr. Chang’s systematic assessment of study quality correctly
 15 identified limitations in a number of studies, she failed to credibly explain how these limitations can
 16 plausibly explain the significant inverse associations that have consistently been found across many
 17 study settings and designs.¹⁹ Although I recognize the issues that Dr. Chang has raised and have fully
 18

19
 20
 21 ¹⁷ The desire to use fluoride in caries prevention programs has sometimes made it difficult
 22 for researchers, including myself, to present findings of potential toxic effects. In addition to my own
 23 personal experiences, published case reports suggest that some studies reporting adverse results have
 24 been suppressed, and, in at least one instance, a respected scientist at the Forsythe Dental Institute lost
 25 her job after publishing evidence of neurotoxicity.

26 ¹⁸ A search of PubMed for “CNKI database” shows that many systematic reviews include
 27 CNKI as one of the databases to retrieve studies, and the Institute of Medicine recommendations for
 28 systematic review (which Chang relies on) calls for searching for foreign language studies when
 appropriate (IOM 2011, p. 8). CNKI is publicly available online at:
<http://oversea.cnki.net/kns55/default.aspx>.

¹⁹ Unable to explain why so many studies have found significant associations between
 fluoride and IQ, Dr. Chang claims that “most published scientific research findings are anticipated to be
 false” (p. 38, citing Ioannidis (2005)). Although the original report by John Ioannidis (Ioannidis 2005)

1 considered them in my assessment, it remains extremely unlikely, if not impossible, that the
2 overwhelming evidence of fluoride neurotoxicity is a mirage caused by bias, as Dr. Chang apparently
3 believes. A far more likely and plausible explanation for the consistent findings in the epidemiological
4 studies is that fluoride is a developmental neurotoxicant that reduces IQ and that this association is
5 strong enough to be apparent also in studies with less-than-ideal designs.

6 **C. Bradford Hill Aspects Support, Rather than Detract from, the Causal Nature of**
7 **Fluoride's Association with Neurodevelopmental Harm**

8 111. Dr. Chang used the Bradford Hill aspects to evaluate the causal relationship between
9 fluoride and neurotoxicity. As I explained in my rebuttal report, her causal analysis is superficial and
10 pays lip service only to Sir Austin's wise advice. An appropriate and systematic assessment of the
11 Bradford Hill guidelines supports, rather than refutes, the causal relationship between elevated fluoride
12 exposure and IQ loss. I will summarize here:

13 112. *Strength*: Dr. Chang dismissed the strength of the association between fluoride and IQ on
14 the grounds that a loss of 3 to 5 IQ points is relatively small in comparison with normal, expected
15 variation (p. 69). Under this arbitrarily high standard, other well-known neurotoxicants (e.g., lead,
16 methylmercury, arsenic) would fail Dr. Chang's strength criterion. By failing to consider the strength of
17 association of other well-known neurotoxicants, Dr. Chang subjectively analyzed the data on fluoride in
18 a meaningless vacuum. Had Dr. Chang considered the strength of association for other neurotoxicants,
19 she would have found that the effect size for fluoride actually is actually large, not small (i.e., it rivals
20 the effects of lead), which *supports*, rather than detracts, from a causal relationship.

21 113. *Consistency*: One of the most compelling aspects about the epidemiological research on
22
23
24
25 did provide some stunning examples of how clinical medicine could be misled by single reports, it
26 would be reckless and counterproductive if we were to ignore all published reports, as Dr. Chang seems
27 to prefer. This nihilistic view was also not the intent of the author. In a more recent paper in the same
28 journal, Dr. Ioannidis highlighted the need for balanced review of scientific evidence in the interest of
inspiring responsible policy decisions (Ioannidis 2018).

1 fluoride is how consistent it has been in finding significant associations with IQ (Choi et al. 2012). Dr.
2 Chang obscured this by highlighting non-informative studies that made no attempt to measure or
3 investigate prenatal or early postnatal fluoride exposures (Barberio et al. 2017; Broadbent et al. 2015;
4 Morgan et al. 1998; Shannon et al. 1986; Spittle 1998) as being on the same level as, and contradicting,
5 the highly significant findings from the prospective ELEMENT (Bashash et al. 2017) and MIREC
6 (Green et al. 2019) prospective birth cohort studies (pp. 70-71). A particularly poor judgment by Dr.
7 Chang was to place the Spittle abstract on the same level as the ELEMENT and MIREC studies despite
8 the fact that Spittle's abstract does not describe *any* confounder adjustment. Dr. Chang cited the "mixed"
9 nature of the findings as a basis to conclude that the consistency factor has not been met, while failing to
10 acknowledge the inappropriate apples-to-oranges nature of comparing the prospective
11 ELEMENT/MIREC studies to much, much weaker studies.
12

13 114. In her assessment of consistency, Dr. Chang failed to mention the fact that every single
14 prospective birth cohort study with prenatal exposure measurements has found a significant adverse
15 effect of prenatal fluoride on neurodevelopment (Bashash et al. 2017; Bashash et al. 2018; Green et al.
16 2019; Valdez Jimenez et al. 2017). Dr. Chang also gave short shrift to the consistent association between
17 fluoride exposure and reduced IQ reported in the numerous cross-sectional studies (Choi et al. 2012;
18 Duan et al. 2018; Tang et al. 2008). This latter shortcoming may be a result of Dr. Chang's critical
19 misunderstanding of our meta-analysis (Choi et al. 2012), which I will now address.
20

21 115. Dr. Chang claimed that our meta-analysis found an average loss of 0.45 IQ points in the
22 high-fluoride areas and characterizes this as a 10-fold difference with the Tang meta-analysis (Tang et
23 al. 2008). This, however, is not what we reported (see paragraph 78). Because different intelligence
24 scales had been used in the studies considered, we expressed the outcome as a random-effect
25 standardized weighted mean difference estimate, as we clearly explained (Choi et al. 2012). In order to
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1 translate this measure to a difference on the same IQ scale, the joint result must be multiplied by the
2 standard deviation of the IQ scale, i.e., 15. An SMD of -0.45 thus corresponds to a loss of 6.75 IQ
3 points. Contrary to Dr. Chang's mischaracterization, therefore, the results of our meta-analysis are
4 consistent with the Tang meta-analysis, a fact that we actually mention in our published paper (Choi et
5 al. 2012).

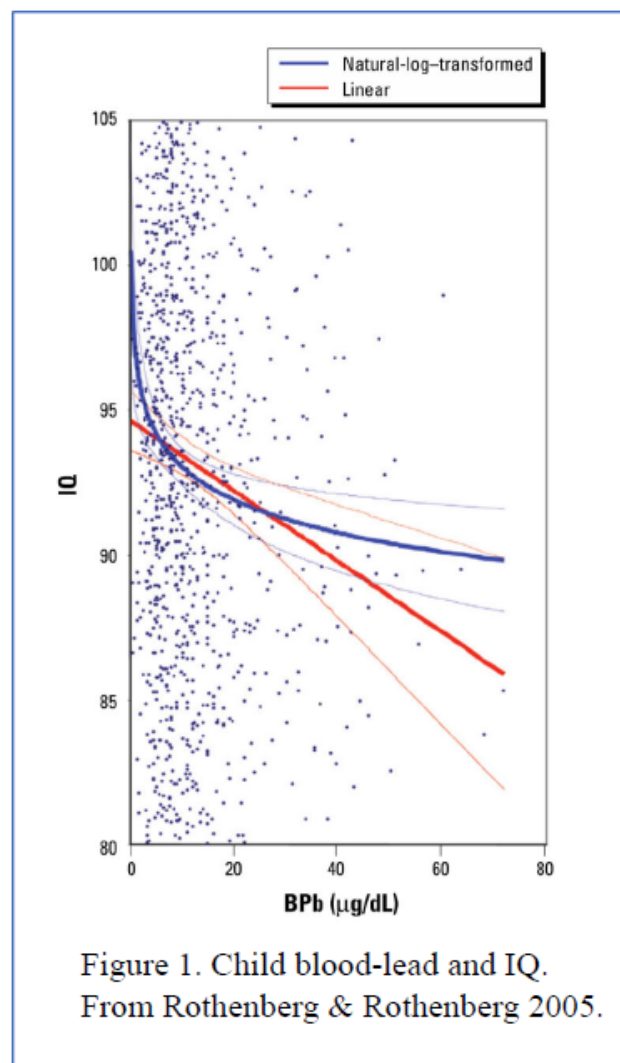
6 116. Dr. Chang's assessment of consistency also entirely ignored the findings from
7 occupational studies, as well as the neuropathology data from examinations of fetal brains in endemic
8 fluorosis areas. As I explained in my report, each of these types of studies is consistent with, and provide
9 support for, fluoride being a neurotoxic agent.
10

11 117. *Specificity*: As Kenneth Rothman (2012) and others (Neutra 2018) have emphasized, and
12 as Dr. Chang recognized, lack of specificity between an exposure and an outcome (e.g., asbestos and
13 mesothelioma) does not weigh against or in favor of a causal conclusion.

14 118. *Temporality*: Dr. Chang's assessment of temporality mirrored her assessment of
15 consistency in that she cited the two New Zealand studies as contradicting the findings from the
16 ELEMENT and MIREC cohorts. Once again, Dr. Chang fails to acknowledge the absence of prenatal or
17 early postnatal fluoride exposure assessments in the New Zealand studies, nor any of the other serious
18 shortcomings of these studies. Instead, Dr. Chang focused on non-differential measurement uncertainties
19 of the urine-fluoride data in the far superior ELEMENT and MIREC cohorts to cast doubt on the
20 findings of these studies. As already discussed in my report, however, the imprecision of the fluoride
21 exposure parameters would likely *bias the results toward the null*, not the reverse. The temporality
22 requirement is thus met with fluoride, as each of the prospective birth cohort studies has found a
23 significant association between early-life exposure to fluoride and the offspring's subsequent
24 performance on neurobehavioral testing. The exposure preceded the effect in these studies, which is
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what the temporality factor is supposed to assess.

119. *Biological Gradient*: The ELEMENT and MIREC studies have reported monotonic dose-response relationships between elevated prenatal fluoride exposure and IQ deficits in the offspring (Bashash et al. 2017, Green et al. 2019), as well as ADHD behaviors (Bashash et al. 2018). Dr. Chang dismissed the biological gradient of these effects by showing scatterplots from the ELEMENT and MIREC cohorts without the trend lines. However, this approach proves little insight, other than illustrating the undisputed fact that there is substantial natural variation in IQ across the population and that an appropriate statistical analysis is needed to extract a reliable estimate of the average effect of the toxicant exposure. Similar scatterplots have been published showing the effects of lead and IQ, as can be seen in the figure to the right (Rothenberg & Rothenberg 2005, Figure 1). Lead would thus fail the biological gradient test that Dr. Chang has used for fluoride. Dr. Chang also argued that outliers may have distorted the effects seen in the ELEMENT and MIREC cohorts (p. 77-78), without acknowledging that statistical analyses on the impact of outliers have been conducted and that the results did not meaningfully change (Bashash et al. 2017).



120. *Plausibility*: Dr. Chang limited her assessment of biologic plausibility to NTP's assessment of learning and memory (NTP 2016) in animal models, and to Dr. Tsuji's expert report. In so doing, Dr.

1 Chang completely ignored the large body of animal literature showing adverse neuroanatomical and
2 neurochemical effects from fluoride exposure, as already reviewed by the National Research Council
3 (NRC 2006) and by Dr. Thiessen in her report. The NRC concluded that the neuroanatomical and
4 neurochemical effects are sufficient to determine that fluoride interferes with brain function (NRC
5 2006). Dr. Chang ignored this information in favor of the NTP's more narrow assessment on
6 learning/memory, but even the NTP assessment found suggestive evidence that fluoride impairs learning
7 and memory. In contrast to Dr. Chang's assessment, EPA's own experts on developmental
8 neurotoxicity, including internationally recognized scientists such as William R. Mundy and Kevin M.
9 Crofton (Mundy et al. 2015), have identified fluoride as a chemical with substantial evidence of
10 developmental neurotoxicity.
11

12 121. *Coherence*: Dr. Chang dismissed the coherence of fluoridated water reducing IQ on the
13 grounds that IQ scores in US children steadily improved throughout the 20th century (the so-called
14 "Flynn Effect"). Dr. Chang even went so far as to suggest that fluoridation may be responsible for the
15 increased scores, although more plausible explanations are known. Under Dr. Chang's simplistic
16 framework, leaded gasoline could not have reduced IQ and may have increased it, as it was introduced
17 in the early part of the 20th century and IQ scores continued to increase during the entire duration of its
18 use. It is well accepted, however, that low-level lead exposure reduces IQ, and thus the Flynn Effect
19 argument—while perhaps superficially appealing—does *not* demonstrate "incoherence."
20

21 122. In her assessment of coherence, Dr. Chang failed to consider other relevant considerations,
22 including the association between neonatal fluoride exposure mediated by infant formula feeding and
23 reduced IQ (Till et al. 2020), as further discussed below. While the studies prior to the recent Canadian
24 analysis did not evaluate the potential role of neonatal fluoride exposure, formula feeding is well
25 established to increase a baby's fluoride exposure, even in areas without fluoridated water (Harriehausen
26
27
28

et al. 2019; Zohoori et al. 2019). Although other factors are of likely importance, the relationship between formula-feeding and reduced IQ is coherent with maternal fluoride exposure during pregnancy being associated with a lowered IQ in the child and supports a causative relationship between early-life exposure to fluoride and IQ deficits.

123. *Experiment:* Dr. Chang ignored the NRC’s observation (NRC 2006) that case reports of fluoride toxicity constitute “experimental studies” of neurologic symptomatology following fluoride exposure (NRC, p. 208). The case reports involve “one or more individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under ‘blind’ conditions.” In most cases, the symptoms (which included lethargy, weakness, and impaired ability to concentrate) “disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated.” Although experimental support is not an obligatory criterion (Neutra 2018), the existence of such support should not be missed in what is dubbed a systematic assessment.

124. *Analogy:* I agree with Dr. Chang that “analogies can be drawn to other naturally occurring elements, especially certain metals” like lead (p. 85). As discussed above, many of the exaggerated criteria that she uses to reject a causal relationship between fluoride exposure and IQ could be equally used to erroneously dismiss the causal relationship between low-level lead exposure and IQ.

125. In summary, after correcting for Dr. Chang’s errors and biases in judgment, the Bradford-Hill aspects support, rather than detract from, a causal relationship between fluoride in water and neurotoxicity. After analyzing and considering Dr. Chang’s systematic review, I have more, not less, confidence that developmental neurotoxicity is a serious risk of elevated fluoride exposure.

VIII. BENCHMARK DOSE (BMD) ANALYSIS

A. Selection of Source Data

126. Regulatory agencies are in overall agreement in using Benchmark Dose (BMD) analyses to

1 calculate non-cancer health-based limits for dietary intakes of contaminants, such as those found in
2 drinking water (EFSA 2009; EPA 2012).

3 127. As with the Faroe Islands cohort that the EPA relied upon in its risk assessment for
4 methylmercury, the ELEMENT and MIREC studies are high-quality birth cohorts suitable for dose-
5 response analysis (Bashash et al. 2017; Green et al. 2019). Further, as the data refer to the critical effect
6 in a highly vulnerable population, they constitute appropriate data to use for identifying a safe exposure
7 limit for fluoride. I worked, therefore, with my colleague, Dr. Budtz-Jorgensen, on BMD analyses of
8 these studies, which I describe below.

9
10 128. Our selection of the ELEMENT and MIREC studies for BMD analysis is consistent with
11 an analogous assessment conducted by both Dr. Chang and her colleague, Dr. Joyce Tsuji (Tsuji et al.
12 2015) for another neurotoxicant. In their paper, Drs. Chang and Tsuji sought to determine if the existing
13 RfD for arsenic is adequately protective of neurotoxicity. To answer this question, they conducted a
14 systematic review of the literature to see if there were any studies that would permit a dose-response
15 analysis for quantitative risk assessment. After reviewing the literature, they found a study that, in their
16 judgment, was suitable for the purpose: a study from Bangladesh by Hamadani et al. (2011).

17
18 129. The ELEMENT and MIREC studies are at least equally suitable for dose-response analysis
19 as the one study Dr. Chang and Dr. Tsuji found sufficiently reliable to use for their risk assessment of
20 arsenic exposure. As with the Hamadani study, the ELEMENT and MIREC studies have a (i)
21 prospective birth cohort design; (ii) large sample size; (iii) control for potential confounders;²⁰ (iv) urine
22 measurements²¹ of the toxicant of interest during pregnancy; (v) and extended follow-up (up to 5 years
23

24
25 ²⁰ Drs. Chang and Tsuji considered studies to have sufficiently controlled for potential
confounders if they controlled for SES or HOME Score and parental education/IQ (Tsuji et al. 2015, p.
93).

26 ²¹ As with the ELEMENT and MIREC studies, the Bangladesh study measured prenatal
exposure through several samples of maternal urine (adjusted for specific gravity) (Hamadani 2011).
27 The Bangladesh study collected urine twice during the pregnancy (at gestational weeks 8 and 30), which
28

1 after birth). In fact, the ELEMENT and MIREC studies have an important advantage: the average
2 arsenic exposure in Bangladesh substantially exceeded exposures in the U.S.,²² which is not the case
3 with the North American fluoride cohort studies.

4 130. My calculations of benchmark values for fluoride from the ELEMENT and MIREC
5 cohorts are therefore in accordance with the criteria that Drs. Chang and Tsuji have previously used
6 when generating benchmark calculations for arsenic (where adverse effects were seen in girls, but not
7 boys, at 5 years of age).

8 **B. Selection of Benchmark Response (BMR)**

9
10 131. The benchmark dose (BMD) is defined as the dose that leads to a specific loss (or degree
11 of abnormality) known as the benchmark response (BMR) in the outcome variable. The BMR must be
12 defined before the analysis (EPA 2012), and general guidelines been developed for the selection of a
13 BMR (EFSA 2009).

14 132. According to the EPA Clean Air Scientific Advisory Committee, a 1-to-2 IQ point
15 reduction at the population level is “highly significant from a public health standpoint,” and should be
16 prevented in up to 99.5% of the population (EPA 2008). Consistent with this, previous BMD analyses of
17 human neurotoxicity have selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-
18 Jorgensen et al. 2013; EFSA 2010; Tsuji et al. 2015).

19
20 133. Economists have calculated the substantial losses in lifetime incomes from a decrease of 1
21 IQ point²³ (Gould 2009), as also practiced by economists at the EPA in regulatory impact analyses (EPA
22 2008).

23
24 134. Research on other neurotoxicants (Grandjean 2013) has shown that shifts to the left of IQ
25 is a lower number of samples than the MIREC cohort, and roughly the same as the ELEMENT study.

26 ²² The Bangladesh study addressed a population with mean urinary arsenic levels ranging
from 35 to 80 ug/L, which is about 10-to-40 times the levels measured in the US population.

27 ²³ In terms of 2006-dollars, the value of 1 IQ point was calculated to be about \$18,000
(Gould 2009; Spadaro and Rabl 2008).

distributions in a population (i.e., reductions in average IQ) can have substantial impacts, especially among those in the high and low ranges of the distribution (Bellinger 2007).

135. Consistent with prior analyses, including our own, we therefore selected 1 IQ point as the BMR (Budtz-Jorgensen et al. 2000; Budtz-Jorgensen et al. 2013).

C. Analyses of ELEMENT and MIREC Data

136. For our BMD analysis, we used the same formula that we used in our prior assessment of lead (Budtz-Jorgensen et al. 2013). The formula is as follows:

The BMD is defined by

$$f(0) - f(\text{BMD}) = \text{BMR} \rightarrow \text{BMD} = f^{-1}(-\text{BMR})$$

In a linear model, $(Y = \alpha + \beta d + \epsilon)$, from which we get $\text{BMD} = -\text{BMR}/\beta$.

Likewise, the BMDL is defined as a lower one-sided 95% confidence limit of the BMD. In the linear model,

$$\text{BMDL} = -\text{BMR}/\beta_{\text{lower}}$$

where β_{lower} is the one-sided lower 95% confidence limit for β . Information on the (linear) regression coefficients and their standard deviations, from which the confidence intervals can be calculated, is available from the published articles on the two major prospective cohort studies.

137. For the ELEMENT study (Bashash et al. 2017), a linear dose-response model could be used for the effect of urine-fluoride concentrations on both measures of childhood IQ (i.e., the General Cognitive Index (GCI) results at age 4 and IQ results at ages 6-12). In this model, the BMD and BMDL can be calculated based only on the regression coefficient and its precision. In Table 4 of the publication (Bashash et al. 2017), this information is available both for a crude model and for a model A with confounder adjustment. The table below shows the benchmark results for these two models for both the age-4 GCI and school-age IQ.

Table 2. Benchmark dose results (mg/L urine adjusted for creatinine) obtained from the ELEMENT study results (Bashash et al. 2017).

Model	GCI		IQ	
	BMD	BMDL	BMD	BMDL
Crude	0.133	0.085	0.211	0.121
Adjusted	0.159	0.099	0.200	0.130
Read from plot	0.159	0.102	-	-

138. As these calculations are based on assumptions of Gaussian distributions, we checked the validity by scanning the numbers from the plot in the published article. We tentatively used the *WebPlotDigitizer* software to read the plot shown in the published paper (see Figure 1, page 22) (Bashash et al. 2017), to obtain the individual adjusted GCI results for more accurate BMD calculations. Of the original 287 observations, the software provided 286 observations, probably due to two overlapping observations. Thus, missing a single point only, our calculations based on the scanned data should be considered fairly reliable.

139. Using the standard benchmark approach to epidemiological data and a linear dependency, we find that the BMD for GCI is approximately 0.16 mg/L, and that the BMDL is 0.10 mg/L (bottom line of Table 2). These results are in excellent agreement with the results calculated only from the regression data presented in Table 4 of Bashash et al. (2017).

140. To assess the robustness of the calculation, we included a logarithmic conversion of the exposure parameter. We also used a split linear dose-response curve as in one of our previous studies (Budtz-Jorgensen et al., 2013). These sensitivity analyses showed BMD results that deviated only marginally from the calculation using the default linear association. In conclusion, Table 2 shows

reliable BMD results that have been calculated in accordance with standard EPA procedures.

141. We also conducted a BMD analysis of the MIREC data. As with the ELEMENT study, we calculated the BMD and BMDL from the reported regression coefficients and standard deviations, with the assumption of a Gaussian distribution (Green 2019, Table 2). In addition to calculating the BMD and BMDL from the urine-fluoride data (U-F), we also calculated a BMD and BMDL from the maternal fluoride intake data. Our results are shown in the table below:

Table 3. Benchmark dose results (mg/L urine adjusted for specific gravity, or mg estimated daily intake) obtained from MIREC study results on IQ (Green et al. 2019).

Study	Exposure	Sex	BMD	BMDL
MIREC	Maternal U-F	Both sexes	0.51	0.21
	Maternal U-F	Boys	0.22	0.13
	Maternal U-F	Girls	(–)	0.58
	Maternal F intake	Both sexes	0.27	0.15

142. As shown in the above table, the prenatal BMD for girls is not defined when relying on urine-fluoride, but the BMDL is still meaningful and is, as expected, higher than the other estimates obtained. No sex difference was found when relying on estimated fluoride intake.

143. Overall, the results derived from the two studies are comparable. In the ELEMENT study, the BMDL for maternal urine among ~4-year olds is approximately **0.1 mg/L** (both sexes), while in the MIREC study, it is **0.13 mg/L** (boys) and **0.21 mg/L** (both sexes).²⁴ The respective BMDL for the 6-to-12-year olds from the ELEMENT study is **0.13 mg/L**, thus overall approximately 0.15 mg/L. Consistent with these maternal urinary excretion values, the BMDL for maternal fluoride *intake* in the MIREC

²⁴ Based on how the authors reported the data, our BMDL values from the ELEMENT cohort are creatinine-adjusted, while our BMDL values from the MIREC cohort are specific gravity-adjusted.

study is **0.15 mg/day** (both sexes).

IX. ASSESSMENT OF RISK

A. Comparing BMDLs with Current Exposures in Fluoridated Areas

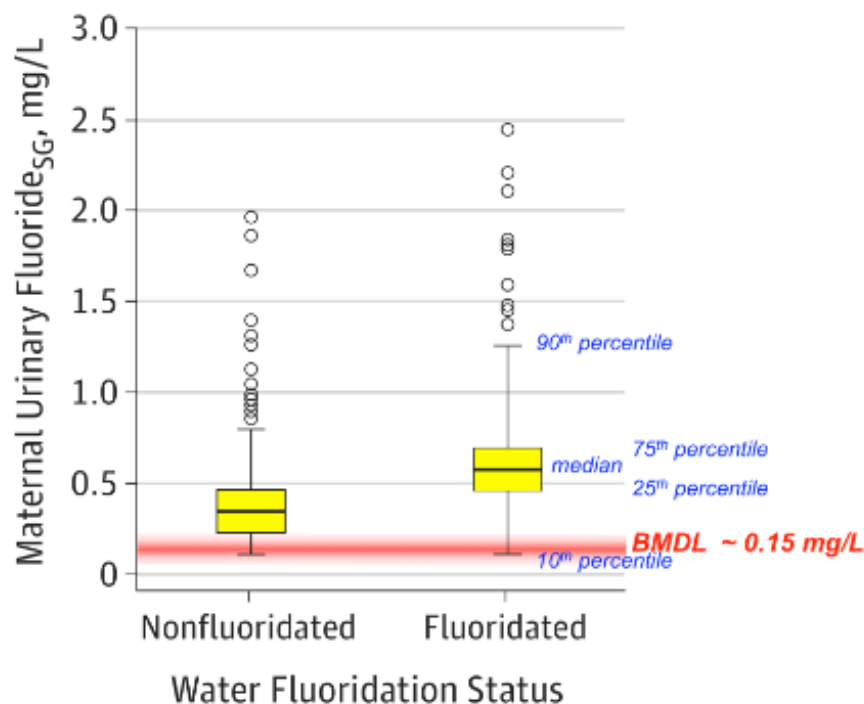
144. As benchmark dose calculations constitute a routine approach applied by the EPA for establishing safe limits on chemical exposure, the above calculations that rely on overall associations between fluoride exposure and cognitive deficits provide a basis for assessing the risk of cognitive deficits from current fluoride exposure levels.

145. Typically, the EPA uses the BMDL to calculate a Reference Dose (RfD) by dividing by an uncertainty factor for the purpose of accounting for variations in human susceptibility. The default value that EPA uses for the uncertainty factor is 10. Here, if we round up the overall BMDL to **0.2 mg/L**, or about 0.2 mg/day, the RfD would likely be 0.02, which is very much below current exposure levels, especially in communities with fluoridation programs (Till et al. 2018). But, *even if no uncertainty factor is applied, and even if relying on the BMD rather than the BMDL* (both of which would be unusual), the RfD would still be well below current exposure levels in fluoridated areas (Till et al. 2018).

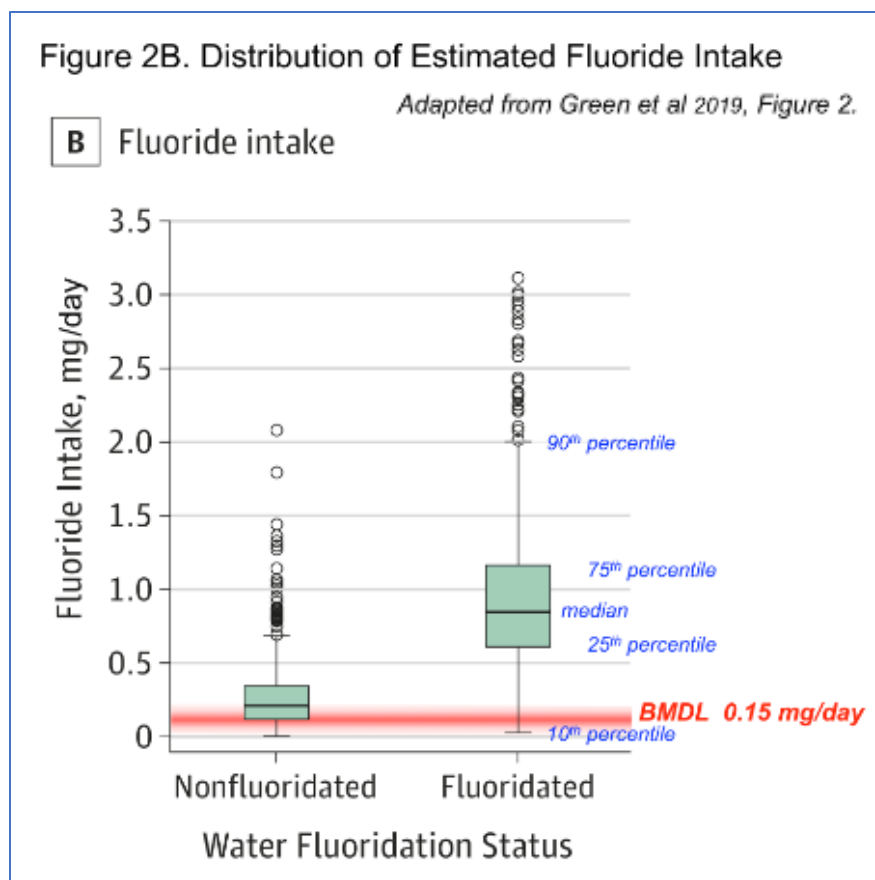
146. The serious risk that we are confronted with can be appreciated by visually comparing the BMDLs against documented exposure levels in fluoridated communities. The following Figure 2A, adapted from Green et al. (2019), compares an overall BMDL for maternal urine-fluoride (0.15 mg/L) with the maternal urine-fluoride concentrations reported in the study. As can be seen, the urine-fluoride levels far surpass the levels associated with IQ loss.

Figure 2A. Distribution of Maternal Urinary Fluoride

Adapted from Green et al 2019, Figure 2.

A Maternal urine

147. The below Figure 2B compares the approximate BMDL for maternal fluoride *intake* from beverages (0.15 mg/day) against the reported fluoride intakes in Green et al (2019). As can be seen, the estimated fluoride intakes in fluoridated areas far surpass the fluoride intake level associated with a clear IQ loss.



148. There are no contemporary large-scale studies of urine-fluoride concentrations in the United States, as the CDC has not yet reported urinary fluoride excretion levels as part of its ongoing National Health and Nutrition Examination Survey (NHANES) studies. One can reasonably infer, however, that urinary fluoride excretion levels in fluoridated areas of the U.S. are generally comparable to those in fluoridated areas of Canada. The reasonableness of this inference is supported by the following facts:

149. Canada and the U.S. add fluoride to water to reach the same target concentration (0.7 mg/L), although empirical data suggests Canadian cities only reach 0.6 mg/L which is slightly less than the U.S. (Till et al. 2018).

150. Fluoridated water is recognized as the largest source of fluoride exposure for adults, particularly when indirect sources are accounted for, such as beverages and foods prepared with the

1 water, including commercially prepared beverages such as soda and reconstituted juice (EPA 2010).

2 151. Urine-fluoride has been shown to be a good indicator of total daily fluoride intake, and has
3 a close, linear correlation with the fluoride content in water (Villa et al. 2000; McClure 1944; Smith et
4 al. 1950).

5 152. The largest study of urine-fluoride levels in the U.S. found that pooled urine samples from
6 healthy young males generally mirrored the fluoride concentration in the drinking water (McClure
7 1944). Based on U.S. data, therefore, a person drinking water with 0.7 mg/L fluoride would be expected
8 to have about 0.7 mg/L in their urine, which is similar to what was found in the MIREC cohort (Till et
9 al. 2018). Although these U.S. data were published prior to widespread fluoridation, the levels today
10 would, if anything, tend to be *higher* today, not lower because fluoride is now available from more
11 sources than was the case in the 1940s (e.g., including commercial beverages made with fluoridated
12 water, dental products, etc.).
13

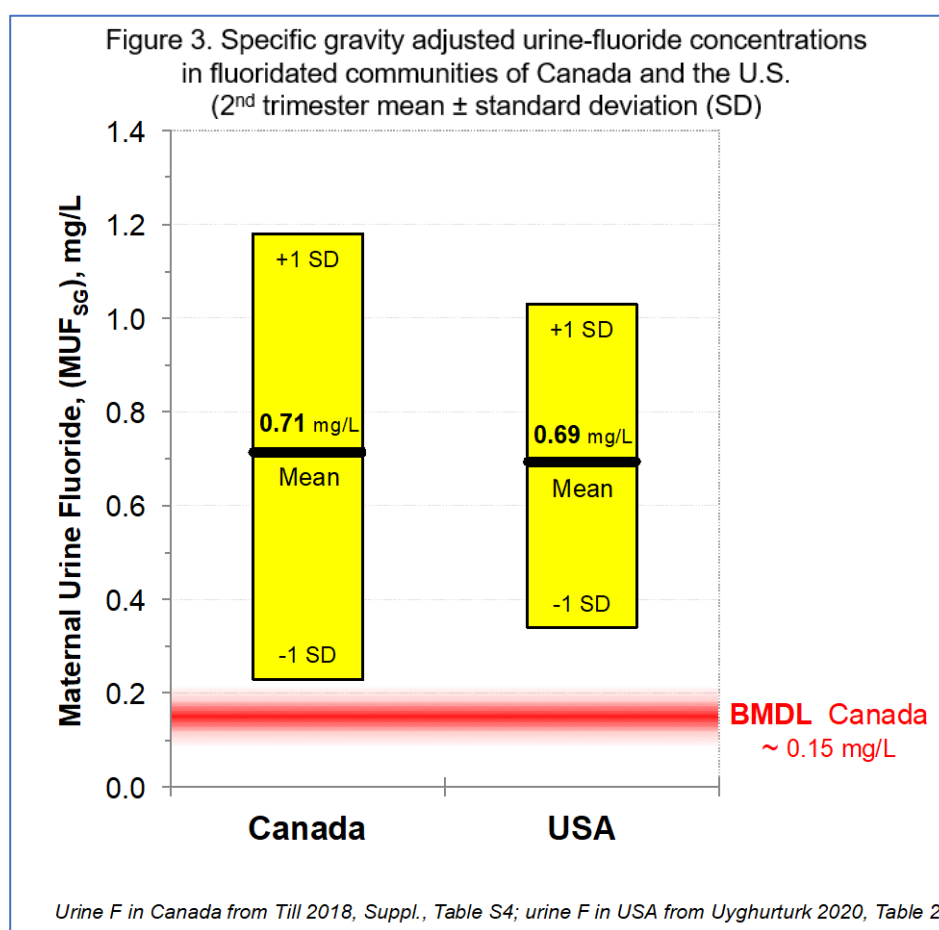
14 153. To address the lack of contemporary US data on fluoride exposures in pregnant women,²⁵
15 the recent UCSF study measured the concentrations of fluoride in urine (and blood²⁶) of 48 pregnant
16 women living in fluoridated and non-fluoridated areas of California. As with the Canadian study, the
17 UCSF team had the urine tested by Dr. Angeles Martinez-Mier at the University of Indiana and adjusted
18 the fluoride measurements for specific gravity. The study found an average (specific gravity-adjusted)
19 urine-fluoride concentration of **0.69 mg/L** among pregnant women in areas with at least 0.7 mg/L in the
20 community water, which is clearly in the same range as the MIREC team found in Canada (Uyghurturk
21
22

23 ²⁵ As noted by the UCSF team, there is only one prior published study of urine-fluoride
24 levels among pregnant women in the US: this is the study by Shen & Taves (1974) that I discussed in
25 my expert report. This study found an average of 1.02 mg/L in maternal urine among a group of 16
26 pregnant women, but the authors did not report the concentrations of fluoride in water.

²⁶ The study found an average of 0.021 mg/L fluoride in the blood (=1.1 µmol/L) of the
27 women from fluoridated areas (~0.8 mg/L), which is higher than the predicted value (0.015 mg/L = 0.8
28 µmol/L). As discussed by the NRC, it has been historically estimated that adult populations will have 1
µmol/L in their blood for each 1 mg/L of fluoride in the water (NRC 2006).

2020, Table 2). While the small-scale nature of the study likely introduced some random scatter in the results of the UCSF study,²⁷ the study supports the general similarity in fluoride exposures in the Canadian and U.S. populations.

154. Finally, the relevance of the Canadian IQ data (Green et al., 2019) to the US can be appreciated by comparing the BMDL to the maternal urine-fluoride concentrations reported by the UCSF team (Uyghurturk 2020). As can be seen in the following Figure 3, maternal urine-fluoride concentrations found in pregnant women in the Californian cohort greatly exceed the BMDL for fluoride-associated IQ loss. This, ultimately, is the most important consideration.



²⁷ The study found some high levels of urine-fluoride in the mid-range fluoride communities (0.3-0.5 mg/L), which slightly skewed the distribution (Uyghurturk 2020, Fig. 2). As the authors note, this may be the result, in part, of the fact that the women had their urine tested while visiting a clinic in San Francisco, which is fluoridated (Uyghurturk 2020, p. 6-7). In the areas with >0.3 mg/L in water, the average (specific-gravity adjusted) fluoride level was 0.74 mg/L (Uyghurturk 2020, Table 5).

B. Comparing Fluoride's Population-Level Effects with Other Causes of IQ Loss

155. In order to compare fluoridation's population-level effects with other neurotoxicant exposures, some approximate estimates of fluoride-associated IQ losses can be made. The calculations rely on several assumptions that are necessary in the absence of actual data and are therefore meant only to identify relative orders of magnitude. On the conservative side, I shall assume that all children are equally vulnerable and that the dose-dependent IQ losses observed in the recent prospective studies can be used to assess the impact on the population at large (i.e., that genetic and other predisposition can be ignored).

156. My analysis focuses on the average difference in maternal urine-fluoride levels between fluoridated and non-fluoridated areas. The Canadian study (Till et al. 2018) showed that this difference is approximately 0.4 mg/L. It bears emphasizing that this difference likely understates the true contribution of fluoridated water because part of the exposure in "non-fluoridated" areas comes from the "halo" effect. The halo effect refers to the fact that many commercial beverages and foods made in fluoridated areas are shipped to and consumed in non-fluoridated areas and that residents from non-fluoridated communities may work or spend time in fluoridation areas.²⁸

157. Given the BMD results, an average increase of 0.4 mg/L in maternal fluoride concentrations is above the threshold for developmental neurotoxicity, even if assuming a zero background exposure. Using the dose-dependent losses observed in the recent prospective studies (Bashash et al. 2017; Green et al. 2019), this elevated exposure will correspond to an IQ loss of approximately 2 IQ points.

158. Because about two-thirds of the U.S. population receives fluoridated drinking water, one can assume that a similar proportion of the 4 million annual U.S. births (i.e., more than 2.5 million

²⁸ This widespread dispersal of fluoridated water in commercial products helps to explain the relatively high urine-fluoride levels now seen in non-fluoridated communities versus the situation back in the 1940s (Till et al. 2018).

1 births) are affected by fluoridation-associated exposure increases. With the 2-point average IQ loss
2 associated with fluoridation, the 2.5 million births will lose a total estimated number of 5 million IQ
3 points annually.

4 159. This approximate estimate can be compared with calculations made by Professor David
5 Bellinger on IQ losses due to major pediatric diagnoses affecting 0-to-5-year-old children (Bellinger
6 2012). According to CDC data and Bellinger's calculations, the top pediatric etiologies for IQ loss are
7 preterm birth at 34 million IQ points lost and lead exposure representing 23 million IQ points lost. For
8 fluoridation, the estimate for children aged 0 to 5 years is approximately 25 million IQ points. Even if
9 this estimate is somewhat imprecise, and unevenly distributed, the order of magnitude is likely to be
10 correct and is very considerable.

12 160. Finally, even if we assume that a threshold exists at approximately 0.8 mg/L in maternal
13 urine (as suggested by mere inspection of the IQ plots in the ELEMENT study for the 6-to-12-year-old
14 cohort members), water fluoridation would still result in substantial IQ losses. As documented in the
15 MIREC study, the 75th percentile maternal urine-fluoride levels (adjusted for creatinine) are 1.04 mg/L
16 in the fluoridated areas versus 0.52 mg/L in the non-fluoridated areas (Till et al. 2018, Table S4). In
17 fluoridated areas, pregnant women above the 75th percentile are already at least 0.29 mg/L above the
18 hypothetical threshold, and thus 25% of the children would then experience an average IQ loss of at
19 least 1.5 points. This would amount to over 4.5 million lost IQ points among 0-to-5-year-olds. Even this
20 smaller amount of IQ losses exceeds the IQ losses attributed to methylmercury exposure in the U.S.
21 (Grandjean et al. 2012).

23 161. I have made these calculations only to illustrate the significance and impact of
24 neurotoxicity outcomes from fluoridation exposures, and I offer these crude estimates to emphasize my
25 concern that developmental neurotoxicity due to early-life exposure to fluoride is a serious public health
26

1 hazard with substantial societal impacts that must be controlled.

2
3 **X. CONCLUSIONS**

4 162. Recent research has shown that the most vulnerable life stage for many toxicants,
5 particularly those that adversely affect the brain, is during intrauterine and early postnatal development.
6 Fluoride fits into this paradigm, and efforts to control human fluoride exposures must therefore focus on
7 pregnant women and small children.

8 163. Research on fluoride-exposed workers and laboratory animals suggest that elevated
9 fluoride exposure is toxic to the brain and nerve cells. Epidemiological studies have identified links to
10 learning, memory, and intelligence deficits, though most of the past studies focused on populations with
11 fluoride exposures higher than those typically provided by U.S. water supplies.

12 164. Epidemiology studies of birth cohorts from the most recent years document that adverse
13 effects on brain development happen at elevated exposure levels that occur widely in North America, in
14 particular in communities with fluoridated drinking water. These new prospective studies are of very
15 high quality and show very similar results, thus leaving little doubt that developmental neurotoxicity is a
16 serious risk associated with elevated fluoride exposure. This evidence shows that community water
17 fluoridation is associated with IQ losses that are substantial and of economic and societal concern.

18 165. Applying methods for standards setting routinely used by the EPA (i.e., Benchmark Dose
19 analysis), the recent studies on IQ deficits in children allow the estimation of a recommended limit that
20 would protect against neurotoxicity. Such calculations show that current allowable limits for fluoride in
21 drinking water and the levels of fluoride added in community water fluoridation programs both greatly
22 exceed a science-based limit that would protect against developmental neurotoxicity.

23 166. The evidence on fluoride neurotoxicity in the general population is fairly recent and
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1 unlikely to represent the full toxicological perspective, including adverse effects that may occur at
2 longer delays. As has been seen on numerous occasions, the evidence available today may well
3 underestimate the true extent of the fluoride toxicity. With a reasonable degree of scientific certainty, I
4 therefore consider the elevated levels of fluoride exposure in the U.S. population as a serious public
5 health concern.

6
7 I declare under penalty of perjury, under the laws of the United States, that the foregoing is true
8 and correct to the best of my knowledge and belief.
9

10 Executed on May 20, 2020, in Copenhagen, Denmark.

11 
12
13 PHILIPPE GRANDJEAN, MD, DMSc

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development delay in infants. *Neurotoxicology* 59:65-70.

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- Wang S, Wang L, Hu P, Guo S, Law S. 2001. Effects of high iodine and high fluorine on children's intelligence and thyroid function (in chinese). *Chin J Endemiol* 20:288-290.
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- Xiang Q, Wang Y, Yang M, Zhang M, Xu Y. 2013. Level of fluoride and arsenic in household shallow well water in Wamiao and Xinhuai villages in Jiangsu Province, China. *Fluoride* 46:192-197.
- Xiang Q. 2015. Correspondence. *Fluoride* 48:78-89.
- Yazdi SM, Sharifian A, Dehghani-Beshne M, Momeni VR, Aminian O. 2011. Effects of fluoride on psychomotor performance and memory of aluminum potroom workers. *Fluoride* 44:158-162.

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2 changes in the brains of fetuses from areas of endemic fluorosis. *Fluoride* 41:134-138.
- 3 Yu X, Chen J, Li Y, et al. 2018. Threshold effects of moderately excessive fluoride exposure on
4 children's health: A potential association between dental fluorosis and loss of excellent
intelligence. *Environ Int* 118:116-124.
- 5 Zhao L, Liang G, Zhang D, Wu X. 1996. Effect of a high fluoride water supply on children's
6 intelligence. *Fluoride* 29:190-192.
- 7 Zhou G, Tang S, Yang L, Niu Q, Chen J, Xia T, et al. 2019. Effects of long-term fluoride
8 exposure on cognitive ability and the underlying mechanisms: Role of autophagy and its
association with apoptosis. *Toxicol Appl Pharmacol* 378:114608.
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10 behaviour of children and adolescents in China. *Int Dent J* 53:289-298.
- 11 Zohoori FV, Omid N, Sanderson RA, Valentine RA, Maguire A. 2019. Fluoride retention in
12 infants living in fluoridated and non-fluoridated areas: effects of weaning. *Brit J Nutr* 121:74-81.
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**CURRICULUM VITAE OF
PHILIPPE GRANDJEAN, MD, DMSc**

PHILIPPE GRANDJEAN, M.D.

Office address

Institute of Public Health
University of Southern Denmark
Winsløwparken 17
DK-5000 Odense C, Denmark
Tel. (+45) 6550.3769
Fax (+45) 6591.1458
Email: pgrand@health.sdu.dk
<http://www.sdu.dk/staff/PGrandjean.aspx>

Harvard School of Public Health
Department of Environmental Health
665 Huntington Avenue
Building 1, room 1312
P.O. Box 15697
Boston, MA 02115
Tel: 617-384-8907
Fax: 617-384-8994
Email: Pgrand@hsph.harvard.edu
<http://www.hsph.harvard.edu/faculty/philippe-grandjean/>

Academic degrees

1974, M.D., University of Copenhagen
1975, Diploma in basic medical research, University of Copenhagen
1979, D.M.Sc. (dr.med.), University of Copenhagen

Chronology of employment

1974-1975	Postgraduate training fellowship, University of Copenhagen
1975-1978	Research fellow, Institute of Hygiene, Univ. Copenhagen
1978-1980	Senior research fellow, University of Copenhagen Visiting fellow, Department of Community Medicine, Mount Sinai School of Medicine, New York
1980-1982	Director, Department of Occupational Medicine, Danish National Institute of Occupational Health
1982-	Professor of Environmental Medicine, Odense University
1983-2017	Consultant in Toxicology, Danish Health Authority
1994-2002	Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston
2003-	Adjunct Professor of Environmental Health, Harvard T.H. Chan School Public Health, Boston

Awards and honors

Prize essay in medicine, University of Copenhagen (1972)
Fulbright senior research scholarship (1978)
Keynote speaker, Odense University anniversary (1983)
Gitlitz Memorial Lecture, Association of Clinical Scientists, USA
(1985)

Fellow, Collegium Ramazzini (1987)
Knight of the Dannebrog, awarded by the Queen of Denmark (1990)
The Dannin prize for medical research (1991)
Fellow, American Association for the Advancement of Science (1994)
Irish Congress Lecturer, Royal College of Physicians of Ireland and
Irish Society of Toxicology (1996)
Knight of the Dannebrog, First Degree, awarded by the Queen of Denmark
(2003)
'Mercury madness award' for excellence in science in the public
interest from eight US environmental organizations (2004)
Emeritus Fellow, International Union of Pure and Applied Chemistry,
IUPAC (2009)
Honorary Research Award, International Order of Odd Fellows (2010)
Science Communication Award, University of Southern Denmark (2012)
Bernardino Ramazzini Award (2015)
Basic & Clinical Pharmacology & Toxicology Nordic Award (2015)
Margrethegaarden honorary prize (2016)
John R. Goldsmith Award, International Society for Environmental
Epidemiology (2016)

Editorial boards

American Journal of Industrial Medicine (1987-2017)
Applied Organometal Chemistry (1985-1991)
Arbejdsmiljø (Occupational Environment, in Danish, 1983-1990)
Archives of Environmental Health (European Editor, 1986-1992)
Archives of Toxicology (1987-)
Biomarkers (1996-2001)
Central European Journal of Occupational and Environmental Medicine
(2015-)
Critical Reviews in Toxicology (1985-2012)
Danish Medical Bulletin (1994-2003)
Environmental Health (Editor-in-Chief, 2002-)
Environmental Health Perspectives (2003-)
Environmental Research (1981-1994 and 2014-2017, Associate Editor,
1995-2014)
Industrial Health (2000-2005)
International Journal of Hygiene and Environmental Health (2001-)
International Journal of Occupational and Environmental Health (1994-
2011)
International Journal of Occupational Medicine & Environ Health (1991-
Journal of Clean Technology, Environmental Toxicology, and
Occupational Medicine (1992-1998)
Journal of Environmental Medicine (1998-1999)
Naturens Verden (Natural Science, in Danish) (1987-1991)
Ugeskrift for Læger (Danish Medical Journal, in Danish) (1991-2007)

Scientific societies

American Association for the Advancement of Science (Fellow, 1994)
American Public Health Association
Collegium Ramazzini (Fellow, 1987; Member of the Council, 2005-2013)
Danish Medical Association

Danish Societies of Clinical Chemistry, Epidemiology, Occupational and Environmental Medicine, and Public Health
Faroese Society of Science and Letters
International Society for Environmental Epidemiology

Teaching experience

Professor of Environmental Medicine, Odense University (University of Southern Denmark) (1982-). Member of curriculum committee.

Coordinator, Global Health class.

Adjunct Professor of Public Health (Environmental Health) and Neurology, Boston University School of Medicine, Boston (1994-2002)

Adjunct Professor of Environmental Health, Harvard T.H.Chan School of Public Health, Boston (2003-)

Invited teacher, École des hautes études en santé publique (EHESP, French school of public health) (2009-)

International: Numerous teaching assignments, including guest lectures at universities and related tasks, e.g. as external examiner, National University of Singapore (1995). External evaluator of PhD theses from other universities, including University of Sydney and University of South Pacific (Fiji).

Research support as Principal Investigator since 2000

2000-2006 NIEHS

Mercury associated neurobehavioral deficit in children

2001-2003 Nordic Arctic Research Programme (NARP)

Changing patterns of biomagnified pollutants in the northern marine environment

2001-2004 Danish Medical Research Council

Exposure assessment for endocrine disruptors

2002-2004 Danish Medical Research Council

Environmental epidemiology research

2003-2004 European Commission

Assessment of Neurobehavioral Endpoints and Markers of Neurotoxicant Exposures (ANEMONE)

2003-2005 Danish Medical Research Council

Research in hormone related substances

2003-2006 NIEHS ES11687

Effects of perinatal disruptors in children

2003-2007 EPA STAR RD-83075801-0

Children's vulnerability to environmental immunotoxicant

2004-2011 NIEHS ES12199

Epidemiology of immunotoxicant exposure in children

2006-2011 NIEHS ES13692

Health effects of lifetime exposure to food contaminants

2006-2012 NIEHS ES14460

Three-generation human study of reproductive effects of marine food contaminants

2008-2012 Danish Council for Strategic Research

Environmental pollutant impact on antibody production against current and new childhood vaccines

2007-2013 NIEHS ES009797

Mercury associated neurobehavioral deficit in children

2011-2017 NIEHS ES012199

Epidemiology of immunotoxicant exposure in children

2012-2020 NIEHS ES021993 and NSF OCE-1321612

Immunotoxicity in Humans with Lifetime Exposure to Ocean Pollutants

2013-2019 NIEHS ES021477

Glucose Metabolism in Adults Prenatally Exposed to Diabetogenic Pollutants

2013-2018 NIEHS ES021372

Pollutant-related diabetes in the Nurses' Health Study II

2014-2020 NIEHS ES023376

Gut Microbiome in Adults with Early Life Exposures to Environmental Chemicals

Major Current Funding as Principal Investigator

2017-2020 NIEHS ES026596

Inflammation and metabolic abnormalities in pollutant-exposed children

2017-2022 NIEHS P42ES027706

Sources, Transport, Exposure and Effects of PFASs (STEEP)

2019-2024 ATSDR TS000313

Assessment of PFAS exposures and health effects in two Massachusetts communities with PFAS drinking water contamination

2019-2023 NIEHS ES030394

Vulnerability During Infancy to Immunotoxic Contaminant Exposures

Major committees, boards and elective offices

Danish:

Danish Medical Association: Member, Prevention Council (2011-2014)

Danish Medical Research Council: Consultant on environmental medicine (1985-1990); Member, Joint Research Council Committee on Environmental Research (1986-1991); Member of DMRC (1992-1998)

Danish Society of Community Medicine: Secretary (1977-1978)

Danish Society of Industrial Medicine: Board Member (1974-1983)

Ministry of Education: Member, Committee on Toxicology (1984-1986); Member, Committee on Environmental Education (1986-1987)

Ministry of the Environment: Member, Council on Environmental Chemicals (1983-1989); Member, Environmental Appeal Board (1986-2010); Member, Environmental Research Council (1990-1992); Member, Advisory Committee on Pesticide Research (1995-2004 and 2018-2020); Member, Advisory Committee on Arctic Research (1996-2004)

Ministry of Health: numerous committee appointments; Chair, Committee on Risk Perception (2000-2001)

Ministry of Labour: Consultant on Occupational Health, Council on Occupational Safety and Health (1983-1993); Member, Occupational Health Council Research Committee (on behalf of the Danish Medical Research Council) (1984-1990 and 1999-2003)

Ministry of Research: Chair, Committee on Research at the Faroe Islands (1995-1996); Member, Committee on Scientific Dishonesty (2004-2006); Chair, Program Committee on Non-Ionizing Radiation (2004-2009)

Odense University (from 2000 University of Southern Denmark), elected

offices: Chairman, Institute of Community Health (1982-1985; 1996-1999); Member of Executive Committee, Institute of Community Health (from 2000 Institute of Public Health) (1986-1995; 2000-2005); Member, Faculty Research Committee (1983-1985); Member, Curriculum Committee (1984-1986); Member, Faculty Council (1985-1993); Vice-Dean (1991-1993); Member, Scientific Integrity Committee (2003-2022)

United States and international:

Academy of Finland: member of panel evaluating the National Institute of Public Health (1995), site visit of center of excellence (2001)
 Agency for Toxic Substances and Disease Registry: Workshop Rapporteur, Neurobehavioral Test Batteries for Use in Environmental Health Field Studies (1992); Member, Expert Panel of Mercury (1998)
 Association of Schools of Public Health in the European Region: Treasurer (1975-1977)
 BioMedCentral: Member, Editors Advisory Group (2011-2013)
 Boston Environmental Hazards Center: Consultant (1994-1999)
 Collegium Ramazzini: President, International Conference, The precautionary principle: Implications for research and prevention in environmental and occupational health (2002); Member, Executive Council (2005-2013)
 Commission of the European Communities: National Expert, Working Party on Environmental and Lifestyle-Related Diseases (1988-1990); ad hoc Consultant for evaluation of research applications; ad hoc Scientific Advisor on Risk Assessment (2009-); Member, Scientific Committee on Emerging and Newly Identified Health Risks; - Working group on Dental Amalgam (Human Health)(2012-2013)
 European Environment Agency: Member, Scientific Committee (2012-2020)
 European Food Safety Authority: Member, Panel on Contaminants in the Food Chain responsible for 85 opinions (2003-2009); Member of Working Groups on mercury, polychlorinated biphenyls, cadmium, lead, and benchmark dose
 Food Advisory Committee, U.S.FDA, Methylmercury: invited expert (2002)
 INMA (Infancia y Medio Ambiente), Spain: Member, Project Steering Committee (2010-)
 Institut de Recherche Santé, Environnement et Travail, France: Member, Board of Advisers (2015-)
 International Agency for Research on Cancer: Member of Task Group, Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47 (1988), Vol. 49 (1989), as chairman, Vol. 58 (1993), and as Subgroup chair, Vol. 100C (2009)
 International Commission on Occupational Health: Danish Delegation Secretary (1982-90); Member, Scientific Committee on the Toxicology of Metals (1987-); Member of the Board (1990-1996)
 International Programme on Chemical Safety: Member of Task Group, Environmental Health Criteria, Vol. 36 (1984) and 72 (1986)
 International Society for Environmental Epidemiology: Councillor (1991-1994)
 International Union of Pure and Applied Chemistry: Member, Subcommittee on the Toxicology of Nickel (1979-1989); Titular

Member (1985-1991) and Chairman (1987-1991), Commission on Toxicology; Chairman, Subcommittee on Risk Assessment (1985-1989)
Instituto de Saude Ambiental, Lisboa, Portugal: Member, External Advisory Committee (2018-2020)
Karolinska Institute (Stockholm, Sweden): Member of international evaluation panel on environmental medicine (1993)
Ministry for Scientific Policy (Belgium): Consultant on national research program on health hazards (1990 and 1994)
National Institutes of Health (USA): Member of Special emphasis panels (2009-)
NATO Priority Area Panel on Environmental Security: Member (1996-1997)
Norwegian Research Council: ad hoc reviewer (2001-2008); Chairman of Environment and Health Review Group (2009-2010); member of steering committee (2011-2015)
Prenatal Programming and Toxicity (PPTOX) conferences: Organizer/Chair/Co-chair, Torshavn (2007), Miami (2009), Paris (2012), Boston (2014), Kita-Kyushu (2016), Torshavn (2018)
Society of Occupational and Environmental Health: Member, Governing Council (1990-1993)
Swedish Council for Work Life Research: Member, Priority Committee on Chemical Health Risks (1997-1998)
U.N.Environment Programme: Member, Global Mercury Assessment Working Group (2002)
U.S. Environmental Protection Agency: Member, SAB/SAP Endocrine Disruptor Screening Program Subcommittee (1998-1999); Member, Food Quality Protection Act (FQPA) Science Review Board (SRB)(1999-2003)
White House Office of Science and Technology Policy: Team leader and presenter, Workshop on Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury (1998)
World Health Organization: Temporary Adviser or Consultant on several occasions, five times elected Rapporteur; Member, European Advisory Committee on Health Research (2011-2017)

Books

1. Grandjean P, ed. Standards setting. Copenhagen: Occupational Health Foundation, 1977, 210 pp.
2. Grandjean P, Nielsen T. Organiske blyforbindelser, forurening og toksikologi (Organolead compounds, pollution and toxicology, in Danish). Report No. SNV PM 879. Stockholm: Naturvårdsverket, 1977, 78 pp.
3. Grandjean P. Occupational health aspects of construction work. EURO Reports and Studies 86. Copenhagen: World Health Organization, Regional Office for Europe, 1983, 28 pp. (also published in German, French and Russian)
4. Grandjean P, ed. Biological effects of organolead compounds. Boca Raton, FL: CRC Press, 1984, 278 pp.
5. Grandjean P, Tarkowski S, eds. Toxic oil syndrome: mass food poisoning in Spain. Copenhagen: World Health Organization, Regional Office for Europe, 1984, 92 pp. (also published in Spanish)
6. Grandjean P. Miljø og forebyggelse. (Environment and prevention, student's guide in Danish). Copenhagen: F.a.d.L.'s Forlag, 1984, 109 pp.
7. Gilioli R, Grandjean P, Johnson B, Seppäläinen AM, Tarkowski S, eds. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 3. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 209 pp.
8. Grandjean P, ed. Neurobehavioural methods in occupational and environmental health. Environmental Health No. 6. Copenhagen: World Health Organization, Regional Office for Europe, 1985, 72 pp.
9. Grandjean P, ed. Miljømedicin (Environmental medicine, textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1986, 257 pp.
10. Grandjean P, ed. Trace elements in human health and disease: extended abstracts. Environmental Health No. 20. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 230 pp.
11. Grandjean P, ed. Trace elements in human health and disease: symposium report. Environmental Health No. 26. Copenhagen: World Health Organization, Regional Office for Europe, 1987, 134 pp.
12. Grandjean P, Kimbrough RD, Rantanen J, Tarkowski S, Yrjänheikki E. Assessment of health risks in infants associated with exposure to PCBs, PCDDs and PCDFs in breast milk. Environmental Health No. 29. Copenhagen: World Health Organization, Regional Office for Europe, 1988, 116 pp.
13. Grandjean P, ed. Miljømedicin, 2. udg. (Environmental medicine, 2nd ed., textbook in Danish). Copenhagen: F.a.d.L.'s Forlag, 1988, 311 pp.
14. Kimbrough RD, Mahaffey KR, Grandjean P, Sandø SH, Ruttstein DD. Clinical Effects of Environmental Chemicals: A Software Approach to Etiologic Diagnosis. New York: Hemisphere, 1989, 110 pp. and one floppy disk.
15. Grandjean P. Skin Penetration: Hazardous Chemicals at Work. (Published on behalf of the Commission of the European Communities.) London: Taylor and Francis, 1990, 187 pp.
16. Grandjean P, ed. Ecogenetics: Genetic Predisposition to Toxic

Effects of Chemicals. London: Chapman & Hall, 1991, 288 pp.

17. Grandjean P, ed. Miljø, sundhed og samfund (Environment, health and society, in Danish). Copenhagen: Nyt Nordisk Forlag, 1991, 453 pp.
18. Grandjean P, Brown SS, Reavey P, Young DS, Rej R (eds). Biomarkers of Chemical Exposure. Proceedings of the Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1994; 40 (issue 7B).
19. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ, Jr, Jégou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajper-DeMeyts E, Scheike T, Sumpter J, Skakkebaek N. Male reproductive health and environmental chemicals with estrogenic effects. Copenhagen: Danish Environmental Protection Agency, 1995, 166 pp.
20. Grandjean P, Brown SS, Reavey P, Young DS, Sampson E (eds). Biomarkers. Proceedings of the Second Arnold O. Beckman/IFCC European Conference on Environmental Toxicology. Clin Chem 1995; 41 (issue 12B).
21. Grandjean P. Farlig forurening (Dangerous pollution, in Danish). Copenhagen: Nyt Nordisk Forlag and National Board of Health, 1998, 174 pp.
22. Grandjean P ed. Human health effects of environmental mercury exposure (special issue). Environ Res 1998; 77 (67-177).
23. Grandjean P, Sofritti M, Minardi F, Brazier J (eds). The Precautionary Principle. Implications for research and prevention in environmental and occupational health. Eur J Oncol Library 2003; 2: 1-245. Also published in Int J Occup Med Environ Health 2004; 17: 3-201.
24. Grandjean P (ed). Prenatal programming and toxicity. Basic Clin Pharmacol Toxicol. 2008; 102(2): 71-273.
25. Gee D, Grandjean P, Hansen SF, van den Hove S, MacGarvin M, Martin J, Nielsen G, Quist D, Stanners D, eds. Late Lessons from Early Warnings, volume II (EEA Report No 1/2013). Copenhagen, European Environment Agency, 2013, 746 pp.
26. Grandjean P. Only one chance. How Environmental Pollution Impairs Brain Development – and How to Protect the Brains of the Next Generation. New York: Oxford University Press, 2013 (232 pp.).
27. Grandjean P, Hermann P. Kemi på hjernen – går ud over enhver forstand. København: Gyldendal, 2015 (334 sider).
28. Grandjean P. Cerveaux en danger (Brains in danger, in French). Translated by Odile Demange. Paris: Buchet Chastel, 2016 (336 pp.).
29. Kishi R, Grandjean P, eds. Health Impacts of Developmental Exposure to Environmental Chemicals. Singapore: Springer, 2020 (555 pp.)

Publications in international peer-reviewed journals

1. Grandjean P, Holma B. A history of lead retention in the Danish population. *Environ Biochem Physiol* 1973; 3: 268-73.
2. Grandjean P. Lead in Danes, historical and toxicological studies. *Environ Qual Saf* 1975; Suppl. Vol. 2: 6-75.
3. Grandjean P. Possible effect of lead on egg-shell thickness in kestrels 1874-1974. *Bull Environ Contam Toxicol* 1976; 16: 101-6.
4. Grandjean P. Regional distribution of lead in human brains. *Toxicol Lett* 1978; 2: 65-9.
5. Nielsen T, Jensen KA, Grandjean P. Organic lead in normal human brains. *Nature (Lond.)* 1978; 274: 602-3.
6. Grandjean P. Lead concentration in single hairs as a monitor of occupational lead exposure. *Int Arch Occup Environ Health* 1978; 42: 69-81.
7. Grandjean P, Lintrup J. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. *Scand J Clin Lab Invest* 1978; 38: 669-75.
8. Grandjean P, Arnvig E, Beckmann J. Psychological dysfunctions of lead-exposed workers: Relation to biological parameters of exposure. *Scand J Work Environ Health* 1978; 4: 295-303.
9. Grandjean P. Widening perspectives of lead toxicity, a review of health effects of lead exposure in adults. *Environ Res* 1978; 17: 303-21. (Also published as a special report to the U.S. National Institute of Environmental Health Sciences)
10. Grandjean P. Occupational lead exposure in Denmark: Screening with the haematofluorometer. *Br J Ind Med* 1979; 36: 52-8.
11. Grandjean P, Nielsen OV, Shapiro IM. Lead retention in ancient Nubian and contemporary populations. *J Environ Path Toxicol* 1979; 2: 781-7.
12. Grandjean P, Nielsen T. Organolead compounds, environmental health aspects. *Residue Rev* 1979; 72: 97-148.
13. Arnvig E, Grandjean P, Beckmann J. Neuropsychological effect of heavy lead exposure determined with psychological tests. *Toxicol Lett* 1980; 5: 399-404.
14. Hertz MM, Bolwig TG, Grandjean P, Westergaard E. Lead poisoning and the blood-brain barrier. *Acta Neurol Scand* 1981; 63: 286-96.
15. Grandjean P, Selikoff IJ, Shen SK, Sundermann FW Jr. Nickel concentrations in plasma and urine of shipyard workers. *Am J Ind Med* 1981; 1: 181-9.
16. Olsen NB, Hollnagel H, Grandjean P. Indicators of lead exposure in an adult Danish suburban population. *Dan Med Bull* 1981; 28: 168-76.
17. Grandjean P, Olsen NB, Hollnagel H. Influence of smoking and alcohol consumption on blood lead levels. *Int Arch Occup Environ Health* 1981; 48: 391-7.
18. Grandjean P, Kon SH. Lead exposure of welders and bystanders in a ship repair yard. *Am J Ind Med* 1981; 2: 65-70.
19. Grandjean P, Lintrup J. Sources of variation in fluorometry of zinc-protoporphyrin in blood. *Scand J Work Environ Health* 1981; 7: 311-2.
20. Grandjean P, Olsen NB, Hollnagel H. Occupationally related lead exposure in the general population. *Scand J Work Environ Health* 1981;

7: 298-301.

21. Grandjean P. Occupational fluorosis through 50 years: clinical and epidemiological experiences. *Am J Ind Med* 1982; 3: 227-36.
22. Nielsen OV, Grandjean P, Bennike P. Chemical analyses of archaeological bone samples: Evidence for high lead exposure on the Faroe Islands. *J Dan Archaeol* 1982; 2: 145-8. (also published in Faroese: Blyggj i føroyingum, *Mondul* 1983; 9: 27-31)
23. Grandjean P. Storage depots in the body: Passive retention or time bomb? (Editorial) *Am J Ind Med* 1983; 4: 489-90.
24. Grandjean P, Wulf HC, Niebuhr E. Sister chromatid exchange in response to variations in occupational lead exposure. *Environ Res* 1983; 32: 199-204.
25. Grandjean P, Thomsen G. Reversibility of skeletal fluorosis. *Br J Ind Med* 1983; 40: 456-61.
26. Grandjean P. Lead poisoning: Hair analysis shows the calendar of events. *Hum Toxicol* 1984; 3: 223-8.
27. Grandjean P, Hansen ON, Lyngbye K. Analysis of lead in circum-pulpal dentin of deciduous teeth. *Ann Clin Lab Sci* 1984; 14:270-5.
28. Eskildsen J, Grandjean P. Lead exposure from lead pellets: Age-related accumulation in mute swans. *Toxicol Lett* 1984; 21: 225-9.
29. Grandjean P, Juel K, Jensen OM. Mortality and cancer morbidity after heavy occupational fluoride exposure. *Am J Epidemiol* 1985; 121: 57-64.
30. Lyngbye T, Hansen ON, Vangberg L, Grandjean P. Lead as a cause of SIDS. *N Engl J Med* 1985; 10: 954-5.
31. Grandjean P. Reference intervals for toxic metals: Problems and prospects. *Ann Clin Lab Sci* 1986; 16: 67-74.
32. Grandjean P, Bach E. Indirect exposures: The significance of bystanders at work and at home. *Am Ind Hyg Assoc J* 1986; 47: 819-24.
33. Grandjean P, Lyngbye T, Hansen ON. Lead concentration in deciduous teeth: Variation related to tooth type and analytical technique. *J Toxicol Environ Health* 1986; 19: 437-45.
34. Grandjean P. After Chernobyl (Editorial). *Arch Environ Health* 1986; 41: 277.
35. Andersen O, Grandjean P. Effects of inorganic and organic lead compounds on chromosomal length in human lymphocytes. *Appl Organomet Chem* 1987; 1: 15-19.
36. Grandjean P, Andersen O, Nielsen GD. Carcinogenicity of occupational nickel exposures: An evaluation of the epidemiological evidence. *Am J Ind Med* 1988; 13: 193-209.
37. Christoffersen J, Christoffersen MR, Larsen R, Rostrup E, Tingsgaard P, Andersen O, Grandjean P. Interaction of cadmium ions with calcium hydroxyapatite crystals: A possible mechanism contributing to the pathogenesis of cadmium-induced diseases. *Calcif Tissue Int* 1988; 42: 331-9.
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Expert Declaration
of
Kathleen M. Thiessen, Ph.D.

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Food & Water Watch et al. v. Environmental Protection Agency
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Oak Ridge Center for Risk Analysis, Inc.
102 Donner Drive
Oak Ridge, TN 37830



TABLE OF CONTENTS

I.	SUMMARY OF QUALIFICATIONS	3
II.	SUMMARY OF OPINIONS	4
III.	SUMMARY OF METHODOLOGY	5
	A. Risk Assessment	5
	B. Materials Relied Upon	7
	C. Literature Search for Animal Neurotoxicity Data	8
	D. Systematic Review.....	9
IV.	HISTORIC CONTEXT: 1930s to 2006.....	9
V.	HAZARD CHARACTERIZATION	11
	A. The “Sufficient Evidence” Standard.....	11
	1 Sufficient Evidence from Human Data.....	12
	2 Sufficient Evidence from Animal Data.....	12
	3 Data that EPA Has Found Sufficient for Hazard Determination.....	14
	B. Human Studies on Fluoride Neurotoxicity	17
	C. Animal Studies on Fluoride Neurotoxicity	19
	1 Studies Indexed by the National Library of Medicine (PubMed).....	19
	2 NTP Systematic Review (2015).....	22
	3 NTP Systematic Review (2016).....	23
	4 Assessment of NTP’s Review.....	24
	5 Developmental Studies Published Since NTP Review.....	25
	6 McPherson (2018) and Other “No Effect” Studies.....	25
	D. Other Considerations	27
	1 Dose Response	27
	2 Neuroendocrine Effects	28
	3 Toxicokinetics.....	30
	4 Mode of Action	31
	5 <i>In Vitro</i> Studies	32
	6 Validity of the Database.....	32
	7 Data Gaps.....	35
	E. Conclusion: Neurotoxicity Is a Hazard of Fluoride Exposure.....	35
VI.	QUANTITATIVE DOSE RESPONSE	36
	A. Basis for Using Animal Data	37
	B. Selecting Points of Departure (PODs)	39
	C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day).....	44
	D. Selecting the Uncertainty Factors	45
	1 <i>Intraspecies</i> Variability (UF _H).....	46
	2 <i>Interspecies</i> Variability (UF _A)	47
	3 LOAEL to NOAEL	51
	4 Composite Uncertainty Factor	51
	E. RfD Calculations from Animal Data	52
VII.	EXPOSURE ASSESSMENT	53

VIII.	RISK CHARACTERIZATION	56
A.	Characterization of Highly Exposed and/or Highly Susceptible Populations	56
1	Pregnant Women (Fetus)	57
2	Bottle-Fed Infants	59
3	Elderly	66
4	Renal Impairment.....	68
5	Other Predisposing Factors	68
B.	Margin of Exposure	70
1	Introduction to the MOE Approach and Similarity to the RfD Approach.....	70
2	MOE Analysis.....	71
C.	Assumptions and Key Sources of Uncertainty	77
IX.	RISK DETERMINATION	82
A.	Effects of Fluoridation Chemicals Under the Condition of Use.....	83
B.	Number of People Exposed to Fluoridation Chemicals.....	84
C.	Exposure of Susceptible Subpopulations to Fluoridation Chemicals	85
D.	The Severity of the Hazard (Cognitive Deficits/IQ Loss)	85
E.	Uncertainties	86
	REFERENCES	88
	APPENDIX A. Recent animal studies of fluoride neurotoxicity (Tables A-1 and A-2).....	112
	APPENDIX B. Resume of Kathleen M. Thiessen, Ph.D.	125

I, Kathleen Thiessen Ph.D., declare that:

1. I am a risk assessment scientist at Oak Ridge Center for Risk Analysis in Oak Ridge, Tennessee. For more than 30 years, I have been involved in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment, including fluoride, and in the use of uncertainty analysis for environmental and health risk assessment.

2. I was asked to apply risk assessment frameworks used by the Environmental Protection Agency (EPA) to the current scientific literature on fluoride neurotoxicity to determine whether neurotoxicity is a hazard of fluoride exposure, and whether this hazard is a risk at the levels of fluoride added to drinking water for fluoridation (0.7 mg/L).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 7 and attached herein.

4. In the course of my work as a risk assessment scientist, I have done work for the U.S. Environmental Protection Agency (EPA), the U.S. Department of Energy, the Centers for Disease Control and Prevention, the U.S. Nuclear Regulatory Commission, the National Cancer Institute, and the National Institute for Occupational Safety and Health, as well as a number of other government and private clients.

5. I have authored several reports for the EPA on the health effects of specific environmental contaminants, including Health Issue Assessments of fluorides (hydrogen fluoride and related compounds) and mercuric chloride.

6. More recently, I served on two subcommittees of the National Research Council, one which was asked by EPA to review the toxicologic literature on fluoride (which resulted in the 2006 publication *Fluoride in Drinking Water: A Scientific Review of EPA's Standards*), and one

dealing with guidance levels for air contaminants in submarines. For the latter review, published in 2009, the NRC asked me to write much of the chapter on hydrogen fluoride.

7. Recently, I led the Working Group on Assessment of Exposures and Countermeasures in Urban Environments for the International Atomic Energy Agency's (IAEA) program on Development, Testing and Harmonization of Models and Data for Radiological Impact Assessment. I was also involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity.

8. Throughout my career, I have authored or contributed to a number of open literature publications in peer-reviewed journals such as *Environmental Science and Technology*, *Environmental Pollution*, *Atmospheric Environment*, *Journal of Environmental Radioactivity*, and the *International Journal of Occupational and Environmental Health*. I have also served as a peer reviewer for journals such as *American Journal of Preventive Medicine*, *Environment International*, *Environmental Pollution*, *Risk Analysis*, *Science of the Total Environment*, *Environmental Health Perspectives*, and *Journal of Environmental Radioactivity*, among others.

II. SUMMARY OF OPINIONS

9. Under EPA's *Guidelines for Neurotoxicity Risk Assessment*, there is sufficient evidence to conclude that neurotoxicity is a hazard of fluoride exposure.

10. The animal data on fluoride neurotoxicity are consistent with the epidemiological data in showing a risk of cognitive deficits at doses of fluoride ingested from fluoridated water.

11. Fluoridation chemicals present an "unreasonable risk" of neurotoxic effects, including IQ loss, if assessed under the same risk characterization and risk determination framework that EPA uses in its evaluations of other chemicals under TSCA.

III. SUMMARY OF METHODOLOGY

A. Risk Assessment

12. EPA has stated it “will follow” its *Guidelines on Neurotoxicity Risk Assessment* (hereafter, *Guidelines*) when “evaluating data on potential neurotoxicity associated with exposure to environmental toxicants.”¹ I conducted a risk assessment in accordance with these *Guidelines*, including a Hazard Characterization, Quantitative Dose Response Analysis, Exposure Assessment, and Risk Characterization.

13. Hazard Characterization: Pursuant to the *Guidelines*, I conducted a Hazard Characterization, in which I considered: (1) the animal studies on neuroanatomical, neurochemical, and behavioral effects, including effects on learning and memory; (2) human case reports, including clinician observations of occupationally exposed workers; (3) human epidemiology studies of fluoride and cognitive deficits, including all prospective cohort studies; (4) the literature on fluoride’s neuroendocrine effects; (5) animal and human research on possible modes of action (direct and indirect) by which fluoride affects the brain; (6) dose-response data on fluoride and neurotoxic outcomes in animal and epidemiological studies; (7) the toxicokinetics of fluoride, including data on placental transfer and uptake into the brain; and (8) *in vitro* studies investigating fluoride’s effects on brain cells, including several that used low concentrations.

14. Quantitative Dose Response Analysis: Since the literature demonstrates with high confidence that neurotoxicity is a hazard of fluoride exposure, I turned to the second step of an EPA neurotoxicity risk assessment: Quantitative Dose Response. In a quantitative dose-response analysis, a “Point of Departure” (POD) is identified from the available animal and human data in order to derive a dose that will be without appreciable risk (i.e., a Reference Dose, or RfD). For

¹ EPA (1998a), p. 1.

my analysis, I focused on the animal data, as I understood that Dr. Grandjean had already calculated a POD (i.e., BMDL) from the human birth cohort data.

15. To increase confidence in the risk characterization (a later step in the analysis, discussed below), I did not identify just one POD from the animal data. Instead, I identified the full range of PODs that can be justified, including the *least protective*. After converting these PODs into Human Equivalent Doses (HED), I applied different combinations of uncertainty factors (from non-conservative to conservative) to derive the *full range of reference doses that can be justified from the animal literature*.

16. Exposure Assessment: Consistent with the *Guidelines*, I conducted an Exposure Assessment that focused solely on the condition of use at issue in this case: fluoridation of drinking water. For my initial assessment, I relied primarily, but not solely, on the National Research Council's estimates of fluoride intake from water from the 2006 report. In response to criticisms that NRC's data may no longer be representative of contemporary exposures, I considered EPA's 2019 assessment of water intake data, in which the Agency identified the most scientifically sound and up-to-date data to use for risk assessment. I compared these updated values from EPA with the values I initially used to see if they have any material effect on my risk estimates (they did not).

17. Risk Characterization: Consistent with the *Guidelines*, I integrated the information on hazards and exposures in a risk characterization by, among other things, conducting a "Margin of Exposure" analysis for each of the PODs identified through the Quantitative Dose Response analysis.

18. Risk Determination: For the risk determination, I considered the risk-related factors that EPA has identified as relevant for risk determinations under TSCA. At the time of my initial report, EPA had not yet issued any draft risk evaluations under Section 6 of TSCA, so I relied for

guidance on risk evaluations that EPA had completed under Section 5. In response to criticism on this point, I reviewed the draft risk evaluations that EPA has subsequently issued under Section 6 to assess whether the factors EPA considers under Section 6 affect my initial determination (they do not).

B. Materials Relied Upon

19. For my risk assessment, I have relied upon my background, training and expertise in risk assessment, as well as my existing familiarity with the scientific literature on fluoride, which I first developed through extensive literature reviews for both the EPA and NRC. I also considered the following materials:

20. EPA documents, including (i) the *Guidelines* and other guidance documents that EPA has issued on risk assessment; (ii) risk assessments that EPA has conducted pursuant to the *Guidelines*;² (iii) risk evaluations that EPA has conducted under TSCA; and (iv) EPA's water intake data.

21. The NRC's review of the toxicologic literature on fluoride (NRC 2006), which I co-authored.

22. Animal studies on fluoride neurotoxicity that have been published since the NRC's 2006 review, which I obtained through a search of the National Library of Medicine's online database PubMed, as described further below.

23. The NTP's systematic review of studies addressing fluoride's impact on learning and memory in animals (NTP 2015, NTP 2016).

24. All prospective cohort studies on fluoride and neurodevelopment in humans

²I obtained the complete list of risk assessments that EPA has conducted pursuant to the *Guidelines* via an interrogatory response produced by EPA, which was provided to me by counsel.

(Bashash et al. 2017; Bashash 2018; Broadbent et al. 2015; Green et al. 2019; Shannon et al. 1986; Till et al. 2020; and Valdez-Jiminez et al. 2017).

25. Meta-analyses of the cross-sectional studies on fluoride and IQ (Choi 2012, Duan 2018).

26. The deposition of Dr. Kristina Thayer, the Director of EPA's Integrated Risk Information System (IRIS) and principal author of the NTP's 2015 and 2016 systematic reviews.

27. The deposition of Casey Hannan, the Acting Director of the Oral Health Division of the Centers for Disease Control and Prevention.

28. The deposition of Dr. Tala Henry, the Deputy Director of EPA's Office of Pollution Prevention and Toxics.

29. Studies provided by counsel—much of which I was already familiar with—which I understand were also provided to EPA's experts as well, including Dr. Tsuji.

C. Literature Search for Animal Neurotoxicity Data

30. For the animal literature, I conducted a search of the National Library of Medicine's online database PubMed to identify studies published since the NRC's 2006 review. The search terms used were: "fluoride and brain," "fluoride and learning," and "fluoride and memory."

31. The titles of all studies published since 2006 were reviewed to identify potentially relevant primary studies, and, among potentially relevant studies, abstracts were reviewed to verify relevance. Reviews, studies in Chinese for which translations were not available, and *in vitro* studies were excluded. Full-text copies of all relevant studies were obtained. In total, the search identified 110 papers. Papers that appeared to be reporting effects from the same underlying rodent experiment were treated as one study, leaving 105 distinct studies.

32. The 105 studies I identified are not an exhaustive list of the studies published since

2006, as they do not include studies that were not indexed in PubMed (e.g., studies published in the journal *Fluoride* or in certain Chinese-language journals such as the *Chinese Journal of Endemiology*). In addition, the search terms probably did not identify all relevant studies available on PubMed.

Nevertheless, the studies obtained through this pre-defined search protocol should be a reasonably representative sample of the recent literature.

D. Systematic Review

33. I did not conduct a formal systematic review, but a risk assessment under the *Guidelines* has been considered the effective equivalent of a systematic review.

IV. HISTORIC CONTEXT: 1930s to 2006

34. The early epidemiological studies in the U.S. that claimed to establish the safety of waterborne fluoride (fluoride concentrations ranging from 1 to 8 mg/L in drinking water) did not address the potential for fluoride to cause neurological effects, including IQ loss.³ The primary focus of these early studies was, instead, on skeletal health.

35. Although largely overlooked, some of the early studies of occupationally exposed workers,⁴ as well as some of the early studies of fluoride-exposed animals,⁵ reported central nervous system effects from fluoride exposure. In a 1953 study of monkeys, Wadhwani and Ramasway reported that monkeys with chronic fluorosis “did not conduct themselves with intelligence and agility of mind normally associated with them. There was a significant lack of co-ordination in their behaviour.”⁶ These early observations, some of which remained unpublished,

³ Call et al. (1965); Leone et al. (1954; 1955a; 1955b); McCauley and McClure (1954); McClure (1944); Schlesinger et al. (1956a; 1956b); Stevenson and Watson (1957).

⁴ Roholm (1937); Popov et al. (1974); Duan et al. (1995); Guo et al. (2001); Yazdi et al. (2011).

⁵ Wadhwani and Ramasway (1953); Lu et al. (1961); Rice and Lu (1963); Sadilova et al. (1968).

⁶ Wadhwani and Ramasway (1953).

were largely ignored at the time.

36. The first known study of fluoride and intelligence in humans was published in 1989 by Ren and colleagues in China.⁷ A flurry of similar studies were published in China in the 1990s.⁸ Most of these studies were published in Chinese, and they remained largely unknown outside of China until English translations started to become available after the NRC's report in 2006.

37. In 2006, the NRC concluded that "fluorides have the ability to interfere with the functions of the brain and the body by direct and indirect means."⁹ The NRC reached this conclusion based on the histological, biochemical, and molecular findings from animal studies published in the 1990s and early 2000s.¹⁰ The NRC also reviewed two studies that examined the impact of fluoride on learning and memory in animals, but the data were not yet sufficient to draw conclusions on cognitive effects.¹¹

38. As part of its report, the NRC also reviewed the 4 studies on fluoride and intelligence that were then available in English.¹² Various methodological limitations were identified with these studies, but the NRC concluded that the consistency of the results (i.e., reduced intelligence among children exposed to elevated fluoride) warranted further epidemiological research into the potential of fluoride to lower IQ.

39. The NRC also reviewed the toxicologic literature on fluoride's effects on the endocrine system, including the thyroid gland. The NRC concluded that fluoride is an endocrine-disrupting chemical which can alter thyroid function at estimated average intakes as low as 0.01 to

⁷ Ren et al. (1989).

⁸ Qin et al. (1990); Chen et al. (1991); Guo et al. (1991); Lin et al. (1991); Sun et al. (1991); An et al. (1992); Li et al. (1994); Xu et al. (1994); Yang et al. (1994); Duan et al. (1995); Li et al. (1995); Wang et al. (1996); Yao et al. (1996; 1997); Zhao et al. (1996).

⁹ NRC (2006), p. 222.

¹⁰ NRC (2006), pp. 221-222.

¹¹ NRC (2006), pp. 215-216, 221.

¹² Li et al. (1995); Zhao et al. (1996); Lu et al. (2000); Xiang et al. (2003a; 2003b).

0.03 mg/kg/day in individuals with iodine deficiency.¹³ The NRC recognized the potential relevance of fluoride's endocrine effects to neurotoxicity, noting that depressed thyroid function during pregnancy can lower the IQ of the offspring.¹⁴

40. The NRC's findings on the neurotoxic potential of fluoride have been accepted as an accurate summary of the hazard by the EPA and other federal agencies, including the CDC.

41. My risk assessment builds upon NRC's hazard determinations by considering the large volume of additional research that has been published since the NRC findings were released.

V. HAZARD CHARACTERIZATION

A. The "Sufficient Evidence" Standard

42. The focus of the Hazard Characterization is whether, at some level of exposure, the chemical has a credible potential to cause neurotoxic effects (i.e., whether neurotoxicity is a *hazard* of the chemical). The question of whether this hazard is a *risk* at environmentally relevant exposures is a separate question that is addressed in the Risk Characterization phase (as discussed below).

43. Under the *Guidelines*, hazard assessment is a qualitative determination in which the risk assessor must determine whether "sufficient evidence" of a neurotoxicity hazard exists.¹⁵ A "sufficient evidence" finding "can be based on either human or animal data."¹⁶ EPA has a preference for using human data if suitable data exist;¹⁷ in practice, however, animal data are almost always used.¹⁸

¹³ NRC (2006), pp. 262-263, 266.

¹⁴ NRC (2006), p. 263.

¹⁵ EPA (1998a), pp. 11, 53, 55-56.

¹⁶ EPA (1998a), p. 11.

¹⁷ EPA (2018a), p. 2-1.

¹⁸ EPA (1998a), p. 20.

1. Sufficient Evidence from Human Data

44. For human data, “sufficient evidence” of a neurotoxic hazard exists if epidemiologic studies show that “some neurotoxic effect is *associated* with exposure.”¹⁹ EPA contrasted this requirement of an “association” with what the Agency recognized to be the “more stringent requirement” of “causality.”²⁰ Under the *Guidelines*, there is no requirement to prove causality; evidence of an association is enough.

45. In assessing whether epidemiological studies demonstrate an association with neurotoxicity, EPA has stated that prospective cohort studies “should weigh heavily” in the assessment.²¹ The *Guidelines* recognize that prospective studies are “invaluable for determining the time course for development of dysfunction” and permit “direct estimate of risks attributed to a particular exposure.”²² The only drawback of prospective studies that the *Guidelines* identify are that they “can be very time-consuming and costly.”²³

2. Sufficient Evidence from Animal Data

46. For animal data, “sufficient evidence” of a neurotoxic hazard exists if experimental studies demonstrate a potential neurotoxic hazard in humans.²⁴ The “minimum evidence” necessary to demonstrate a potential hazard is “a single appropriate, well-executed study in a single experimental animal species.” If no individual study is sufficient to establish a hazard, “the total

¹⁹ EPA (1998a), p. 53.

²⁰ EPA (1998a), pp. 53.

²¹ EPA (1998a), pp. 18.

²² EPA (1998a), pp. 17.

²³ EPA (1998a), pp. 17.

²⁴ EPA (1998a), p. 53.

available data may support such a conclusion” including data on toxicokinetics²⁵ and mechanisms of action.²⁶

47. Neurotoxic endpoints in animal studies fall into several categories, including neuroanatomical, neurochemical, and behavioral.²⁷

48. Neuroanatomical endpoints include changes to the brain, including damage to brain cells, that are detectable under a microscope (i.e., “histological”).²⁸ The *Guidelines* consider neuroanatomical changes to be “of concern,” and EPA has established reference doses for chemicals based on neuroanatomical effects.

49. Neurochemical effects include biochemical changes, such as alterations in neurotransmitter function and effects on enzymes. The *Guidelines* state that neurochemical changes “may be regarded as adverse because of their known or presumed relation to neurophysiological and/or neurobehavioral consequences.”²⁹

50. Behavioral changes include alterations to motor activity, changes in sensory abilities or motor coordination, and impairments in learning, memory, and attention.³⁰ EPA has repeatedly based reference doses on behavioral alterations documented in animals, including learning and memory impairments.

51. In considering the relevance of the animal data to humans, the *Guidelines* provide four default assumptions. First, EPA assumes that “an agent that produces detectable adverse

²⁵ The *Guidelines* use the term pharmacokinetics. Both pharmacokinetics and toxicokinetics refer to the uptake, distribution, and retention of chemicals, with the former term being more frequently used in the context of pharmaceuticals, and the latter term more frequently used in the context of toxicants.

²⁶ EPA (1998a), p. 56.

²⁷ EPA (1998a), pp. 20-21.

²⁸ EPA (1998a), p. 21.

²⁹ EPA (1998a), p. 55.

³⁰ EPA (1998a), p. 21.

neurotoxic effects in experimental animal studies will pose a potential hazard to humans.”³¹ Second, EPA assumes that neuroanatomical, neurochemical, and behavioral changes “are of concern.”³² Third, EPA assumes that “the neurotoxic effects seen in animal studies may not always be the same as those produced in humans” due to “species-specific differences in maturation of the nervous system, differences in timing of exposure, metabolism, or mechanisms of action.”³³ Fourth, EPA assumes that “humans are as sensitive as the most sensitive animal species tested.”³⁴ These four assumptions are “plausibly conservative,” meaning that “they are protective of public health and are also well founded in scientific knowledge about the effects of concern.”³⁵

3. Data that EPA Has Found Sufficient for Hazard Determination

52. EPA has conducted 10 risk assessments pursuant to the *Guidelines*. In 9 of these risk assessments, EPA found sufficient evidence to make a hazard determination and established Reference Doses (RfDs) or Reference Concentrations (RfCs)³⁶ to protect against the hazard.³⁷ In each of these 9 assessments, EPA based its hazard determination on animal data. For 6 of these 9 assessments, the chemicals had *no* human data on neurotoxicity (Table 1). For the 3 chemicals with some human data, no prospective cohort studies were available.

53. The principal studies³⁸ which EPA has used to establish RfDs have not been

³¹ EPA (1998a), p. 6.

³² EPA (1998a), p. 6.

³³ EPA (1998a), p. 7.

³⁴ EPA (1998a), p. 7.

³⁵ EPA (1998a), p. 7.

³⁶ Reference Doses refer to oral exposures, while Reference Concentrations refer to inhalational exposure. Eight of the 9 neurotoxicity risk assessments established RfDs, while 1 set an RfC. For purposes of simplicity, I will refer to Reference Doses for the remainder of this declaration when discussing these assessments.

³⁷ These 9 risk assessments were performed for BDE-47 (EPA 2008a), BDE-99 (EPA 2008b), BDE-153 (EPA 2008c), BDE-209 (EPA 2008d), Chlorine Dioxide and Chlorite (EPA 2000b), 2-Hexanone (EPA 2009b), Methanol (EPA 2013a), RDX (EPA 2018a), and Trimethylbenzenes (EPA 2016).

³⁸ A principal study is the study that contributes most significantly to the assessment of risk and is generally the basis for the Point of Departure from which a reference value is derived.

“perfect” studies. In fact, in most of the neurotoxicity risk assessments, EPA has identified a number of methodological limitations with the studies. Some of the principal studies did not conform to EPA’s testing guidelines for animal studies; some used relatively small numbers of animals (e.g., 10 per group); and the principal studies that investigated effects from prenatal exposures did not always control for “litter effects,” a methodological deficiency that can skew the effect size in developmental studies. In light of these limitations, EPA had “low confidence” for the studies it relied upon for several of its risk assessments (see Table 1). This did not stop EPA from establishing RfDs for these chemicals.

54. In several of EPA’s neurotoxicity risk assessments, EPA established an RfD despite a relatively small number of animal studies. In the RDX risk assessment, for example, EPA identified 16 animal studies, only two of which had been published. EPA characterized these studies as showing “consistent evidence” of neurotoxicity because 11 of the 16 studies reported neurological effects³⁹ and the effects were generally dose-related (although inconsistencies existed across the studies in terms of the doses that produced effects).⁴⁰ EPA has thus recognized that “consistency” of the evidence is not synonymous with unanimity.

³⁹ EPA (2018a), p. 1-23.

⁴⁰ EPA (2018a), pp. 1-12, 1-18.

Table 1. Chemicals with oral RfDs based on neurological endpoints, assessed according to EPA's Guidelines for Neurotoxicity Risk Assessment.^a

Name of Chemical	Human Neurotoxicity Data? ^b	Principal Study	Confidence in Principal Study	Known Mode of Action?	Effect	Reference
BDE-47	No	Animal	Not given ^c	Inadequate data	Changes in spontaneous motor activity and habituation	EPA (2008a)
BDE-99	No	Animal	Not given ^d	Inadequate data	Neurobehavioral developmental effects; changes in motor activity	EPA (2008b)
BDE-153	No	Animal	Not given ^e	Inadequate data	Spontaneous behavior, learning and memory	EPA (2008c)
BDE-209	No	Animal	Low	Inadequate data	Changes in spontaneous behavior and habituation	EPA (2008d)
Chlorine Dioxide and Chlorite	No	Animal	Medium	No	Neurodevelopmental delay; lowered auditory startle amplitude	EPA (2000b)
2-Hexanone	No	Animal	Medium	Yes	Axonal swelling in peripheral nerves	EPA (2009b)
RDX	One cross-sectional study, 16 case reports	Animal	High	Yes	Convulsions	EPA (2018a)
Trimethylbenzenes	Occupational studies of solvent mixtures, controlled experiments with healthy adults	Animal	Low to Medium	Tentative, based on structurally similar compounds	Decreased pain sensitivity	EPA (2016)

^a EPA (1998a); Federal Register (1998). In addition, an inhalation RfC was derived for methanol based on animal data (EPA 2013a); the confidence in the RfC was considered medium to high.

^b Human studies of neurotoxicity endpoints.

^c Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment of BDE-47 is low" (EPA 2008a, p. 48).

^d Confidence in the principal study was not stated, but the "overall confidence in the RfD [for BDE-99] is low" (EPA 2008b, p. 67).

^e Confidence in the principal study was not stated, but the "overall confidence in the RfD assessment for BDE-153 is low" (EPA 2008c, p. 37).

55. EPA has taken a similar approach to animal data in some of its draft risk evaluations under Section 6 of TSCA. In its NMP risk evaluation, for example, EPA based its risk calculations for chronic exposures in humans on animal data linking NMP to reduced fertility, despite the fact that there were only six animal studies available, three of which found no effect.⁴¹ These contradictory findings were considered a source of uncertainty, but did not stop EPA from using these animal data to assess risk in humans. In fact, EPA made findings of unreasonable risk in humans exposed to lower doses of NMP based on this small body of contradictory data.

B. Human Studies on the Neurotoxicity of Fluoride

56. As noted earlier, the *Guidelines* state that prospective cohort studies “should weigh heavily in the risk assessment process.”⁴² The *Guidelines* also identify other types of human studies that can inform the assessment, including case reports and cross-sectional studies.⁴³

57. In contrast to 9 chemicals for which EPA has established reference doses under the *Guidelines*, there are abundant human data on fluoride neurotoxicity, including 4 high-quality prospective cohort studies with individualized measurements of exposure during the prenatal period.⁴⁴

58. I understand that Dr. Hu and Dr. Lanphear will be addressing the ELEMENT and MIREC birth cohort studies, and I understand that Dr. Philippe Grandjean will be addressing the other epidemiological studies, so I will forego repeating the details here.

⁴¹ EPA (2019d), pp. 173-174.

⁴² EPA (1998a), p. 17.

⁴³ EPA (1998a), pp. 15-16.

⁴⁴ Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

59. As I described in my expert report, the human data on fluoride *strongly* support a hazard determination. Most importantly, each of the 4 prospective studies with measurements of *prenatal* exposure has found large and significant adverse associations with neurodevelopment, including IQ loss and inattention. An additional prospective study has found an association between IQ deficits and fluoride exposure during *infancy*.⁴⁵ These studies—which have consistently detected a significant association between early-life fluoride exposure and cognitive deficits using the most reliable study design identified by the *Guidelines*—are by themselves enough to constitute “sufficient evidence” of a hazard.

60. The consistency of the inverse association between fluoride and IQ in cross-sectional studies also adds important weight to the hazard assessment. Although cross-sectional studies are limited in their capacity to establish causal relationships, this limitation is lessened where the study examines stable populations and stable water fluoride levels.⁴⁶ In any event, the focus of the *Guidelines* is on assessing whether there is a reliable *association* with neurotoxicity, not on definitively proving causality.⁴⁷ As several meta-analyses have demonstrated, the cross-sectional studies show large and significant inverse *associations* between fluoride and IQ, with an average loss of about 7 IQ points.⁴⁸

61. Finally, the case reports of neurological symptoms following fluoride exposure (e.g., general malaise, fatigue, headaches, and difficulties with concentration and memory) add

⁴⁵ Till et al. (2020).

⁴⁶ Under these conditions, measurement of current water fluoride levels may be a reasonable, albeit imperfect, proxy for exposure from the prenatal period onward, and thus the temporality requirement for a causal inference is partially met. A number of the cross-sectional studies on fluoride and IQ have, in fact, expressly limited the study population to children who lived in the same area since birth, which increases the basis for inferring causation. Chen et al. (1991); Choi et al. (2015); Ding et al. (2011), Karimzade et al. (2014a; 2014b); Khan et al. (2015); Lu et al. (2000); Nagarajappa et al. (2013); Rocha Amador et al. (2007); Seraj et al. (2012); Sudhir et al. (2009); Wang et al. (2007); Yao et al. (1996; 1997); Zhang et al. (2015b).

⁴⁷ EPA (1998a), p. 53.

⁴⁸ Choi et al. 2012; Duan et al. 2018.

additional support to the hazard determination. While case reports are generally not sufficient, by themselves, to establish a hazard, the *Guidelines* consider them “useful when corroborating epidemiological data are available.”⁴⁹ Further, as the NRC noted, several of the case reports on fluoride can be characterized as “experimental studies,” since they involved “individuals who underwent withdrawal from their source of fluoride exposure and subsequent re-exposures under ‘blind’ conditions. In most cases, the symptoms disappeared with the elimination of exposure to fluoride and returned when exposure was reinstated.”⁵⁰ There is credible evidence, therefore, that for some sensitive individuals, fluoride exposure may cause overt neurological symptoms, although the NRC called for more research to better understand the issue.

C. Animal Studies on Fluoride Neurotoxicity

62. The animal research on fluoride neurotoxicity was sufficient to permit the NRC to conclude, in 2006, that fluoride interferes with the functions of the brain.⁵¹ The NRC based this finding on the neuroanatomical and neurochemical changes produced by fluoride in laboratory animals. These changes include: reduced protein and phospholipid content; inhibition of acetylcholinesterase; interference with neurotransmitters; increased production of free radicals in the brain (i.e., oxidative stress); neuronal deformations; increased uptake of aluminum; and enhancement of reactive microglia.⁵²

63. Many animal studies have been published since the NRC review which add further support to the hazard determination, as I will now discuss.

1. Studies Indexed by the National Library of Medicine (PubMed)

64. In my search of PubMed, I identified 105 studies that have been published since

⁴⁹ EPA (1998a), p. 15.

⁵⁰ NRC (2006), pp. 208-209.

⁵¹ NRC (2006), p. 222.

⁵² NRC (2006), pp. 221-222.

2006. Of these studies, all but 4 reported associations between fluoride exposure and neurotoxic outcomes.⁵³

65. Table A-1 in Appendix A to this declaration provides data from the 88 animal studies which investigated neuroanatomical and neurochemical endpoints (i.e., “structural” effects), while Table A-2 provides data from the 36 animal studies which investigated learning and memory endpoints (i.e., “functional” effects).⁵⁴ Twenty-nine studies investigated both types of effects and are in both lists.⁵⁵

66. As can be seen in Table A-1, rodent studies published since the NRC review have continued to document structural (e.g., neuroanatomical and neurochemical) changes in the brains of fluoride-treated rodents. These changes include oxidative stress, neuronal degeneration, mitochondrial disturbances, reductions in nicotinic receptors, impaired synaptic plasticity, and neuroinflammation.

67. Among the studies that have investigated both structural and functional effects of fluoride, the former have sometimes (but not always) occurred at lower exposures, suggesting that fluoride can cause cellular and biochemical changes in the brain prior to the manifestation of outwardly demonstrable deficits.⁵⁶ Put another way, deficits in learning and memory likely represent a relatively advanced stage of fluoride neurotoxicity. Nevertheless, both structural and

⁵³ Negative results were reported by Whitford et al. (2009), Pulangan et al. (2018), McPherson et al. (2018), and Jia et al. (2019, which I discuss later).

⁵⁴ For purposes of simplicity, I have used the term “structural” to refer to both neuroanatomical and neurochemical effects. While neurochemical effects are technically “functional” in nature, I use the word “functional” to refer solely to outward manifestations of neurotoxicity (i.e., learning/memory deficits). In this declaration, therefore, “structural” changes refer to all changes observed *in the brain*, while functional effects refer to all changes in *outward behavior* (e.g., learning and memory test performance, etc).

⁵⁵ To facilitate comparisons across these studies, Tables A-1 and A-2 exclude 2 studies of non-rodents as well as four studies in which the fluoride exposure was part of a mixture involving other potentially neurotoxic chemicals, one study involving exposure by a route other than ordinary ingestion, and two behavioral studies with endpoints that did not specifically involve learning and memory.

⁵⁶ See, for example, Agustina et al. (2018); Ma et al. (2015); Niu et al. (2018a); Sun et al. (2018); Wang et al. (2018a); Zhang et al. (2019); Zhao et al. (2019).

functional harms have repeatedly been observed in rodents at water fluoride concentrations between 5 mg/L and 23 mg/L.⁵⁷ As with the RDX literature,⁵⁸ there are some inconsistencies across the studies in the reported doses that can cause certain types of harm; these differences likely result, at least in part, from differences in study design, including differences in timing of exposure, duration of exposure, and strain and sex of animal.

68. Most of the animal studies to date have used subchronic exposure scenarios, which would tend to understate the effect from lifetime exposure. EPA's testing guidelines define a chronic exposure study in rodents as one that lasts at least 12 months.⁵⁹ None of the recent learning studies has lasted 12 months, and only 1 of the recent structural studies has lasted 12 months or more.⁶⁰ Among the studies that have tested animals at multiple points in time, the effects have tended to worsen with time, with some effects not appearing at all until 3 to 6 months of chronic exposure.⁶¹ Since most of the studies on fluoride neurotoxicity have lasted no longer than 3 months, the studies are likely not detecting the full spectrum of fluoride's effects.

69. I understand that EPA is asserting that systemic toxicity, as reflected by reduced body weight, may explain fluoride's observed effect on learning/memory in animals. The *Guidelines* provide that, "If several neurological signs are affected, but only at the high dose and in conjunction with other overt signs of toxicity, including systemic toxicity, *large decreases in body weight*, decreases in body temperature, or debilitation, there is less persuasive evidence of a direct neurotoxic effect."⁶² The *Guidelines* further provide that "At doses causing moderate

⁵⁷ These concentrations of fluoride *ion* correspond to a concentration of approximately 10 to 50 mg/L of *sodium* fluoride, as there are 2.2 parts sodium for each 1 part fluoride.

⁵⁸ EPA (2018a).

⁵⁹ EPA (1998b), p. 1.

⁶⁰ Teng et al. (2018).

⁶¹ For example, Güner et al. (2016); Liu et al. (2011); Yang et al. (2018a); Zhang et al. (2015a).

⁶² EPA (1998a), p. 38.

maternal toxicity (i.e., 20% or more reduction in weight gain during gestation and lactation), interpretation of developmental effects may be confounded.”⁶³ The fact that there is some effect on body weight, therefore, does not, by itself, negate a direct neurotoxic effect; the effect on body weight must be relatively large (i.e., >20%). While some of the animal studies on fluoride do show some body weight reductions, many do *not*—particularly at the lowest doses causing the effects. Systemic toxicity is thus an unlikely explanation of the neurotoxic effects reported.

2. NTP Systematic Review for Australian Government (2015)

70. In 2015, the National Toxicology Program (NTP) completed a systematic review of the animal literature on fluoride neurotoxicity and submitted a report to the Australian government.⁶⁴ The NTP limited its review to studies that have measured learning, memory, and other behavioral effects.⁶⁵ In total, the NTP identified 44 studies of learning and memory, 14 of which were excluded due to risk of bias from lack of randomization, lack of blinding at outcome assessment, or other design deficiencies.⁶⁶ From the remaining 30 studies, NTP concluded that there was “a moderate level-of-evidence for a pattern of findings suggestive of an effect on learning and memory in rats treated during development or adulthood.”⁶⁷ Moderate level of evidence is the second highest level of evidence under NTP’s 5-grade classification criteria.⁶⁸

⁶³ EPA (1998a), p. 46.

⁶⁴ NTP (2015a).

⁶⁵ NTP (2015a), pp. 1, 28.

⁶⁶ In addition to PubMed, NTP searched several additional databases. NTP (2015a), p. 1.

⁶⁷ NTP (2015a), p. 1.

⁶⁸ NTP (2015a), p. 11. Under NTP’s Hazard Identification Scheme, a chemical that has a moderate level of evidence of neurotoxicity in animals and a moderate level of evidence of neurotoxicity in humans is a “presumed” neurotoxicant (NTP 2015b, p. 67, Figure 8).

3. NTP Systematic Review (2016)

71. In 2016, the NTP published an updated version of its systematic review.⁶⁹ In the updated review, NTP identified an additional four studies on learning and memory, two of which were excluded for bias, resulting in a total of 32 studies for its analysis.⁷⁰ NTP maintained its conclusion that the animal evidence is “suggestive” that fluoride impairs learning and memory, but downgraded its confidence in the developmental studies to “low.”⁷¹ NTP had less confidence in the developmental studies due to their general failure to control for litter effects, as well as the relatively few developmental studies that used fluoride concentrations lower than 25 mg/L in drinking water.⁷²

72. The NTP identified several common methodological limitations with the learning and memory studies, including failure to rule out fluoride-induced motor effects as the cause of the apparent cognitive deficits; failure to control for “litter effects” in the developmental studies; lack of blinding; and lack of reported information on the study conditions, including the purity of the fluoride added to the water and the concentrations of fluoride in the rodent chow.

73. In contrast to NTP’s 2015 report, the 2016 report considered the absence of animal studies using 0.7 mg/L (the current recommended fluoride concentration for human drinking water⁷³) to be an important limitation in the research in terms of its relevance to human exposure levels.⁷⁴

⁶⁹ NTP (2016).

⁷⁰ NTP (2016), p. vi.

⁷¹ NTP (2016), p. vii.

⁷² NTP (2016), p. 57.

⁷³ USDHHS (2015).

⁷⁴ NTP (2016), pp. 55, 58.

4. Assessment of NTP's Review

74. The suggestion by NTP that rodent studies should use fluoride concentrations of 0.7 mg/L in order to be relevant to human exposures is at odds with EPA's approach to risk assessment.⁷⁵ As I discuss later, humans are considered much more sensitive to toxicants than are rats and mice, and the EPA has developed procedures to account for this increased sensitivity. The net effect of EPA's procedures is that what might initially seem to be a "high" dose in animal studies may be very relevant to assessing risk in humans at lower doses.

75. By limiting its review to studies investigating learning and memory, the NTP did not consider the much larger number of studies that have investigated neuroanatomical and neurochemical effects, endpoints that are more sensitive and also potentially less susceptible to bias associated with outcome assessment.

76. The NTP correctly identified a number of methodological limitations in the learning/memory studies. The lack of blinding in some studies, for example, does create some uncertainty because lack of blinding can bias results in the direction of the anticipated effect.⁷⁶ Some of the limitations, however, would not be expected to skew the results in a consistent direction across laboratories (e.g., lack of information on the purity of the fluoride compounds). Similarly, litter effects can produce false negatives as well as false positives, and can both inflate and deflate the true effect size.⁷⁷ The impact of these limitations on the reported results is thus unclear, particularly when considering that the studies also have limitations that will make it harder

⁷⁵ The principal author of the NTP study, Kristina Thayer, testified at her deposition that she is no longer comfortable with the assumption of a 1-to-1 equivalence between fluoride exposures in animals and humans; Thayer testified that she would approach the issue differently today, with greater attention to interspecies differences in toxicokinetics and toxicodynamics. (Thayer Deposition at 151:9-152:3, 302:21-303:23). These issues are discussed further below.

⁷⁶ Holman et al. (2015).

⁷⁷ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

to detect effects, including the absence of chronic studies and the absence of studies investigating neonatal exposures that are comparable to formula-feeding exposures in human infants, as discussed further below.

77. Although the NTP expressed concern about the difficulty of distinguishing fluoride's effects on learning/memory from its effects on the motor/sensory system, each of these effects is neurotoxic and a matter of concern.

5. Developmental Studies Published Since the NTP Review

78. Subsequent to the NTP's review, 11 additional developmental studies have reported learning and memory outcomes.⁷⁸ Ten of these studies found deficits in the fluoride-treated groups. Notably, the Bartos et al. studies, which controlled for litter effects, found impairments in learning and memory at a fluoride concentration of just 5 mg/L. I will discuss these studies further in the Quantitative Dose Response section below.

6. McPherson (2018) and Other "No Effect" Studies

79. McPherson et al. (2018) is the one developmental study published since the NTP review that did not find clear adverse effects on learning and memory, although it did find a significant increase in pain sensitivity (a neurotoxic effect).

80. There are several features of the McPherson study that may help to explain the absence of a clear effect on learning and memory. First, unlike the overwhelming majority of previous studies on fluoride neurotoxicity, the McPherson study used Long Evans Hooded rats, which some have suggested may have lower sensitivity to fluoride than other strains.⁷⁹ To date,

⁷⁸ Bartos et al. (2018; 2019); Chen et al. (2018a); Cui et al. (2017); Ge et al. (2018); McPherson et al. (2018); Sun et al. (2018); Wang et al. (2018a); Zhao et al. (2019); Zhu et al. (2017); Zhou et al. (2019).

⁷⁹ Elliott (1967).

three studies⁸⁰ have examined the effect of fluoride on learning in Long Evans rats, and all three have failed to find an effect.⁸¹

81. Second, in contrast to most of the other developmental studies, McPherson et al. did not start the exposure until the 6th day of gestation.⁸² As pregnancy in rats lasts approximately 21 days, any effects due to exposures early in, or preceding, the pregnancy may not have been detected by McPherson's study design.

82. Third, the offspring in the McPherson study had virtually no fluoride exposure during the neonatal period because the rat pups were breastfed during the pre-weaning period. This is important because the fluoride content of breast milk in rats (as with other mammals, including humans) is negligible, even when the mother is consuming large quantities of fluoride.⁸³ The rats in the McPherson study thus missed a potentially key period of vulnerability (early infancy)—an important limitation given the widespread use of infant formula among human neonates.⁸⁴

83. In addition to the McPherson study, three other studies (with weaker study designs) reported no neurotoxic effects from fluoride exposure.⁸⁵ These three studies include Whitford et al. and Pulungan et al. which started with adult animals, and an unusual study by Jia et al. which started at gestational day 9. All or part of the gestational period was thus missed in each of these studies.

⁸⁰ Elliott (1967); Varner et al. (1994); McPherson et al. (2018).

⁸¹ The plausibility of strain-specific differences between Long Evans and other rats is supported by other research which has found that Long Evans Hooded rats have different sensitivities to teratogenic substances in utero than Sprague-Dawley rats (Kang et al. 1986).

⁸² McPherson et al. (2018).

⁸³ Fluoride concentrations in mammalian milk are very low in comparison to the mother's fluoride intake, even when the mother's fluoride intake is quite high (NRC 2006, pp. 33, 36; Drinkard et al. 1985).

⁸⁴ This limitation is not unique to the McPherson study, as all other developmental studies on fluoride have failed to supplement the pup's exposure during the breastfeeding stage.

⁸⁵ Whitford et al. (2009); Pulungan et al. (2018); Jia et al. (2019).

84. According to the *Guidelines*, “To judge that an agent is unlikely to pose a hazard for neurotoxicity, the minimum evidence would include data from a host of endpoints that revealed no neurotoxic effects.”⁸⁶ This evidence does not exist for fluoride. To the contrary, almost all studies, including McPherson et al. (2018), have reported adverse effects on at least one of the endpoints measured.

D. Other Considerations

1. Dose Response

85. The *Guidelines* recognize that “determining a hazard often depends on whether a dose-response relationship is present,”⁸⁷ and thus “dose-response evaluation is a critical part of the qualitative characterization of a chemical’s potential to produce neurotoxicity.”⁸⁸ Because “human studies covering a range of exposures are rarely available,” the *Guidelines* state that the dose-response evaluation will typically be limited to animal data.⁸⁹

86. In contrast to the chemicals that EPA has evaluated under the *Guidelines*, there is abundant dose-response data for fluoride from *human* studies. Most importantly, the ELEMENT and MIREC birth cohort studies have found linear dose-response relationships between maternal urinary fluoride and IQ in the offspring.⁹⁰ The linearity of the dose-response relationships in these studies was not simply assumed—it was scrutinized through several methods, which I understand Drs. Hu and Lanphear will be explaining as part of their testimony.

87. Dose-response trends have also been observed in cross-sectional studies as a function of childhood urine and serum fluoride levels, although these are inherently less certain.⁹¹

⁸⁶ EPA (1998a), pp. 55-56.

⁸⁷ EPA (1998a), p. 2.

⁸⁸ EPA (1998a), p. 50.

⁸⁹ EPA (1998a), p. 50.

⁹⁰ Bashash et al. (2017; 2018); Green et al. (2019).

⁹¹ Cui et al. (2018); Ding et al. (2011); Xiang et al. (2011); Zhang et al. (2015b).

An important limitation with dose-response data from cross-sectional studies is that the exposures are tested after the effect (reduction in IQ) has occurred. The data, however, are not without value, as current exposures can be reflective of developmental exposures in areas with stable populations and stable water fluoride concentrations. In the Zhang study, for example, most of the children had been living in the same household and drinking from the same wells since birth.⁹²

88. In addition to dose-response data from human studies, there is also considerable dose-response data from animal studies. A prerequisite for dose-response analysis in animal studies is that there be multiple treatment groups with different exposures to the test substance. Many of the animal studies on fluoride have used multiple treatment doses, and thereby permit evaluation of dose response. Of the studies published since the NRC review (summarized in Table A-1), 1 used four treatment doses, 17 used three treatment doses, and 16 used two treatment doses (in addition to the control groups). Of these 34 studies, 30 show visually apparent dose-response trends for at least one of the effects being investigated.

2. Neuroendocrine Effects

89. EPA's *Guidelines* recognize the relevance of a chemical's ability to alter the function of the thyroid gland.⁹³ According to the *Guidelines*, "the development of the nervous system is intimately associated with the presence of circulating hormones such as thyroid hormone."⁹⁴ A thyroid disturbance during a specific developmental period may cause a "nervous system deficit, which could include cognitive dysfunction, altered neurological development, or visual deficits, [depending] on the severity of the thyroid disturbance and the specific developmental period when exposure to the chemical occurred."⁹⁵ Elsewhere, EPA has recognized

⁹² Zhang et al. (2015b), p. 4.

⁹³ EPA (1998a), p. 50.

⁹⁴ EPA (1998a), p. 50.

⁹⁵ EPA (1998a), p. 50.

that “thyroid hormones are essential for normal brain development in humans and that hypothyroidism during fetal and early neonatal life may have profound adverse effects on the developing brain.”⁹⁶

90. Thyroid toxicity may be a significant mechanism by which fluoride affects neurodevelopment. In 2006, the NRC had enough information to conclude that fluoride is an “endocrine disrupter” which may lower thyroid function.⁹⁷ Sodium fluoride was once prescribed as a therapeutic agent for *lowering* thyroid activity in cases of *hyperthyroidism*.⁹⁸ The NRC reported that fluoride can lower thyroid function at estimated average intakes of 0.05-0.13 mg/kg/day in humans with adequate iodine intake, and at estimated average intakes as low as 0.01 to 0.03 mg/kg/day in individuals with iodine deficiency.⁹⁹ Put differently, fluoride affects thyroid function at lower doses in people with iodine deficiency than in those with optimal intake of iodine.

91. Epidemiological research published subsequent to the NRC’s report is consistent with and further supports NRC’s findings. In 2018, Malin et al. reported a relationship between urinary fluoride and elevated TSH (thyroid stimulating hormone) among iodine-deficient adults in Canada, but not in the general population as a whole (excluding those with known thyroid disease and excluding pregnant individuals).¹⁰⁰ Elevated TSH is indicative of a decrease in thyroid function. Ten percent of women of child-bearing age in the US are iodine deficient.¹⁰¹

⁹⁶ EPA (2008a), p. 40, citing Morreale de Escobar et al. (2000) and Haddow et al (1999). See also EPA (2008b), p. 54, citing Morreale de Escobar et al. (2000). EPA’s Science Advisory Board in 2013 found that “the most sensitive life stages are the fetus, neonates and infants because these are the stages when thyroid-dependent brain development occurs” (EPA 2013b, cover letter, p. 2).

⁹⁷ NRC (2006), pp. 262-263.

⁹⁸ Galletti and Joyet (1958). Consistent with this thyroid use (i.e., lowering thyroid function), fluoride exposure has been associated with hypothyroidism in animal and human studies (Hillman et al. 1979; Peckham et al. 2015; Yang et al. 2019).

⁹⁹ NRC (2006), pp. 262-263.

¹⁰⁰ Malin et al. (2018). Barberio et al. (2017) found no association between fluoride exposure and thyroid status, but the iodine-deficient part of the population was not specifically addressed.

¹⁰¹ CDC (2008), Chapter 4a, pp. 91-100; see also Pearce (2015); Caldwell et al. (2011).

92. In 2015, a nationwide study from England reported a significant association between water fluoridation and increased prevalence of hypothyroidism.¹⁰²

3. Toxicokinetics

93. Under the *Guidelines*, consideration should be given to the toxicokinetics of the chemical with “particular importance” given to the chemical’s capacity to get through the blood-brain barrier.¹⁰³ The permeability of the blood brain barrier is particularly important when a chemical, such as fluoride, is able to make it through the placenta. Studies in humans have repeatedly demonstrated that fluoride crosses the placenta and reaches the fetus,¹⁰⁴ and thus it is generally accepted that “fluoride readily crosses the placenta.”¹⁰⁵ In general, measured concentrations of fluoride in umbilical cord blood and in blood of neonates are similar to concentrations in maternal blood.¹⁰⁶ In short, the fluoride that a mother ingests will cause exposure to the fetus.

94. Fluoride is also known to cross the blood-brain barrier,¹⁰⁷ and passage of fluoride into the brain can be expected to be higher during the fetal and neonatal life stages when the blood brain barrier is not yet fully developed.¹⁰⁸ As the EPA has recognized, “Because the blood-brain barrier limits the passage of substances from blood to brain, in its absence, toxic agents can freely enter the developing brain.”¹⁰⁹ Consistent with EPA’s observation, the recent rat study by

¹⁰² Peckham et al. (2015).

¹⁰³ EPA (1998a), p. 47.

¹⁰⁴ See for example, Feltman and Kosel (1961); Gedalia et al. (1964); Blayney and Hill (1964); Armstrong et al. (1970); Hanhijärvi et al. (1974); Forsman (1974); Shen and Taves (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Brambilla et al. (1994); Shimonovitz et al. (1995).

¹⁰⁵ NRC (2006), p. 193.

¹⁰⁶ Feltman and Kosel (1961); Gedalia et al. (1964); Hudson et al. (1967); Armstrong et al. (1970); Hanhijärvi et al. (1974); Ron et al. (1986); Malhotra et al. (1993); Gupta et al. (1993); Shimonovitz et al. (1995).

¹⁰⁷ Geeraerts et al. (1986); Mullenix et al. (1995); Zhang et al. (2013c); Niu et al. (2015b).

¹⁰⁸ EPA (2009b), p. 58.

¹⁰⁹ EPA (2009b), p. 58.

McPherson et al. found sharply elevated concentrations of fluoride in the brain following prenatal exposure.¹¹⁰

4. Mode of Action

95. EPA's *Guidelines* recognize that hazard identification is strengthened by, but not dependent upon, an identifiable mechanism by which the chemical can exert neurotoxic effects.¹¹¹ For most of the chemicals for which EPA has established RfDs pursuant to the *Guidelines*, the mode of action has not been known (see Table 1). As noted recently by the NAS, "solid conclusions about causality can be drawn without mechanistic information, for example, when there is strong and consistent evidence from animal or epidemiology studies."¹¹² The NAS added that "mechanistic frameworks today could probably be completed for only a few chemicals."¹¹³

96. Several plausible mechanisms—both indirect and direct—have been identified that could help explain the neurotoxicity of fluoride.

97. *Indirect Mechanisms:* Depression of thyroid function is likely a principal indirect mechanism and could account for some of the neurotoxic effects reported in the literature. A thyroid mechanism is particularly plausible as a cause of IQ loss among offspring born to women with suboptimal iodine intakes.

98. *Direct Mechanisms* A recent study by Zhao et al. provides *in vitro*, *in vivo*, and epidemiological data that, together, suggest that disturbances in hippocampal mitochondrial dynamics (marked by fission inhibition and fusion promotion) play an important role in fluoride-induced cognitive loss.¹¹⁴ The hippocampus is an important region in the brain for learning and

¹¹⁰ McPherson et al. (2018).

¹¹¹ EPA (1998a), pp. 10, 53.

¹¹² NAS (2018), p. 9.

¹¹³ NAS (2018), p. 9.

¹¹⁴ Zhao et al. 2019.

memory, and many of the studies investigating the neuroanatomical and neurochemical effects of fluoride exposure have identified adverse effects in this region (see Table A-1). Other potential modes of action have also been identified, including signaling disruption, oxidative stress, and selective reductions in nicotinic receptors.¹¹⁵

5. In Vitro Studies

99. EPA's *Guidelines* also call for consideration of *in vitro* data. While positive *in vitro* data are not sufficient, by themselves, to demonstrate a neurotoxic hazard in humans, the existence of such data helps enhance the reliability of *in vivo* data.¹¹⁶

100. Fluoride's ability to damage brain cells has been documented in *in vitro* experiments. While most of the *in vitro* studies have used high concentrations that are unlikely to be present in the human brain, several studies have examined environmentally realistic fluoride concentrations. Gao et al. found increased lipid peroxidation and reduced $\alpha 7$ nicotinic acetylcholine receptors in brain cells at fluoride concentrations (i.e., 9.5 parts per billion) that are commonly found in the blood of people living in fluoridated areas.¹¹⁷ Increases in markers of neuroinflammation have also been found at low concentrations.¹¹⁸ Under the *Guidelines*, these data do not demonstrate a hazard in humans, but they do enhance the reliability of the animal studies, as similar effects have been reported in fluoride-treated rodents.¹¹⁹

6. Validity of the Database

101. Under the *Guidelines*, the validity of the database should be evaluated by assessing

¹¹⁵ Bartos et al. (2018); Chen et al. (2003; 2018a); Gao et al. (2008); Liu et al. (2010); Long et al. (2002); Shan et al. (2004); Zhang (2017b); Zhu et al. (2017).

¹¹⁶ EPA (1998a), p. 49.

¹¹⁷ Gao et al. (2008), Figures 1A, 3A.

¹¹⁸ Goschorska et al. (2018).

¹¹⁹ Bartos et al. (2018); Dong et al. (2015); Yang et al. (2018a); Yan et al. (2016); Zhao et al. (2019).

the content validity, construct validity, concurrent validity, and predictive validity of the data.¹²⁰

102. *Content validity* addresses “whether the effects result from exposure.”¹²¹ This factor weighs decisively in favor of a neurotoxicity hazard determination for fluoride. The NRC concluded that fluoride interferes with the brain,¹²² and the evidence has gotten stronger since. Kristina Thayer, the Director of EPA’s IRIS Division, has explained that “experimental animal studies are designed to let you draw causal inferences,” and that the animal studies show that fluoride damages the brain at some level of exposure.¹²³ Further, while the human cross-sectional studies are limited in their ability to produce causal inferences, the *Guidelines* provide that prospective cohort studies permit “direct estimates of risk attributable to a particular exposure.”¹²⁴

103. *Construct validity* addresses whether the neurologic effects that have been observed “are adverse or toxicologically significant.”¹²⁵ This factor is satisfied in the fluoride database. Animal studies have linked fluoride to learning and memory deficits, which are an adverse effect upon which EPA has established reference doses for other neurotoxicants (e.g., BDE-153).¹²⁶ Further, the human epidemiological data have linked fluoride with IQ detriments, including an approximate 5 to 6 point drop in IQ as maternal urinary fluoride increased from 0 to 1 mg/L.¹²⁷ EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,¹²⁸ and EPA’s Clean Air Science Advisory Council has stated that “a population loss of 1-2 IQ points

¹²⁰ EPA (1998a), pp. 10-11.

¹²¹ EPA (1998a), pp. 10-11.

¹²² NRC (2006), p. 222.

¹²³ Thayer Deposition at 225:8-15, 226:13-16, 270:23-25.

¹²⁴ EPA (1998a), p. 17.

¹²⁵ EPA (1998a), pp. 10-11.

¹²⁶ EPA (2008c), p. 36. Effects on memory were also noted in the RfD determination for BDE-99 (EPA 2008b, p. 27).

¹²⁷ Bashash et al. (2017); Green et al. (2019).

¹²⁸ EPA (2008e), p. 5-28.

is highly significant from a public health perspective” and should be prevented in 99.5% of the population.¹²⁹

104. *Concurrent Validity* addresses “whether there are correlative measures among behavioral, physiological, neurochemical, and morphological endpoints.¹³⁰ Studies have correlated fluoride’s cognitive effects in animals with various neurochemical and neuroanatomical changes,¹³¹ and a few studies have correlated fluoride-associated cognitive loss in humans with increased TSH and alterations in mitochondrial dynamics.¹³² For example, Zhao et al.¹³³ reported lower circulating levels of a mitochondrial protein (fission-related protein-1, Fis1) in children from high fluoride areas (compared with children in low fluoride areas), and higher circulating levels of a second mitochondrial protein (mitofusin-2, Mfn2) in the same children. The levels of circulating Fis1 were positively associated with children's IQ scores, while the levels of circulating Mfn2 were negatively associated with the IQ scores. In addition, several plausible mechanisms of fluoride neurotoxicity have been described (discussed above).

105. *Predictive validity* addresses “whether the effects are predictive of what will happen under various conditions.”¹³⁴ The condition of perhaps greatest interest with respect to prediction of fluoride neurotoxicity is exposure during the prenatal period. Studies in both animals and humans have, with one exception,¹³⁵ reported neurologic effects following prenatal exposure. The database, therefore, does have some degree of predictive validity, although further research remains necessary to determine to what extent other conditions (e.g., nutrition, genetics, neonatal

¹²⁹ Federal Register (2008), p. 67000.

¹³⁰ EPA (1998a), pp. 10-11.

¹³¹ For example, see Bartos et al. (2018); Zhao et al. (2019); Zhou et al. (2019).

¹³² For example, Zhang et al. (2015b); Zhao et al. (2019).

¹³³ Zhao et al. (2019).

¹³⁴ EPA (1998a), pp. 10-11.

¹³⁵ McPherson et al. (2018).

exposure, and kidney function) may modify or predict outcomes. Exposure during the early postnatal period also requires further research.

7. Data Gaps

106. EPA's *Guidelines* point to the need to address "significant data gaps."¹³⁶ One of the major data gaps for fluoride is the lack of research on the impact of fluoride during the neonatal and early infancy period. EPA has recognized that the neonatal period represents a critical window of vulnerability to neurotoxicants,¹³⁷ yet most developmental rodent studies do not address neonatal exposures to fluoride (due to exclusive breastfeeding of the rat or mouse pups and absence of gavage exposures). Other data gaps include the absence of long-term animal studies, and the scarcity of epidemiological research into fluoride's neurologic effects in the elderly. Data gaps also remain with respect to how the dose which causes neurologic effects varies across susceptible subsets of the population, including those with nutrient deficiencies, genetic polymorphisms, kidney disease, and the elderly.

E. Conclusion: There Is Sufficient Evidence that Neurotoxicity Is a Hazard of Fluoride

107. The large and substantial body of evidence that now exists for fluoride, from both animal and human studies, satisfies EPA's "sufficient evidence" standard for hazard determination.

108. The *Guidelines* provide that "the minimum evidence sufficient would be data on a single adverse endpoint from a well-conducted study."¹³⁸ The *Guidelines* also recognize that prospective cohort studies are the optimal type of epidemiological study that permit direct

¹³⁶ EPA (1998a), p. 12.

¹³⁷ See for example, EPA (2008a), p. 42.

¹³⁸ EPA (1998a), p. 55.

estimates of risk. The minimum evidence threshold is thus met for fluoride because there is not just one, but *four* high-quality prospective cohort studies that support the endpoint of IQ loss, and another high-quality prospective cohort study that supports the endpoint of inattention.¹³⁹

109. EPA's *Guidelines* also permit consideration of the collective evidence when no study, by itself, is sufficient to permit a hazard determination. This, again, supports a hazard determination for fluoride because the prospective studies are most compelling when viewed in the context of (i) the toxicokinetic data showing that fluoride crosses the placenta and enters the fetal brain; (ii) animal data showing neurochemical and neuroanatomical damage following fluoride exposure; (iii) animal data finding impairments in learning and memory following prenatal exposure to fluoride; (iv) cross-sectional studies consistently finding reductions in IQ in communities with elevated fluoride exposure; (v) *in vitro* studies reporting effects on brain cells at concentrations of fluoride found in the blood of individuals living in fluoridated communities; and (vi) animal and human studies finding that fluoride can depress thyroid function, a known risk factor for neurodevelopmental harm.

110. Based on the collective data—which are far more robust than the data EPA has relied upon for prior hazard determinations—I conclude with a reasonably high degree of confidence that neurotoxicity is a hazard of fluoride exposure.

VI. QUANTITATIVE DOSE RESPONSE

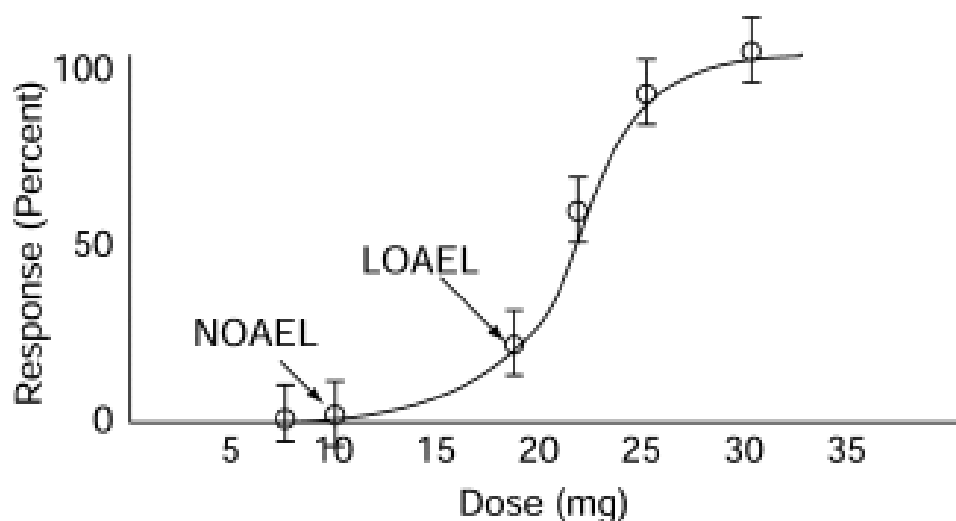
111. If a chemical is identified as posing a neurotoxic hazard, EPA's *Guidelines* call for a quantitative dose-response analysis to determine the reference dose (RfD). The RfD is “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the

¹³⁹ Bashash et al. (2017; 2018); Green et al. (2019); Till et al. (2020); Valdez-Jiménez et al. (2017).

human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”¹⁴⁰

112. In the Quantitative Dose Response analysis, human or animal data are assessed to determine an appropriate “Point of Departure” (POD). As the name implies, the Point of Departure (POD) is the datapoint from which the RfD is ultimately derived. The POD can be one of three types of values: the No Observed Adverse Effect Level (NOAEL), the Lowest Observed Adverse Effect Level (LOAEL) or the Benchmark Dose Level (BMDL). While EPA now has a preference for using BMD, it still uses both the NOAEL and LOAEL approaches in its assessments.

113. The following figure provides a visual illustration of the difference between a NOAEL and LOAEL on a dose-response curve.



A. Basis for Using Animal Data

114. When human data are available, EPA’s preference is to use human data for the Point of Departure.¹⁴¹ In the case of fluoride, the recent prospective cohort studies¹⁴² with individual-level biomonitoring data provide suitable data for this purpose. If one had to choose,

¹⁴⁰ EPA (1998a), p. 57. See also EPA (2009a).

¹⁴¹ EPA (2018a), p. 2-1.

¹⁴² Bashash et al. (2017; 2018); Valdez-Jiménez et al. (2017); Green et al. (2019).

therefore, between deriving the POD for fluoride from the human or animal data, *the choice would clearly be to use the human data*. But this does not mean that the animal data are without value. In EPA's assessment of methylmercury, for example, the EPA derived its RfD from human prospective cohort data, but it also considered what the RfD would be if it were derived from the animal literature.¹⁴³ As the EPA noted, "[i]t is informative to compare RfDs derived from animal studies with those derived from the epidemiological literature."¹⁴⁴ In the case of methylmercury, the animal-based RfD supported the human-based RfD, and EPA cited this as a factor that increased its "confidence" in the assessment.¹⁴⁵

115. In this case, Dr. Philippe Grandjean conducted a dose-response analysis of the prospective cohort data where he derived a BMDL. To avoid duplication of Dr. Grandjean's effort, and to determine whether Dr. Grandjean's BMDL is consistent with potential RfDs derived from the animal data, I focused my assessment on the animal literature.

116. In this assessment, I did not seek to select a single value for the RfD. Instead, I sought to identify the full range of RfDs that can be derived, including the *least* protective. If human exposures exceed RfDs that use non-protective assumptions, there would be greater confidence that a human risk does, in fact, exist.

117. There are several considerations that support the use of animal data to establish an RfD for fluoride. First, EPA has used animal studies as the principal studies for each of the neurotoxicity risk assessments it has thus far conducted under the *Guidelines*. Second, EPA has used impairment in learning and memory in rodents as the adverse effect upon which to base the RfD for other chemicals,¹⁴⁶ thus this is an accepted endpoint to use in deriving an RfD. Third, a

¹⁴³ EPA (2001), pp. 17-18.

¹⁴⁴ EPA (2001), pp. 17.

¹⁴⁵ EPA (2001), pp. 18-19.

¹⁴⁶ For example, BDE-153 (EPA 2008c, p. 36).

substantial number of animal studies of fluoride neurotoxicity have used 2 or 3 treatment groups (in addition to control groups), and EPA has found this to be sufficient for identifying Points of Departure,¹⁴⁷ including in animal studies with as few as 10 rats per group (2-Hexanone).¹⁴⁸

B. Selecting Points of Departure

118. In the literature review discussed earlier, 37 rodent studies were identified that have investigated fluoride's impact on learning and memory since the NRC report (Table A-2). All but 3 of these studies found adverse effects in the fluoride-treated rodents, including 16 of the 17 studies that investigated prenatal fluoride exposures. Since the prenatal period represents a point of heightened vulnerability to neurotoxicants, the prenatal studies are a logical candidate for the point of departure.

119. To avoid studies at high risk of bias, the three studies that did not specifically mention using a randomization procedure were excluded from further consideration.¹⁴⁹ Further, in order to focus the analysis on those studies best suited for identifying a Point of Departure (POD), four studies that only used one treatment dose were excluded.¹⁵⁰

120. Table 2 and the figures below summarize the 10 prenatal studies that remained for POD consideration. Most of the studies used a similar dosing regimen with 2 or 3 treatment groups and at least 10 rodents per group, which is consistent with several of the principal studies that EPA has used to establish an RfD. The figures show the lowest-observed and no-observed effect levels in each study and help to visually compare the data across studies.

121. Nine of the 10 studies found dose response trends for one or more effects, which

¹⁴⁷ EPA (2000b; 2008a; 2008c; 2008d; 2009b).

¹⁴⁸ EPA (2009b).

¹⁴⁹ Bera et al. (2007); Basha et al. (2011b); Ge et al. (2018).

¹⁵⁰ Niu et al. (2014); Banala and Karnati (2015); Dong et al. (2015); Zhu et al. (2017).

adds confidence to a causative role of the fluoride treatment.¹⁵¹ Six of these studies also provide data on the body weights of the pups, and no bodyweight changes were seen in any of the studies at the lowest concentrations producing the effects.¹⁵² Only one of the six studies found any bodyweight changes among pups in the higher-dose groups.¹⁵³ Of the two studies that reported maternal weight, neither found any changes.¹⁵⁴

122. One limitation with these studies is that only three of them specifically mention controlling for litter effects,¹⁵⁵ which introduces some uncertainty since the failure to control for litter effects can result in false positives, as well as false negatives.¹⁵⁶ While a source of uncertainty, the failure to control for litter effects does not preclude use for risk assessment purposes. As noted earlier, EPA has used studies that do not control for litter effects as the principal studies upon which it has based RfDs for developmental neurotoxicity.¹⁵⁷

¹⁵¹ See for example, Jiang et al. (2014b), Table 3; Cui et al. (2017), Table 3; Chen et al. (2018a), Figure 1d,e; Sun et al. (2018), Tables 2 and 3; Wang et al. (2018a), Figure 4b,c; Zhao et al. (2019), Figure 5e.

¹⁵² Bartos (2018; 2019); Cui et al. (2017); Jiang et al. (2014b); Wang et al. (2018a). The study by McPherson (2018) also showed no changes in bodyweight, although it did not find effects on learning/memory.

¹⁵³ Jiang (2014b) found reduced body weight gain among the pups in the 23 mg/L and 45 mg/L groups.

¹⁵⁴ Bartos (2018; 2019).

¹⁵⁵ Bartos et al. (2018; 2019); McPherson et al. (2018).

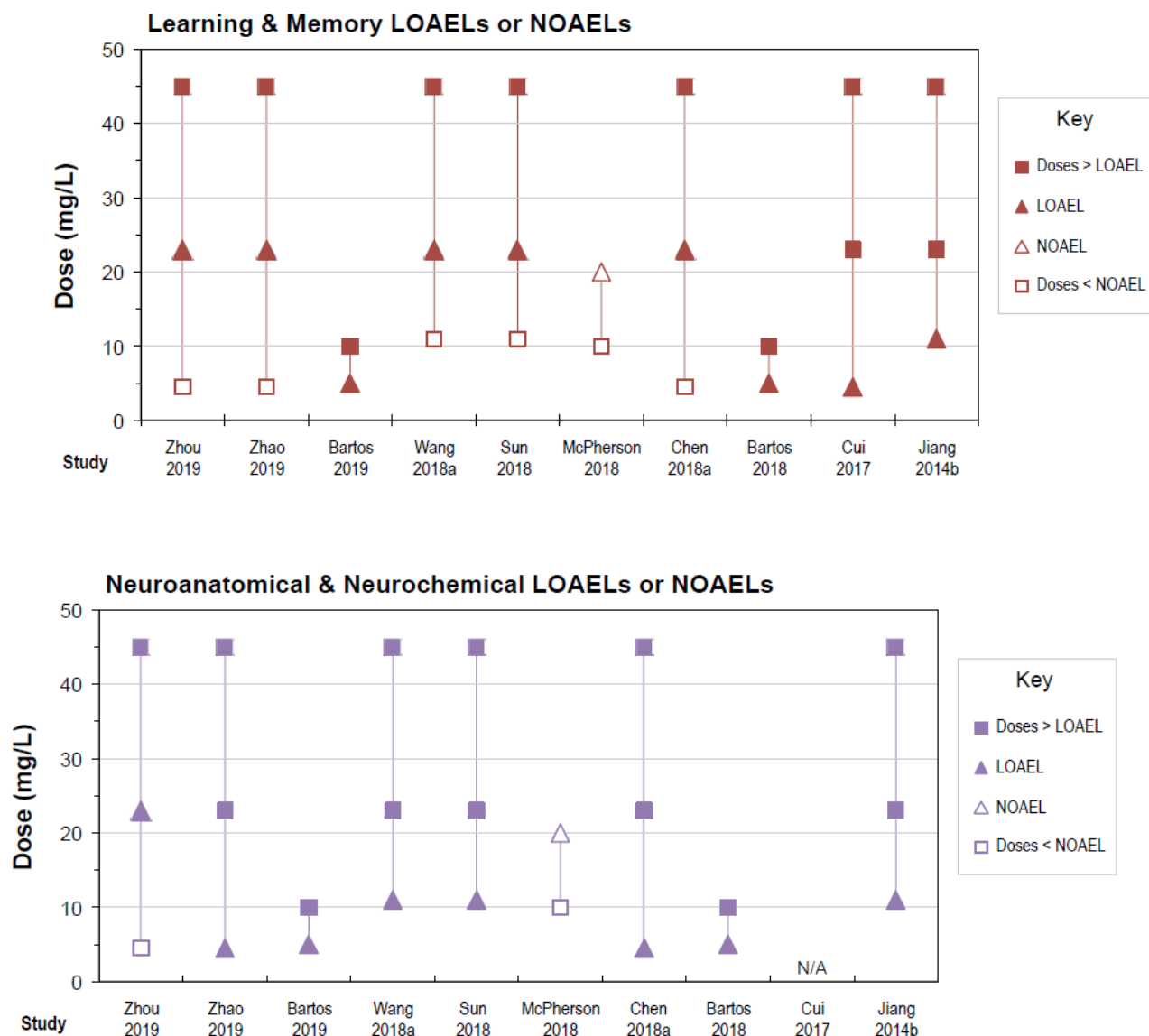
¹⁵⁶ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

¹⁵⁷ See for example EPA (2008a), pp. 44, A-4; EPA (2008b), pp. 59, A-3; EPA (2008c), pp. 32, A-3.

Table 2. Examples of rodent studies of prenatal exposure to fluoride that could provide LOAELs or NOAELs for neurotoxicity.

Study	Animal	Exposure period	[F ⁻] in drinking water ^a (mg/L)	Number of animals per group (n)	Learning and memory		Neuroanatomical or neurochemical effects	
					LOAEL (mg/L)	NOAEL (mg/L)	LOAEL (mg/L)	NOAEL (mg/L)
Zhou et al. (2019)	Rats, Sprague- Dawley	Prenatal ^b + 6 months	4.5, 23, 45	6	23	4.5	23	4.5
Zhao et al. (2019)	Rats, Sprague- Dawley	Prenatal ^b + 60 days	4.5, 23, 45	5	23	4.5	4.5	None
Bartos et al. (2019)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Wang et al. (2018a)	Mice, ICR (female)	Prenatal (from day 7) + 21 days	11, 23, 45	15	23	11	11	None
Sun et al. (2018)	Mice, Kunming	Prenatal + 21 days	11, 23, 45	6	23	11	11	None
McPherson et al. (2018)	Rats, Long Evans Hooded (male)	Prenatal (from day 6) + 90 days	10, 20 ^c	11-23	None	20	None	20
Chen et al. (2018a)	Rats, Sprague- Dawley	Prenatal ^b + 6 months	4.5, 23, 45	6	23	4.5	4.5	None
Bartos et al. (2018)	Rats, Wistar (female)	Prenatal + 21 days	5, 10	9-10	5	None	5	None
Cui et al. (2017)	Rats, Sprague- Dawley	Prenatal ^b + 60 days	4.5, 23, 45	12	4.5	None	N/A	N/A
Jiang et al. (2014b)	Rats, Sprague- Dawley	Prenatal ^b + 2 months	11, 23, 45	12	11	None	11	None

^a Treatment groups in addition to the control group.^b Exposure of the mother began before pregnancy.^c Animals were given 0, 10, or 20 mg/L fluoride in drinking water, plus 3.24 ppm fluoride in feed. An additional control group had 0 mg/L fluoride in drinking water plus 20.5 ppm fluoride in feed (McPherson et al. 2018).



123. Based on the dose-response data from these studies, the following values could be used as the Point of Departure.

124. **LOAEL of 5 mg/L:** The lowest observed adverse effect levels in the studies were fluoride concentrations of 4.5 and 5 mg/L. Of the six studies that used this concentration, three

found adverse effects on learning,¹⁵⁸ and two of the other three studies, which did not find effects on learning, *did find alterations in the brain*.¹⁵⁹ Two of the three studies reporting effects on learning at 5 mg/L controlled for litter effects, which suggests that the failure to control for litter effects is unlikely to explain the reported effects at this concentration.¹⁶⁰ A 5 mg/L LOAEL was selected, therefore, as one of the Points of Departure (PODs) for learning impairment from prenatal fluoride exposure.

125. **LOAEL of 23 mg/L**: Seven of the 10 studies used 23 mg/L as one of the treatment doses, and all 7 of these studies found impaired performance on the cognitive tests, with 6 of the 7 studies finding changes in the brain as well. 23 mg/L appears, therefore, to be a reliable “Observed Adverse Effect Level,” particularly in light of the six studies (discussed above) which found adverse effects at < 5 mg/L. Although not the *lowest* observed effect level, it is assumed to be one for purposes of this Point of Departure.

126. **LOAEL of 45 mg/L**: As can be seen in the above figures, 45 mg/L is clearly an “observed adverse effect level,” just as it has been in many other animal studies on fluoride neurotoxicity. It would be difficult to justify selecting 45 mg/L as the LOAEL because it is the *highest* observed adverse effect level in this group of studies, not the *lowest*. Nevertheless, for purposes of capturing the broadest possible range of RfDs that can be derived from the animal literature, a 45 mg/L LOAEL was selected as one of the Points of Departure.

¹⁵⁸ Cui et al. (2017); Bartos et al. (2018; 2019). In the Chen study (which had only six rats per group), there is some indication of an effect on learning in the 4.5 mg/L group, albeit not statistically significant (Chen et al. 2018a, Figure 1).

¹⁵⁹ Chen et al. (2018a); Zhao et al. (2019). Other studies have also found alterations in the brain at ≤ 5 mg/L, including Liu et al. (2010; 2011); Zhang et al. (2015a); Niu et al. (2018a); Varner et al. (1998); and Yu et al. (2019).

¹⁶⁰ Bartos et al. (2018; 2019).

127. **NOAEL of 11 mg/L:** Four of the prenatal studies used 10 or 11 mg/L for the low-dose group.¹⁶¹ The two studies of mice failed to find a significant effect on learning at this level,¹⁶² and, as such, 11 mg/L could be selected as a NOAEL. The fact that the two studies that did not find effects at 11 mg/L found them at higher concentrations (23 and 45 mg/L) would be a factor weighing in favor of this choice, as the animal models were sensitive enough to find an effect. It bears considering, however, that the two studies finding no effects on learning at 11 mg/L did find alterations in the brain at this level,¹⁶³ which is consistent with 11 mg/L being a LOAEL, rather than a NOAEL. However, for purposes of reflecting the spectrum of RfDs that can be derived from the animal literature, 11 mg/L was treated as a NOAEL for one of the PODs.

128. **NOAEL of 20 mg/L:** The highest possible NOAEL that can be selected from these prenatal studies is the 20 mg/L no-effect finding from McPherson et al.¹⁶⁴ As discussed earlier, there are limitations with the McPherson study that may have made it less sensitive to detecting an effect, including strain of rat used and lack of first trimester exposure. Further, the study did find an adverse neurotoxic effect in the 20 mg/L group (i.e., increased pain sensitivity), and, as such, 20 mg/L is not a true NOAEL in the study. Nevertheless, for the purpose of illustrating the upper-bound range of RfDs that can be derived from the animal literature, a 20 mg/L NOAEL will be treated as a POD for the analysis.

C. Conversion of POD Concentrations (mg/L) to Doses (mg/kg/day)

129. Reference Doses (RfDs) are expressed in terms of dose (i.e., milligrams per kilogram of bodyweight, or mg/kg/day), not in terms of water concentration. To calculate RfDs from the Points of Departure, therefore, the unit of measurement (i.e., water fluoride concentration)

¹⁶¹ Wang et al. (2018a); Sun et al. (2018); McPherson et al. (2018); Jiang et al. (2014b).

¹⁶² Sun et al. (2018); Wang et al. (2018a).

¹⁶³ Sun et al. (2018); Wang et al. (2018a).

¹⁶⁴ McPherson et al. (2018).

needs to be converted into a dosage metric.

130. The NTP's 2016 review provides data that facilitate this analysis.¹⁶⁵ In its review, the NTP estimated the doses for dozens of rodent studies by using EPA's default water consumption rates and body weight data for the species, strain, and sex of the animals studied.¹⁶⁶ A review of NTP's data shows that the average ratio of fluoride concentration (mg/L) to intake rate or dose (mg/kg/day) is 6.8, and that this ratio is generally higher for rats (typically 6 to 10) than for mice (typically 3.8 to 5). For purposes of this analysis, the low end of this range was chosen for each species (6 for rats, 3.8 for mice). The practical effect of selecting the low-end of this range, is that the estimated doses will likely *overestimate* the actual dose, and thereby *inflate* the RfDs derived from these Points of Departure.¹⁶⁷ The net result of this non-conservative approach will be RfDs that are *less* protective of human health.

D. Selecting the Uncertainty Factors

131. Consistent with EPA's standard risk assessment procedures,¹⁶⁸ the *Guidelines* provide that "uncertainty factors" (UFs) should be applied to the point of departure (POD) to ensure that the resulting RfD is protective of health.¹⁶⁹

132. Uncertainty factors are applied to account for expected variations in susceptibility among humans (*intraspecies* variability, or UF_H), expected differences in susceptibility between animals and humans (*interspecies* variability, or UF_A), and, where applicable, differences in the

¹⁶⁵ NTP (2016), Appendix 19.

¹⁶⁶ NTP (2016), p. 118.

¹⁶⁷ For example, using this method gives an intake rate of 0.83 mg/kg/day for rats for the 5 mg/L fluoride concentration (Table 5). However, Bartos et al. (2018; 2019) give an estimate of 0.6 mg/kg/day for their rats at this fluoride concentration. Using the same approach described below with Table 5 for a LOAEL of 5 mg/L, equivalent to an intake rate of 0.6 mg/kg/day, gives an RfD of 0.0005, compared with 0.0007 in Table 5.

¹⁶⁸ EPA (2018a), pp. xvii-xxiv.

¹⁶⁹ EPA (1998a), pp. 58-59.

length of exposure between the study and human conditions (subchronic to chronic, or UF_S), research gaps in the overall database (database deficiency, UF_D), and converting from a LOAEL to a NOAEL.¹⁷⁰ These uncertainty factors are “typically multiples of 10,” although they can be reduced to factors of 3 or 1 if warranted by available information.^{171,172}

1. Intraspecies Variability (UF_H)

133. EPA recognizes that susceptibility to toxic substances is not uniform across the human population, and that due to differences in *toxicokinetics* and/or *toxicodynamics* some subsets of the population will be more vulnerable to harm than others.¹⁷³

134. *Toxicokinetics* refers to the “processes which determine the extent and duration of exposure of the target organ or site of toxicity to the active chemical species,” while *toxicodynamics* refers to the “processes involved in the translation of such exposure of the target organ or site of action into the generation of a toxic effect.”¹⁷⁴ Put more simply, toxicokinetics governs how much of the chemical gets to the target site (i.e., access), while toxicodynamics governs how much of the chemical is necessary at the target site to cause the adverse effect (i.e., sensitivity).

135. If there are no chemical-specific data on toxicokinetics and toxicodynamics, EPA uses a default UF_H of 10.¹⁷⁵ This default factor of 10 is “considered to be appropriate in the absence of convincing data to the contrary.”¹⁷⁶ Consistent with this, EPA has used a UF_H of 10 in each of

¹⁷⁰ EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), pp. xix-xx.

¹⁷¹ EPA (1998a), p. 59; EPA (2018a), p. xxii; EPA (2016), p. xix.

¹⁷² As discussed by Martin et al. (2013), default uncertainty factors, while sometimes viewed as overly protective, do not represent worst-case situations and cannot be safely assumed to be adequately protective of the most exposed individuals or the most susceptible individuals, nor can they be safely assumed to be protective for effects of mixtures of chemicals.

¹⁷³ EPA (2011b), p. 14; EPA (2016), p. 2-15; EPA (2018a), p. 2-12.

¹⁷⁴ Renwick (1993), p. 276.

¹⁷⁵ EPA (2018a), pp. 2-12, 2-13.

¹⁷⁶ EPA (2013a), p. 5-17.

the nine risk assessments where it has established an RfD or RfC pursuant to the *Guidelines* (Table 3).

136. In the case of fluoride, there is evidence that affirmatively demonstrates substantial variability in how humans respond to fluoride, including differences in retention (toxicokinetics) and differences in response (toxicodynamics). These data are discussed below in the Risk Characterization. While the magnitude of this variability is difficult to quantify, the data *support* the need for an uncertainty factor as opposed to providing “convincing data” *against* one. Accordingly, pursuant to standard EPA procedure, a value of 10 for UF_H was assigned.

Table 3. Summary of RfDs or RfCs developed in compliance with EPA's Guidelines for Neurotoxicity Risk Assessment.

Chemical	LOAEL	NOAEL	Uncertainty Factors					RfD or RfC ^a	Reference
			UF _H	UF _A	UF _S	UF _D	Composite		
BDE-47	10.5 mg/kg	0.7 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008a)
BDE-99	0.8 mg/kg	0.4 mg/kg	10	10	3	10	3000	0.1 µg/kg/day	EPA (2008b)
BDE-153	0.9 mg/kg	0.45 mg/kg	10	10	3	10	3000	0.2 µg/kg/day	EPA (2008c)
BDE-209	20.1 mg/kg	2.22 mg/kg	10	10	3	1	300	7 µg/kg/day	EPA (2008d)
Chlorine Dioxide and Chlorite	6 mg/kg/day	3 mg/kg/day	10	10	1	1	100	0.03 mg/kg/day	EPA (2000b)
2-Hexanone	143 mg/kg/day	Not observed	10	10	1	10	1000	0.005 mg/kg/day	EPA (2009b)
Methanol	1000 ppm (1310 mg/m ³)	500 ppm (655 mg/m ³)	10	3	1	3	100	20 mg/m ³	EPA (2013a)
RDX	8 mg/kg/day	4 mg/kg/day	10	3	1	10	300	0.004 mg/kg/day	EPA (2018a; 2018h)
Trimethylbenzenes	492 mg/m ³	123 mg/m ³	10	3	3	3	300	0.01 mg/kg/day	EPA (2016)

^a Where EPA established both an RfD (mg/kg/day) and an RfC (mg/m³) for a chemical, the RfD is presented.

Table 4. Comparison of BW^{1/1} and BW^{3/4} in estimating oral exposure in humans from a 10 mg/kg exposure to rats, mice, and a dog.^a

Absolute animal intake or administered dose	Species	BW(h)/BW(a)	Scaling = BW ^{1/1}		Scaling = BW ^{3/4}	
			BW scaling factor	BW scaled human intake or oral dose (mg/kg)	BW scaling factor	BW scaled human intake or oral dose (mg/kg)
0.25 mg / 0.025 kg	Mouse	70 / 0.025 = 2800	2800 ^{1/1} = 2800	(2800 × 0.25 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	2800 ^{3/4} = 385	(385 × 0.25 mg = 96 mg) 96 mg / 70 kg = 1.4 mg/kg
2.5 mg / 0.25 kg	Rat	70 / 0.25 = 280	280 ^{1/1} = 280	(280 × 2.5 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	280 ^{3/4} = 68	(68 × 2.5 mg = 170 mg) 170 mg / 70 kg = 2.4 mg/kg
120 mg / 12 kg	Dog	70 / 12 = 5.8	5.8 ^{1/1} = 5.8	(5.8 × 120 mg = 700 mg) 700 mg / 70 kg = 10 mg/kg	5.8 ^{3/4} = 3.7	(3.7 × 120 mg = 444 mg) 444 mg / 70 kg = 6.4 mg/kg

^a Taken from Table A-1 in EPA (2011b), p. 29.

2. Interspecies Variability (UFA)

137. EPA recognizes that susceptibility to toxic substances can differ across species. As with human-to-human variability, animal-to-human variability is also rooted in principles of toxicokinetics and toxicodynamics.

138. To adjust for differences in toxicokinetics between animals and humans, EPA has developed a hierarchical framework of approaches for ascertaining the “human equivalent dose” (HED) of doses given to animals.¹⁷⁷ EPA’s “optimal” approach for determining the HED is to use a physiologically based toxicokinetic model (PBTk).¹⁷⁸ Where a PBTk model is not available, the “intermediate” approach is to use chemical-specific information that, while falling short of a full PBTk model, provides some reliable guidance.¹⁷⁹ Where there is no reliable chemical-specific information on kinetics, EPA uses a default allometric scaling method.¹⁸⁰

139. Allometric scaling is “scaling of physiological rates or quantities to relative growth and size (mass or volume) of one animal species relative to another species.”¹⁸¹ Under EPA’s recommended method for allometric scaling (BW^{3/4} Method), the HED equates to 24% of the dose given to rats, and 14% of the dose given to mice (see Table 4 above).¹⁸²

140. The BW^{3/4} Method “predominantly addresses factors involved in estimating toxicokinetics, as well as some toxicodynamic factors.”¹⁸³ EPA thus maintains a residual default UF of 3 to allow for residual uncertainty from toxicodynamics, unless there is chemical-specific information available.¹⁸⁴

¹⁷⁷ EPA (2011b), pp. 18-21; EPA (2018a), p. 2-10.

¹⁷⁸ EPA (2011b), p. 19.

¹⁷⁹ EPA (2011b), p. 19.

¹⁸⁰ EPA (2011b), p. 19.

¹⁸¹ EPA (2011b), p. 1.

¹⁸² EPA (2011b), p. 29, Table A-1; EPA (2018a), p. 2-12.

¹⁸³ EPA (2011b), p. 17.

¹⁸⁴ EPA (2011b), p. 21; EPA (2016), p. 2-15; EPA (2018a), pp. 2-12, 2-13.

141. The following factors were considered to account for interspecies differences in both the toxicokinetics and toxicodynamics of fluoride.

142. *Toxicokinetic Considerations:* A full PBTK model has not yet been developed for fluoride that would allow for the calculation of HEDs from doses given to animals. As such, EPA's preferred approach for controlling for interspecies toxicokinetics is not available. By contrast, there is chemical-specific information for fluoride that could support application of EPA's intermediate approach. As discussed by the NRC, rats require higher levels of fluoride in their water to achieve the same level of fluoride in their blood.¹⁸⁵ Dunipace estimated that rats require about 5 times more fluoride in water than humans to reach the same plasma concentration of fluoride,¹⁸⁶ while Den Besten's team has reported a larger margin for mice, with a difference of about a factor of 10.¹⁸⁷ The data from Dunipace and Den Besten support a toxicokinetics adjustment of 5 for rats and 10 for mice, which are slightly *higher* than, but roughly consistent with, the adjustments under the default BW^¾ Method (4 for rats, 7 for mice). The chemical-specific information for fluoride thus supports the general validity of the BW^¾ Method, but would be more protective. The BW^¾ Method, which is roughly consistent with the chemical-specific information, but slightly *less* protective, was selected as the method for the toxicokinetics adjustment.

¹⁸⁵ NRC (2006), pp. 98-99; pp. 442-446, Appendix D; NRC (2009), pp. 88-89.

¹⁸⁶ NRC (2006), pp. 98, 442.

¹⁸⁷ Zhang et al. (2014).

143. *Toxicodynamic Considerations*: It has long been recognized that rodents are less susceptible (i.e., more resistant) to certain toxic effects from fluoride ingestion than are humans.¹⁸⁸ Rats, for example, have been reported to require 10 to 25 times more fluoride than humans to develop dental fluorosis.¹⁸⁹ Differences in toxicokinetics contribute to rodents being less sensitive to fluorosis, but the differences appear larger than would be expected if they were due solely to kinetics. The fluorosis data support the existence of differential toxicodynamics between rodents and humans, but it is unclear if this difference would also apply to neurotoxicity, as this has not yet been the subject of study. Conversely, there are no data to suggest that humans are *more resistant* to fluoride neurotoxicity than animals. In the absence of data, EPA's default uncertainty factor of 3 was selected to account for interspecies differences in toxicodynamic differences.

3. LOAEL to NOAEL

144. When EPA uses a LOAEL from animal data as the Point of Departure, it applies an additional uncertainty factor of 10 to convert the LOAEL into an estimated NOAEL.¹⁹⁰ Consistent with EPA practice, the three LOAEL-based PODs were adjusted by a factor of 10.

4. Composite Uncertainty Factor

145. The "composite" uncertainty factor is the product of all uncertainty factors used in an analysis. The composite uncertainty factor applied here to the NOAEL-based PODs is **30**, which is the same value that EPA has been using in its draft risk evaluations under TSCA.¹⁹¹ The

¹⁸⁸ Roholm (1937), pp. 265, 318; Lehman and Fitzhugh (1954), p. 33; Angmar-Mansson and Whitford (1982), p. 339.

¹⁸⁹ Roholm (1937), pp. 265, 318; Angmar-Mansson and Whitford (1982), p. 339.

¹⁹⁰ EPA (1998a), p. 59.

¹⁹¹ In my expert report, I also calculated alternate RfDs where I applied additional uncertainty factors that EPA uses to account for subchronic animal exposures and deficiencies in the fluoride database (e.g. no data on formula-feeding during the neonatal period). For purposes of simplicity, I have not included those calculations in this declaration.

composite uncertainty factor applied here to the LOAEL-based PODs is **300**, which is on the low-end of the range of the composite uncertainty factors that EPA has used in its neurotoxicity risk assessments (see Table 3 above).

E. RfD Calculations from Animal Data

146. Table 5 summarizes the RfD calculations for each of the five Points of Departure (POD) listed above. The RfDs range from 0.0007 to 0.006 mg/kg/day for the LOAEL-based PODs, and 0.01 to 0.03 mg/kg/day for the NOAEL-based PODs. The least protective RfD that can be derived from the literature in a manner consistent with EPA practice is thus **0.03 mg/kg/day**.

Table 5. Calculation of the RfD from the selected Points of Departure (POD), based on the studies summarized in Table 2.

A Observation	B Intake rate	C POD _{HED}	D NOAEL	E UF _H = 10	F UF _A = 3	G RfD
LOAEL or NOAEL from Table 6 mg/L	Column A / 6 (rats) or 3.8 (mice) mg/kg/day	Column B × 0.24 (rats) or 0.14 (mice) mg/kg/day	Column C / 10 (LOAEL) or 1 (NOAEL) mg/kg/day	Column D / 10 mg/kg/day	Column E / 3 mg/kg/day	Column F mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	0.020	0.0020	0.00067	0.0007
23 mg/L, LOAEL (rats)	3.8	0.91	0.091	0.0091	0.0030	0.003
45 mg/L, LOAEL (rats)	7.5	1.8	0.18	0.018	0.0060	0.006
11 mg/L, NOAEL (mice)	2.9	0.41	0.41	0.041	0.014	0.01
20 mg/L, NOAEL (rats)	3.3	0.79	0.79	0.079	0.026	0.03

Column A: The observed LOAEL or NOAEL from Table 2.

Column B: The observed LOAEL or NOAEL converted from mg/L to an intake rate (dose) in mg/kg/day. For rats, the LOAEL or NOAEL is divided by 6; for mice, the NOAEL is divided by 3.8 (see explanation in text).

Column C: The intake rate for rats or mice converted to a human equivalent dose (HED) using the BW^{3/4} method (see explanation in text). The HED = 24% of the intake rate for rats or 14% of the intake rate for mice.

Column D: NOAEL as already obtained (NOAEL / 1) or as estimated from a LOAEL (LOAEL / 10).

Column E: The estimated NOAEL after application of an intraspecies uncertainty factor (UF_H), where UF_H = 10. The NOAEL from Column D is divided by UF_H (i.e., NOAEL / 10).

Column F: The estimated NOAEL after application of an additional uncertainty factor for interspecies variability (UF_A), where UF_A = 10. The adjusted NOAEL from Column E is divided by UF_A (i.e., NOAEL / 3).

Column G: The value of the Reference Dose (RfD) obtained with only UF_H and UF_A. RfD = the NOAEL value in Column F, rounded to 1 significant digit.

VII. EXPOSURE ASSESSMENT

147. The only condition of use at issue in this case, as I understand it, is the addition of fluoridation chemicals to drinking water. Because of this, I limited the scope of my exposure assessment to exposures directly attributable to fluoridated water (0.7 mg/L). The purpose of my assessment was to enable a comparison of the doses people ingest from fluoridated water with the toxicity values (LOAELS and NOAELs) derived from the animal studies. I did not consider fluoride intake from dental products, pesticides, industrial pollution, occupational exposures, black tea, or other sources.

148. In my assessment, I considered fluoride exposures among both the general public as well as subsets of the population known to consume elevated amounts of water. For the source data, I relied primarily on the NRC's 2006 report which presented estimates of fluoride intake from water containing 0.7 mg/L fluoride. The NRC's estimates were based on an EPA analysis of community water intake data that were collected in a national survey by the US Department of Agriculture (USDA) in the 1990s.¹⁹² The USDA survey was "designed to obtain a statistically representative sample of the United States population," and EPA stated that data from this survey "may be used in risk assessment analyses where exposures that occur through ingestion of water are of concern."¹⁹³

149. Based on NRC's data, human exposure to fluoride from fluoridated water is estimated to range from an average of 0.011 mg/kg/day for adults to a "high" of 0.14 mg/kg/day for 95th percentile-exposed infants.

150. Following my initial report, a criticism was raised that I should have conducted a

¹⁹² The USDA survey is called the "Continuing Survey of Food Intakes by Individuals," or CSFII for short.

¹⁹³ EPA (2000a), p. 5-5.

systematic review of all water intake data published subsequent to the NRC's report. In response to this criticism, I reviewed an updated and comprehensive review of water intake data that EPA published in 2019. The review was published as an update to EPA's *Exposure Factors Handbook* ("*Handbook*"), which is a document "intended for use by exposure and risk assessors both within and outside the U.S. EPA as a reference tool and primary source of exposure factor information."¹⁹⁴

151. In its 2019 report, EPA presented the results of its "comprehensive review of the scientific literature [on water intake] through 2017" and provided EPA's determination as to "the most up-to-date and scientifically sound" data¹⁹⁵ to use for tap water consumption in the US.¹⁹⁶ The report thus provides the community water intake values¹⁹⁷ that EPA now recommends using for risk assessment for each age group in the population.¹⁹⁸

152. The water intake data that EPA identifies in its 2019 report are consistent with EPA's older water intake data that I relied upon in my initial assessment. For example, whereas I selected 0.011 mg/kg/day as an average adult exposure, the EPA's updated data produce mean intakes by adults of 0.011-0.013 mg/kg/day (i.e., the same as or slightly higher than my estimate).¹⁹⁹ Further, whereas I selected 0.14 mg/kg/day as the 95th percentile exposure among

¹⁹⁴ EPA (2011a), p. 1-3.

¹⁹⁵ EPA (2019b), p. 1-5.

¹⁹⁶ EPA selected its own analysis of water intake data from NHANES's 2005-2010 surveys as the "key study" to use for all age groups in the general population and for pregnant and lactating women. For formula-fed babies, EPA selected an analysis by Kahn of the USDA's CSFII survey, which is the same survey that the NRC relied upon for its estimates in 2006.

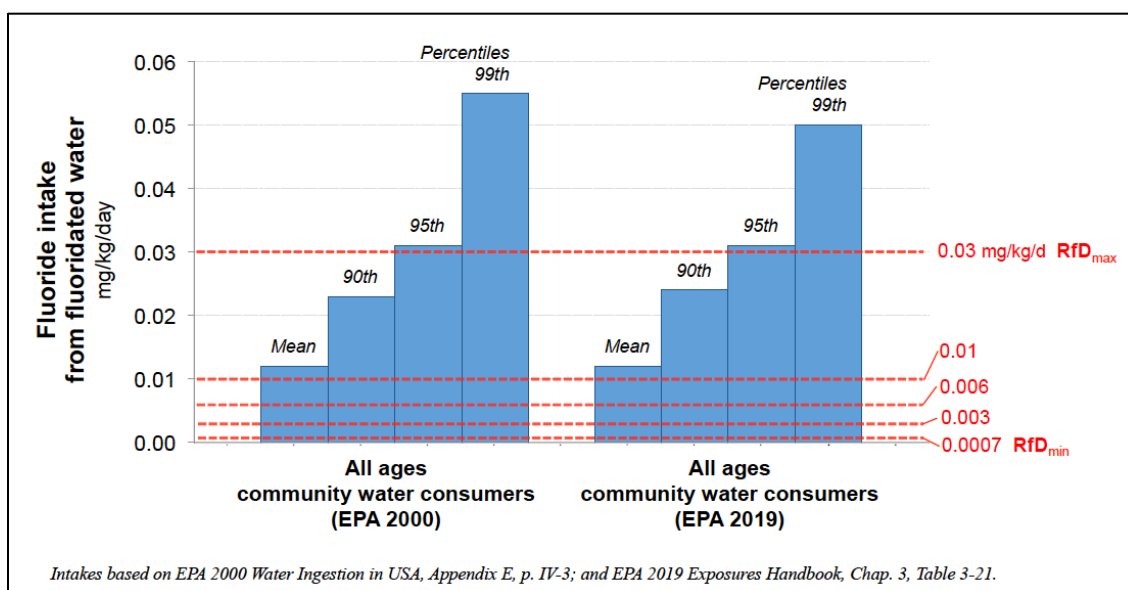
¹⁹⁷ EPA's report presents water intake in terms of milliliters of water consumed per kilogram of bodyweight per day (mL/kg/day). This permits a direct estimation of fluoride exposure from fluoridated water because the concentration of fluoride is known (0.7 micrograms per milliliter). By way of example, if a person drinks 100 milliliters of fluoridated water per kilogram of bodyweight, they will receive a dose of 70 micrograms of fluoride per kilogram, which is more commonly expressed as 0.07 milligrams per kilogram (i.e., 0.07 mg/kg/day).

¹⁹⁸ EPA (2019b), pp. 3-1, 3-4, 3-7, & 3-9.

¹⁹⁹ EPA (2019b), pp. 3-4.

bottle-fed infants, EPA's updated data produce 95th percentile values ranging from 0.13 mg/kg/day to 0.2 mg/kg/day (i.e., higher than my estimate).²⁰⁰

153. The similarity between the two EPA datasets can be seen in the following figure. The figure shows the fluoride exposure from water for *all* community water consumers for *all* age groups combined. The left side of the figure shows EPA's 2000 data (that NRC and I relied upon), while the right side of the figure shows EPA's 2019 data. To help put these exposures in context, the figure also shows the five reference doses from the animal neurotoxicity data (Table 5).



154. As can be seen in the figure, the two datasets show that a *substantial* percentage of the population that consume fluoridated tap water exceed each of the 5 RfDs for neurotoxicity, including the least protective RfD.

155. One limitation with EPA's water intake data (from both 2000 and 2019) is that they do not include consumption of community water that is added to commercial beverages, such as soda and juice.²⁰¹ This underestimates actual exposure to fluoridated water, since commercial

²⁰⁰ EPA (2019b), pp. 3-9.

²⁰¹ EPA (2000a), p. viii.

beverages have become a significant source of exposure to fluoridated water for many people.²⁰²

156. Another limitation with EPA's water intake data is that they are based on short-term surveys (i.e., surveys taken on two non-consecutive days), which creates a source of uncertainty when extrapolating to long-term exposures. This uncertainty is minimized, however, by the large numbers of people surveyed in the studies, and the use of non-consecutive days for the survey. While not perfect, EPA has recognized these data as the most scientifically sound data to use for risk assessment.

VIII. RISK CHARACTERIZATION

157. The risk characterization step of a risk assessment integrates the evidence of hazard, exposure, and dose-response in a clear and transparent manner, and provides a description of the risk. The *Guidelines* recognize multiple ways of describing risk, including (i) characterization of highly-exposed and/or susceptible individuals; (ii) estimation of the number of individuals exposed; (iii) comparing human exposures against the RfD; and (iv) "Margin of Exposure" analysis.²⁰³

A. Characterization of Highly Exposed and/or Highly Susceptible Populations

158. Susceptibility to a chemical may be "intrinsic" (biological, e.g., life stage) or "extrinsic" (acquired, e.g., lifestyle),²⁰⁴ although many individuals may have *both* intrinsic *and* extrinsic susceptibility.

159. EPA has recognized that life stage is an important source of intrinsic susceptibility to neurotoxicants, and has identified the prenatal, infant, and elderly stages of life as "critical periods for exposure."²⁰⁵ According to the EPA, "It is a well-established principle that there are

²⁰² E.g., Heilman et al. (1999); Kiritsy et al. (1996); Turner et al. (1998).

²⁰³ EPA (1998a), pp. 63-66.

²⁰⁴ EPA (2017).

²⁰⁵ EPA (1998a), p. 65.

critical developmental periods for the disruption of functional competence, which include both the prenatal and postnatal periods to the time of sexual maturation, and the effect of a toxicant is likely to vary depending on the time and degree of exposure.”²⁰⁶ In light of this, a “population subgroup is susceptible if exposure occurs during a period of sensitivity.”²⁰⁷

160. As described below, there are large, identifiable subsets of the population that are likely more susceptible to the neurotoxic effects of fluoride than the general population, including pregnant women and their fetuses, bottle-fed infants, the elderly, and individuals with renal impairment.

1. Pregnant Women and Their Fetuses

161. Multiple converging lines of evidence support the fetal period as a critical period of susceptibility to fluoride’s neurotoxic effects. First, it is well established that fluoride crosses the placenta and reaches the fetus.²⁰⁸ Second, due to the absence of an effective blood brain barrier,²⁰⁹ the fluoride that reaches the fetus also reaches the brain—a fact that has been confirmed by both animal and human studies.²¹⁰ Third, fluoride has the capacity to lower thyroid function, particularly among individuals with low iodine intakes, and EPA has recognized that alterations to thyroid function (e.g., reductions in thyroid hormone concentrations) during pregnancy can cause cognitive disorders and other neurological harm to the child.²¹¹ Fourth, most studies of prenatal fluoride exposures in animals have documented neuroanatomical, neurochemical, and/or cognitive problems. Fifth, all prospective cohort studies that included individual measurements of

²⁰⁶ EPA (1998a), p. 46.

²⁰⁷ EPA (2008a), p. 42.

²⁰⁸ NRC (2006), p. 193.

²⁰⁹ EPA (2009b), p. 58.

²¹⁰ E.g., McPherson et al. (2018); Mullenix et al. (1995); Du et al. (1992).

²¹¹ EPA (1998a), p. 50; EPA (2008a), p. 40; EPA (2008b), p. 54; EPA (2013b), cover letter, p. 2. See also Rodier (1995); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Bellinger (2018).

prenatal fluoride exposure have found significant adverse associations with neurocognitive harm, including IQ loss and inattention.²¹²

162. The number of pregnant women exposed to fluoridated water each year is large. The CDC estimates that there are approximately 4 million children born in the U.S. each year, and therefore about 4 million pregnancies.²¹³ With approximately two-thirds of the U.S. population living in communities where fluoridation chemicals are added to water, about 2.5 million pregnancies can be expected to occur each year in fluoridated areas.

163. Of paramount concern are pregnant women who have an iodine deficiency. The CDC considers the average iodine status (median urinary iodine concentration) of women of childbearing age (12-19 years and 20-39 years) in the U.S. to be in the “adequate intake” range, but the 10th percentiles by ethnicity and for the total population are in the “insufficient intake” range, indicating that more than 10% of women of childbearing age in the U.S. are deficient in iodine.²¹⁴ Caldwell et al. report that 35% of pregnant women and 38% of nonpregnant women in the U.S. have urinary iodine concentrations below the level considered adequate.²¹⁵ In addition, the CDC notes that even higher intakes of iodine are required for pregnant and lactating women; thus an even greater percentage of American women are likely to be deficient in iodine with respect to the demands of pregnancy and lactation.²¹⁶ Pearce suggests that iodine deficiency in the U.S. may be becoming more prevalent, especially among pregnant women.²¹⁷

164. While the effects of fluoride exposure among pregnant women with iodine

²¹² Bashash et al. (2017; 2018); Green et al. (2019); Valdez-Jiménez et al. (2017).

²¹³ Centers for Disease Control. Births and Natality. Available at: <http://www.cdc.gov/nchs/fastats/births.htm>

²¹⁴ CDC (2008), Chapter 4a, pp. 90-100.

²¹⁵ Caldwell et al. (2011).

²¹⁶ CDC (2008), Chapter 4a, pp. 90-100.

²¹⁷ Pearce (2015).

deficiency have not yet been specifically studied, there is a clear basis for concern. The NRC reported that high fluoride intake appears to exacerbate the effects of low iodine intake on thyroid function in both animals and humans.²¹⁸ Consistent with this, Malin et al. found that an increase in urinary fluoride was associated with an increase in thyroid stimulating hormone (TSH)—an indicator of decreased thyroid function—among iodine-deficient adults in Canada.²¹⁹ A decrease in thyroid function during pregnancy, even in the absence of clinical symptoms in the mother, is associated with reduced IQ and other neurological effects in the offspring.²²⁰

2. Bottle-Fed Infants

165. A bottle-fed infant has a combination of *both* intrinsic *and* extrinsic susceptibility to fluoridated water.

166. *Intrinsic Susceptibility:* The blood brain barrier does not finish developing until 6 months of age,²²¹ and, as such, the fluoride ingested during early infancy will likely reach the brain more readily than during the later childhood and adult years. The brain is also undergoing “rapid development” during infancy, with the growth rate of the brain peaking at 4 months of age.²²² The EPA has thus described the neonatal stage of life as “a critical window of development.”²²³

167. *Extrinsic Susceptibility:* Infants have the highest intake of fluid per unit body weight of any age group among humans, given their mostly liquid diet at that age. This can be seen in the following figure, which uses EPA’s 2000 water intake data to compare the community water

²¹⁸ NRC (2006), pp. 227, 234, 262.

²¹⁹ Malin et al. (2018).

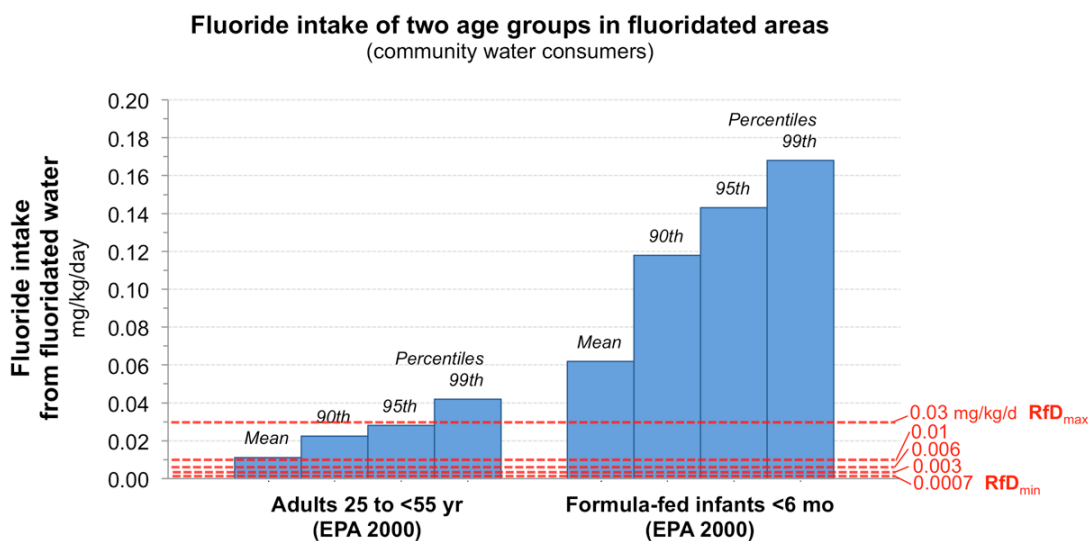
²²⁰ For example, see Haddow et al. (1999); Pop et al. (1999; 2003); Morreale de Escobar et al. (2000; 2004); Klein et al. (2001); Vermiglio et al. (2004); LaFranci et al. (2005); Kooistra et al. (2006); Roman (2007); Zoeller and Rovet (2004); Patel et al. (2011); Suárez-Rodríguez et al. (2012); Modesto et al. (2015); Moleti et al. (2016).

²²¹ EPA (2009b), p. 58.

²²² EPA (2013a), p. 5-4; EPA (2008a), p. 42.

²²³ EPA (2008a), p. 42.

intake of adults (on the left) with the community water intake of bottle-fed infants (on the right).



168. According to the CDC, 75% of infants born in 2015 were formula-fed at least partially during their first six months, including 17% of infants who were *exclusively* formula-fed.²²⁴ Data vary by ethnicity, with Hispanics, whites and Asians having breastfeeding rates similar to or greater than the national averages and African Americans having substantially lower rates. Breastfeeding rates tend to be highest for higher family income and maternal education levels.

169. Breastfeeding rates in the U.S. have increased substantially in recent years from a low point in the early 1970s.²²⁵ While increased breastfeeding rates are to be encouraged for a number of reasons, it is important to remember that for many infants in the U.S., breastfeeding is not an option; these include cases of infant adoption or fostering, as well as cases of death or illness of the mother.

²²⁴ CDC (2018; n.d.).

²²⁵ DHEW (1979), pp. 2-6, especially Tables A and B.

170. Most commercial infant formula, historically and currently, has been in powder form, for which the cost is approximately half that of ready-to-feed formula, per unit volume of formula as fed.²²⁶ Based on national data collected during 2005-2007, the CDC reported that approximately 83-93% of babies are fed formula prepared from powder from cans.²²⁷ For approximately 70-78% of infants in the same national survey, formula is reconstituted with tap water at least some of the time.²²⁸

171. Based on the available information, it can reasonably be assumed that the majority of formula-fed infants in the U.S. are fed powdered formula reconstituted with water, often or usually tap water. Especially for low-income homes (where breastfeeding is less likely), it is reasonable to assume that many or most infants are fed formula prepared from powder using tap water, which in much of the country is fluoridated. In addition, for approximately 20% of infants, tap water is boiled before it is used to prepare formula;²²⁹ if this tap water is fluoridated, the resulting fluoride concentration in the formula will be higher than if the water had not been boiled.²³⁰

172. Fomon et al. estimated that infants consuming powdered formula prepared with fluoridated water (1 mg/L) will ingest between 0.116 and 0.164 mg/kg/day.²³¹ If Fomon's estimate is adjusted to account for the lower concentration of fluoride now added to water (0.7 mg/L), the result is a daily intake of 0.08 to 0.115 mg/kg/day, which is 80 to 115 times higher than the amount that Fomon et al. estimated for breast-fed infants (0.001 mg/kg/day).²³² By Fomon's estimates,

²²⁶ O'Connor (2009).

²²⁷ CDC (2017), Table 3.16.

²²⁸ CDC (2017), Table 3.97.

²²⁹ CDC (2017), Table 3.98.

²³⁰ For example, see Juárez-López et al. (2011).

²³¹ Fomon et al. (2000), Table 2.

²³² Fomon et al. (2000), Table 2.

essentially all formula-fed infants will exceed the RfDs for neurotoxicity if their formula is prepared with fluoridated tap water.

173. Fomon's estimates agree well with recent data from Harriehausen et al., who surveyed 114 parents in Houston to determine brand and type of formula, total volume of formula consumed over 24 hours, and infant weight.²³³ Most of the parents in the study (corresponding to 92.1% of the infants) reported using powdered formula, which is consistent with the literature described above.²³⁴ Harriehausen et al. estimated that over 50% of infants fed formula made with fluoridated water will exceed 0.1 mg/kg/day during the first 4 months of life (Table 6).

Table 6. Estimated fluoride ingestion from infant formula, assuming fluoridated water at 0.7 mg/L.^a

Category	Age				
	2 months	4 months	6 months	9 months	12 months
Number of infants	32	23	27	21	11
Predicted fluoride intake					
Mean (mg/kg/day)	0.110	0.112	0.090	0.066	0.053
Variance	0.0033	0.0016	0.0018	0.0012	0.0009
Standard deviation ^b	0.057	0.040	0.042	0.035	0.03
Distribution of fluoride intake					
> 0.1 mg/kg/day (%)	59.4	56.5	33.3	14.3	9.1
< 0.1 mg/kg/day (%)	40.6	43.5	66.7	85.7	90.9

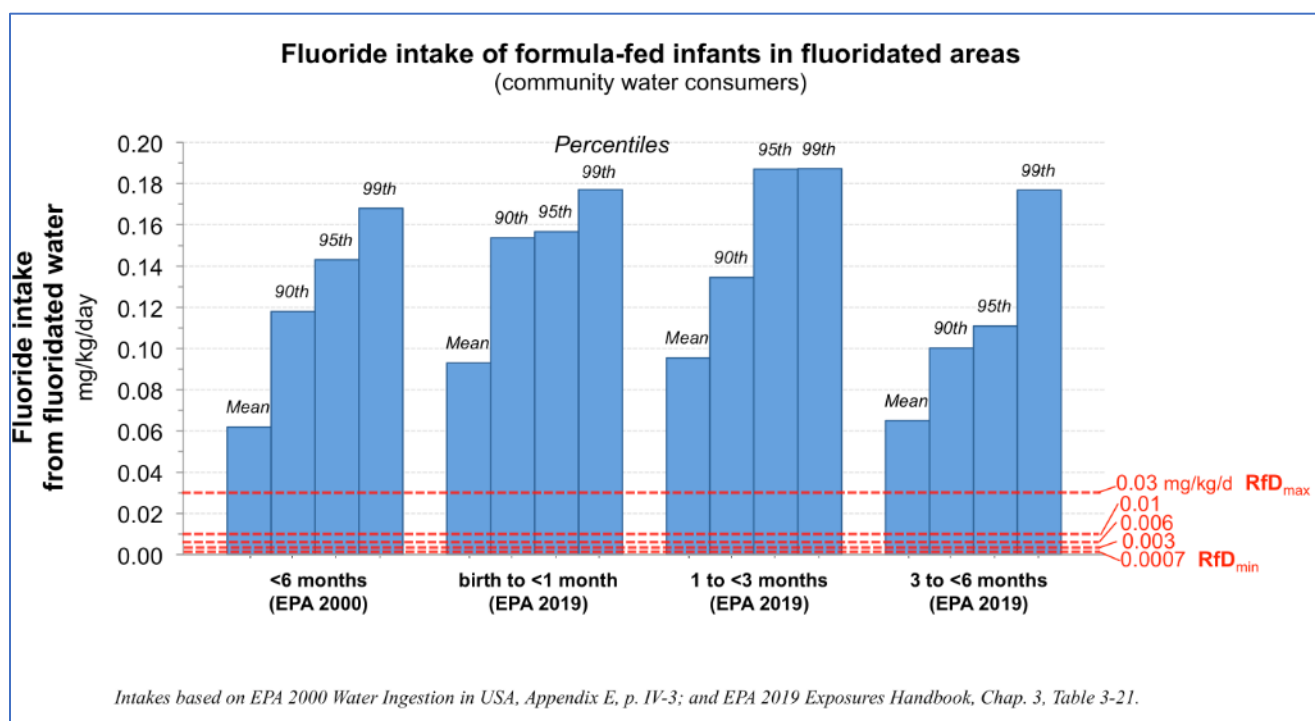
^a Data from Harriehausen et al. (2019), Table 3.

^b Calculated from the variance reported by Harriehausen et al. (2019), Table 3.

²³³ Harriehausen et al. (2019).

²³⁴ Harriehausen et al. (2019), Table 2.

174. The estimates from both Harriehausen and Fomon are consistent with EPA's most up-to-date and scientifically sound estimates for formula-fed infants.²³⁵ According to EPA's updated estimates, mean fluoride exposures during the first 6 months of life for infants receiving formula reconstituted with fluoridated water are **0.07 to 0.10 mg/kg/day** (age-dependent), with 95th percentile exposures of **0.13 to 0.2 mg/kg/day** for the first 3 months and **0.13 mg/kg/day** for the next three months.²³⁶ These intakes are very high, and far exceed even the least protective RfD, as shown in the following figure.



175. In its *Guidelines*, EPA considers the potential for postnatal toxicant exposures to interact with breastmilk composition.²³⁷ EPA was referring to animal studies, but the principle would apply to humans as well: Replacement of the mother's milk with a substitute that contains a toxic agent would be an extremely important source of postnatal exposure for infants and children

²³⁵ EPA (2019b), p. 3-9.

²³⁶ EPA (2019b), p. 3-9.

²³⁷ EPA (1998a), p. 46.

to that toxic agent. Few, if any, animal studies reproduce the effect of formula-feeding of human infants, in terms of a water-based formula containing fluoride being substituted for the mother's milk; thus this very important developmental period is routinely missed in most developmental studies on fluoride.

176. Consistent with the high fluoride intakes produced by formula feeding, studies have found that bottle-fed babies have higher rates of dental fluorosis (a disorder of enamel caused by excess fluoride intake) in their permanent teeth.²³⁸ Studies have also documented an increased prevalence and severity of dental fluorosis in the African American community, which is consistent with the high rate of formula feeding in this population.²³⁹

177. While fluoride exposure during infancy is known to produce abnormal physiological changes in the body (e.g., dental fluorosis), there has been a paucity of research on the neurodevelopmental effects of this exposure. In the developmental studies on fluoride neurotoxicity to date, the pups have been *breastfed*. Consequently, the existing animal data do not reflect the neurotoxic effects that may occur during the neonatal period.

178. Studies in humans have found lower IQ scores among formula-fed babies versus breastfed babies,²⁴⁰ but up until this year,²⁴¹ no study had investigated the role that fluoridated water may have in this association. Specific differences in brain activation and regional volumes of gray matter have been reported among formula-fed children, indicating developmental changes in children in comparison with breastfed children.²⁴² Such effects (and other adverse effects of

²³⁸ Hong et al. (2006a; 2006b); Forsman (1977); Walton and Messer (1981); Fomon and Ekstrand (1999); Fomon et al. (2000).

²³⁹ EPA (2010), pp. 33-34; Exhibit 34 to Casey Hannan Deposition; CDC (2005), Table 23.

²⁴⁰ For example, see Fomon (2001); Wolf 2003; Belfort et al. (2013); Horta et al. (2015; 2018); Victora et al. (2015; 2016); Kanazawa (2015); Boutwell et al. (2018). Many studies have controlled for possible confounders such as maternal IQ, maternal education, and family income.

²⁴¹ Till et al. (2020).

²⁴² Ou et al. (2016).

formula-feeding compared with breastfeeding, especially compared with exclusive breastfeeding for at least the first several months) could, in principle, be due to loss of the enhanced mother-child bonding associated with breast-feeding,²⁴³ to deficiency of an essential nutrient (e.g., long-chain saturated fatty acids) in the formula,²⁴⁴ to the presence of a toxic contaminant in the water used to prepare the infant formula,²⁴⁵ or to some combination of these factors.

179. Given the *a priori* basis for concern that fluoridated water may adversely affect the neurological system of bottle-fed infants, the recent findings from Till et al. must be taken very seriously.²⁴⁶ Using a prospective cohort study design, Till et al. found that fluoridated water consumption during infancy is associated with a large and significant reduction in non-verbal IQ at age 4 (i.e., a loss of 9.3 non-verbal IQ points for each 0.5 mg/L increase in exposure). Although the study did not find a statistically significant association with Full-Scale IQ after excluding several outliers, this could be a result of imprecision in the exposure estimates, or might reflect differential impacts of pre- and post-natal exposure.

180. As noted earlier, CDC data indicate that 17% of babies are *exclusively* fed formula for their first six months of life (i.e., never breast-fed).²⁴⁷ Assuming 2.5 million live births per year in fluoridated areas, approximately 1.9 million infants living in fluoridated areas will be formula-fed for at least part of the time during their first six months, including 425,000 infants who are *exclusively* formula-fed.²⁴⁸ Approximately 70-78% of these infants will have their formula made

²⁴³ Horta et al. (2018).

²⁴⁴ Horta et al. (2018).

²⁴⁵ Goyer (1995).

²⁴⁶ Till et al. (2020).

²⁴⁷ CDC (2018; n.d.).

²⁴⁸ CDC (2018; n.d.).

with fluoridated tap water (some of which will be boiled and have higher concentrations), at least part of the time.²⁴⁹

3. Elderly

181. The elderly have also been identified by the EPA as an at-risk group for neurotoxicity.²⁵⁰ According to the EPA, the elderly are “at particular risk because of the limited ability of the nervous system to regenerate or compensate to neurotoxic insult.”²⁵¹

182. The NRC has described the possible relationship of fluoride exposure, especially exposure to aluminum fluoride complexes, to the development of Alzheimer’s disease.²⁵² The NRC based its concern, in part, on studies reporting pathological lesions in the brain of fluoride-treated rodents that parallel the changes in humans with dementia.²⁵³ A recent study by Cao et al. found that exposure to fluoride for 3 months among mice genetically prone to degenerative brain changes, produced more severe, and earlier development of, neuropathological lesions than in controls, including lesions associated with Alzheimer’s.²⁵⁴ Goschorska et al. have recently postulated that fluoride plays a likely role in the initiation and progression of Alzheimer’s disease, based largely on the neuroanatomical and neurochemical changes seen in the brains of fluoride-treated animals.²⁵⁵

183. While epidemiological data on fluoride and cognition in the elderly remain relatively sparse, Li et al. reported a very high rate of cognitive impairment (81.1%) in an endemic fluorosis area.²⁵⁶ Li did not find a linear relationship between urinary fluoride and the severity of

²⁴⁹ CDC (2017), Table 3.97; Juárez-López et al. (2011).

²⁵⁰ EPA (1998a), p. 65; see also NRC (2006), p. 351.

²⁵¹ EPA (1998a), p. 65.

²⁵² NRC (2006), pp. 210-212.

²⁵³ NRC (2006), pp. 222.

²⁵⁴ Cao et al. (2019).

²⁵⁵ Goschorska et al. (2018).

²⁵⁶ Li et al. (2016), p. 59.

cognitive impairment within the endemic fluorosis area; however urinary fluoride levels among those with any form of cognitive impairment were significantly higher than those with normal cognition.²⁵⁷ Russ et al. described a longitudinal study involving nearly all people born in Scotland in 1921, who were passively followed for diagnoses of dementia after 2004.²⁵⁸ Residential locations after age 60 (or at death or at time of diagnosis of dementia) were used to estimate exposure to aluminum and fluoride (separately) in drinking water. The authors found that even relatively low levels of aluminum and fluoride were associated with an increased prevalence of dementia and suggested further research.²⁵⁹

184. While more research is needed to clarify fluoride's effects in the elderly population, there are a multitude of factors which support an increased vulnerability to fluoride's neurological effects among the elderly. Studies have found that water fluoridation significantly increases the level of fluoride in bone, and these levels increase with age.²⁶⁰ In the post-menopausal and elderly years, the fluoride that is taken into bone can be released back into the blood stream as bones begin to break down, leading to increased levels of fluoride in the blood.²⁶¹ Compounding this, renal function declines with age, and because of this the elderly kidney can be expected to be less efficient in clearing fluoride from the bloodstream. The net result is that more fluoride will be circulating in the bloodstream, and due to age-related increases in the permeability of the blood-brain barrier, will reach the brain more readily.²⁶²

185. Although the impact of fluoride on the elderly brain has not received as much

²⁵⁷ Li et al. (2016), Figure 2, Table 3.

²⁵⁸ Russ et al. (2019).

²⁵⁹ Russ et al. (2019).

²⁶⁰ Alhava et al. (1980); Arnala et al. (1985); Eble et al. (1992); Chachra et al. (2010).

²⁶¹ Itai et al. (2010).

²⁶² Increased permeability of the blood-brain barrier is associated with ordinary aging, as well as with diseases such as Alzheimer's and Parkinson's, both of which are common among elderly people. For example, see Mooradian (1994); Zeevi et al. (2010); Rosenberg (2014); and Pan and Nicolazzo (2018).

scholarly attention as the impact on the developing brain, this population is likely at higher risk of toxicity than healthy adults, particularly among those with elevated accumulation of fluoride in the bone following long-term residence in a fluoridated area.

Renal Impairment

186. It is well recognized that people with renal impairment (kidney disease) are less able to excrete fluoride, resulting in higher concentrations of fluoride in the body and greater susceptibility to adverse health effects from fluoride exposure.²⁶³ The World Health Organization states that it “is known that persons suffering from certain forms of renal impairment have a lower margin of safety for the effects of fluoride than the average person.”²⁶⁴ In addition, a number of papers report an association between renal impairment and reduced IQ or other cognitive impairment,²⁶⁵ which is consistent with higher fluoride retention (and often higher water intake and consequent higher fluoride intake). The role of fluoride in these IQ deficits has not yet been the subject of epidemiological study.

4. Other Predisposing Factors

187. There are a number of other factors that are known, or reasonably anticipated, to increase susceptibility to the chronic toxic effects of fluoride exposure, including neurotoxicity. These factors include:

188. *Diseases that Increase Water Intake*: The NRC identified population subgroups whose water intake “is likely to be substantially above the national average for the corresponding sex and age group” as susceptible subpopulations with respect to fluoride exposure.²⁶⁶ Health

²⁶³ For example, see Marumo and Iwanami (2001); NRC (2006), pp. 30, 292, 351; Ibarra-Santana (2007); Schiff (2008).

²⁶⁴ WHO (2004), p. 6.

²⁶⁵ For example, see Madero et al. (2008); Mendley et al. (2015); Chen et al. (2018b).

²⁶⁶ NRC (2006), p. 30.

conditions that affect water intake include “diabetes mellitus, especially if untreated or poorly controlled; disorders of water and sodium metabolism, such as diabetes insipidus; [and] renal problems resulting in reduced clearance of fluoride.”²⁶⁷ According to the NRC, adults with diabetes mellitus can ingest 0.05 mg/kg/day from fluoridated water alone, while children with diabetes mellitus can have fluoride intakes as high as 0.07 mg/kg/day.²⁶⁸ For children and adults with nephrogenic diabetes insipidus, NRC estimated waterborne fluoride intakes of 0.11 mg/kg/day.^{269,270} Each of these intakes exceeds the least protective RfD.

189. *Nutrient Deficiencies:* Nutritional deficiencies can contribute to increased susceptibility to fluoride toxicity.²⁷¹ Calcium deficiency and iodine deficiency are expected to be particularly important in terms of vulnerability to neurotoxic effects of fluoride, but deficiencies of magnesium, vitamin C, protein, and other nutrients have also been associated with increased susceptibility to the effects of fluoride exposure.

190. *Genetic Susceptibilities:* A number of studies have shown associations between specific genetic arrangements and a greater susceptibility to the chronic effects of fluoride exposure,²⁷² including dental fluorosis and alterations to reproductive hormones.²⁷³ While a complete picture of the relationship between genes, gene regulation, and adverse effects of fluoride exposure remains to be developed, it is already quite clear that some people or groups of people

²⁶⁷ NRC (2006), p. 30.

²⁶⁸ NRC (2006), p. 35, Table 2-4.

²⁶⁹ NRC (2006), p. 35, Table 2-4.

²⁷⁰ Consistent with this, case reports have documented moderate to severe dental fluorosis among children with diabetes insipidus who drank water with 0.5 to 1 mg/L NRC (2006), p. 33.

²⁷¹ See for example, NRC (2006), p. 265; Pandit et al. (1940); Marier (1977).

²⁷² Reviewed by Pramanik and Saha (2017). See also Lavryashina et al. (2003); Tu et al. (2011); Liu et al. (2006); Huang et al. (2008); Ba et al. (2011); Zhao et al. (2015); Zhou et al. (2016); Zhang et al. (2013b); Pei et al. (2017); Jiang et al. (2015); Zhang et al. (2015b); Cui et al. (2018); K  chler et al. (2018); Bhagavatula Naga (2009).

²⁷³ Zhao et al. (2015); Zhou et al. (2016); Ma et al. (2017); An et al. (2019).

are inherently more vulnerable than others to adverse effects of fluoride exposure and require a greater level of protection from fluoride exposures.²⁷⁴ The implications to neurotoxicity have not yet been extensively studied, but two recent studies from China, including one with extensive control for covariates, suggest that certain genotypes may significantly magnify fluoride's impact on IQ in some individuals.²⁷⁵ A third, smaller study reported a contrary result.²⁷⁶ More research is needed to clarify this issue, but in light of the broader literature on genetic susceptibility to chronic fluoride toxicity, it is reasonable to suspect that genetics plays a role in rendering some individuals more vulnerable to fluoride's neurological effects.

B. Margin of Exposure (MOE)

1. Introduction to the MOE Approach and Its Similarity to the RfD Approach

191. Under the *Guidelines*, neurotoxic risk can be described either through a comparison of the human exposures to the RfD, or by calculating the “Margin of Exposure” (MOE).²⁷⁷ Although the two approaches use slightly different frameworks, they produce the same results. If comparison of human exposure with the RfD shows a risk, a risk will be shown by MOE as well, and vice versa.

192. RfD and MOE analyses produce the same results because they use the same Point of Departure (i.e., NOAEL, LOAEL, or BMDL) for the toxicity value, the same data for human exposure, and the same composite uncertainty factor to assess whether human exposure poses a risk. Where the two methods differ is in how they put these three pieces together and the terminology they use, as will now be discussed.

193. In an RfD analysis, human exposure is compared against the Reference Dose. As

²⁷⁴ Wu et al. (2015); Yang et al. (2016); Pei et al. (2017); Li et al. (2017); Yang et al. (2018b).

²⁷⁵ Cui et al. (2018); Zhang et al. (2015b).

²⁷⁶ Pang et al. (2018).

²⁷⁷ EPA (1998a), pp. 65-66; Federal Register (1998), pp. 26949-26950.

discussed earlier, the Reference Dose is the Point of Departure (i.e., NOAEL, LOAEL, or BMDL) divided by the composite uncertainty factor. In an MOE analysis, by contrast, human exposure is *compared directly against the Point of Departure*. If the ratio (i.e., Actual MOE) between the Point of Departure and human exposure is less than the composite uncertainty factor (i.e., Acceptable MOE), an unacceptable risk is presumed to exist.^{278,279} In short, the composite uncertainty factor is the standard for judging whether human exposure is unacceptably close to the toxicity value under both frameworks.

2. MOE Analysis

194. As part of the risk assessment, I conducted an MOE analysis to characterize risk because this is EPA's preferred method to characterize non-cancer risk under TSCA, as evident by its risk evaluations under both Section 5 (new chemicals)²⁸⁰ and Section 6 (existing chemicals).²⁸¹

195. *Points of Departure*: The same five Points of Departure (converted into Human Equivalent Doses) that were used for the derivation of the Reference Doses, as discussed above (see Table 5), were used for the MOE analysis.

196. *Acceptable MOEs (Benchmark MOEs)*: The same composite uncertainty factors that were used for the RfD derivation were selected as the Acceptable MOEs: 30 for the NOAEL-based PODs, and 300 for the LOAEL-based PODs. In EPA's draft risk evaluations under Section 6 of TSCA, EPA has used composite uncertainty factors of 30 for NOAEL-based PODs, and has

²⁷⁸ EPA (2016), p. 61; EPA (2012), p. 13-8.

²⁷⁹ EPA sometimes refers to the risk as a "risk of concern." EPA (2007), p. 13; EPA (2000c), p. C-12.

²⁸⁰ See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

²⁸¹ In its draft risk evaluations under Section 6 thus far, EPA has used MOE to characterize non-cancer risk. (EPA 2019c; 2019d; 2020). In its Final Rule for Risk Evaluation under Section 6, however, EPA described the MOE method as "just one of several approaches to risk characterization" that may be used under TSCA (Federal Register 2017, p. 33735).

characterized this as a relatively small uncertainty factor that “indicates greater certainty in the data (because fewer of the default UFs relevant to a given POD . . . were applied).”²⁸² EPA has contrasted this with a composite uncertainty factor of 1,000, which “would indicate more uncertainty in risk estimation and extrapolation.”²⁸³

197. *Human Exposure:* At the time I conducted this analysis, EPA had not yet released any of its Section 6 draft risk evaluations. I relied, therefore, on EPA’s risk evaluations under Section 5 for guidance on the human exposure assessment. In the Section 5 risk evaluations, EPA considers the highest-exposed group in the population. When dealing with chemicals that may be present in drinking water, therefore, EPA’s MOE analyses separately consider the exposures of *infants*.²⁸⁴

198. Based on the guidance from the Section 5 risk evaluations, I relied on the NRC’s 2006 data to calculate a range of exposures representing the general adult population along with highly exposed population subgroups, including bottle-fed infants and individuals with high water intakes (for example, due to medical conditions or to physical exertion).²⁸⁵

199. In EPA’s draft risk evaluations under Section 6, EPA has used the 95th percentile exposure to represent highly exposed individuals.²⁸⁶ This is the same percentile exposure I used

²⁸² EPA (2019d), p. 301.

²⁸³ EPA (2019d), p. 301.

²⁸⁴ See for example EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

²⁸⁵ For the general adult population, I combined NRC’s estimates for adult consumers of municipal water, ages 20-24 and 25-54 years (0.011 mg/kg/day). As an example of elderly adults (ages 65+), I included the 90th percentile of adult consumers of municipal water (0.022 mg/kg/day). To account for individuals with high water intakes, I used the NRC’s waterborne fluoride intake estimates (at 0.7 mg/L) for adult athletes and physical laborers (0.05 mg/kg/day), children with diabetes mellitus (0.07 mg/kg/day), and individuals with nephrogenic diabetes insipidus (0.1 mg/kg/day). For bottle-fed infants, I estimated a typical (0.1 mg/kg/day) and high (0.14 mg/kg/day) exposure based on the data from Fomon et al. (2000), Harriehausen et al. (2019), and NRC (2006). None of these exposure estimates, even those labeled “high,” is an upper bound or maximum exposure.

²⁸⁶ E.g., EPA (2019d), pp. 266, 300; EPA (2020), p. 108.

for high exposures among bottle-fed infants, and a higher percentile exposure than I used for the elderly (90th percentile).

200. Table 7 and the two figures below show the results of the MOE analyses. The first figure shows the results using the three LOAEL-Based PODs, while the second figure shows the results using the NOAEL-based PODs. As can be seen, the Actual MOEs are below the Acceptable MOEs for each group using every POD (including the least protective), with the exception of *average* adults and 90th percentile elderly when using the NOAEL-based PODs. If EPA's recommended 95th percentile exposure data (0.031 mg/kg/day) is used as the exposure for adults, risks are present even when using the least protective PODs.

201. The margins between the neurotoxicity levels in animals and the exposure levels in humans are far smaller than what EPA considers "acceptable." In fact, the Actual MOEs are so small that unacceptable risks would still be indicated for infants for each POD if the doses from animal studies had no adjustment to convert to the Human Equivalent Doses (HEDs) (i.e., no allometric scaling). Under EPA's framework for characterizing risk, therefore, it is apparent that fluoridation chemicals in drinking water present an unacceptable risk of neurotoxicity.²⁸⁷

²⁸⁷ EPA (2016), p. 61.

Table 7. Calculated Margins of Exposure (MOEs)^a for selected subgroups of the human population for the NOAELs and LOAELs for fluoride in Table 5.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Estimated human exposures ^e					
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

^a A Margin of Exposure (MOE) is equal to the LOAEL or NOAEL (mg/kg/day) divided by an estimated human exposure (mg/kg/day). Usually, the benchmark MOE = 1000 for assessments based on a LOAEL and 100 for assessments based on an NOAEL. Since allometric scaling between animals and humans has been used to obtain the Human Equivalent Dose, the benchmark MOE is 300 for LOAELs and 30 for NOAELs. An MOE less than the benchmark MOE indicates an “unacceptable risk.”

^b These LOAEL and NOAEL values (mg/L) for fluoride are summarized in Table 2.

^c The intake rates (mg/kg/day) in this column correspond to the LOAELs and NOAELs in the first column (mg/L), converted to intake rates (mg/kg/day) as summarized in Table 5. For rats, the intake rate equals the LOAEL or NOAEL divided by 6. For mice, the intake rate equals the NOAEL divided by 3.8.

^d The Human Equivalent Dose (HED) is calculated from the intake rate for rats or mice as summarized in Table 5. The HED = the intake rate for rats × 0.24 or the intake rate for mice × 0.14.

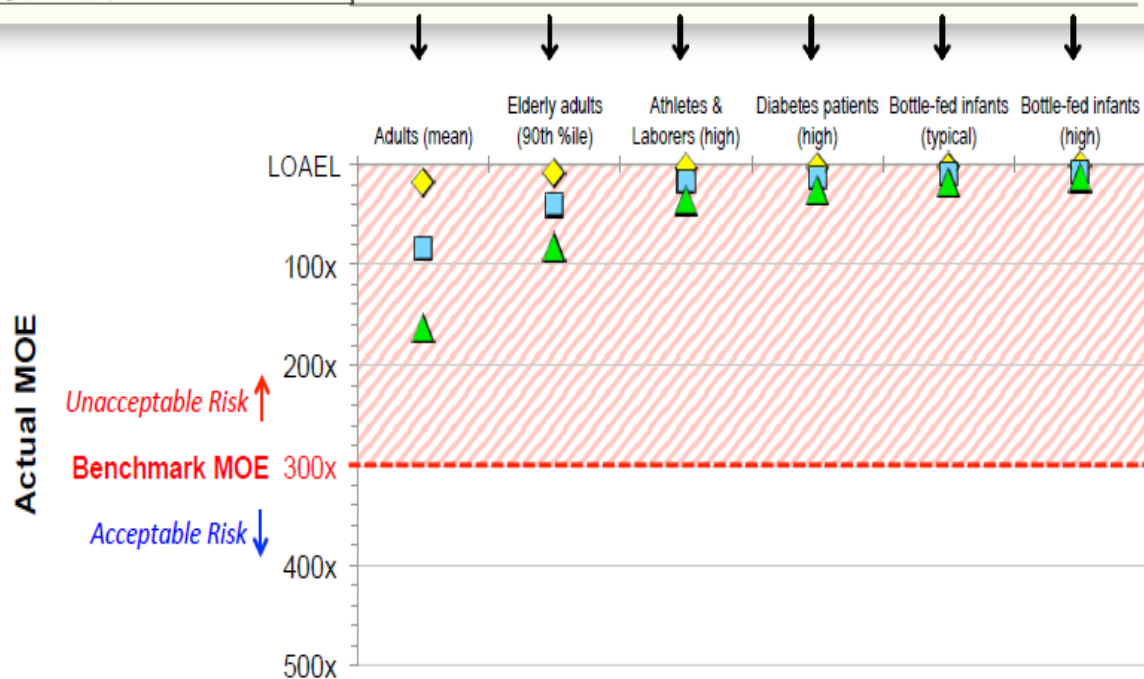
^e The estimated human exposures are for fluoride exposures from drinking water alone, assuming a fluoride concentration of 0.7 mg/L in the drinking water. Sources are as follows: Adults (average), NRC (2006), p. 430, Table B-11, average consumers ages 20-54; Elderly adults (90th percentile), NRC (2006), p. 431, Table B-12, 90th percentile consumers ages 65+; Athletes and laborers (high), NRC (2006), p. 35, Table 2-4, high consumers (but not upper bound); DM patients (high), NRC (2006), p. 35, Table 2-4, patients with diabetes mellitus, high consumers (but not upper bound); Bottle-fed infants (typical), based on Fomon et al. (2000) and Harriehausen et al. (2019); NDI patients (high), NRC (2006), p. 35, Table 2-4, patients with nephrogenic diabetes insipidus, high consumers (but not upper bound); and Bottle-fed infants (high), NRC (2006), p. 432, Table B-13, infants < 0.5 years old, 95th percentile consumers (but not upper bound).

Food and Water Watch v. EPA

Thiessen Report

Table 8. Calculated Margins of Exposure (MOEs)^a for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Actual MOEs					
			Estimated human exposures ^e					
LOAELs from animal studies								
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats) 	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats) 	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats) 	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice)	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats)	3.3	0.79	72	36	16	11	7.9	5.6

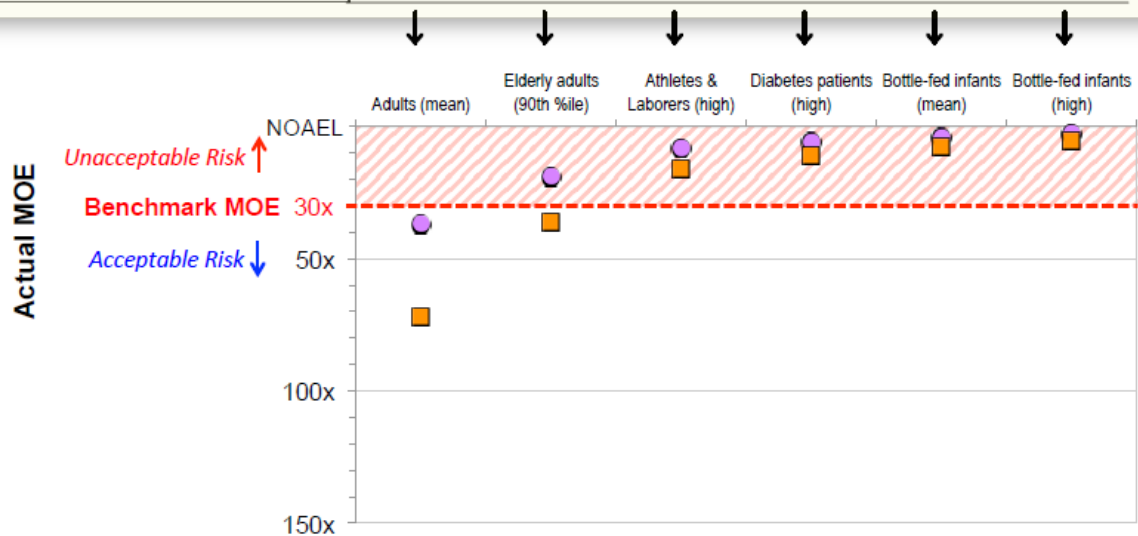


Food and Water Watch v. EPA

Thiessen Report

Table 8. Calculated Margins of Exposure (MOEs)^a for selected human population subgroups for the NOAELs and LOAELs for fluoride in Section 4.

Observation ^b	Intake rate ^c	Human Equivalent Dose (HED) ^d	Actual MOEs					
			Estimated human exposures ^e					
NOAELs from animal studies								
LOAEL or NOAEL	LOAEL or NOAEL	LOAEL or NOAEL	Adults (average)	Elderly adults (90th percentile)	Athletes and laborers (high)	DM patients (high)	Bottle-fed infants (typical) NDI patients (high)	Bottle-fed infants (high)
mg/L	mg/kg/day	mg/kg/day	0.011 mg/kg/day	0.022 mg/kg/day	0.05 mg/kg/day	0.07 mg/kg/day	0.1 mg/kg/day	0.14 mg/kg/day
5 mg/L, LOAEL (rats)	0.83	0.20	18	9.1	4.0	2.9	2.0	1.4
23 mg/L, LOAEL (rats)	3.8	0.91	83	41	18	13	9.1	6.5
45 mg/L, LOAEL (rats)	7.5	1.8	163	82	36	26	18	13
11 mg/L, NOAEL (mice) 	2.9	0.41	37	19	8.2	5.9	4.1	2.9
20 mg/L, NOAEL (rats) 	3.3	0.79	72	36	16	11	7.9	5.6



C. Assumptions and Key Sources of Uncertainty

202. Uncertainties are inherent to the field of risk assessment; they are to be expected. As discussed throughout my expert report, there are uncertainties involved in a risk assessment of fluoride neurotoxicity,²⁸⁸ including:

203. *Uncertainties in the Animal Data:* The Points of Departure for both the RfDs and MOEs are derived from developmental animal studies that, while published in the peer-reviewed biomedical literature, have methodological limitations, including lack of control for litter effects, lack of blinding, lack of exposure during the full window of vulnerability (in utero *and* infancy), lack of long-term chronic exposures, and failure to rule out a contributing role of motor and sensory effects in the observed learning/memory deficits. As discussed earlier, the net effect of these limitations is uncertain. On one hand, lack of blinding can inflate the effect size, while on the other hand, lack of exposure during the full window of vulnerability and lack of chronic exposures can deflate it. Similarly, while lack of control for litter effects can create false positives, it can also create false negatives as well.²⁸⁹ Further, to the extent that fluoride is causing the learning/memory deficits indirectly through a motor/sensory mechanism,²⁹⁰ this would still be a neurotoxic effect and is thus not a basis to forego risk assessment, particularly since body weight changes do not appear to be a mediating mechanism in the studies from which the Points of Departure have been derived.

²⁸⁸ For purposes of brevity, my initial expert report did not reiterate each of these uncertainties in the risk characterization section, although I considered them as part of my assessment.

²⁸⁹ Zorrilla (1997), p. 144; Lazic and Essioux (2013), p. 3.

²⁹⁰ NTP (2016), p. vii.

204. While there are some uncertainties in the animal data (which is not unusual²⁹¹), there is reasonable confidence that the observed effects are both real and relevant. First, the animal studies have been overwhelmingly consistent—across numerous laboratories and study designs—in finding adverse effects on the brain, both structural and functional, which supports the conclusion that the effects are not an artifact of a methodological limitation. Second, the effect of fluoride on cognition has been detected in studies that have specifically controlled for litter effects and body weight changes, thus suggesting that fluoride’s effect on the brain is independent of these concerns.²⁹² Third, there are extensive human epidemiological data reporting associations between fluoride and reduced IQ, and the existence of these data adds plausibility to the animal data, and vice versa. Fourth, the finding of unacceptable risk through an MOE analysis of the animal toxicity values is consistent with Dr. Grandjean’s BMD analysis of the human data, which shows that the level of exposure associated with reduced IQ in humans is well below the levels of exposure produced by fluoridation. The confluence of the animal and human data thus adds strong overall confidence to the assessment.

205. *Uncertainties in the Extrapolation to Humans:* As discussed above, the extrapolation of animal data to humans involves some inherent uncertainty. There does not yet exist a physiologically based toxicokinetic model (PBTK) for fluoride, which would be the optimal method for adjusting for toxicokinetics.²⁹³ This uncertainty has been accounted for by EPA’s use of allometric scaling method which accounts for the expected difference in

²⁹¹ As discussed earlier, the principal animal studies that EPA has relied upon for its neurotoxicity risk assessments have also had methodological limitations, including failure to control for litter effects. There was also significant uncertainty in the animal data that EPA used for its unreasonable risk determinations for its draft NMP evaluation (e.g., there were only 6 studies available for the endpoint of concern, and three found no effect).

²⁹² Bartos (2018; 2019).

²⁹³ EPA (2011b), p. 19.

toxicokinetics), and use of an uncertainty factor of 3 (to address the expected difference in toxicodynamics). The use of default allometric scaling for fluoride is consistent with chemical-specific research on fluoride showing that rats and mice require approximately 5 to 10 times more fluoride, respectively, to obtain the same concentration of fluoride in the blood.²⁹⁴ The allometric scaling thus has a chemical-specific justification for fluoride, which provides confidence to the assessment. But, importantly, even if *no* allometric scaling is done to assess the risk of infant exposures, the MOEs still indicate unacceptable risks for *all* PODs.

206. The use of non-protective (i.e., non-conservative) assumptions provides additional confidence to the assessment. These non-protective assumptions include: (1) the use of 45 mg/L as a LOAEL, despite the fact that studies have found adverse effects well below this concentration; (2) the use of 20 mg/L as a NOAEL in McPherson (2018), despite the fact that the study found a neurotoxic effect at this concentration (i.e., increased pain sensitivity); and (3) conversion of water fluoride concentrations (mg/L) into doses (mg/kg/day) using the lowest end of the reported ratio, which results in Points of Departure that are likely higher than the actual dosages the animals received.

207. *Uncertainties in the Exposure Assessment:* As discussed above, I obtained most of my initial exposure estimates from the NRC's 2006 report, which in turn were based on EPA's own water intake data from 2000,²⁹⁵ and have also reviewed EPA's 2019 report in which the Agency identified the "most up-to-date and scientifically sound" water intake data to use for risk assessment. Both of EPA's water intake reports (from 2000 and 2019) are based on short-term (2-day) surveys, which introduces some uncertainty when extrapolating to long-term exposures.

²⁹⁴ NRC (2006), pp. 98, 442; Zhang et al. (2014).

²⁹⁵ NRC (2006), Appendix B; EPA (2000a).

Long-term surveys, however, do not exist, and the uncertainty of using 2-day surveys is minimized by the large, nationally-representative scale of the survey data. EPA has stated that it has medium-to-high confidence in the reliability of these data, and that the data are well suited for risk assessment of water-based exposures.²⁹⁶

208. *Uncertainties in the Human Data:* One of the major strengths of the database on fluoride neurotoxicity is that there is a large body of human data, including five prospective cohort studies that have individual measurements of exposure during the fetal and neonatal period. The large extent of human data for fluoride far surpasses what EPA has used for its draft risk assessments of other chemicals under Section 6,²⁹⁷ where the Agency has often had to rely *solely* on animal data.

209. The emergence of prospective cohort data on early life exposures to “optimal” levels of fluoride (from salt and water fluoridation programs)²⁹⁸ addresses the two primary criticisms that have been made with respect to the cross-sectional studies of populations with elevated levels of fluoride in water: i.e., (1) that cross-sectional studies are limited in establishing causation because the exposures are measured after the effect (i.e., IQ loss) has occurred; and (2) the cross-sectional studies involve exposures that are generally higher than what people receive through artificially fluoridated water. The fact that the prospective cohort studies have found cognitive deficits at “optimal” levels of exposure that are consistent with the effects observed in the cross-sectional studies adds *substantial* confidence to the risk characterization.

210. While the human data are very robust, data gaps do remain, particularly with

²⁹⁶ EPA (2000a), p. 5-5; EPA (2019b), pp. 3-6 & 3-10.

²⁹⁷ As discussed earlier, the data available for fluoride are also substantially more robust than the data EPA has considered in making hazard determinations for other neurotoxicants.

²⁹⁸ I understand that Dr. Hu and Dr. Lanphear will be addressing the criticisms with respect to imprecise exposure estimates, and thus I do not address that issue here.

respect to how the causative doses may vary across the population based on life-stage (e.g., the elderly), and other intrinsic sources of susceptibility, such as renal impairment, nutritional deficiencies, and genetic predisposition. These data gaps make it difficult to quantify the extent to which susceptibility varies across the population; the available data on chronic fluoride toxicity, however, provide a high level of confidence that human susceptibility to fluoride varies by a considerable margin, particularly in a population as large and diverse as the United States. Of particular concern are individuals with co-existing susceptibilities, such as pregnant women with iodine deficiencies, neonates that are bottle-fed with fluoridated water, and elderly individuals with diabetes.

211. To account for the *known* (but not yet quantified) variability in human susceptibility, I utilized EPA's default uncertainty factor of 10. This is consistent with EPA's standard practice, including EPA's Section 6 risk evaluations under TSCA. While I derived the Points of Departure from studies on susceptible (i.e., prenatally exposed) animals, the studies did not account for the full range of expected susceptibility in the human population. The studies did not, for example, attempt to replicate the formula-feeding practices of human infants, as all rodents were breast-fed during the critical neonatal period. Nor did the studies attempt to examine the effect of a co-existing iodine deficiency in the mother, or any other factor (e.g., renal impairment, calcium deficiency, etc) that would be expected to exacerbate the effects of prenatal fluoride exposure. Since hundreds of millions of Americans are now exposed to fluoridation chemicals on a regular basis, the spectrum of susceptibility will likely exceed the susceptibility examined in the available animal studies. An uncertainty factor of 10 is thus appropriate and necessary.

IX. RISK DETERMINATION

212. Under TSCA, a risk evaluation has a fifth and final step that is not included within the *Guidelines*: the Risk Determination. In the Risk Determination, EPA assesses whether the risks identified by the Margin of Exposure (MOE) analysis are “unreasonable.” In making this determination, EPA considers “relevant risk-related factors,” including (i) the effects of the chemical substance under the conditions of use; (ii) number of people exposed; (iii) whether susceptible subpopulations are exposed; (iv) the severity of the hazard; and (v) uncertainties in the data.

213. In practice, EPA’s Risk Determination analyses do not address each of the “relevant risk factors” identified above. Severity of the hazard, for example, is rarely discussed. Assessments of uncertainties in EPA’s Risk Determinations has also been rather cursory. In the NMP risk evaluation, for instance, the discussion of uncertainties in the analysis was largely limited to the assumptions involved in estimating worker exposure to chemicals in the absence of actual monitoring data.²⁹⁹ Although EPA’s risk estimates were based on an endpoint for which there were only 6 animal studies (with only 3 showing an effect), EPA did not re-address the underlying uncertainties in these data. The Risk Determination should thus not be mistaken as an exhaustive re-examination of all issues previously addressed; instead they tend to be brief and written in summary form.

214. At the time I conducted my initial assessment in this case, EPA had not yet released any risk evaluations under Section 6. For guidance, therefore, I relied on the risk characterization

²⁹⁹ EPA (2019d), pp. 301-335.

considerations identified in the *Guidelines*,³⁰⁰ as well as risk evaluations that EPA had recently completed on “new chemicals” under Section 5.

215. The factors that EPA considers under Section 5 substantially overlap with the factors that EPA considers under Section 6. Specifically, EPA considers the following three factors: (i) the hazardous nature of the chemical (as determined by toxicity values in animal studies);³⁰¹ (ii) the extent of human exposure to the chemical, and (iii) the Margin of Exposure (MOE). As I described in my report, fluoride meets each of these three criteria for unreasonable risk.

216. Importantly, whether one considers the factors under Section 5 or Section 6, the risk of neurotoxicity posed by fluoridation chemicals constitutes a clear and unreasonable risk, as will now be discussed.

A. Effects of Fluoridation Chemicals Under the Condition of Use

217. In most of the risk evaluations that EPA has conducted thus far under Section 6, the Agency did not have actual human data on health effects associated with the condition of use. EPA had to rely, therefore, on animal data alone. This is not the case with fluoridation. Critically, there are four prospective cohort studies that have examined the impact of optimal fluoride exposures, including two that examined the specific condition of use (water fluoridation) at issue.³⁰² Under the *Guidelines*, prospective cohort data permit “direct estimates of risks attributed to a particular

³⁰⁰ EPA (1998a), pp. 63-66.

³⁰¹ Under Section 5, a chemical is “considered to have high human health hazard if there is evidence of adverse effects in humans or conclusive evidence of severe effects in animal studies with a NOAEL of less than or equal to 10 mg/kg/day.” EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a). This criterion is readily satisfied with fluoride, as the LOAELs for cognitive deficits and brain abnormalities are below 10 mg/kg/day. Fluoride is thus a “high human health hazard” under Section 5.

³⁰² Bashash et al (2017, 2018); Green et al. (2019); Till et al. (2020).

exposure.”³⁰³ The effects of fluoridation chemicals under the condition of use are thus well characterized, particularly in comparison to chemicals (e.g., NMP, 1-BP) for which EPA has made unreasonable risk findings under TSCA.

B. Number of People Exposed to Fluoridation Chemicals

218. EPA has recognized that “the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and *the extent of exposure* to the substance.”³⁰⁴ Although EPA made this statement in the context of Section 5, EPA considers the extent of exposure to be a relevant factor under Section 6 as well. In the Section 6 risk determinations, the number of people (usually workers) who are exposed to the chemical are identified under each condition of use.³⁰⁵

219. This factor weighs in favor of an unreasonable risk finding for fluoridation chemicals. The extent of human exposure to fluoridation chemicals is nothing short of massive, much like lead exposure was during the era of leaded gasoline. Today, approximately 200 million Americans, or nearly 2/3 of the population, have municipal water to which fluoridation chemicals are added. Moreover, most of the remaining population living in “non-fluoridated” areas will routinely consume fluoridation chemicals in processed beverages and foods, as many beverages and foods are produced in fluoridated areas.³⁰⁶ To put these numbers in perspective, EPA has found unreasonable risks for conditions of use involving as few as 1,046³⁰⁷ and 1,900 occupationally-

³⁰³ EPA (1998a), p. 17.

³⁰⁴ EPA (2018b; 2018c; 2018d; 2018e; 2018f; 2018g; 2019a).

³⁰⁵ EPA (2019d), pp. 299, 303-335; EPA (2019c), pp. 255-289.

³⁰⁶ See, for example, Kiritsy et al. (1996); Turner et al. (1998); Heilman et al. (1999).

³⁰⁷ EPA (2019c), p. 264.

exposed workers.³⁰⁸ With such widespread exposure to fluoridation chemicals among the general population, even small risks can amount to widespread harm.

C. Exposure of Susceptible Subpopulations to Fluoridation Chemicals

220. One of the consequences from widely dispersing a toxicant through the environment (versus the use of industrial chemicals *within* manufacturing facilities) is that susceptible members of the general public may be exposed. This is the case with fluoridation chemicals. Each year, there are approximately **2.5 million pregnancies** in fluoridated areas; *in utero* exposures are thus widespread. Many of those exposed *in utero* will also be exposed during the sensitive neonatal period, with upwards of **1.9 million infants** living in fluoridated areas being fed formula at least part of the time, including **400,000 infants** who are *exclusively* formula-fed for their first six months. While these numbers do not account for those who use bottled water, the numbers will be substantial regardless.

D. The Severity of the Hazard (Cognitive Deficits/IQ Loss)

221. The principal hazard at issue from exposure to fluoridation chemicals is IQ loss. The prospective studies have found an approximate 5 to 6 point drop in IQ as maternal urinary fluoride levels increase from 0 to 1 mg/L.³⁰⁹ To put this in perspective, EPA has recognized that a loss of a single IQ point is associated with a loss in lifetime earnings,³¹⁰ and EPA's Clean Air Science Advisory Council has stated that "a population loss of 1-2 IQ points is highly significant from a public health perspective" and should be prevented in 99.5% of the population.³¹¹

³⁰⁸ EPA (2019d), pp. 307, 311.

³⁰⁹ Bashash et al. (2017); Green et al. (2019).

³¹⁰ EPA (2008e), p. 5-28.

³¹¹ Federal Register (2008), p. 67000.

Consistent with this, EPA has established reference doses for chemicals based on observed cognitive deficits in animal studies (see Table 1 above). Cognitive deficits, including in the range observed in fluoridated areas, are a sufficiently severe effect on human health to warrant prevention, as EPA has recognized in other contexts.

E. Uncertainties

222. Uncertainties are a pervasive aspect of risk assessment; their existence does not negate a finding of risk. As would be expected, there are uncertainties in the fluoride dataset, arising in part from methodological limitations in the available animal studies (e.g., lack of control for litter effects, lack of blinding, lack of studies on neonatal exposures, lack of chronic experiments, etc.). The impact of these limitations on the observed learning and memory deficits is not yet defined. The clear suggestion from the observed findings, however, is that fluoride causes alterations to the brain and behavior. Further, the uncertainties that remain in the animal data are largely offset by the existence of high-quality prospective studies that have *consistently* detected significant associations between “optimal” fluoride exposures and cognitive deficits. While I understand that EPA’s experts in this case question whether the “causal” relationship between fluoridation and IQ loss has been proven, the *Guidelines* do not require proof of causation; they require sufficient evidence of association.³¹²

223. Another factor weighing in favor of an unreasonable risk finding is that the exposure estimates are more straightforward—and permit greater confidence—than the exposure estimates that EPA has had to extrapolate for other chemicals under TSCA. In its NMP risk evaluation, for example, EPA had to make “assumptions about glove use, glove effectiveness,

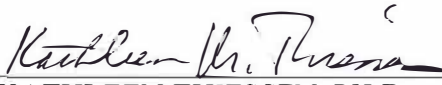
³¹² EPA (1998a), p. 53.

duration of contact with NMP, concentration of NMP, and amount of skin surface contact with NMP” in order to come up with estimates of human exposure under the conditions of use.³¹⁵ Estimating exposure to fluoridation chemicals involves much less uncertainty, as the concentration of fluoride in the water is defined (0.7 mg/L), and the EPA has extensive empirical data on water consumption in the U.S. that the Agency has described as “scientifically sound.”

224. Based on the available scientific evidence that now exists on the hazards, exposures, and risks of fluoride ingestion, the widespread addition of fluoridation chemicals to drinking water and processed foods in the United States presents an unreasonable risk to human health.

I declare under penalty of perjury, under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and belief.

Executed on May 20, 2020, in Oak Ridge, Tennessee.


KATHLEEN THIESSEN, PH.D.

³¹⁵ EPA (2019d), Table 5-1.

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Appendix A

Recent Animal Studies of Fluoride Neurotoxicity (Tables A-1 and A-2)

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity.

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Adebayo et al. 2013	Albino Rats	Male	Post-Weaning ^f	1 week	6
Adedara et al. 2017a & b	Wistar Rats	Male	8 weeks old	45 days	12
Agustina et al. 2018	Wistar Rats	Male	Adults	30 days	8
Akinrinade et al. 2015a & b	Wistar Rats	Male	Adults	30 days	5
Ameeramja et al. 2018	Wistar Albino Rats	Female	2 to 3 months old	30 days	6
Atmaca et al. 2014	Wistar Rats	Male	Post-Weaning ^f	21 days	7
Balaji et al. 2015	Swiss Albino Mice	Female	Adults	30 days	6 (of 7)
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 14, 21 & 30 days	5
Banji et al. 2013	Wistar Rats	Both	Gestational day 6	Prenatal + 15 days	6
Bartos et al. 2018	Wistar Rats	Female	Prenatal	Prenatal + 21 days	5
Bartos et al 2019	Wistar Rats	Both	Pre-Pregnancy	Prenatal + 21 days	5
Basha and Madhusudhan 2010	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 21 days	6
Basha et al. 2011a & b	Wistar Albino Rats	Both	Multigenerational	Prenatal + 12 weeks (3rd generation)	6
Basha and Sujitha 2012a & b	Wistar Rats	Male	3 months old	1 month	6
Basha and Saumya 2013	Albino Mice	Both	Adults	45 days	6
Bharti and Srivastava 2009	Wistar Rats	Female	Adults	28 days	6
Bharti et al. 2012	Wistar Rats	Female	Adults	7 days	6
Chauhan et al. 2013	Sprague-Dawley Rats	Female	6 months old	3 to 6 weeks	4 (of 8)
Chen et al. 2018a	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Chouhan and Flora 2008	Albino Rats	Male	Adults	10 weeks	6
Chouhan et al. 2010	Wistar Albino Rats	Male	Adults	12 weeks	5-6 (of 6)
Dec et al. 2019	Wistar Rats	Males	Pre-Pregnancy	Prenatal + 90 days	6 (of 12)
Dong et al. 2015	Sprague-Dawley Rats	Both	1 month old	>10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1, 7, 14, 21, & 28 days	10
Flora et al. 2009	Swiss Mice	Male	Adults	10 weeks	5
Flora et al. 2012	Swiss Mice	Male	Adults	28 weeks	5 (of 12)
Ge et al. 2011	Wistar Albino Rats	Both	Pre-Pregnancy	Prenatal + 20 days	8
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 90 days	6
Güner et al. 2016	Wistar Albino Rats	Both	Adult	Prenatal + 1, 3, & 5 months	5

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Treatment groups	LOAEL ^b	Specific Effect	Hippocampus?
Adebayo et al. 2013	100 mg/L	100 mg/L	Oxidative stress, reduced brain weight	No
Adedara et al. 2017a & b	6.8 mg/L	6.8 mg/L	Oxidative stress, reduced AChE activity, inflammation, Caspase-3 activity	No
Agustina et al. 2018	2.3, 4.5 & 9 mg/kg/day	4.5 mg/kg/day	Reduced number of Purkinje cells	No
Akinrinade et al. 2015a & b	1 & 5 mg/L	1 mg/L	Oxidative stress, inflammation, neuronal damage	No
Ameeramja et al. 2018	136 mg/L	136 mg/L	Oxidative stress	No
Atmaca et al. 2014	100 mg/L	100 mg/L	Oxidative stress & neuronal degeneration	Yes
Balaji et al. 2015	45 & 90 mg/L	45 mg/L	Inhibition of cholinesterase & increased oxidative stress	No
Banala and Karnati 2015	9 mg/L	9 mg/L	Oxidative stress	No
Banji et al. 2013	9 mg/kg/day	9 mg/kg/day	Oxidative stress	No
Bartos et al. 2018	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Decreased nicotinic receptors & oxidative stress	Yes
Bartos et al. 2019	5 & 10 mg/L (=0.6 & 1.2 mg/kg/d)	5 mg/L	Increased oxidative stress as reflected by decreased CAT, GPT, and GOT	Yes
Basha and Madhusudhan 2010	50 & 150 mg/L	50 mg/L	Oxidative stress & reduced brain protein content	No
Basha et al. 2011a & b	100 & 200 mg/L	100 mg/L	Oxidative stress, reduced brain weight, and histological changes	Yes
Basha and Sujitha 2012a & b	270 mg/L	270 mg/L	Oxidative stress & decreased acetylcholinesterase activity	No
Basha and Saumya 2013	270 mg/L	270 mg/L	Mitochondrial disturbances & Oxidative stress	No
Bharti and Srivastava 2009	150 mg/L	150 mg/L	Oxidative stress	No
Bharti et al. 2012	150 mg/L	150 mg/L	Decreased acetylcholinesterase activity	No
Chauhan et al. 2013	11.3 mg/kg/day	11.3 mg/kg/day	Oxidative stress	No
Chen et al. 2018a	4.5, 23, 45 mg/L	4.5 mg/L	Impaired synaptogenesis	Yes
Chouhan and Flora 2008	10, 50, & 100 mg/L	100 mg/L ^c	Oxidative stress	No
Chouhan et al. 2010	1, 10, 50 & 100 mg/L	1 mg/L	Oxidative stress, alterations in neurotransmitters, neuronal lesions, & increased AChE activity	No
Dec et al. 2019	23 mg/L	23 mg/L	Evidence of inflammatory processes (reduced activity of cyclooxygenases (COX1 & COX2) and increase in prostaglandins)	Yes
Dong et al. 2015	50 mg/L (adults)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Dong et al. 2015	50 mg/L (offspring)	50 mg/L	Decrease in muscarinic nicotinic receptors	No
Flora et al. 2009	50 mg/L	50 mg/L	Oxidative stress, alteration in neurotransmitters, DNA damage, increased AChE activity	No
Flora et al. 2012	50 mg/L	50 mg/L	Oxidative stress, neuronal degeneration, DNA damage, Protein interaction	Yes
Ge et al. 2011	100 mg/L (+25 mg/kg in food)	100 mg/L	Alteration in protein expression	No
Ge et al. 2018	50 & 100 mg/L	50 mg/L	Alterations of synapse-related proteins	No
Güner et al. 2016	13.6 & 45 mg/L	13.6 mg/L	Neurodegenerative changes & catalase immunoreactivity	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity - *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Hamza et al. 2015	Wistar Albino Rats	Male	Adults	30 days	10
Han et al. 2014	Kumming Mice	Male	Sexually matured mice	180 days	4 (of 15)
Hassan and Abdel-Aziz 2010	Wistar Albino Rats	Male	Adults	5 weeks	6
Inkielwicz-Stepniak and Czarnowski 2010	Wistar Han Rats	Male	6 weeks old	4 weeks	6
Jia et al. 2019	CD1 Mice	Both	Prenatal	Prenatal (day 9) + 19 days	5 (of 20)
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	3-12 (of 12)
Jiang et al. 2019	Sprague-Dawley Rats	Male	Post-weaning ^f	10 weeks	7
Kaur et al. 2009	Sprague-Dawley Rats	Female	Adults	8 weeks	6-7 (of 8)
Khan et al. 2018	Wistar Rats	Both	Post-weaning ^f	28 days	6
Kinawy 2019	Rats	Male	Prenatal (6th day)	Prenatal + Weaning or 70 days	8
Li et al. 2019	Kumming Mice	Both	Adults	90, 120 & 150 days	8 (of 30)
Liu et al. 2010	Sprague-Dawley Rats	Both	Post-weaning ^f	6 months	10 (of 24)
Liu et al. 2011	Sprague-Dawley Rats	Both	Post-weaning ^f	3 & 6 months	12 (of 24)
Lou et al. 2013	Sprague-Dawley Rats	Both	Post-weaning ^f	6 months	20
Ma et al. 2015	C57/BL Mice	Male	4 weeks old	4 weeks	8
Mansour and Tawfik 2012	Albino Rats	Male	Adults	5 weeks	6
McPherson et al. 2018	Long Evans Hooded Rats	Male	Prenatal	Prenatal (day 6) + 90 days	6 (of ~23)
Nabavi et al. 2012a	Wistar Rats	Male	8 to 12 weeks old	1 week	10
Nabavi et al. 2012b	Wistar Rats	Male	Post-weaning ^f	1 week	10
Nabavi et al. 2013	Wistar Rats	Male	7 days old	7 days	10
Niu et al. 2009	Wistar Albino Rats	Both	Day of birth	6, 8, 10, & 12 weeks	8
Niu et al. 2014	Kumming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2015a	Kumming Mice	?	Adults	60 days	5 (of 15)
Niu et al. 2015b	Kumming Mice	Both	Prenatal	Prenatal + 56 days	6
Niu et al. 2018a	Sprague-Dawley Rats	Female	Post-weaning ^f	60 days	3 (of 10)
Niu et al. 2018b	Kumming Mice	Both	Adults	60 days	5 (of 12)

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Hamza et al. 2015	4.7 mg/kg/day	4.7 mg/kg/day	Increased oxidative stress	No
Han et al. 2014	11, 23, and 45	23 mg/L ^c	Altered mRNA expression	Yes
Hassan and Abdel-Aziz 2010	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
Inkielwicz-Stepniak and Czarnowski 2010	25 mg/L	25 mg/L	Oxidative stress	No
Jia et al. 2019	6 & 113 mg/L	None	No reduction in neuronal density	No
Jiang et al. 2014a	54 mg/L	54 mg/L	Decreased glutamate levels	Yes
Jiang et al. 2014b	11, 23, and 45 mg/L	11 mg/L	Neuronal degeneration, decreased glucose utilization	Yes
Jiang et al. 2019	23 & 45 mg/L	23 mg/L	Impaired neurogenesis & synaptic plasticity	Yes
Kaur et al. 2009	125 mg/L	125 mg/L	Oxidative stress, alteration in neurotransmitters, & neuronal degeneration	No
Khan et al. 2018	20 mg/L	20 mg/L	Inhibition of AChE and increase in oxidative stress	No
Kinawy 2019	678 mg/L	678 mg/L	Oxidative stress	Yes
Li et al. 2019	68 mg/L	68 mg/L	Altered mRNA expression of anxiety & depression-related genes	Yes
Liu et al. 2010	5 & 50 mg/L	5 mg/L	Reductions in nicotinic receptors & activation of photoho-ERK1/2	No
Liu et al. 2011	5 & 50 mg/L	5 mg/L	Increased apoptosis & phosphorylation	No
Lou et al. 2013	10 & 50 mg/L	10 mg/L	Mitochondrial disturbances in neurons, altered protein expression	No
Ma et al. 2015	23 & 45.6 mg/L	23 mg/L	Increased BDNF expression	Yes
Mansour and Tawfik 2012	4.7 mg/kg/day	4.7 mg/kg/day	Oxidative stress	No
McPherson et al. 2018	10 & 20 mg/L (+ food exposure group)	None	No neuronal damage or glia reactivity	Yes
Nabavi et al. 2012a	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2012b	270 mg/L	270 mg/L	Oxidative stress	No
Nabavi et al. 2013	270 mg/L	270 mg/L	Oxidative stress	No
Niu et al. 2009	68 mg/L	68 mg/L	Decreased glutamate levels & altered enzyme activity	Yes
Niu et al. 2014	68 mg/L	68 mg/L	Altered protein expression	Yes
Niu et al. 2015a	11, 23, and 45 mg/L	23 mg/L	Microtubule lesions in neurons	Yes
Niu et al. 2015b	68 mg/L	68 mg/L	Alterations in protein expression	No
Niu et al. 2018a	4.5, 23, and 45 mg/L	4.5 mg/L	Endoplasmic reticulum stress	Yes
Niu et al. 2018b	11, 23, and 45 mg/L	11 mg/L	Myelin damage, and alteration to synaptic structure	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Pal and Sarkar 2014	Wistar Rats	Male	Post-weaning ^f	30 days	6 to 8
Pan et al. 2015	Sprague-Dawley Rats	Male	3 weeks after weaning	30 days	15
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	4-10 (of 15)
Pulungan et al. 2018	Wistar Rats	Male	12-16 weeks old	30 days	8
Qian et al. 2013	Sprague-Dawley Rats	Male	Newly weaned	6 months	2-20 (of 20)
Reddy et al. 2009	Swiss Albino Mice	Female	Adults	14 days	6
Reddy et al. 2014	Wistar Rats	Male	4 months old	90 days	6
Rogalska et al. 2017	Wistar Rats	Both	8 weeks old	4 weeks	6-8
Samanta et al. 2016	Sprague-Dawley Rats	Female	Post-weaning ^f	16 weeks	5
Sarkar et al. 2014	Wistar Rats	Male	Post-weaning ^f	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2014	Swiss Albino Mice	Male	1.5 months old	30 days	7
Sharma et al. 2018	Swiss Albino Mice	Both	1 month old	30 days	7
Shen et al. 2019	Wistar Rats	Both	1 month old	12 & 24 weeks	30
Sun et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	10
Sun et al. 2018	Kumming Mice	Female	Prenatal	Prenatal + 21 days	6 (of 12)
Teng et al. 2018	Sprague-Dawley Rats	Male	Recently weaned	18 months	6-7 (of 13)
Trivedi et al. 2007	Swiss Albino Rats	Male	Young adults	30 days	10
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (7th day) + 21 days	6 (of 15)
Wang et al. 2018b	Wistar Albino Rats	Male	12-weeks old	8 weeks	10 (of 24)
Wei et al. 2018	Sprague-Dawley Rats	Both	1 month old	>6 months	15
Wei et al. 2018	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 28 days	6-10 (of 10)
Yan et al. 2016	Wistar Rats	Both	5 weeks old	10 weeks	20
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 & 12 weeks	4-6 (of 10)
Yu et al. 2019	ICR Mice	Male	Newly weaned	3 & 6 months	20
Yuan et al. 2019	Kumming Mice	Male	7 weeks old	90 days	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2015a	Sprague-Dawley Rats	Both	2 months old	3 months & 6 months	10 (of 20)

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Pal and Sarkar 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, altered neurotransmitters, reduced protein content	No
Pan et al. 2015	9 mg/kg/day	N/A ^d	Altered protein expression	Yes
Pereira et al. 2011	45 mg/L	45 mg/L	Alterations in neurotransmitters	Yes
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	none	No reduction in number of pyramidal cells in medial prefrontal cortex	No
Qian et al. 2013	23 mg/L	23 mg/L	Impaired synaptic plasticity, oxidative stress, altered protein expression	Yes
Reddy et al. 2009	9 mg/kg/day	9 mg/kg/day	Oxidative stress & altered enzyme activity	No
Reddy et al. 2014	9, 27, & 45 mg/L	9 mg/L	Oxidative stress, alterations in neurotransmitters, and immunosuppression	No
Rogalska et al. 2017	4.5 & 23 mg/L	23 mg/L ^c	Increased glucose uptake	Yes
Samanta et al. 2016	5.9 mg/kg/day	5.9 mg/kg/day	Oxidative stress, cellular degeneration, apoptosis	No
Sarkar et al. 2014	9 mg/kg/day	9 mg/kg/day	Oxidative stress, inhibited enzymes, & reduced protein content	No
Shalini and Sharma 2015	10 mg/L	10 mg/L	Oxidative stress, reduced protein content & AChE activity	No
Sharma et al. 2014	120 mg/L	120 mg/L	Oxidative stress & cellular degeneration	Yes
Sharma et al. 2018	54 mg/L	54 mg/L	Oxidative stress and neuronal damage	Yes
Shen et al. 2019	200 mg/L	200 mg/L	Apoptosis and degeneration of nerve cells in spinal cord	No
Sun et al. 2017	45 mg/L	45 mg/L	Altered gene expression & apoptosis	Yes
Sun et al. 2018	11, 23, and 45 mg/L	11 mg/L (Fig 3b)	Altered mRNA expression	Yes
Teng et al. 2018	8.25, 16.5, & 33 mg/L	16.5 mg/L ^c	Elevated calcium in hippocampus	Yes
Trivedi et al. 2007	2.7 & 5.4 mg/kg/day	2.7 mg/kg/day	Reduced protein content	No
Wang et al. 2018a	11, 23, and 45 mg/L	11 mg/L (Fig 4b)	Altered expression of mi-RNAs	No
Wang et al. 2018b	45 mg/L	45 mg/L	Cellular degeneration, DNA damage	Yes
Wei et al. 2018	50 mg/L (adults)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Wei et al. 2018	50 mg/L (offspring)	50 mg/L	Neuronal injury (as evident by damage to Nissl bodies)	No
Yan et al. 2016	60 & 120 mg/L	60 mg/L	Increased apoptosis & inflammation	Yes
Yang et al. 2018a	60 & 120 mg/L	60 mg/L	Apoptosis, altered protein expression, increased inflammation	Yes
Yu et al. 2019	2.3 & 13.6 mg/L	2.3 mg/L	Alterations of L-type calcium channels	Yes
Yuan et al. 2019	23, 45, 68 mg/L	23 mg/L	Reduced brain protein content, impaired insulin signaling pathway, reduced brain organ coefficient	Yes
Zhang et al. 2013a	45 mg/L	45 mg/L	Oxidative stress, neuronal loss, altered protein expression	Yes
Zhang et al. 2015a	5 & 50 mg/L	5 mg/L	Increased oxidative stress & activation of AGE/RAGE Pathway	Yes

Table continued next page

Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Animal	Sex	Maturity at Start of Exposure	Length of Exposure	Animals per group
Zhang et al. 2017a	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 14 or 28 days	15-20 (of 20)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	2-3 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	2-5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2011 & Zhang et al. 2011	Sprague-Dawley Rats	Male	Just weaned	9 months	6 (of 12)
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 21 or 42 days	6 (of 8)

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Table A-1. Summary of animal studies that have investigated neuroanatomical and neurochemical endpoints of fluoride toxicity – *Continued*

Paper	Treatment groups	LOAEL	Specific Effect	Hippocampus?
Zhang et al. 2017a	45 mg/L	45 mg/L	Impaired synaptic plasticity	No
Zhang et al. 2019	25, 50, 100 mg/L	50 mg/L ^e	Autophagy in hippocampus	Yes
Zhao et al. 2019	4.5, 23, 45 mg/L	4.5 mg/L [Fig 6e]	Mitochondrial disturbances	Yes
Zheng et al. 2016	45 mg/L	45 mg/L	Increased apoptosis	Yes
Zhou et al. 2019	4.5, 23, 50 mg/L	23 mg/L ^c	Decreased neurons, suppressed autophagy, and enhanced apoptosis in hippocampus	Yes
Zhu et al. 2011 & Zhang et al. 2011	7, 13.6, & 27 mg/L	13.6 mg/L ^c	Decrease in synaptic membrane fluidity & increased calcium	Yes
Zhu et al. 2017	34 mg/L	34 mg/L	Altered protein expression in ERK/CREB signaling pathway	Yes

^a Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

^b A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

^c At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

^d The authors did not perform a statistical analysis to determine if the observed changes were statistically significant.

^e Ultrastructural observations of the rat hippocampal CA1 cells identified changes in the 25 mg/L group (i.e., increased lipofuscin content), but a statistical analysis of these changes was not performed.

^f Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning.

Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory

Paper	Strain	Sex ^a	Maturity at Start of Exposure	Length of Exposure	Animals per group
Banala and Karnati 2015	Wistar Rats	Both	Prenatal	Prenatal + 30 days	5
Bartos et al. 2018	Wistar Rats	Female	Prenatal (day 0)	Prenatal + 21 days	9-10
Bartos et al. 2019	Wistar Rats	Both	Prenatal (day 0)	Prenatal + 21 days	9-10
Basha et al. 2011b	Wistar Albino Rats	Both	Prenatal/Multigenerational	Prenatal + 30 days	6
Basha & Sujitha 2012b	Wistar Rats	Male	3 months old	1 month	6
Bera et al. 2007	Wistar Rats	Both	Prenatal (day 1)	Prenatal (day 1) + 9 days	6-12
Chen et al. 2018a	Sprague-Dawley Rats	Female	2 months pre-gestation	Prenatal + 6 months	6
Chioca et al. 2008	Wistar Rats	Male	Adult	30 days	15 (of 18)
Cui et al. 2017	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	12
Dong et al. 2015	Sprague-Dawley Rats	Both	One month old	10 months	30
Dong et al. 2015	Sprague-Dawley Rats	Both	10 months pre-birth	Prenatal + 1 to 28 days	10
Ge et al. 2018	ICR Mice	Both	Pre-Pregnancy	Prenatal + 60 days	6
Han et al. 2014	Kunming Mice	Male	Sexually matured mice	180 days	15
Jetti et al. 2016	Wistar Rats	Male	Adult	30 days	6
Jiang et al. 2014a	Sprague-Dawley Rats	Male	Weaned	3 months	8
Jiang et al. 2014b	Sprague-Dawley Rats	Both	Pre-pregnancy	Prenatal + 2 months	12
Liu et al. 2010	Sprague-Dawley Rats	Both	Adult	6 months	10 (of 24)
Liu et al. 2014	BaB/C Mice	Male	4 weeks old	4 weeks	11-12 (of 12)

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Strain	Sex ^a	Maturity at Start of Exposure	Length of Exposure	Animals per group
McPherson et al. 2018	Long-Evans Hooded Rats	Male	Prenatal (day 6)	Prenatal (day 6) + 90 days	11-23 (of ~23)
Niu et al. 2009	Wistar Albino Rats	Both	Postnatal (day 0)	6 to 12 weeks	8
Niu et al. 2014	Kunming Mice	Male	Prenatal	Prenatal + 56 days	15
Niu et al. 2018a	Sprague Dawley Rats	Female	Post-weaning ^g	2 months	6 (of 10)
Pereira et al. 2011	Wistar Rats	Male	30 days old	30 days	14-15
Pulungan et al. 2018	Wistar Rats	Male	12 to 16 weeks old	30 days	8
Raghu et al. 2013	Wistar Rats	Male	1 month old	30 days	6
Shalini and Sharma 2015	Wistar Albino Rats	Female	Adults	60 days	10
Sharma et al. 2018	Swiss Albino Mice	Male	1 month old	30 days	7
Sun et al. 2018	Kunming Mice	Both	Prenatal	Prenatal + 21 days	6 (of 12)
Wang et al. 2018a	ICR Mice	Female	Prenatal	Prenatal (day 7) + 21 days	15
Whitford et al. 2009	Sprague-Dawley Rats	Female	8 days after weaning	8 months	8
Yang et al. 2018a	Wistar Rats	Male	6 weeks old	4 to 12 weeks	10
Yuan et al. 2019	Kunming Mice	Male	7 weeks old	12 weeks	12 (of 24)
Zhang et al. 2013a	Wistar Rats	Male	6 weeks old	3 months	3 (of 10)
Zhang et al. 2019	Wistar Rats	Both	4 weeks old	3 months	15 (of 20)
Zhao et al. 2019	Sprague-Dawley Rats	Both	Pre-Pregnancy	Prenatal + 60 days	5 (of 15)
Zheng et al. 2016	Sprague-Dawley Rats	Male	Newly weaned	3 months	20
Zhou et al. 2019	Sprague-Dawley Rats	Female	Pre-Pregnancy	Prenatal + 6 months	6
Zhu et al. 2017	Sprague-Dawley Rats	Both	Prenatal	Prenatal + 42 days	8

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL ^b
Banala and Karnati 2015	20 mg/L	Maze Learning	20 mg/L
Bartos et al. 2018	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Bartos et al. 2019	5 & 10 mg/L	Step Down Inhibitory Avoidance	5 mg/L
Basha et al. 2011b	100 & 200 mg/L	T Maze	100 mg/L
Basha & Sujitha 2012b	270 mg/L	T Maze	270 mg/L
Bera et al. 2007	1.13 & 2.3 mg/kg/day	Active Avoidance / Novel Object Recognition	2.3 mg/kg
Chen et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Chioca et al. 2008	23 & 45 mg/L (5.15 & 10.77 mg/kg/day)	Open Field / Two-Way Active Avoidance	23 mg/L
Cui et al. 2017	4.5, 23, & 45 mg/L	Morris Water Maze	4.5 mg/L
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (adults)
Dong et al. 2015	50 mg/L	Morris Water Maze	50 mg/L (pups)
Ge et al. 2018	50 & 100 mg/L	Morris Water Maze	50 mg/L
Han et al. 2014	11, 23, and 45 mg/L	Novel Object Recognition / Open Field	45 mg/L ^d
Jetti et al. 2016	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Jiang et al. 2014a	55 mg/L	Morris Water Maze	55 mg/L
Jiang et al. 2014b	11, 23, & 45 mg/L	Morris Water Maze	11 mg/L
Liu et al. 2010	2.3 & 23 mg/L	Morris Water Maze	2.3 mg/L
Liu et al. 2014	0.9, 2.3, and 4.5 mg/L	Morris Water Maze / Novel Object Recognition / Elevated-Plus Maze	2.3 mg/L ^c

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Table A-2. Summary of animal studies that have investigated toxic effects of fluoride on learning and memory - *Continued*

Paper	Treatment groups	Selected Tests	LOAEL ^b
McPherson et al. 2018	10 & 20 mg/L (+food exposure group)	Open Field / Elevated Plus Maze / Passive Avoidance / Morris Water Maze / Y Maze	None
Niu et al. 2009	68 mg/L	Y Maze	68 mg/L
Niu et al. 2014	68 mg/L	Novel Object Recognition	68 mg/L ^e
Niu et al. 2018a	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Pereira et al. 2011	45 mg/L	Open Field	45 mg/L
Pulungan et al. 2018	2.3, 4.5 & 9 mg/kg/day	Y Maze	None ^f
Raghu et al. 2013	100 mg/L	T Maze / Passive Avoidance	100 mg/L
Shalini and Sharma 2015	10 mg/L	Maze Test	10 mg/L
Sharma et al. 2018	68 mg/L	Morris Water Maze / Classic Maze	68 mg/L
Sun et al. 2018	11, 23, & 45 mg/L	Radial Arm Maze / Open Field	23 mg/L ^c
Wang et al. 2018a	11, 23, & 45 mg/L	Open Field / Eight-Arm Maze	23 mg/L ^c
Whitford et al. 2009	2.9, 5.7, & 11.5 mg/kg/day	Appetitive Based Learning	None
Yang et al. 2018a	60 & 120 mg/L	Morris Water Maze / Open Field	60 mg/L
Yuan et al. 2019	23, 45, & 68 mg/L	Y Maze	23 mg/L
Zhang et al. 2013a	45 mg/L	Y Maze	45 mg/L
Zhang et al. 2019	25, 50, & 100 mg/L	Morris Water Maze	100 mg/L ^c
Zhao et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L
Zheng et al. 2016	45 mg/L	Morris Water Maze / Open Field	45 mg/L
Zhou et al. 2019	4.5, 23, & 45 mg/L	Morris Water Maze	23 mg/L ^c
Zhu et al. 2017	45 mg/L (8 to 11 mg/kg/day)	Morris Water Maze	45 mg/L

^a Where the study does not identify the sex of the animals, it is assumed that both sexes were studied.

^b A LOAEL refers to the lowest observed adverse effect level where a statistically significant result was observed.

^c At least one effect was seen at lower treatment doses (as reflected by a visually apparent dose-related trend), but the effect(s) at the lower treatment levels did not reach statistical significance.

^d At least one statistically significant effect was seen at lower treatment doses but for a neurological endpoint that is not specific to learning or memory impairments.

^e The effect in the fluoride + lead treatment group was statistically significant, but the effect in the fluoride-only treatment group did not reach statistical significance.

^f A statistically significant effect was observed in the low treatment dose group (5 mg/kg/day) when compared to the control, but there were no significant differences between the control and mid/high dose treatment groups (10 mg/kg/day & 20 mg/kg/day).

^g Where the study does not identify the age of the animal at the start of the experiment, it is assumed that the animals had already completed weaning

Appendix B

KATHLEEN M. THIESSEN, Ph.D.
Senior Scientist
Oak Ridge Center for Risk Analysis, Inc.

Education

Ph.D. 1986 Genetics, University of Tennessee-Oak Ridge, Graduate School of Biomedical Sciences, Oak Ridge, TN
B.A. 1981 Biology and Chemistry (*Summa cum laude*), Covenant College, GA

Capabilities

Health Effects Assessment
Dose and Risk Assessment
Analysis of Environmental Transport and Exposure Pathways
Uncertainty and Sensitivity Analysis
Technical Writing/Editing, Technical and Public Presentations

Experience Summary

Dr. Thiessen is experienced in the evaluation of exposures, doses, and risks to human health from trace levels of contaminants in the environment and in the use of uncertainty analysis for environmental and health risk assessment. She has served on two National Research Council subcommittees, one charged with the review of fluoride exposure and toxicology, and one dealing with guidance levels for air contaminants (including hydrogen fluoride) in submarines. Dr. Thiessen has also written two reports for the U.S. Environmental Protection Agency, one on the health effects of hydrogen fluoride and related compounds, and one on the health effects of mercuric chloride. Dr. Thiessen has led several working groups on urban contamination and dose reconstruction for the International Atomic Energy Agency's programs on environmental transport modeling and has served on the coordinating committees of the programs; she currently leads a working group on assessment of exposures and countermeasures in urban environments. She also serves on a committee for the preparation of a new International Atomic Energy Agency report on modeling the impacts of planned discharges or radioactivity, and she is involved in the preparation of an IAEA guidance document on implementation of remediation strategies following accidental releases of radioactivity. Dr. Thiessen participated in two symposia on reconstruction of internal doses from Fukushima releases organized by Japan's National Institute of Radiological Sciences, and she has served as a consultant on environmental modeling issues to the Korea Atomic Energy Research Institute and on uncertainty analysis to the National Council on Radiation Protection and Measurements. Dr. Thiessen contributed to the development of a risk-based screening approach to prioritize further investigation of contaminants and exposure situations in various assessment contexts, and she led in the application of risk-based screening techniques for the reconstruction of doses and health risks associated with releases of chemicals and radionuclides from the U.S. Department of Energy's Oak Ridge (Tennessee) facilities. Dr. Thiessen also led an analysis of human exposures, doses, and health risks to off-site individuals associated with historic releases of radionuclides to the Clinch River from the Oak Ridge facilities.

Experience

- 1992-present Senior Scientist and Director, Oak Ridge Center for Risk Analysis, Inc. (Formerly *SENES* Oak Ridge, Inc., Center for Risk Analysis), Oak Ridge, TN.
- Review of data on contaminant exposure and toxicology.
 - Analysis of environmental transport and exposure pathways.
 - Screening techniques for environmental assessment.
 - Dose reconstruction.
 - Uncertainty analysis for environmental assessment.
 - International model validation using Chernobyl data sets.
 - Working Group Leader for International Atomic Energy Agency research programs.
 - Project coordination.
 - Technical review.
- 1991-1992 Consultant and Technical Writer. Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN.
- 1987-1992 Lecturer in Genetics. University of Tennessee, Oak Ridge Graduate School of Biomedical Sciences.
- 1986-1989 Oak Ridge National Laboratory, Health and Safety Research Division, Chemical Hazard Evaluation Program.
- Assessment of health effects from chemicals.
 - Risk assessment.
 - Technical review.

Publications and Technical Reports

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C. ANDREW WATERS, ESQ., CA Bar No. 147259
MICHAEL CONNETT, ESQ., CA Bar No. 300314
WATERS, KRAUS & PAUL
222 N. Pacific Coast Hwy, Suite 1900
El Segundo, CA 90245
310-414-8146 Telephone
310-414-8156 Facsimile

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al.,

Plaintiffs,

vs.

U.S. ENVIRONMENTAL PROTECTION
AGENCY, et al.

Defendants.

Civ. No. 17-CV-02162-EMC

**DECLARATION OF
BRUCE LANPHEAR, MD, MPH**

DECLARATION OF BRUCE LANPHEAR, MD, MPH

TABLE OF CONTENTS

I. SUMMARY OF QUALIFICATIONS1

II. SUMMARY OF OPINIONS3

III. BASIS FOR OPINIONS.....4

 A. The Growing Problem with Brain-Based Disorders4

 B. The MIREC Cohort Is a Comprehensively Characterized Birth Cohort5

 C. Urinary Fluoride Study (Till 2018).....6

 1. Methodological Strengths6

 2. Fluoridated Water Has a Large and Significant Effect on Urinary Fluoride.....7

 3. Pregnant Women in Water-Fluoridated Areas of the MIREC Cohort Have Similar Urinary Fluoride Levels as the ELEMENT Cohort.....8

 D. Prenatal Fluoride/IQ Study (Green 2019).....8

 1. Methodological Strengths8

 2. Prenatal Fluoride Exposure Is Associated with Large and Significant Reductions in IQ in the MIREC Cohort.....11

 3. Convergent Findings of ELEMENT and MIREC Cohorts.....13

 E. Infant Fluoride/IQ Study (Till 2020)13

 1. Methodological Strengths14

 2. Fluoride Exposure During Infancy Is Associated with Significant Reductions in Non-Verbal IQ in the MIREC Cohort15

 F. The Limitations of Our Studies Do Not Provide a Likely Explanation for the Results.....16

IV. CONCLUSION.....18

REFERENCES19

I, Bruce Lanphear, MD, MPH, declare that:

1. I am a Clinical Investigator at the BC Children's Hospital Research Institute, BC Children's Hospital, and Professor in the Faculty of Health Sciences at Simon Fraser University in Vancouver, British Columbia.

2. I am also the Co-Principal Investigator of an ongoing study to examine the impact of early-life fluoride exposures on intellectual abilities in a cohort of mothers and offspring from Canada known as the MIREC Study. Our study of fluoride and IQ in the MIREC cohort was funded by a grant from the U.S. National Institutes of Health (NIH).

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 6 and attached herein.

4. I have studied the impact of toxic chemicals, including lead and pesticides, on children's brain development for over 20 years. My research has been almost exclusively funded by federal agencies, including the Environmental Protection Agency (EPA), Centers for Disease Control and Prevention, the Department of Housing and Urban Development, Health Canada, National Institute of Allergy and Infectious Diseases, National Institute for Child Health and Human Development, National Institute of Environmental Health Sciences, National Institute of Neurologic Diseases, and the National Heart, Lung and Blood Institute.

5. My research has been published in leading medical and scientific journals, including *Journal of the American Medical Association*, *New England Journal of Medicine*, and *Pediatrics*, and has been extensively relied upon by environmental and public health agencies, including the EPA. My pooled analysis of blood lead and IQ (Lanphear 2005) was cited by the EPA as the critical study upon which the Agency based the current national air standard for lead.

1 6. I have served on the editorial boards of seven academic journals, including *Public Health*
2 *Reports* (the official journal of the U.S. Surgeon General), *PLoS Medicine* (a peer-reviewed medical
3 journal published by the Public Library of Science), and *Environmental Health Perspectives* (a journal
4 funded by the National Institutes of Environmental Health Sciences).

5 7. I have served on numerous scientific committees on environmental health issues impacting
6 children, including multiple scientific advisory boards for the EPA and the Executive Council on
7 Environmental Health for the American Academy of Pediatrics. My work with the EPA has included
8 invited expert advisory roles on EPA's (i) Science and Research Work Group of the Children's Health
9 Protection Advisory Committee (1998-2001); (ii) Workshop on Assessing Environmental Exposures to
10 Children (2000-2002); (iii) Clean Air Scientific Advisory Committee (2006-2008); (iv) Science Advisory
11 Board for Evaluating Dust Lead Standards (2010-2012); and (v) Science Advisory Board for Evaluating
12 Hazards of Partial Water Line Replacement (2011-2012).

13
14 8. My research has earned various awards and honors, including the Research Integrity Award
15 from the International Society for Environmental Epidemiology in 2012, the Public Policy and Advocacy
16 Award from the Academic Pediatric Association in 2013, and the Research Award from the Academic
17 Pediatric Association in 2015.

18
19 9. I have been involved with the MIREC Study for over 10 years. I was a Co-Principal
20 Investigator for the neurobehavioral assessments conducted when the children were 3 to 4 years old and I
21 oversaw the neurodevelopmental assessments in Vancouver. I have been a coauthor of twelve publications
22 from the MIREC Study, including three publications on fluoride described below.

23
24 10. In light of the consistent association between elevated fluoride and IQ reported in cross-
25 sectional studies (Choi, et al. 2012), we received a grant from the NIH to study the association between
26 prenatal and early-life measures of fluoride and IQ in children in the MIREC cohort. To date, we have
27

1 published three peer-reviewed studies, including the most extensive assessment of fluoride exposure
2 during pregnancy ever conducted and prospective studies on early life fluoride exposure on IQ. These
3 studies have been published in *Environmental Health Perspectives*, *JAMA Pediatrics*, and *Environment*
4 *International* (Till 2018, Green 2019, Till 2020). Our study on prenatal fluoride and IQ was the highest
5 scoring study in *JAMA Pediatrics* in 2019 (Christakis 2020).

6 11. I agreed to participate as a non-retained expert in this case because I believe it is a public
7 duty to present the results of studies that suggest substantial risk to public health. I have asked *not* to be
8 compensated for this work.

9 **II. SUMMARY OF OPINIONS**

10 12. Our study of prenatal fluoride and IQ in the MIREC cohort (Green 2019) further enhances
11 the quality of data related to the neurotoxicity of fluoride. As with the ELEMENT cohort, we employed a
12 prospective cohort design, had extensive control for potential confounders, and had multiple measures of
13 fluoride exposure during pregnancy, including three types of urinary fluoride measurements for each
14 trimester of pregnancy.

15 13. The maternal urinary fluoride levels in the MIREC cohort were significantly associated
16 with lower intellectual abilities in 3-4-year-old children. These associations remain large and significant
17 when controlling for relevant covariates.

18 14. Converging results from the MIREC and ELEMENT cohorts indicate that exposure to
19 “optimal” levels of fluoride during fetal development is associated with diminished intelligence in
20 childhood.

21 15. In the MIREC cohort, exposure to fluoridated water in infancy, particularly among
22 formula-fed infants, was also associated with diminished intelligence (Till 2020). This association remains
23 significant after controlling for fetal fluoride exposure and other relevant covariates, suggesting that
24
25
26
27

1 susceptibility to fluoride's adverse neurological effects may extend into infancy.

2 **III. BASIS FOR OPINIONS**

3 **A. The Growing Problem with Brain-Based Disorders**

4 16. As I have discussed elsewhere, the causes of death and disability in children have shifted
5 over the past century (Lanphear 2015). Concerted public health efforts to control tuberculosis, cholera,
6 typhoid, and other infectious agents in the early twentieth century led to a dramatic reduction in child
7 mortality, followed by a rise in life expectancy. By the end of the twentieth century, the 'new morbidities
8 of childhood' had emerged: attention deficit hyperactivity disorder (ADHD), autism, asthma, obesity, and
9 preterm birth. Learning disabilities and neurodevelopmental disorders are now two of the most prevalent
10 morbidities in children. About 7.6% of US children are estimated to have a learning disability, and 13%
11 are estimated to have a neurodevelopmental disorder, including anxiety, autism, conduct disorder,
12 depression, or ADHD (Lanphear 2015). These data indicate that we are in the midst of an epidemic of
13 brain-based disorders.
14

15 17. Neurotoxicants can have a lifelong impact on brain function. Children who have higher
16 blood lead concentrations, for example, may never meet the same peak cognitive ability in adulthood as
17 that in less exposed children. At the other end of the age spectrum, cognitive decline is accelerated in
18 adults who have higher bone lead concentrations and some evidence has shown that lead exposure is a
19 risk factor for the development of late-onset Alzheimer's disease. Few birth cohorts have been studied
20 into adulthood; however, it would be surprising if the effects of other neurotoxicants observed in school-
21 aged children do not persist into adulthood (Lanphear 2015). The cumulative impact of exposures to
22 various toxins that only modestly impact intellectual abilities can be substantial (Lanphear 2015).
23

24 18. The high reported prevalence of learning disabilities and neurodevelopmental disorders has
25 fueled research to better understand the role of environmental chemicals, including the use of prospective
26
27

1 cohort studies that collect individualized biomarkers of exposure to environmental toxins. Biologic
2 markers, or biomarkers, of exposure, which can enhance our ability to quantify an individual's internal
3 dose of a contaminant, are revolutionizing the study of environmental toxins in the same way genetic tests
4 are revolutionizing the study of heritability (Lanphear 2015).

5 **B. The MIREC Cohort Is a Comprehensively Characterized Birth Cohort**

6 19. The MIREC¹ cohort in Canada was developed to obtain biomonitoring data for pregnant
7 women and their infants to examine potential adverse health effects of early-life exposure to
8 environmental chemicals.

9 20. The MIREC cohort is a geographically diverse and comprehensively characterized birth
10 cohort. Women were recruited during the first trimester of pregnancy from 10 cities across Canada,
11 including cities that add fluoride to water for caries prevention purposes (e.g., Toronto), and cities that do
12 not (e.g., Vancouver). Women were followed through delivery and their offspring have undergone
13 periodic neurodevelopmental tests, including IQ testing.

14 21. We administered questionnaires during pregnancy and early childhood to collect
15 information on demographics, occupation, lifestyle, medical history, environmental exposures and diet.
16 Dietary questions included whether the mother drank tap water during pregnancy, how many glasses of
17 water and other beverages she consumed, and duration of breastfeeding.

18 22. Information on the pregnancy and the infant was abstracted from medical charts. Maternal
19 urine was collected at multiple points throughout pregnancy, as was blood, urine, hair, breast milk, cord
20 blood and infant meconium. These samples have been archived in a biobank.

21 23. Study staff from each participating study site completed a 3-day training session that was
22

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¹ MIREC stands for Maternal-Infant Research on Environmental Chemicals. It is an
26 interdisciplinary collaboration between Health Canada scientists and clinical and academic researchers,
27 and was funded by Health Canada, the Ontario Ministry of the Environment, and a grant from the
28 Canadian Institutes of Health Research.

led by a PhD-level psychologist and focused on specialized training of the neurodevelopmental tests. The training emphasized the importance of providing an ideal and standardized environment in the home by ensuring that the test area was well-lit, quiet, and free from distractions and interruptions.

C. Urinary Fluoride Study (Till 2018)

24. In 2018, we published the most comprehensive study of urinary fluoride during pregnancy that has ever been conducted (Till 2018). Our study included 1,566 pregnant women from the MIREC cohort who had urine samples for each trimester of pregnancy. It was the first study of its kind in water-fluoridated areas of North America. A similar study has recently been published of a smaller pregnancy cohort in California (Uyghurturk 2020), but our study remains the largest and most thorough.

1. Methodological Strengths

25. Our study of urinary fluoride was conducted in accordance with sound and objective science practices. Important strengths of the study include: (1) a large study size, with over 1,500 women and over 5,000 urine samples; (2) collection of urine samples from each trimester for each mother; (3) empirical data on the actual measured water fluoride levels for each mother's water treatment plant boundary (WTP) during the course of the pregnancy; (4) control for other factors that have potential to influence urinary fluoride excretion, including tea consumption, alcohol use, pre-pregnancy BMI, maternal age, maternal education, annual household income, and race; (5) control for fluctuations that can occur in urine fluoride during the day by adjusting for dilution using two methods (specific gravity and creatinine) and controlling for time of void and time since last void; and (6) measurement of fluoride in urine using the same scientist (Dr. Martinez-Mier), method (microdiffusion), and laboratory (University of Indiana) as the ELEMENT cohort, thereby enhancing the comparability of the data.

26. Dr. Martinez-Mier's lab at the University of Indiana is considered a gold-standard lab for the testing of fluoride in urine and blood. EPA appears to recognize Dr. Martinez-Mier's expertise as she

was approached by EPA to serve as an expert in this case.

2. Fluoridated Water Has a Large and Significant Effect on Urinary Fluoride

27. In our study, fluoride in water had the strongest correlation with urine fluoride of all the factors that we measured, thus confirming that fluoridated water remains a major source of fluoride intake (Till, 2018).

28. The average urinary fluoride level among pregnant women in fluoridated areas is almost two times higher than the average levels in nonfluoridated areas (Till 2018).

29. The average creatinine-adjusted² maternal urinary fluoride level in the fluoridated areas is 0.87 mg/L, versus 0.46 mg/L in the non-fluoridated areas.³

30. Our data suggests that, for every 0.5 mg/L increase in water fluoride level, urinary fluoride levels will increase by 74-82%.

31. Our findings are consistent with prior studies showing that, among adults, fluoride levels in urine are closely correlated with the concentration of fluoride in water.

32. As part of our study, we attached a table showing the full distribution of urinary fluoride levels, including the 75th and 95th percentile exposures for each trimester (Till et al. 2018, Table S4). At the second trimester, 95th percentile values in the fluoridated areas were 2 mg/L (adjusted for creatinine), and 1.63 mg/L (adjusted for specific gravity).

² Creatinine-adjustment of spot urine samples adjusts for dilution and has been found to have good agreement with 24-hour fluoride values (WHO 2014, Zohouri 2006). We used the same method for creatinine adjustment as Bashash (2017). We also adjusted for dilution by correcting for specific gravity. Our adjustments for creatinine and specific gravity produced results that were highly correlated ($r = 0.91$) and interchangeable in our analyses of the factors that increase urinary fluoride.

³ The average specific gravity-adjusted concentration in the fluoridated areas was 0.71 mg/L (SD 0.38 mg/L), with a range of 0.10 to 3.12 mg/L.

3. Pregnant Women in Water-Fluoridated Areas of the MIREC Cohort Have Similar Urinary Fluoride Levels as the ELEMENT Cohort

33. One of the key findings from our 2018 study is that pregnant women who live in water-fluoridated areas of Canada have urinary fluoride levels that are essentially the same as the urinary fluoride levels documented in the ELEMENT cohort.

34. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts can be appreciated when comparing the respective mean values (0.87 vs. 0.91 mg/L), standard deviations (0.50 vs. 0.40 mg/L), and ranges (0.14-3.80 vs. 0.02-3.67 mg/L) of the study participants in the water fluoridated areas of the MIREC cohort vs. the ELEMENT cohort.

35. The similarity in maternal urinary fluoride levels between the MIREC and ELEMENT cohorts is of scientific and public health relevance given the findings of Bashash (2017) showing an inverse association between maternal urinary fluoride and offspring IQ.

D. Prenatal Fluoride/IQ Study (Green 2019)

36. In 2019, we published our findings on the relationship between prenatal fluoride exposure and IQ in the MIREC cohort. The study, which was published in *JAMA Pediatrics*, provides reliable and unbiased results and was conducted in accordance with sound and objective science practices.

1. Methodological Strengths

37. ***Prospective Birth Cohort Study Design:*** A key strength with our study is that we used a prospective cohort study design, also known as a longitudinal study. Prospective studies are the best available method for investigating the impact of environmental chemicals and, as noted earlier, have helped to revolutionize our understanding of how chemicals impact childhood health.

38. ***Extensive Control for Potential Confounders:*** The MIREC cohort is one of the most comprehensively characterized birth cohorts, with abundant individualized data on factors that may influence neurodevelopment. We took full advantage of this data. We excluded study participants if there

was a known fetal abnormality, if they had any medical complications (i.e., cancer, renal disease, cardiovascular disease), or if there was known maternal alcohol or drug abuse during pregnancy. For analyses using water fluoride, we excluded women if they did not drink tap water during their pregnancy. For those not excluded, we controlled for the following factors: maternal education; maternal age; quality of the child's home environment (HOME); child sex; mother's race; city of residence; secondhand smoke; maternal blood or urinary concentrations of other neurotoxicants, such as lead, arsenic, mercury, manganese, and PFOA. Additionally, we controlled for the diurnal fluctuations that may occur in urinary fluoride levels by including time of day that the urine sample was collected and time since last void.

39. ***Individualized Measures of Fluoride Exposure:*** Another important strength of our study is that we had multiple individualized measures of prenatal fluoride exposure, including: (1) urinary fluoride samples averaged across each trimester of pregnancy and corrected for urinary dilution; (2) measured water fluoride levels from within each participant's water treatment plant boundary during the course of their pregnancy;⁴ and (3) questionnaire data about how much water each woman drank from tap water and water-based beverages.

40. ***Large, Multi-Center Cohort:*** Our study included 512 mother-offspring pairs which is a robust sample size for statistical analyses. Further, the mother-offspring pairs came from 6 cities across Canada, some of which fluoridate their water (average F = 0.59 mg/L), and some of which do not (average F = 0.13 mg/L).⁵ Our study thus permitted us to examine the impact of fluoride exposures on IQ in communities with water fluoridation, thus addressing what some have perceived to be a limitation of prior

⁴ Water treatment plants measured fluoride levels daily if fluoride was added to municipal drinking water and weekly or monthly if fluoride was not added to water. We matched participants' postal codes with water treatment plant zones, allowing an estimation of water fluoride concentration for each woman by averaging water fluoride concentrations (in milligrams per liter) during the duration of pregnancy.

⁵ Pregnant women in the fluoridated areas tended to have higher incomes and more education, which may help explain the lack of difference in average *unadjusted* IQs between fluoridated and non-fluoridated areas (Green 2019, Table 1).

studies of fluoride neurotoxicity.

41. ***Reliable and Objective IQ Test:*** We assessed children’s intellectual abilities with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). This is a validated IQ test with excellent internal reliability ($r = 0.96$), and good test-retest reliability ($r = 0.86$). We used Full Scale IQ (FSIQ), which is a measure of global intellectual functioning, as the primary outcome. The FSIQ score is comprised of two composite scores: Verbal IQ (VIQ)—representing verbal reasoning and comprehension—and Performance IQ (PIQ)—representing nonverbal reasoning, spatial processing, and visual-motor skills.

42. ***Blinded Assessments:*** As with the ELEMENT cohort, our study was “blinded,” meaning the examiners were not aware of the mother’s fluoride exposure status at the time of the examination. This eliminates the potential for examiner bias.

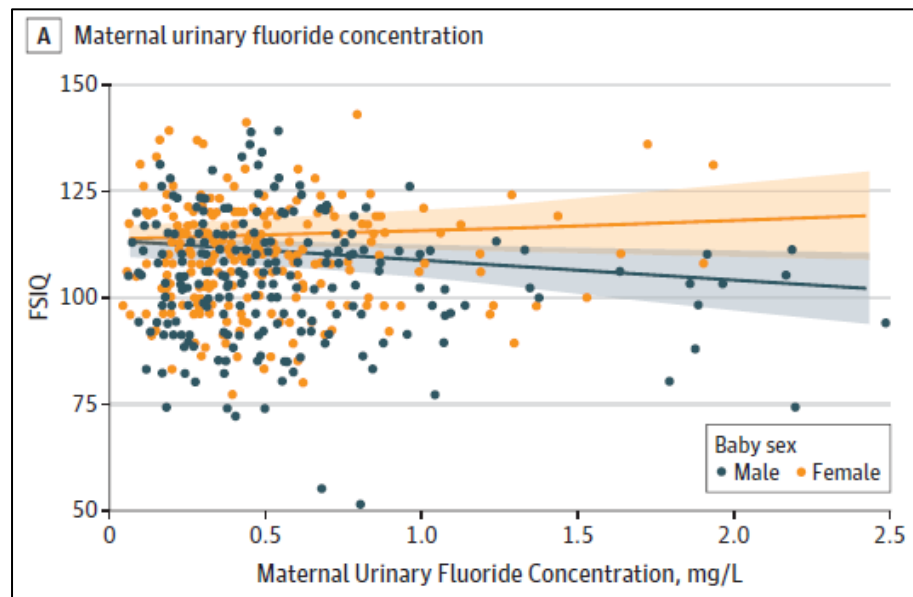
43. ***Statistical Analyses that Did Not Assume Linearity:*** We conducted sound, objective, and rigorous statistical analyses that: (i) controlled for the impact of the large number of measured covariates; (ii) examined the data for collinearity, outliers, and influential points; and (iii) scrutinized the shape of the relationship between fluoride and IQ. With respect to linearity and possible threshold effects, we conducted sensitivity analyses that used quadratic and natural log effect models as well as ran spline analyses that examined the relationship below 0.5 mg/L, 0.8 mg/L, and 1.0 mg/L in urine (and below 0.4 mg/day and 0.8 mg/day in fluoride intake). We did *not* assume that statistical associations between fluoride and IQ were linear and without threshold.

44. Short of intentionally dosing pregnant mothers with fluoride, we maximized the power of environmental epidemiology to investigate whether prenatal fluoride exposure is associated with neurocognitive deficits in a prospective, observational cohort study.

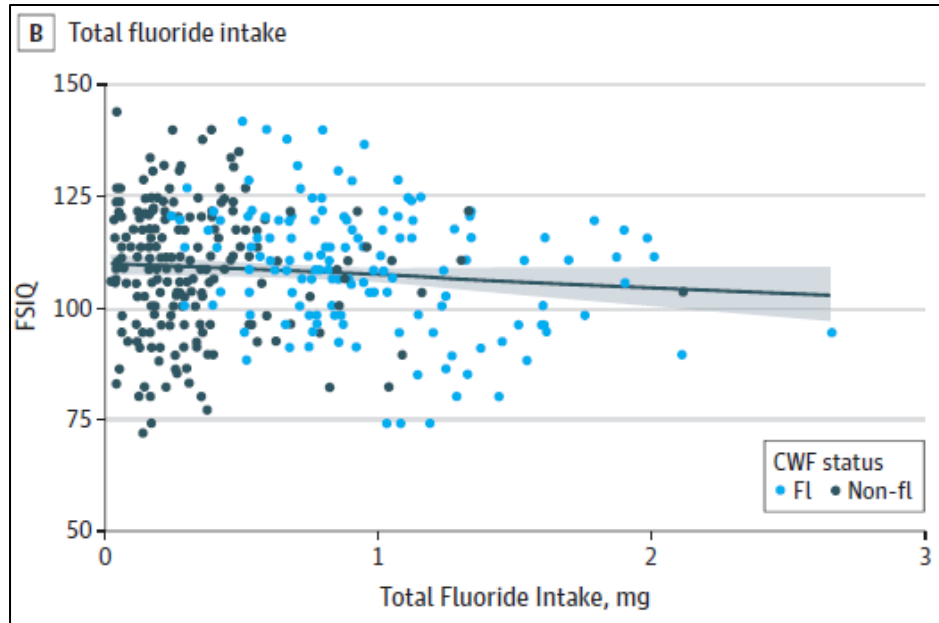
2. Prenatal Fluoride Exposure Is Associated with Large and Significant Reductions in IQ in the MIREC Cohort

45. All three measures of prenatal fluoride exposure—(i) maternal urinary fluoride, (ii) maternal fluoride intake from beverages, and (iii) water fluoride concentration during pregnancy—were associated with large, statistically significant decreases in IQ among the 3 to 4-year old children in the MIREC cohort.

46. After controlling for covariates, a 1-mg/L increase in maternal urinary fluoride⁶ was associated with a **4.49 lower IQ** score (in boys); a 1-mg higher daily intake of fluoride from beverages was associated with a **3.66 lower IQ** score (in boys and girls); and a 1 mg/L higher water fluoride concentration was associated with a **5.29 lower IQ** score (in boys and girls). These fluoride-associated reductions in IQ that we found showed a linear, dose-response relationship with no apparent indication of a threshold (see figures below).



⁶ We used specific gravity (SG) as the primary adjustment method for this study. The average SG-adjusted concentration among women from the fluoridated areas was 0.69 mg/L (SD = 0.42), which is consistent with the concentration in fluoridated areas from the larger cohort (0.71 mg/L, SD = 0.38) (Till 2018). Sensitivity analyses using the creatinine-adjusted urinary fluoride values did not change the results between fluoride and IQ (Green 2019, eTable 2).



47. The effect sizes that we found are large and rival the impact of a population blood lead concentration of 5 $\mu\text{g}/\text{dL}$.⁷ Fourteen percent of the women had urinary fluoride concentrations exceeding 1.0 mg/L, and thus the impact for some children may exceed the ranges identified above.

48. Although maternal urinary fluoride was associated with significant reduction in full-scale IQ in boys, it was not associated with diminished full-scale IQ in girls. As is often the case, the reason for this discrepancy is not currently known. It is known, however, that boys have a higher prevalence of neurodevelopmental disorders such as ADHD, learning disabilities, and intellectual disabilities than girls. It is also known that boys and girls may respond differently to some neurotoxicants. In our studies of the MIREC cohort, for example, we found that low levels of blood lead correlate with a loss of IQ in boys, but not girls (Desrochers-Couture 2018).

49. The possibility that boys are more sensitive to prenatal fluoride exposure than girls is

⁷ My pooled analysis of blood lead and IQ found that an increase in childhood blood lead from <1 to 10 $\mu\text{g}/\text{dL}$ was associated with a 6.9 IQ point decrement (Lanphear 2015, p. 814). General population exposures to lead today are now on the low-to-mid range of this spectrum, with relatively few children having blood lead levels as high as 10 $\mu\text{g}/\text{dL}$.

supported by at least one animal study, in which males had greater deficits from prenatal exposure and females had greater deficits from postnatal exposure (Mullenix et al 1995). While we did not find sex-specific differences with our other two exposure measures (water F concentration and water F intake), these other measures may better correlate with chronic or postnatal exposure and thereby reflect distinct risks.

3. Convergent Findings of ELEMENT and MIREC Cohorts.

50. The significant associations we observed between prenatal fluoride and IQ in the MIREC cohort are consistent with the findings from the ELEMENT cohort (Bashash, 2017).

51. In the ELEMENT study, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 6.3 IQ points among 4-year olds, as measured by General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities. In our analysis, an increase of 1 mg/L in creatinine-adjusted maternal urine was associated with a loss of 4.96 IQ points among 3- to 4-year old boys, as measured by the WPPSI-III test (Green 2019, eTable 2). These effect sizes are generally consistent with each other.

52. The consistency of results in both population cohorts adds further confidence that the association is real, particularly when viewed in the context of other studies that have reported inverse associations between fluoride and IQ in many different locations in other countries, as well as general knowledge about the vulnerability of the developing brain.

E. Infant Fluoride/IQ Study (Till 2020)

53. We recently completed and published a study that examined whether fluoride exposures during infancy have an influence on IQ at 3-4 years (Till 2020).

54. Concerns have been raised about the use of fluoridated water in baby formula due to the high intake of water by bodyweight during infancy. These high intakes have been associated with

significant increases in dental fluorosis, including in the permanent teeth.

55. In our study, we obtained information about fluoride intake of infants through questionnaires that the mothers completed when the children were 30 to 48 months of age.⁸ The questionnaire included the question, “How old was your baby when you ceased breastfeeding exclusively?” Women who breastfed exclusively for six months or longer were included in the breastfeeding (BF) group; those who reported introducing formula within the first six months (never breastfed or partial breastfeeding) were included in the formula-feeding (FF) group.

56. As a separate measure of infant fluoride exposure, we estimated fluoride intake by obtaining the measured water fluoride levels within the water treatment plant boundary during infancy. We took the average of these levels, multiplied by the amount of time that the infant was not exclusively breast-fed during the first year,⁹ and divided it by the estimated average water intake among Canadian formula-fed infants (0.8 L). We excluded any mother-offspring pair if the mother reported not drinking tap water.

1. Methodological Strengths

57. Our study of infants shares many of the same methodological strengths as our prenatal study, including: (i) prospective cohort design; (2) extensive control for potential confounders (discussed below); (3) blinded assessment; (4) relatively large cohort (398 mother-offspring pairs) from both fluoridated and non-fluoridated areas; (5) the same validated and standardized IQ test that we used for the prenatal study (i.e., Wechsler Primary and Preschool Scale of Intelligence-III); and (6) rigorous statistical

⁸ The answers to these questions correlated well with the contemporaneous infant feeding practices that were reported among 11% of the cohort. Among women with breastfeeding questionnaire data and infant feeding observation data, the median difference for when breast-feeding ceased was 0 months, with two-thirds being within 1.5 months of each other.

⁹ The mean duration of exclusive breastfeeding was 4.98 months; 13.6% of women reported never breastfeeding, 8% reported discontinuing breastfeeding after the first three months, and 50.2% reported continuing to breastfeed at six months or longer. Average water fluoride concentration did not significantly differ between the BF (mean=0.32 mg/L) and FF groups (mean=0.29 mg/L; p=.18).

analyses that tested for sex-specific effects and scrutinized the impact of outliers and influential points.

58. We adjusted for potential confounding by selecting covariates *a priori* that have been associated with fluoride, breastfeeding, and children's intellectual abilities. Final covariates¹⁰ included child's sex and age at testing, maternal education, maternal race, second-hand smoke in the home, and quality of the child's home environment (measured at time of testing using the Home Observation for Measurement of the Environment (HOME)). We also controlled for fetal fluoride exposure, using the previously measured maternal urinary fluoride concentrations averaged across each trimester of pregnancy.

2. Fluoride Exposure During Infancy Is Associated with Significant Reductions in Non-Verbal IQ in the MIREC Cohort

59. We found that fluoride exposure during infancy is associated with significant reductions in non-verbal IQ in the MIREC cohort.

60. For each 0.5 mg/L increase in water fluoride concentration, we found a decrease of 4.4 Full-Scale IQ (FSIQ) points among preschool children who were formula-fed in the first six months of life; 0.5 mg/L is the approximate difference in mean water fluoride level between fluoridated (0.59 mg/L) and non-fluoridated (0.13 mg/L) regions. In contrast, we did not find a significant association between water fluoride concentration and FSIQ among children who were exclusively breastfed in the first 6 months.

61. The association between water fluoride concentration and FSIQ must be interpreted with caution, however, because the association became nonsignificant when two outliers were removed.

62. We observed an even stronger association between water fluoride and PIQ (non-verbal intelligence). A 0.5 mg/L increase in water fluoride level predicted a decrement in non-verbal IQ in both

¹⁰ For each analysis, a covariate was retained in the final model if its p-value was <0.20 or its inclusion changed the regression coefficient of water fluoride concentration or fluoride intake from formula by more than 10%.

1 the formula-fed (**9.3-points**) and the breastfed groups (**6.2-points**). Adjusting for fetal exposure or
2 removing two extreme scores did not appreciably alter these results.

3 63. We observed converging results using fluoride intake from formula feeding, which is a
4 continuous, time-weighted exposure estimate. For each 0.5 mg/day of fluoride intake, we found an **8.8-**
5 **point** decrement in non-verbal IQ; adjusting for fetal exposure attenuated the association only slightly
6 (**7.6-point** decrement).

7 64. The time-weighted fluoride intake estimate may reflect a more refined measure of exposure
8 in infancy because it captures differences in both water fluoride level and the proportion of time each child
9 was given formula over the first year of life. Yet, our binary classification of whether a child was
10 exclusively breastfed for the first 6 months may distinguish infants who are exposed to higher amounts of
11 fluoride during the early infancy period when the brain undergoes significant development because breast
12 milk contains minutes amounts of fluoride.

13 65. Taken together, these findings suggest that using “optimally” fluoridated water (0.7 mg/L)
14 to reconstitute infant formula may diminish the development of intellectual abilities in young children,
15 particularly non-verbal abilities. The findings also suggest that both prenatal and early childhood fluoride
16 exposure affect the development of non-verbal intelligence to a greater extent than verbal intelligence.
17 Prior studies examining prenatal exposure to fluoride and IQ showed a similar pattern.
18

19
20 **F. The Limitations of Our Studies Do Not Provide a Likely Explanation for the**
21 **Results**

22 66. As with all epidemiological studies, our fluoride studies have limitations. These
23 limitations, however, are unlikely to explain the large and significant associations that we have found
24 between early-life exposures and IQ.

25 67. Most of the limitations in our studies involve fluoride measurement. These limitations
26
27

1 include: (1) use of spot urine samples instead of 24-hour samples;¹¹ (2) lack of water fluoride
2 measurements from the participant's home; (3) reliance on questionnaire data as to water consumption
3 and breast-feeding; (4) lack of information on the fluoride content of the infant formula concentrate and
4 other sources of fluoride exposure; and (5) use of non-validated methods¹² for estimating total beverage-
5 based intake of fluoride by mothers and water fluoride intake by infants.

6 68. The limitations in our exposure estimates are non-differential, meaning they apply equally
7 to study participants with low fluoride exposure and high fluoride exposure. Non-differential errors in
8 exposure measurement will generally bias the results towards the null (i.e., attenuate, rather than inflate,
9 an association between exposure and outcome). Because of this, the limitations in our exposure estimates
10 do not provide a likely explanation for the significant IQ decrements we observed with fluoride exposures.
11 If anything, these limitations likely attenuated the relationship.

12 69. Another limitation of our studies is that the MIREC cohort tends to be more affluent, more
13 educated, and less ethnically diverse than the general population. Our results may thus not be
14 representative of how fluoride may affect IQ in more disadvantaged populations. On the other hand,
15 affluent populations tend to have less confounders (e.g., less exposure to other stressors and toxicants that
16 can negatively affect neurodevelopment) (Lanphear 2015). We thus worry less about the role of
17 confounders in the MIREC cohort than we would in other cohorts.

18 70. Finally, despite our comprehensive array of covariates included, our studies could not
19 address the possibility of unmeasured residual confounding. This is a limitation in all observational
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23 ¹¹ A 24-hour sample of urine is considered the optimal dosimeter for measuring chronic fluoride
24 exposure (WHO 2014). While we did not have 24-hour samples available to test, we partially controlled
25 for this by adjusting samples by creatinine. Creatine-adjusted urine fluoride measurements have been
26 found to have a strong correlation with 24-hour samples (Villa 2010; Zohouri 2006).

27 ¹² These methods were not validated in the sense that they have not yet been replicated by other
28 authors in other studies. Our method for assessing fluoride intake from beverages did show internal
validity, however, by predicting maternal urinary fluoride levels. This can be seen in the highly significant
correlations that we found ($p < 0.0001$) between maternal urinary fluoride and number of glasses of water
consumed per day and black tea consumption (see Till 2018).

1 studies, and thus inherent to the field. One of the potential confounders for which we lacked data was
2 maternal IQ. We did, however, control for maternal education which is highly correlated with maternal
3 IQ. Moreover, a greater proportion of women living in fluoridated communities (76%) had a university-
4 level degree compared with women living in nonfluoridated communities (66%), and thus it seems
5 unlikely that controlling for maternal IQ would affect our results, particularly since there is no reason to
6 believe that maternal IQ would be correlated with maternal urinary fluoride.

7
8 71. I understand that the EPA has suggested that the location of our study in Canada somehow
9 reduces the relevance of our findings to populations in the US. I disagree. From a biologic standpoint,
10 there is no credible basis to believe that people in the U.S. will respond differently to fluoride than people
11 in Canada. Nor am I aware of any credible reason to conclude, let alone suspect, that people in water-
12 fluoridated areas of the U.S. are exposed to materially less fluoride than people in water-fluoridated cities
13 of Canada.

14 IV. CONCLUSION

15 72. The collective evidence from prospective cohort studies supports the conclusion that
16 fluoride exposure during early brain development diminishes the intellectual abilities in young children,
17 including at the purportedly “optimal” levels of exposure for caries prevention.
18

19
20 I declare under penalty of perjury, under the laws of the United States, that the foregoing is true
21 and correct to the best of my knowledge and belief.

22 Executed on May 20, 2020, in Vancouver, British Columbia, Canada.
23

24
25 

26 BRUCE LANPHEAR, MD, MPH
27

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**CURRICULUM VITAE OF
BRUCE LANPHEAR, MD, MPH**

CURRICULUM VITAE

Bruce Perrin Lanphear, MD, MPH

Office Address

Blusson Hall
8888 University Drive
Burnaby, BC V5A 1S6
Canada
e-mail: blanchear@sfu.ca

Marital status: Married to Nancy Ebbesmeyer Lanphear, M.D., a developmental pediatrician

Citizenship: United States of America and Canada (dual citizenship)

Specialty: Board Certified in General Preventive Medicine & Public Health

Employment

1984-1986	Paramedic, Jackson County Jail, Kansas City, Missouri
1988-1989	Physician, International Travel Clinic, University of Cincinnati, Cincinnati, Ohio
1988-1989	Staff Physician, Sexually Transmitted Disease Clinic, Cincinnati Public Health Department, Cincinnati, Ohio
1989-1992	Assistant Professor of Environmental Health, Associate Director, Medical Center Health Services, University of Cincinnati
1992-1997	Senior Instructor, Departments of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1992-1994	National Research Scholar Award in General Pediatric Research, University of Rochester School of Medicine and Dentistry.
1992-1997	Assistant Professor, Department of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1997-2002	Associate Professor, Department of Pediatrics, Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, Ohio.
1997-2008	Director, General Pediatric Research Fellowship Training Program, Children's Hospital Medical Center and the University of Cincinnati.
1997-2008	Director, Children's Environmental Health Center, Children's Hospital Medical Center and the University of Cincinnati.
1997-2006	Associate Professor (Adjunct), Departments of Pediatrics and of Environmental Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY.
1998-2003	Associate Director for Research, Division of General & Community Pediatrics, Children's Hospital Medical Center.
2001-2002	Associate Professor (tenured), Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
2001-2004	Associate Professor (Adjunct), Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan.
2002-2008	Sloan Professor of Children's Environmental Health, Departments of Pediatrics and Environmental Health, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

2008-2012 Adjunct Professor of Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati.
 2008- Professor of Children's Environmental Health, Faculty of Health Sciences, Simon Fraser University
 2008- Clinician Scientist, Child & Family Research Institute, BC Children's Hospital, University of British Columbia

Education

1980-1985 Bachelor of Arts in Biology
 1980-1986 University of Missouri at Kansas City, Medical Degree (1986)
 1986-1987 Internship, University of Arkansas for Medical Sciences, Little Rock, Arkansas
 1987-1988 Tulane School of Public Health & Tropical Medicine
 Masters in Public Health & Tropical Medicine
 1987-1989 General Preventive Medicine and Public Health Residency
 Tulane School of Public Health & Tropical Medicine
 1992-1995 Postdoctoral Fellowship in General Academic Pediatric Research
 University of Rochester School of Medicine, Rochester, NY

Awards and Honors

2011 Sterling Prize in Controversy, Simon Fraser University
 2012 Research Integrity Award, International Society for Environmental Epidemiology
 2013 Public Policy and Advocacy Award, Academic Pediatric Association
 2015 Research Award, Academic Pediatric Association
 2015 Confederation of Union Faculty Associations of British Columbia (CUFA-BC) Academic of the Year Award
 2018 Lumina Award from the Women for Healthy Environmental Health, Pittsburgh, PA

Teaching Experience

1992-1997 Course Instructor, "Public Health & the Environment", Department of Community & Preventive Medicine, The University of Rochester School of Medicine and Dentistry. A required course for MPH students taught annually.
 1997-2008 Founding Director, NIH-funded, General Academic and Community Pediatric Research Fellowship Training Program, Cincinnati Children's Hospital Medical Center. This interdisciplinary, research training program, which included pediatricians, psychologists and epidemiologists, was the first training program in Children's Environmental Health.
 1998-2008 Course Co-Instructor, "Children's Health & the Environment", Department of Environmental Health, The University of Cincinnati School of Medicine. A course taught every other year to MPH, PhD and postdoctoral trainees in medical subspecialties.
 2008- Course Instructor, "Children's Health and the Environment". A 2-week intensive course taught annually to 4th year undergraduate students at Simon Fraser University.
 2011- Course Instructor, "Plagues, Pollutants and Poverty: The Origins and Evolution of Public Health". An undergraduate course at Simon Fraser University.

Committee and Community Involvement

1993-1997	Lead Poisoning Prevention Task Force, Monroe County Health Department.
1994-1997	Investigational Review Board, Rochester General Hospital
1995-	Scientific Consultant, National Center for Healthy Housing, Columbia, Maryland.
1996-1997	Member, New York State Task Force on Environmental Neurotoxins, University of Rochester School of Medicine
1996-2001	Member, National Institute for Environmental Health Sciences Grant Review Committee for Community-Based Interventions (FG)
1996-1998	Chairman, U.S. Department of Housing and Urban Development Committee on Lead-Contaminated House Dust
1998	Member, Review Group for National Research Service Awards, Health Resources and Services Administration
1998-2000	Member, Cincinnati Board of Health, Cincinnati, Ohio.
1998-2001	Member, Science and Research Work Group, Office of Children's Health Protection Advisory Committee, U.S. EPA
1998-2000	Member, Cincinnati Lead Poisoning Prevention Advisory Task Force, Cincinnati, Ohio.
1999	Member, K23 Grant Review Committee, National Institute for Environmental Health Sciences, August 1999
1999	Member, Expert Panel on Soil Pica Behavior, Agency for Toxic Substance Disease Registry, June 7 th -8 th , Atlanta, Georgia
2000	Member, Panel on Health Disparities: Linking Biological and Behavioral Mechanisms with Social and Physical Environments, National Institute for Environmental Health Sciences, July 14-15 th
2000-2002	Member, Workshop on Assessing Environmental Exposures to Children, U.S. Environmental Protection Agency, July 26-27 th
2000-2004	Member, Children's Environmental Health Project, AAP's Child Health Research Center, Rochester, NY.
2001	Senate Testimony, "Ensuring that Children with Dangerous Levels of Lead in their Blood Receive Care as Early as Possible". Subcommittee on Housing and Transportation of the Committee on Banking, Housing and Urban Affairs, 107 th U.S. Congress, November 13 th , 2001.
2001	Reviewer, National Research Council, National Academy of Science Update of the 1999 Arsenic in Drinking Water Report
2001-2003	Member, Expert Panel on Children's Health and the Environment, North American Commission for Environmental Cooperation
2002-	Member, Scientific Advisory Board, Scientist Communication Network.
2003	Member, "Herculaneum Health Study Workshop" Agency for Toxic Substance Diseases Registry, May 22 nd to 23 rd , 2003
2003-2004	Panel Member, "Lead Poisoning in Pregnant Women", Mt. Sinai for Children's Health and the Environment, New York, NY
2003	Member, "Invitational Workshop on a proposed American Family Study" National Human Genome Research Institute, December 1 st to 3 rd , 2003.

2004-2006 Member, Committee on “Ethical Consideration for Research on Housing-Related Health-Hazards involving Children”, National Research Council and the Institute of Medicine, The National Academies

2004 Congressional Testimony, “Tapped Out? Lead in the District of Columbia and the Providing of Safe Drinking Water”, Subcommittee on Environment and Hazardous Materials of the Committee on Energy and Commerce, U.S. House of Representatives, 108th Congress, July 22nd, 2004

2005 Reviewer, “Superfund and Mining Megasites – Lessons from the Couer d’ Alene River Basin”, National Research Council, The National Academies.

2005 Ad Hoc Member, NIEHS Board of Scientific Counselors Review of the Epidemiology Branch, April 3rd to April 5th, 2005

2005 Senate Briefing, “The Connection of Environmental Chemicals and Learning Disabilities”, U.S. Senate, May 10th, 2005

2006 Invited Participant, NIEHS Strategic Planning Forum, National Institute for Environmental Health Sciences, Chapel Hill, North Carolina, October 17-18th, 2006.

2006-2008 Member, U.S. EPA’s Clean Air Scientific Advisory Committee Lead Review Panel.

2006-2008 Member, National Children’s Study Steering Committee, NICHD

2006 Invited Participant, “How Does Housing Affect Health Outcomes of Children?”, MacArthur Foundation, Chicago, Illinois, June 21st-22nd, 2006.

2006- 2010 Member, External Scientific Advisory Committee, Richmond Center for Excellence in Tobacco Research, American Academy of Pediatrics.

2007 Testimony, Vermont State Legislature, “The Lingering Legacy of Lead Toxicity”, Montpelier, Vermont, February 1st, 2007

2007 Testimony, Connecticut State Legislature, “The Legacy of Lead Toxicity”, Hartford, Connecticut, March 14th, 2007. (PG)

2007 Invited Testimony, United States Senate Hearing, “Lead and Children’s Health”. Committee on Environmental and Public Works, October 18th, 2007

2007-2008 Member, Committee on “Committee on Contaminated Drinking Water at Camp Lejeune”, National Research Council, The National Academies.

2008 Member, Expert Panel on Health and the Environment, Statistics Canada, Ottawa,

2008- Member, Alliance for the Global Elimination of Lead Paint, Intergovernmental Forum on Chemical Safety (IFCS), World Health Organization

2008-2009 Reviewer, Toxicological Review and Recommended Toxicological Reference Values for Environmental Lead Exposure in Canada, Health Canada

2009-2013 Scientific Advisor, Canada Lead Study funded by Health Canada (Patrick Levallois, Principal Investigator).

2009-2014 Board Member, Barro Sin Plomo

2009-2010 Member, Health and Environment Experts Advisory Group of the Canadian Longitudinal Study on Aging, Canadian Institutes of Health Research

2010-2012 Member, US Environmental Protection Agency Science Advisory Board for Evaluating Dust Lead Standards

2010-2013 Advisor, Canada Environmental Health Law and Canadian Partnership for Children’s Health and Environment Retrofit Project

2010-2012 Member, Physicians Advisory Panel, Canada Health Measures Survey

2010 Invited Testimony, United States Senate Hearing, “Research on Environmental Health Factors with Autism and Neurodevelopmental Disorders”, August 3rd, 2010

2010 Member, Joint FAO/WHO Expert Panel for Toxicological and Health Review of Bisphenol A

2010-2015 Board Member, Global Community Monitoring, Oakland, California

2010- Chairman, Scientific Advisory Committee for Dartmouth University’s Program in Children’s Health and the Environment

2011-2016	Member, American Academy of Pediatrics Executive Council on Environmental Health
2011-2012	Member, US Environmental Protection Agency Science Advisory Board for Evaluating Hazards of Partial Water Line Replacement
2011	Invited Testimony, Special Committee on Cosmetic Pesticides, Legislative Assembly, Province of British Columbia, October 7 th , 2011
2011-2012	Member, Panel on Health Effects of Low-level Lead, Office of Health Effects, National Toxicology Program of the National Institutes of Environmental Health Sciences,
2012-	Member, Expert Advisory Committee, Canada Health Measures Survey
2012-	Member, Environmental Defence Fund Science Advisory Committee on Toxics
2015	Reviewer, Review of Clinical Guidance for the Care of Health Conditions Identified by the Camp Lejeune Legislation, Institute of Medicine, The National Academies
2016-	Member, The Lancet Commission on Pollution, Health & Development
2016-	Member, Targeting Environmental Neuro-Developmental Risks (TENDR)
2016	Member, Steering Committee, The National Lead Summit, United States
2017	Rockefeller Foundation Academic Writing Retreat, Bellagio, Italy
2017-	Member, Advisory Committee for the Flint (MI) Cohort Study
2017-	Pure Earth Leadership Council
2018-	Member Project TENDR Advisory Board
2018-	Member, Mercury Disability Board Committee, Health Canada

Editorial Boards

2000-2015	Assistant Editor, <i>Environmental Research</i>
2000-2008	Deputy Editor, <i>Public Health Reports</i>
2004	Associate Editor, <i>Pediatrics</i> supplement on Children's Environmental Health
2004-2017	Editorial Board Member, <i>PLoS Medicine</i>
2005-2014	Editorial Board Member, <i>Breastfeeding Medicine</i>
2007-	Editorial Board Member, <i>Environmental Health</i>
2008-2012	Editorial Review Board Member, <i>Environmental Health Perspectives</i>
2012-2015	Associate Editor, <i>Environmental Health Perspectives</i>
2016-	Advisor, <i>Environmental Health Perspectives</i> News Section

Societies and Organizations

1989-2008	American Public Health Association
1996-2015	Academic Pediatric Association
1997-2012	American Association for the Advancement of Science
2000-2008	Society for Pediatric Research
2001-2008	American Pediatric Society
2001-2016	Specialty Fellow, American Academy of Pediatrics
2006-	Fellow, Collegium Ramazzini
2006-	Member, International Society for Environmental Epidemiology
2008-	Founding Member, International Society for Children's Health & the Environment
2011-2017	Secretary and Treasurer, International Society for Children's Health & the Environment
2012-	Member, International Society for Exposure Science
2017-2018	Vice-President, International Society for Children's Health & the Environment
2019-2020	President, International Society for Children's Health & the Environment

Video and Website Production – www.littlethingsmatter.ca

1. Canadian Environmental Health Atlas: A Portal to Discover the Promise of Environmental Health.
2. Shifting the Curve: The Impact of Toxins on ADHD in U.S. Children (video)
3. Little Things Matter: The Impact of Toxins on the Developing Brain (video)
4. Little Things Matter: The Impact of Toxins on Preterm Birth (video)
5. Prevention Paradox: Why We are Failing to Prevent Disease (video)
6. Little Things Matter: The Deadly Impact of Airborne Particles (video)
7. Cause or Cure: A Plea for Prevention (video)
8. Crime of the Century: The Failure to Prevent the Lead Pandemic (video)

Original Research

1. Lanphear BP. Deaths in Custody. American Journal Forensic Medicine & Pathology 1987;8:299-301.
2. Lanphear BP, Snider DE. Myths of Tuberculosis. J Occ Med 1991;33:501-504.
3. Linnemann CC Jr, Cannon C, DeRonde M, Lanphear BP. Effect of educational programs, rigid sharps containers, and universal precautions on reported needle-stick injuries in healthcare workers. Infection Control Hospital Epidemiology 1991;12:214-20.
4. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. Journal Occupational Med 1992;34:718-721.
5. Lanphear BP, Linnemann CC Jr, Cannon CG, DeRonde MM. Decline of clinical hepatitis B in workers at a general hospital. Clinical Infectious Disease 1993;11:10-14.
6. Lanphear BP, Linnemann CC Jr, Cannon C, DeRonde MM, Pender L, Kerly L. Hepatitis C virus infection in health care workers. Infection Control Hospital Epidemiology 1994;15:745-750.
7. Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.
8. Lanphear BP, Winter NL, Apetz L, Eberly S, Weitzman M. A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 1996;98:35-40.
9. Christy C, Pulcino M, Lanphear BP, McConnochie K. Screening for tuberculosis infection in urban children. Arch Pediatrics Adolescent Med 1996;150:722-726.
10. Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.
11. Lanphear BP, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S, Emond M, Matte TD. Lead-contaminated house dust and urban children's blood lead levels. American Journal of Public Health 1996;86:1416-1421.

12. Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. *Pediatrics* 1997.
<http://www.pediatrics.org/cgi/contents/full99/3/e1>.
13. Emond MJ, Lanphear BP, Watts A, Eberly S for the Rochester Lead-in-Dust Study Group. Measurement error and its impact on the estimated relationship between dust lead and children's blood lead. *Environmental Research* 1997;72:82-92.
14. Lanphear BP, le Cessie S, Atkinson WL, Watelet L. Association of live births and the resurgence of measles. *International Journal Epidemiology* 1997;26:204-211.
15. Rust SW, Burgoon DA, Lanphear BP, Eberly S. Log-additive versus log-linear analysis of lead-contaminated house dust and children's blood lead levels: Implications for residential dust-lead standard. *Environmental Research* 1997;72:173-184.
16. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. *Environmental Research* 1997;74:67-73.
17. Lanphear BP, Byrd RS, Auinger P, Schaffer S. Community characteristics associated with elevated blood lead levels in children. *Pediatrics* 1998;101:264-271.
18. Lanphear BP, Rust SW, Burgoon DA, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. *Environmental Research* 1998;76:120-130.
19. Lanphear BP. The paradox of lead poisoning prevention. *Science* 1998;281:1617-1618.
20. Lanphear BP, Hall CB, Black J, Auinger P. Risk factors for the early acquisition of HHV-6 and HHV-7 infection in children. *Pediatric Infectious Disease Journal* 1998;17:792-795.
21. Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. *Environmental Research* 1998;79:51-68.
22. Marron R, Lanphear BP, Kouides R, Dudman L, Manchester R, Christy C. Efficacy of informational letters on Hepatitis B immunization rates in university students. *J Am College Health* 1998;47:123-127.
23. Howard CR, Howard FM, Lanphear BP, deBlieck EA, Eberly S, Lawrence RA. Effect of early pacifier use on breastfeeding duration. *Pediatrics* 1999;103.
<http://www.pediatrics.org/cgi/contents/full103/3/e33>.
24. Lanphear BP, Howard CR, Eberly S, Auinger P, Kolassa J, Weitzman M, Alexander K, Schaffer S. Primary prevention of childhood lead exposure: A randomized trial of dust control. *Pediatrics* 1999;103:772-777.

25. Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels among the U.S. population. *JAMA* 1999;281:2294-2298.
26. Howard CR, de Blieck EA, ten Hoopen C, Howard F, Lanphear BP, Lawrence RA. Physiologic stability of newborns during cup and bottle-feeding. *Pediatrics* 1999;104:1204-1207.
27. Steiner JF, Curtis P, Lanphear BP, Vu KO, Reid A. Federally-funded fellowship training in primary care research: perspectives of program directors. *Academic Medicine* 2000;75:74-80.
28. Stone KE, Lanphear BP, Pomerantz WJ, Khoury J. Injuries and deaths in children due to window-falls. *Journal of Urban Health* 2000;77:26-33.
29. Mansour M, Lanphear BP, DeWitt TG. Barriers to asthma care among underserved, urban children. *Pediatrics* 2000;106:512-519.
30. Lanphear BP, Eberly S, Howard CR. Long-term effect of dust control on children's blood lead levels. *Pediatrics* 2000 <http://www.pediatrics.org/cgi/contents/full106/4/e48>.
31. Lanphear BP, Dietrich KN, Auinger P, Cox C. Cognitive deficits associated with blood lead levels <10 µg/dl in U.S. children and adolescents. *Public Health Reports* 2000;115:521-529.
32. Lanphear BP, Aligne C, Auinger P, Byrd R, Weitzman M. Residential exposures associated with asthma in U.S. children. *Pediatrics* 2001;107:505-511.
33. Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick S, Naahas R. Contribution of residential exposures to asthma in US children and adolescents. *Pediatrics* 2001. <http://www.pediatrics.org/cgi/content/full/107/6/e98>.
34. Phelan KJ, Kalkwarf H, Khoury J, Lanphear BP. Trends and patterns of playground injuries in U.S. children and adolescents. *Ambulatory Pediatrics* 2001;1:227-233.
35. Mansour M, Lanphear BP, Hornung R, Khoury J, Bernstein DI, Menrath W, Decolongon J. A side-by-side comparison of sampling methods for settled indoor allergens. *Environ Res* 2001;87:37-46.
36. Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of dust control on children's blood lead concentrations: A systematic review. *Env Health Perspect* 2002;110:103-107.
37. Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. *Journal of Pediatrics* 2002;140:40-47.
38. Steiner JF, Lanphear BP, Curtis P, Vu KO. The training and career paths of fellows in the National Research Service Award (NRSA) program for research in primary medical care. *Acad Med* 2002;77:712-718.
39. Steiner JF, Lanphear BP, Curtis P, Vu KO. Indicators of early research productivity among primary care fellows. *J Gen Intern Med* 2002;17:845-851.

40. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake in childhood and adolescence, adult bone density and osteoporotic fractures in U.S. women. *Am J Clin Nut* 2003;77:257-265.
41. Howard CR, Howard FM, Lanphear BP, Eberly S, deBlieck EA, Oakes D, Lawrence RA. A randomized trial of pacifier use and bottle-feeding and their effect on breastfeeding. *Pediatrics* 2003;111:511-518.
42. Curtis P, Dickinson P, Steiner J, Lanphear BP, Vu K. Building capacity for research in family medicine: Is the blueprint faulty? *Family Medicine* 2003;35:124-130.
43. Lanphear BP, Succop P, Roda S, Henningsen G. The effect of soil abatement on blood lead levels in children living near a former smelting and milling operation. *Public Health Reports* 2003;118:83-90.
44. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. *N Engl J Med* 2003;348:1517-1526.
45. Kahn RS, Khoury JC, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactivity-impulsivity, inattentive and oppositional behaviors. *Journal of Pediatrics* 2003;143: 104-110.
46. Auinger P, Kalkwarf HJ, Mansour M, Lanphear BP. Trends in otitis media in US children. *Pediatrics* 2003;112:514-520.
47. Haynes E, Kalkwarf H, Hornung R, Wenstrup R, Dietrich K, Lanphear B. Vitamin D Fok1 polymorphism and blood lead levels in children. *Environ Health Persp* 2003;111:1665-1669.
48. Steiner JF, Curtis P, Lanphear BP, Vu KO, Main DS. Assessing the role of influential mentors in the research development of primary care fellows. *Academic Medicine* 2004;79:865-872.
49. Yolton K, Auinger P, Dietrich KN, Lanphear BP, Hornung R. Exposure to environmental tobacco smoke and cognitive abilities among US children and adolescents. *Environ Health Persp* 2005;113:98-103.
50. Phelan KJ, Khoury J, Kalkwarf H, Lanphear BP. Residential injuries in US children and adolescents. *Public Health Reports* 2005;120:63-70.
51. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in exposure to environmental tobacco smoke among children. *Environ Health Perspect* 2005;113:362-367.
52. Lanphear BP, Hornung R, Ho M. Screening housing to prevent lead toxicity in children. *Pub Health Rep* 2005;120:305-310.
53. Rosner D, Markowitz G, Lanphear BP. J. Lockhart Gibson and the discovery of the impact of lead pigments on children's health: A review of a century of knowledge. *Pub Health Rep* 2005;120:296-300.

54. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. *Environ Health Perspect* 2005;113:894-899.
55. Nagaraja J, Menkedick J, Phelan KJ, Ashley PJ, Zhang J, Lanphear BP. Deaths from residential injuries in US children and adolescents, 1985 to 1997. *Pediatrics* 2005;116:454-61.
56. Eskenazi B, Gladstone EA, Berkowitz GS, Drew CH, Faustman EM, Holland NT, Lanphear BP, Meisel SJ, Perera FP, Rauh VA, Sweeney A, Whyatt RM, Yolton K. Methodologic and logistic issues in conducting longitudinal birth cohort studies: Lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Persp* 2005;113:1419-1429.
57. Eggleston PA, Diette G, Lipsett M, Lewis T, Tager I, McConnell R, Chrischilles E, Lanphear BP, Miller R, Krishnan J. Lessons learned for the study of childhood asthma from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Persp* 2005;113:1430-1436.
58. Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. *J Pediatrics* 2006;149:220-226.
59. Yuan W, Holland S, Cecil K, Dietrich K, Wessel SD, Altaye M, Hornung R, Ris M, Egelhoff J, Lanphear B. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. *Pediatrics* 2006;118:971-977.
60. Howard CR, Lanphear N, Lanphear BP, Eberly S, Lawrence RA. Parental responses to infant crying and colic: the effect on breastfeeding duration. *Breastfeeding Med* 2006;1:146-155.
61. Brinkman W, Geraghty S, Lanphear B, Khoury J, Gonzalez-Del-Rey J, DeWitt T, Britto M. Evaluation of resident communication skills and professionalism: A matter of perspective? *Pediatrics* 2006;118:1371-1379.
62. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect* 2006;114:1904-1909.
63. Brinkman WB, Geraghty SR, Lanphear BP, Khoury JC, Gonzalez-Del-Rey JA, DeWitt TG, Britto MT. Effect of multisource feedback on resident communication skills and professionalism: a randomized controlled trial. *Arch Pediatr Adolesc Med* 2007;161:44-49.
64. Wilson SE, Kahn RS, Khoury J, Lanphear BP. The role of air nicotine in explaining racial differences in cotinine among tobacco-exposed children. *Chest* 2007;131:856-862.

65. Froehlich T, Lanphear BP, Dietrich KN, Cory-Slechta D, Wang N, Kahn RS. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. *Biol Psychiatry* 2007;62:243-249.
66. Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Arch Pediatr Adolesc Med* 2007;161:857-864.
67. Landrigan PJ, Woolf AD, Gitterman B, Lanphear B, Forman J, Karr C, Moshier EL, Godbold J, Crain E. The Ambulatory Pediatric Association Fellowship in Pediatric Environmental Health: A five-year assessment. *EHP* 2007;115:1383-1387.
68. Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, Canfield RL. Blood lead concentrations < 10 µg/dL and child intelligence at 6 years of age. *Environ Health Perspect* 2008;116:243-248.
69. Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. Decreased brain volume in adults with childhood lead exposure. *PLoS Med* 2008;5:e112.
70. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, Lanphear BP, Ho M, Rae MN. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 2008;5:e101.
71. Spanier AJ, Hornung RW, Kahn RS, Lierl MB, Lanphear BP. Seasonal variation and environmental predictors of exhaled nitric oxide in children with asthma. *Pediatr Pulmonol* 2008;43:576-583.
72. Braun JM, Froehlich TE, Daniels JL, Dietrich KN, Hornung R, Auinger P, Lanphear BP. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. *Environ Health Perspect* 2008;116:956-962.
73. Yolton K, Khoury J, Hornung R, Dietrich KN, Succop P, Lanphear BP. Environmental tobacco smoke exposure and child behaviors. *J Dev Behav Pediatr* 2008;29:456-463.
74. Yeoh B, Woolfenden S, Wheeler D, Alperstein G, Lanphear B. Household interventions for prevention of domestic lead exposure in children. *Cochrane Database Syst Rev*. 2008;2:CD006047.
75. Geraghty SR, Khoury JC, Morrow AL, Lanphear BP. Reporting individual test results of environmental chemicals in breastmilk: potential for premature weaning. *Breastfeed Med*. 2008;3:207-213.

76. Spanier AJ, Kahn RS, Hornung RW, Wang N, Sun G, Lierl MB, Lanphear BP. Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children. *Pediatr Pulmonol.* 2009;44:812-819.
77. Hornung RW, Lanphear BP, Dietrich KN. Age of greatest susceptibility to childhood lead exposure: A new statistical approach. *Environ Health Persp* 2009;117:1309-1312.
78. Phelan KJ, Khoury J, Xu Y, Lanphear BP. Validation of a HOME Injury Survey. *Injury Prevention* 2009;15:300-306.
79. Braun J, Yolton K, Dietrich K, Hornung R, Ye X, Calafat AM, Lanphear BP. Prenatal Bisphenol A exposure and early childhood behavior. *Environ Health Persp* 2009;117:1945-1952.
80. Yolton K, Khoury J, Xu Y, Succop P, Lanphear B, Bernert JT, Lester B. Low-level prenatal exposure to nicotine and infant neurobehavior. *Neurotoxicol Teratol.* 2009;31:356-363.
81. Froehlich T, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, Kahn RS. The association of tobacco and lead exposure with attention-deficit/hyperactivity disorder in a national sample of US children. *Pediatrics* 2009;124:e1054-1063.
82. Brubaker CJ, Schmithorst VJ, Haynes EN, Dietrich KN, Egelhoff JC, Lindquist DM, Lanphear BP, Cecil KM. Altered myelination and axonal integrity in adults with childhood lead exposure: A diffusion tensor imaging study. *Neurotoxicology* 2009;30:867-875.
83. Yolton K, Xu Y, Khoury J, Succop P, Lanphear B, Beebe DW, Owens J. Associations between secondhand smoke exposure and sleep patterns in children. *Pediatrics.* 2010;125:e261-268.
84. Brubaker CJ, Dietrich KN, Lanphear BP, Cecil KM. The influence of age of lead exposure on adult gray matter volume. *Neurotoxicology* 2010;31:259-266.
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Presentations

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2. "Common Misconceptions about Tuberculosis". American Lung Association, St. Elizabeth's Hospital, Belleville, IL, March 19, 1991.
3. "Prevention and Control of Infectious Disease in Health Care Workers". Miami Valley Hospital, Dayton, OH, September 5, 1991.

4. "Transmission of Hepatitis B Virus Infection in Health Care Workers". Ohio University, Athens, Ohio, March 21, 1992.
5. "Universal Immunization Against Hepatitis B Virus". Grand Rounds, Dayton Children's Hospital, May 1992, Dayton, Ohio.
6. "Correlation of Blood Lead Levels and Dust Lead Levels Using Three Dust Collection Methods. Environmental Protection Agency, Research Triangle, N.C., January 20, 1994.
7. "Relation of Lead-Contaminated House Dust and Blood Lead Levels in Urban Children" Environmental Protection Agency, Washington, D.C., February, 1994.
8. "Lead-Contaminated House Dust and Blood Lead Concentrations in Children", Society for Pediatric Research, Seattle, Washington May 5, 1994.
9. "EPA Health-Based Standards for Soil and Dust". Alliance to End Childhood Lead Poisoning, Washington, D.C., May 17, 1994.
10. "Epidemiology of Tuberculosis in Health Care Settings". University of Cincinnati, Cincinnati, OH, August 19, 1994.
11. "A Side-by-Side Comparison of Sampling Methods for Lead-Contaminated House Dust". American Public Health Association, Washington, D.C., November 1, 1994.
12. "Trends in Childhood Exposure to Lead: Implications for Prevention". University of Rochester, Pediatric Grand Rounds, February 15, 1995.
13. "Childhood Exposure to Lead". Visiting Professor, Nazareth College, Rochester, New York, March 24, 1995.
14. "Transmission and Control of Infections in Health Care Workers". (Moderator & Speaker) American College of Occupational Environmental Medicine, Las Vegas, Nevada, May 4, 1995.
15. "Lead Exposure Prevention Research at the University of Rochester". New England Lead Conference, Kennebunkport, Maine, August 3, 1995.
16. "Prevention of Childhood Lead Exposure". 1st Annual Midwest Conference on Childhood Lead Poisoning Prevention, Kansas City, MO, September 10-11, 1995.
17. "Childhood Lead Exposure: Implications for Occupational Health". National Institute for Occupational Safety and Health, Cincinnati, OH, May 10, 1996.
18. "Community Characteristics and Children's Blood Lead Concentrations". American Public Health Association, New York City, NY, November 19, 1996.
19. "Evolution of a Disease: The Science of Childhood Lead Exposure Prevention." American Public Health Association, New York City, NY, November 18, 1996.
20. "Childhood Lead Exposure: A Local and National Perspective." Occupational Medicine Grand Rounds, University of Rochester, January 2, 1997.

21. "Prevention of Childhood Lead Exposure: The U.S. Experience". (Keynote) University of the West Indies and Pan American Health Organization, Kingston, Jamaica, January 23, 1997
22. "Lead-Contaminated House Dust and Children's Blood Lead Levels". (Keynote Presentation) Look Out for Lead Conference, Madison, WI, May 22, 1997.
23. "Primary Prevention of Childhood Lead Exposure: A Randomized Trial of Dust Control". American Public Health Association, Indianapolis, November 13, 1997.
24. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Medical University of South Carolina, Charleston, SC, March 20, 1998.
25. "The Science of Childhood Lead Exposure Prevention." Tulane/Xavier Center for Bioenvironmental Research, New Orleans, May 4-5th, 1998.
26. "Lead Hazard Control Research" Conference on Linking Health, Housing & Environment, Centers for Disease Control, Department of Housing and Urban Development, National Institutes of Health, Phoenix, Arizona, June 21-24, 1998.
27. "A Randomized Trial of Dust Control to Prevent Childhood Lead Exposure." Presenter and Co-chairman, Section on Heavy Metals, 1st International Conference on Children's Environmental Health, Amsterdam, The Netherlands, August 11-13th, 1998.
28. "Prevention of Childhood Lead Exposure: A Critique of the EPA's Proposed Residential Lead Standard". Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, D.C., November 5, 1998.
29. "Science and Policy of Lead Poisoning Prevention in the United States". Nicholas School of the Environment, Duke University, Durham, North Carolina, February 22, 1999.
30. "Behaviors in Early Childhood and Exposure to Environmental Toxins". (invited) Pediatric Environmental Health Conference, San Francisco, CA May 4, 1999.
31. "Patterns of Lead Exposure in Early Childhood". International Conference on Lead Exposure, Reproductive Toxicity and Carcinogenicity, Gargnano, Italy, May 7, 1999.
32. "Adverse Effects of Blood Lead Concentrations <10 µg/dL" (Invited), 17th International Conference Neurotoxicology Conference, Little Rock, Arkansas, October 17-20, 1999.
33. "Emerging Research and Implications for Prevention of Childhood Lead Exposure" (Invited), 2nd Annual Syracuse Lead Conference, Syracuse, New York October 27th, 1999.
34. "Prevention of Lead Poisoning in Children" Sierra Club, Omaha, NE, November 16th, 1999.
35. "Children's Environmental Health: A Focus on Residential Hazards" Department of Pediatrics, University of Nebraska Hospital, November 17th, 1999.
36. "Effectiveness of Lead Hazard Controls", New England Lead Conference, New Hampshire, Tufts University School of Medicine, April 25, 2000.

37. "Subclinical Lead Toxicity in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 15, 2000.
38. "Contribution of Residential Exposures to Asthma in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 16, 2000.
39. "The Effect of Soil Abatement on Blood Lead Concentration in Children living near a former Smelter and Milling Operation" (invited). Coeur d'Alene, Idaho, May 24, 2000.
40. "The Paradox of Lead Poisoning Prevention" (invited). National Institute of Justice, Washington, D.C., July 18th, 2000.
41. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Children's Hospital Medical Center, Cincinnati, Ohio, August 22, 2000.
42. "Children's Environmental Health: A Focus on Residential Hazards" Pediatric Grand Rounds, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY, September 20th, 2000.
43. "Prevention of Lead Poisoning in Childhood" 7th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, NY, September 29, 2000.
44. "Excavating the Enigmas of Childhood Lead Exposure". Department of Environmental and Occupational Medicine, Harvard University School of Public Health, Boston, MA, October 16th, 2000.
45. "Contribution of Residential Exposures to Asthma". Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 11th, 2000.
46. "Setting Research Priorities for the Decade". (Moderator & Speaker) Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 13th, 2000.
47. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation) Look Out for Lead Conference, Madison, WI, April 12, 2001.
48. "Environmental Lead Exposure and Children's Intelligence at Blood Lead Concentrations below 10 µg/dl." APA Presidential Plenary Session, Pediatric Academic Society Meeting, Baltimore, MD, April 30, 2001.
49. "Elimination of Childhood Lead Exposure: Obstacles & Opportunities" (Plenary). National Housing Conference and Exposition, New Orleans, LA, May 16th, 2001.
50. "Prevention of Childhood Lead Exposure: A Public Health Perspective" (Keynote Presentation). Philadelphia Health Department, Philadelphia, PA, May 23rd, 2001.

51. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation), Charles Drew University, Los Angeles, California, October 22nd, 2001.
52. "Primary Prevention of Childhood Lead Exposure" (Keynote Presentation), Midwest Regional Lead Conference, Pittsburgh PA, October 29th, 2001.
53. "Prevention of Childhood Lead Exposure: Shifting to Primary Prevention" (Keynote Presentation), Indiana Department of Health, Lead-Safe Conference, November 7th, 2001.
54. "A Strategy for Primary Prevention of Childhood Lead Exposure" A testimony to Housing and Transportation Subcommittee, U.S. Senate, Washington, D.C., November 13, 2001.
55. "Ethical issues of Environmental Research involving Children" (moderator and speaker). Panelists were Jeffrey Kahn, Ph.D., and Leonard Glantz, J.D., Raleigh-Durham, North Carolina, NIEHS Conference of Children's Environmental Health Centers, January 23, 2001.
56. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Omaha Children's Hospital, Omaha, Nebraska, March 1, 2002.
57. "Racial Disparities in Children due to Environmental Hazards" Ohio Commission on Minority Health, Columbus, Ohio March 27, 2002.
58. "Prevention of Childhood Lead Exposure in a Former Mining Community" Tar Creek, Oklahoma, April 4, 2002.
59. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Hasbro Children's Hospital, Brown University, Providence Rhode Island, May 17, 2002.
60. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Dayton Children's Hospital, Wright University, Dayton, Ohio May 22, 2002.
61. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." International Lead Congress, Washington, DC, June 3rd, 2002.
62. "Residential Hazards: A Neglected Health Problem" Agency for Toxic Substances Disease Registry, Centers for Disease Control and Prevention, Atlanta, Georgia, August 19th, 2002.
63. "Control of Residential Exposures to Environmental Neurotoxins" National Center for Healthy Homes (Moderator and Speaker), Annapolis, VA, November 7th, 2003.
64. "The Promises and Potential Pitfalls of Primary Lead Poisoning Prevention" Purchase College, 9th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, New York,, October 4th, 2002.
65. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Syracuse, NY, October 9th, 2002.
66. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." University of Texas at El Paso, El Paso, Texas January 29th, 2003.

67. "Childhood Lead Poisoning" Introduction to Children's Environmental Health, Seattle, Washington, Pediatric Academic Society, May 3rd, 2003.
68. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Chicago Lead Summit, Chicago, Illinois, May 28th, 2003.
69. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Case Western Reserve University, Cleveland, Ohio, June 3rd, 2003.
70. "Housing and Children's Health", Sprawl: The impact on vulnerable populations, University of Cincinnati College of Medicine, Cincinnati, Ohio, July 8th, 2003.
71. "Trials and Tribulations of Protecting Children from Environmental Toxins". Duke University, Nicholas School of the Environment, Durham, NC, November 6th, 2003.
72. "Adverse Effects of Fetal and Childhood Exposures to Prevalent Toxins" Midwest Critical Regional Neonatology Conference, Covington, KY, November 14th, 2003.
73. "Control of Residential Hazards in Children" American Public Health Association, San Francisco, CA, November 18th, 2003.
74. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis". 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 11th, 2004.
75. "Trials and Tribulations of Protecting Children from Environmental Hazards" Workshop on Ethical Issues on Children's Environmental Health, Children's Environmental Health Network, Washington, D.C. March 5, 2004.
76. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis", Pediatric Academic Societies Annual Meeting. Pediatric Research 2004;55:163A.
77. "The Impact of the Environment on Children's Health" Bob Smith Endowed Lecture, Department of Pediatrics, First Gulf Coast Children's Environmental Health Symposium, Baylor University, Houston, Texas.
78. "The Search for Environmental Causes of Learning Disabilities, Learning Disabilities Initiative, Baltimore, MD, May 18th, 2004.
79. "Residential Hazards in Children: A Neglected Public Health Problem", Pediatric Grand Rounds, Boston Medical Center, Department of Pediatrics, Boston University Medical Center, Boston, MA, May 20th, 2004.
80. "Residential Hazards in Children" "Healthier Homes, Stronger Families: Public Policy Approaches to Healthy Housing", National Center for Healthy Housing, Washington, D.C., June 2nd, 2004.

81. "Fetal and Early Childhood Exposures to Prevalent Toxins" Pediatric Grand Rounds, Ste. Justine Children's Hospital, University of Montréal, Montreal, Canada, June 16th, 2004.
82. "Childhood Exposure to Lead-Contaminated Soil: A Problem of the Past or a Problem from the Past?" National Academy of Science Committee on Superfund Site Assessment and Remediation in Coeur d'Alene River Basin", June 17th, 2004, Coeur d'Alene, Idaho.
83. "The Legacy of Lead" (Keynote Speaker). Chicago Lead Summit, Region V EPA Headquarters, September 15th, 2004.
84. "A Tale of Two Toxins: Children's Exposure to Tobacco and Lead" (with Michael Weitzman), The American Academy of Pediatrics, San Francisco, CA, October 10th, 2004.
85. "A Legacy of Childhood Lead Poisoning" University of Washington, Seattle, Washington, October 30, 2004.
86. "Protecting Children from Environmental Toxins", Pediatric Grand Rounds, Seattle Children's Hospital, Seattle Washington, March 10th, 2005.
87. "The Science and Politics of Childhood Lead Poisoning", Northwest Pediatric Environmental Health Conference, University of Washington, Seattle, Washington, March 11th, 2005.
88. "The Effects of Low-level Exposure to Environmental Toxins during Fetal Development and Early Childhood", Children's' Hospital of Fudan University, Shanghai International Pediatric Forum, Shanghai, China, June 16th to 18th, 2005.
89. "The Role of Biomarkers in Revealing Genetic and Environmental Influences of Disease and Disability" Psychiatry Grand Rounds, University of Cincinnati, February 8th, 2006.
90. "Trials and Tribulations of Protecting Children from Environmental Hazards: Ethical Issues", Johns Hopkins University of Medicine, March 17th, 2006.
91. "Key Elements of a Primary Prevention Strategy for Lead Poisoning", Albany Law School, Union University, Albany, New York, March 16th, 2006.
92. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", Case Western Reserve University, City Club of Cleveland, Cleveland, OH March 4th, 2006.
93. Integrating Genetic and Environmental Influences in Pediatric Research" (Moderator and Speaker), Pediatric Academic Societies, San Francisco, CA, April 30th 2006.

94. "Ethical Issues in Housing Health Hazard Research Involving Children" (Topic Symposia) Pediatric Academic Societies, San Francisco, CA, May 2nd 2006.
95. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", International Workshop on Neurotoxic metals: from Research to Prevention, University of Brescia, Italy, June 17th, 2006.
96. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", International Society for Environmental Epidemiology, Paris France, September 6th, 2006.
97. "Protecting Children from Environmental Toxins", Region VIII Children's Environmental Health Summit, Vail, Colorado September 20th, 2006.
98. "Integrating Genetic and Environmental Biomarkers in Pediatric Epidemiology", Visiting Professor, Simon Fraser University and University of British Columbia, Vancouver, British Columbia, October 19th-20th, 2006.
99. "The Legacy of Lead", Indiana Lead Conference, Indianapolis, Indiana, October 24, 2006.
100. "Ethical dilemmas in Children's Environmental Health", Seminar Series in Ethics of Toxicology, University of Champagne-Urbana, Champagne, Illinois, November 19th, 2006.
101. "Low-Level Lead Toxicity: Implications for Prevention", WHO Informal Workshop on Lead, University of Munich, Germany, November 30th, 2006.
102. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold", National Environmental Public Health Conference, National Centers for Disease Control, Atlanta, Georgia, December 4th, 2006.
103. "The Epidemiologic Conquest of Childhood Lead Toxicity: A Pyrrhic Victory". NIEHS Workshop on Children's Environmental Health Research: Past, Present and Future. January 22nd, 2007.
104. "Linking Low-level Exposures to Environmental Toxicants with ADHD". Duke Integrated Toxicology and Environmental Health Program Symposium on Developmental Neurobehavioral Disabilities and Toxic Exposures, March 23, 2007, Durham, North Carolina.
105. "Using Biomarkers to Link Environmental Influences with Disease and Disability", The Channing Laboratory, Harvard University, Boston, Massachusetts, April 4th, 2007.
106. "The Lingering Legacy of Lead Toxicity". Grand Rounds, Department of Pediatrics, St. Louis Children's Hospital, St. Louis University, St. Louis, Missouri, April 11th, 2007.
107. "Protecting Children from Environmental Toxicants", United States Council of Catholic Bishops, Washington, D.C., April 30th, 2007.
108. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", Pediatric Academic Societies, APA Presidential Platform Plenary Session, Toronto, Canada, May 7th, 2007.

109. "The Lingering Legacy of Lead Toxicity" Grand Rounds, Department of Pediatrics, Omaha Children's Hospital, University of Nebraska, Omaha, Nebraska, April 11th, 2007.
110. "Linking Low-level Neurotoxicant Exposures of the Developing Brain to Learning and Behavioral Problems." International Conference on Developmental Programming and Effects of Environmental Toxicants in Human Health and Disease, Faroe Islands, May 20th, 2007.
111. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson", National Policy Consultation Series on Children's Health and Environment, Moncton, New Brunswick, Canada, May 31, 2007.
112. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" Occupational and Environmental Health Seminar Series, Health Canada, Ottawa, Canada, June 6th, 2007.
113. "Linking Low-Level Lead Exposure with Child and Adolescent Psychopathology", 13th Annual International Society for Research in Child and Adolescent Psychopathology, London, England, June 19th, 2007.
114. "The Legacy of Lead Toxicity". Pediatric Grand Rounds, New York Presbyterian Hospital-Weill Cornell Medical Center, September 18th, 2007.
115. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Pediatric Grand Rounds, Children's Hospital at Dartmouth, Dartmouth Medical School, September 19th, 2007.
116. "The Legacy of Lead Toxicity: Effects of Childhood Lead Exposure in Children, Adolescents and Adults". Mid-America Conference, Philadelphia, Pennsylvania, October 4th, 2007.
117. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" International Society for Exposure Analysis (invited plenary session), Raleigh-Durham, North Carolina, October 17th, 2007.
118. The Global Elimination of Lead Toxicity: A Focus on Housing." National Institute of Public Health, Rennes, France, October 22nd, 2007.
119. Linkage of Environmental Lead Exposure with Psychopathology in Children and Adolescents" Ramazzini Collegium, Carpi, Italy, October 25th, 2007.
120. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology", Symposium on Environmental Toxicity and the Brain, University of Toronto, Toronto, Canada, December 7th, 2007.
121. "Linking Exposures to Environmental Toxicants with Child and Adolescent Psychopathology." Pediatric Grand Rounds, Rochester General Hospital and Strong Memorial Hospital, Rochester, New York, April 1&2, 2008.

122. "Rochester's Role in the Ongoing Elimination of Childhood Lead Toxicity." Beaven Lecture, Rochester Academy of Medicine, Rochester, New York, April 1, 2008.
123. "The Lingering Legacy of Lead Toxicity: Lansing Legacy." Michigan's Conference for Lead Safe & Healthy Homes, East Lansing, MI, April 22, 2008.
124. First Annual Controversies in Pediatric Environmental Health, "Should the Centers for Disease Control Lower the Blood Lead Level of Concern". A debate by Bruce Lanphear and George G. Rhoads (James Sargent, Moderator). Pediatric Academic Societies Meeting, Honolulu, Hawaii, May 2nd, 2008.
125. "Linking Exposure to Environmental Toxicants with Psychopathology in Children and Youth". Visiting Professor, Alberta Child and Youth Network, Calgary Children's Hospital, Calgary, Alberta. May 13th-15th, 2008.
126. "Lead Toxicity and the Teenage Brain", Youth Exploring Science Program, St. Louis Science Center, St. Louis, Missouri, June 30th, 2008.
127. "The Legacy of Childhood Lead Toxicity". Health Canada, Ottawa, Canada, October 6th, 2008.
128. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". The 2008 Rachel Carson Legacy Conference: Green Chemistry – Solutions for a Healthy Economy, Duquesne University, Pittsburgh, Pennsylvania, September 20th, 2008.
129. "Trials and Tribulations of Protecting Children from Environmental Hazards", Ethics in Toxicology Seminar Series, University of Champagne-Urbana, Champagne, Illinois, September 22nd, 2008.
130. "Industry's Influence on the Prevention of Childhood Lead Poisoning." In: Symposia on Insulating Environmental Health Research from Conflicting Interests. International Society for Environmental Epidemiology Annual Meeting, Pasadena, California, October 14th, 2008.
131. "The Lingering Legacy of Lead Toxicity: Implications for Research and Policy on Other Environmental Toxicants". (Keynote Presentation) BC Environmental and Occupational Health Research Network, Vancouver, BC, November 7th, 2008.
132. "Effects of Environmental Toxicants on Children's Development". DB-PREP Course, American Academy of Pediatrics, Atlanta, Georgia, December 5th, 2008.
133. "Linking Low-level Environmental Toxicants with New Morbidities of Childhood". BC Children's Grand Rounds, British Columbia, Vancouver, February 6th, 2009.
134. "Using Biomarkers to Link Exposures with Disease and Disability in Children". Workshop on Physical and Chemical Exposures in Canadian Cohort Studies, Canadian Institute of Health Research and Health Canada, February 8th-9th, 2009.

135. "How Dangerous Is Lead In Drinking Water?" An interview on "Around The Water Cooler" with Werner Troesken and Bruce Lanphear. February 18th, 2009.
136. "Linking Environmental Toxicants with ADHD in Children" (invited), Learning Disabilities Association Annual Meeting, February 25th, Salt Lake City, Utah.
137. "The Lingering Legacy of Lead Toxicity", Norfolk Children's Hospital, April 30th, 2009, Norfolk Virginia.
138. Second Annual Controversies in Pediatric Environmental Health Debate, "Should Pediatricians Advise Parents to Feed their Children Organic Foods?" A debate by Joel Forman and Janet Silverstein (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Baltimore, MD, May 4th, 2009.
139. "A Pattern of Pathology: The Population Impact of Environmental Toxicants on Health". Workshop on Endocrine Disruptors, Endocrine Society, Washington, DC, June 9th, 2009.
140. "The Quandary of Environmental Contaminants in Human Milk", 25th Anniversary of US Surgeon General's Report on Breastfeeding, Washington, DC, June 13th, 2009.
141. "Linking Exposures to Environmental Toxicants with Learning Problems and Psychopathology in Children." Northwest Conference on Children's Health and Environment, Tukwila, Washington, October 1st, 2009.
142. "The Second Coming of the Sanitarians", Pediatric Grand Rounds, University of California at Davis Children's Hospital, Sacramento, California, October 9th, 2009.
143. "The Second Coming of the Sanitarians", National Institute of Public Health, Rennes, France, November 4th, 2009.
144. "Linking Exposure to Environmental Toxicants with ADHD in Children." Symposium on ADHD. Riyadh, Saudi Arabia, November 7th, 2009.
145. "The Interplay of Genetic and Environmental Influences in Common Conditions of Children." Macquarie University, Department of Geology, Sydney, Australia, November 18th, 2009.
146. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure." Pacific Basin Consortium Symposium on Environment and Health, Perth, Australia, November 13th, 2009.
147. "The Second Coming of the Sanitarians", SFU President's Lecture, Simon Fraser University, Burnaby, BC, March 4th, 2010.
148. Third Annual Controversies in Pediatric Environmental Health Debate, "Should the American Academy of Pediatrics Sponsor a Ratings Board to Provide Evidence-based Ratings for Media?" A debate by James Sargent and Donald Shifrin (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Vancouver, BC, May 2nd, 2010.

149. "Efficacy of Reducing Lead Hazards in Housing on Lead-Contaminated House Dust, Blood Lead Concentration and Intellectual Abilities in Children." Pediatric Academic Societies Meeting, Vancouver, BC May 1st, 2010.
150. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Pediatric Grand Rounds, Cornell Weill Medical College, New York, New York. May 25th, 2010.
151. "Excavating the Enigmas of Childhood Lead Toxicity", Guest Lecturer, "Introduction to Toxicology, Harvard School of Public Health, Boston, Massachusetts, October 27th, 2010.
152. "The Conquest of Lead Poisoning: A Pyrrhic Victory", Lead Action Collaborative, New England Carpenters Center, Boston, Massachusetts, October 28th, 2010.
153. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson." Academy of Breastfeeding Medicine, San Francisco, California, October 29th, 2010.
154. "Bisphenol A and Behavior Problems in Children". Eastern Perinatal Conference, Kingston, Ontario, November 10th, 2010.
155. "Low-Level Toxicity of Environmental Toxicants: Much Ado about Nothing?" UBC Statistics Department Seminar, November 18th, 2010.
156. "Protecting Children from Environmental Toxicants." Children's Hospital of Quebec, University of Laval, Quebec City, Quebec, December 17th, 2010.
157. "Low-level Toxicity: Implications for Research and Policy", Joint Talks by C. Arden Pope and Bruce Lanphear, SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 7th, 2011.
158. "Crime of the Century: Lead Toxicity in the 20th Century", Panel Presentation and Discussion, UC Davis, Sacramento, California April 7th, 2011.
159. Fourth Annual Controversies in Pediatric Environmental Health Debate, "Should Parent Slather their Children with Sunscreen?" A debate with Russell Chesney, MD and Sophie Balk, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, Denver, Colorado, May 1st, 2011.
160. "The Conquest of Lead Toxicity: A Pyrrhic Victory", Canadian Water Network, Ecole Polytechnique de Montreal, Montreal, Canada, June 9th, 2011.
161. "The Contribution of Environmental Influences on Chronic Disease, Canadian Partnership for Health and Environment, Toronto, Canada, June 16th, 2011.
162. "The Second Coming of the Sanitarians", Environmental and Occupational Health Seminar, University of Washington School of Public Health, Seattle, WA, May 12th, 2011.
163. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Sterling Prize in Controversy, Wosk Centre, Simon Fraser University, Vancouver, BC, October 19th, 2011.

164. "Measuring Exposure: The Benefits and Limits of Biomarkers". Canadian Institute for Human Development, Child and Youth Research, Montreal, Canada, December 6th, 2011.
165. "Rachel Carson: Clarity of Vision". SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA, January 6th, 2012.
166. "The Truth About Toxins: What Parents and Health Professionals Should Know". Environmental Influences on Neurodevelopment: Translating the Emerging Science into Public Health Policy". UCLA School of Public Health, Los Angeles, California, January 12th, 2012.
167. "Protecting Children from Environmental Toxicants: The Neglected Legacy of Rachel Carson". Mattel Children's Hospital, Los Angeles, California, January 13th, 2012.
168. "Why Should We Share Data?", Data Sharing Strategies for Environmental Health Workshop, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, February 6th and 7th, 2012.
169. "The Science and Prevention of Lead Toxicity" (Keynote Presentation), Forum on Lead Toxicity: A Little is Still Too Much", Macquarie University, Sydney, Australia, June 5th, 2012
170. "Canada Environmental Health Atlas Knowledge Translation Workshop", Canadian Public Health Association, Edmonton, Alberta, June 13th, 2012.
171. "First Annual Controversies in Pediatric Environmental Health Debate: Should organophosphate pesticides be reduced or banned?" A debate with Brenda Eskenazi and Bruce Lanphear (Rob McConnell, Moderator). International Society for Environmental Epidemiology, Columbia, SC, August 28th, 2012.
172. "Supralinear Dose-Response Relationship of Environmental Toxicants: Research and Policy Implications." Moderator and Speaker, with Arden Pope, Roel Vermeulen and Bruce Lanphear. International Society for Environmental Epidemiology, Columbia, SC, August 29th, 2012.
173. Tanya Froehlich and Bruce Lanphear, "ADHD and Environmental Toxicants: Time for Prevention?", Society for Development and Behavioral Pediatrics, Phoenix, AZ, September 9th, 2012.
174. "The Epidemic of Childhood Disabilities: A Failure to Regulate". Workshop on Children's Rights and Corporate Responsibility, Green College, University of British Columbia, Vancouver, BC, October 19th, 2012.
175. "Low-level Toxicity: Much Ado About Nothing?", Department of Preventive Medicine Seminar, University of Southern , California, Los Angeles, California, October 23rd, 2012.
176. "Reflections on Silent Spring". (Invited Keynote). International Society for Exposure Sciences, Seattle, Washington, October 28th, 2012.

177. "Randomized Controlled Trials in Children's Environmental Health: Underutilized or Unethical?" The University of Washington Northwest Pediatric Environmental Health Specialty Unit and Center for Child Environmental Health, Seattle, Washington, February 26th, 2013.
178. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". Dali Lana School of Public Health and of School Environment, University of Toronto, Toronto, Ontario, March 26th, 2013.
179. "The Ongoing Search for a Threshold". International Conference of Toxicology, Seoul, Korea, July 1, 2013.
180. "Blood Lead Concentrations and Cardiovascular Mortality in the United States: The NHANES Mortality Follow-up Cohort Study". International Society for Environmental Epidemiology, Basel, Switzerland, August 2, 2013.
181. "The Conquest of Lead Poisoning: A Pyrrhic Victory". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
182. "Striking at the Root: Changing the Narrative on the Causes of Disease". Corporations and Global Health Governance. Simon Fraser University, Burnaby, British Columbia. September 17th, 2013.
183. "Crime of the Century: The Failure to Prevent the Lead Pandemic". Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 26, 2013.
184. "Low-level Toxicity: Policy Implications for the 21st Century". Symposium on Policy Implications of Environmental Exposures in the 21st Century. Pacific Basin Consortium, East-West Center, Honolulu, Hawaii. September 27, 2013.
185. "Excavating the Enigmas of Childhood Lead Toxicity". Network for Soil Contamination Research (INSCR), Delhi University, New Delhi, India. October 22nd, 2013.
186. "The Lingering Legacy of Lead Toxicity: A Call for the Global Elimination of Lead Exposure", World Health Organization, New Delhi, India. October 24th, 2013. "The Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health." National Institute of Environmental Health Sciences, Raleigh-Durham, NC, November 10th, 2013.
187. "Protecting Children from Environmental Toxins". Japan Dioxin and Endocrine Disruptors Preventive Action, Tokyo, Japan, November 24th, 2013.
188. "ADHD: A Preventable Epidemic?" Alberta Children's Hospital, Calgary, Alberta, December 16th, 2013.
189. "Little Things Matter: The Impact of Toxins on the Developing Brain". Early Years Conference, Vancouver, British Columbia, January 30th, 2014.
190. "Little Things Matter: The Impact of Toxins on the Developing Brain". Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.

191. “Low-level Toxicity of Environmental Toxins: Much Ado About Nothing?”. Dalhousie University, Halifax, Nova Scotia, March 6th, 2014.
192. “The Canadian Environmental Health Atlas: A Portal to Discover the Promises of Environmental Health.” School of Occupational and Environmental Health, University of British Columbia, March 28th, 2014.
193. “Little Things Matter: The Impact of Toxins on the Developing Brain”. British Columbia Healthy Child Alliance, Vancouver, British Columbia, April 2nd, 2014.
194. “Sixth Annual Controversies in Pediatric Environmental Health Debate, E-Cigarettes: A weapon in the war against tobacco or a threat to tobacco control. (Moderator). Featuring Greg Connelly and James Sargent. Pediatric Academic Societies, Vancouver, May 4th, 2014.
195. “Striking at the Root Causes of Chronic Disease in Children” (Moderator). James Sargent, Joel Bakan and David Kessler, May 5th, 2014.
196. “Little Things Matter: The Impact of Toxins on the Developing Brain” (Keynote). OHKA Healthy Homes Alliance, Omaha, Nebraska, May 15th, 2014.
197. “Excavating environmental risk factors for autism: Suspects and strategies”. A workshop on examining a multi-systems approach to autism and the environment: challenges and opportunities for research”. Toronto, Ontario, June 23rd-24th, 2014.
198. “Lead Poisoning: Tackling a Global Problem” (Co-Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
199. “Interventions to Reduce Exposures to Environmental Hazards in Pregnant Women and Children”, (Moderator and Speaker). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
200. 3rd Annual ISCHE-Sponsored Debate: Should there be any restrictions on universities or academicians receiving payment from industry or other sources? (Moderator). International Society for Environmental Epidemiology, Seattle, Washington, August 25th, 2014.
201. “Crime of the Century: Our Failure to Prevent the Lead Pandemic”, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, September 5th, 2014.
202. “Environment Matters”, Children’s Environmental Health Panel. Society for Environmental Journalists, New Orleans, Louisiana, September 6th, 2014.
203. “Insidious Influence of Industry on Science: How Corporations Undermine Science”, 5th Annual C. Everett Koop Distinguished Lecture, “Corporate Threats to Children’s Health”, with Joel Bakan and James Sargent, Dartmouth University, New Hampshire, October 6th, 2014.
204. “Crime of the Century: Our Failure to Prevent the Lead Pandemic”, John Rosen Memorial Lecture, Montefiore Medical Center, New York, New York, October 8th, 2014.

205. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). Prenatal Environmental Health Education (PEHE) Conference, University of Ottawa. Ottawa, Ontario, November 21st, 2014.
206. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote). ISEE Asian Regional Meeting, Shanghai, China, November 30th, 2014.
207. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", John Rosen Memorial Lecture, ISEE Asian Regional Meeting, Shanghai, China, November 31st, 2014.
208. "Data Visualization", with Joe Braun and Allan Just, Pediatric Environmental Health Scholars Retreat, Reston, VA, December 6th, 2014.
209. "Victories in Public Health: Progress or Adaptation?" SFU, UBC and UW Annual Occupational and Environmental Health Conference, Semiahmoo, WA January 8th, 2015.
210. "Food in the Industrial Era: Is Backward the Way Forward?" Children's Environmental Health Network, Austin, Texas, February 4th, 2015.
211. "Excavating the enigmas of childhood lead toxicity". Broken Hill City Council and Lead Reference Group, Broken Hill, New South Wales, Australia, March 3rd, 2015.
212. "Prevention Paradox: Why a Little Lead is Too Much". Unequal Exposure Symposium, Climate Change Research Center, University of New South Wales, March 5th, 2015, Sydney, Australia.
213. "Crime of the Century: Our Failure to Prevent the Lead Pandemic". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 23rd, 2015.
214. "The Staggering Cost of Lead Toxicity and the Unbelievable Benefit of Preventing It". 10th Annual Break the Cycle Conference, Emory University, Atlanta, Georgia. April 24th, 2015.
215. Seventh Annual Controversies in Pediatric Environmental Health Debate, "GMOs: A Hazard or Harvest of Health?" A debate with Joel Forman, MD and Daniel Goldstein, MD, (Bruce Lanphear, Moderator and Organizer). Pediatric Academic Societies Meeting, San Diego, California, April 27th, 2015.
216. "Impact of Dwellings on Child Health", Canadian Green Building Council Conference, Vancouver Convention Center, Vancouver, BC, April 28. 2015.
217. "Impact of Tobacco on the Developing Brain", Developmental Effects of Nicotine and Implications for Emerging Tobacco Products, Rockville, Maryland, May 5th, 2015.
218. "Impact of Toxins on the Developing Brain" India Tour (Bengaluru, Trivandrum, Kolkata, and Chandigarh) Sponsored by PAN-India, September 4th-11th, 2015.
219. "Impact of Dwellings on Child Health", Green School Summit, Calgary, Alberta, September 25th. 2015.

220. "Prevention Paradox: Why a Little Lead is Too Much", A debate with George Rhoads, Montefiore Medical Center, Tarrytown, October 2nd, 2015.
221. "Crime of the Century: Our Failure to Prevent the Lead Pandemic" (Keynote Presentation), University of Cincinnati Department of Environmental Health 50th Anniversary Gala, Cincinnati, Ohio, October 9th, 2015.
222. "Impact of Toxins on the Developing Brain" (Keynote Presentation) Children's Environmental Health Centers Annual Meeting, Washington, DC, October 31, 2015.
223. "The Impact of Toxins on the Developing Brain: Our Failure to Prevent Brain-based Disorders in Children", National Core for Neuroethics, UBC November 12th, 2015.
224. "Impact of Dwellings on Child Health", Canada Green Building Council, Toronto, ON Green, December 1st, 2015.
225. "The Tortuous Road to Prevention: Are We There Yet", Air Quality and Impacts on Health: Beyond the Heart and the Lungs, The Lung Association of BC, February 28th, 2016.
226. "Lead's Long Shadow: What the Story of Flint, Michigan Means for All of Us", with Bruce Lanphear, Mona Hanna-Attisha and Marc Edwards. Collaborative on Health and the Environment Webinar, March 8th, 2016.
227. "Little Things Matter: The Impact of Toxins on the Developing Brain", Collaborative on Health and Environmental Alaska Working Group Webinar, March 9th, 2016.
228. "Victories in Public Health: Progress or Adaptation?", Symposium Against Indifference, Ashland University, Ashland, Ohio, April 5th, 2016.
229. "Little Things Matter: The Impact of Toxins on the Developing Brain" (Keynote), Children's Environmental Health: New Findings from California Research, Sacramento, California, April 7th, 2016.
230. "Crime of the Century: Our Failure to Prevent the Lead Pandemic", Distinguished Visiting Professor in Health Law, Loyola University, Chicago, Illinois April 21st, 2016.
231. "The Population Impact of Toxins on Intellectual Abilities: Implications for Policy and Prevention", in Symposia on Environmental Toxins and the Brain: Growing Evidence of Risk, Pediatric Academic Societies, Baltimore, MD, May 2nd, 2016.
232. "Data Visualization and Video Production for Public Consumption", in Symposia on Innovative Tools to Enhance Knowledge Translation of Environmental Health: Data Visualization, Videos and Message Mapping, (co-Moderated by Mark Miller and Bruce Lanphear), Pediatric Academic Societies, Baltimore, MD, April 30th, 2016.
233. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Michigan State University, Flint, MI, May 7th, 2016.

234. "Crime of the Century: Our Failure to Prevent the Lead Epidemic", Johns Hopkins University School of Public Health, Baltimore, MD, May 7th, 2016.
235. "Little Things Matter: The Impact of Toxins on the Developing Brain", Baltimore, MD, International Medical Federation Autism Research (IMFAR), May 8th, 2016.
236. "Public Health Matters: Videos on Toxic Chemicals, Air Pollutants and the Prevention Paradox", Mongolian National University of Medical Sciences, June 23, 2016.
237. "Little Things Matter: The Impact of Toxins on the Developing Brain", USC Annenberg Center for Health Journalism, July 18th, 2016.
238. "Preventing Lead Toxicity", California Environmental Protection Agency, Occupational Environmental Health Hazard Assessment, September 23rd, 2016.
239. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease," World Issues Forum, Fairhaven College, University of Western Washington, (with Bob Lanphear), November 2, 2016.
240. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Pediatric Grand Rounds, Maimonides Hospital, November 15th, 2016.
241. "Little Things Matter: The Impact of Toxic Chemicals on the Child Health" (Keynote), Hudson Valley Perinatal Conference, November 16th, 2016.
242. "Little Things Matter: The Impact of Toxins on the Developing Brain", IPEN, San Francisco, CA, November 18th, 2016.
243. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", SFU, UBC and UW Annual Occupational and Environmental Health Conference Semiahmoo, WA, January 5th, 2017.
244. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", University of New Brunswick, January 25th, 2017.
245. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", New Brunswick Children's Environmental Health Collaborative, January 26th, 2017.
246. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Rockefeller Center, Bellagio, Italy, February 22nd, 2017.
247. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", The Science in Society Speaker Series, Okanagan College, Vernon, BC, April 6th, 2017.
248. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (invited plenary), Vancouver, British Columbia, Canadian Pediatric Society, June 3rd, 2017.
249. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Macquarie University, Sydney, Australia, September 29th, 2017.

250. "Unleashing the Power of Prevention: Creating Video to Re-Imagine our Approach to Disease", Brown University, Providence, Rhode Island, October 13th, 2017.
251. Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Health? University of Alaska, Alaska Tribal Health Consortium, Anchorage, Alaska, November 2nd, 2017.
252. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain" (Keynote), All Alaska Pediatric Conference, Anchorage, Alaska, November 3rd, 2017.
253. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", CINBIOSE 30th Anniversary, University of Quebec at Montreal, Montreal, November 9th, -10th, 2017.
254. "The Legacy of Lead Poisoning: Moving towards Prevention". East Chicago Community Meeting, Illinois, November 26th, 2017.
255. "Cause or Cure", NIEHS Environmental Health Seminar, University of Southern California, Los Angeles, California, December 1st, 2017.
256. "Little Things Matter: The Impact of Lead on Brain Development" (Keynote Presentation), Workshop on Lead-Free Schools, Pew Trust, Washington, DC, December 6th-7th, 2017.
257. "Low-level Toxicity of Chemicals: No Acceptable Threshold?" Risk Modeling, Mitigation and Modeling in Health Sciences, Centre de Recherches Mathematiques, Montreal, QC, December 11th, 2017.
258. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Department of Psychology and Neuroscience, York University, Toronto, ON, December 13th, 2017.
259. "The impact of Pollutants on Human Health: No Safe Levels?", Center for Energy and Environmental Contaminants, Macquarie University, Sydney, Australia, February 13th, 2018.
260. "Cause or Cure: Does the Relentless Pursuit of a Cure Endanger our Children's Health?", Department of Pediatrics, University of Wisconsin at Madison School of Medicine, Madison, Wisconsin, March 1st, 2018.
261. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Wisconsin Environmental Health Network, Madison, Wisconsin, March 2nd, 2018.
262. "Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain", Biennial Atlantic Symposium on Learning Disabilities Association, Fredericton, NB.
263. "Crime of the Century: The Failure to Prevent the Lead Pandemic" (Keynote). 11th UK and Ireland Environmental and Occupational Epidemiology, John Snow Lecture Hall, London School of Hygiene and Tropical Medicine, April 27th, 2018.
264. "The Impact of Pollutants on Human Health: No Safe Levels?" From Toxicology to Planetary Health, London School of Hygiene and Tropical Medicine, April 27th, 2018.

265. Topic Symposium: “Toxic Chemicals and the Rise of Chronic Disease in Childhood: A Preventable Epidemic?” (chair and speaker), Pediatric Academic Societies, May 7th, 2018.
266. “Prevention Paradox; Why a Little Lead is Too Much”, Ontario Water Advisory, Toronto, CA, May 7th, 2018.
267. “How the Secrets of Body Care and Cleaning Products Impact your Health”, Panel with Bruce Lanphear, Muhannad Malas and Janie McConnell, Centre for Free Expression, Ryerson University, Toronto, ON, May 7th, 2018.
268. “Prevention Paradox; Why a Little Lead is Too Much” (Keynote), Pittsburgh, PA, Get the Lead Out Conference, May 9th, 2018.
269. “Low-level Lead Exposure and Mortality”, Global Health Forum, Miami, FL, May 23rd, 2018.
270. “Unleashing the Power of Prevention: Targeting Toxic Chemicals and Pollutants”, Canadian Public Health Association, Montreal, QC, May 28th, 2018.
271. “The Impact of Pollutants on Human Health: No Safe Levels?” Chemicals Management Plan Stakeholder Advisory Council, Health Canada, May 30th, 2018.
272. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Pediatric Grand Rounds, University of California – Davis, Sacramento, CA, June 8th, 2018.
273. “Why a Little Lead is Too Much”, Health Canada, Ottawa, ON, August 29th, 2018.
274. “Unleashing the Power of Prevention: Mobilizing Science to Prevent Disease”, ISEE-ISES Workshop, Ottawa, ON, August 30th, 2018.
275. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, LA Lead Summit: A Strategy for Prevention, University of Southern California, September 14th, Los Angeles, CA.
276. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Children’s Hospital of Orange County, Orange County, CA, September 19th, 2018.
277. “The Lingering Legacy of Lead: Why a Little Lead is Too Much”, Hurley Medical Center, Flint, Michigan, October 3rd, 2018.
278. “Lead and The Mysterious Decline in Coronary Heart Disease”, National Institute of Occupational Safety and Health, Cincinnati, OH, October 11, 2018.
279. “Little Things Matter: The Impact of Toxic Chemicals on the Developing Brain”, Grand Rounds, Oregon State Health University, Portland, OR, October 23, 2018.
280. “The Impact of Pollutants on Human Health: No Safe Levels?” Oregon Environmental Council, Portland, OR, October 23, 2018.
281. “Little Things Matter: The Impact of Toxic Chemicals and Organic Food on Children’s Health”, HIPP Scientific Symposium on Organic Food, Kranzberg, Germany, October 30, 2018.

282. “The Mysterious Decline in Coronary Heart Disease”, Harvard University Lead Summit, Cambridge, MA, November 15th, 2018.
283. “The Impact of Pollutants on Human Health: No Safe Levels?” Department of Epidemiology, UMass, Amherst, MA, November 16th, 2018.
284. “Little Things Matter: The Impact of Toxic Chemicals on Human Health”, School of Public Health, Oregon State University, Corvallis, Oregon, April 12th, 2019.
285. Why A Little Lead is Too Much: An Intimate History”, “The Impact of Pollutants on Human Health: No Safe Levels?”, Graduate Course in Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.
286. “The Impact of Pollutants on Human Health: No Safe Levels?”, Department of Environmental Health, School of Public Health, University of California, Berkeley, April 17th, 2019.

Grants

Active Grant Awards

1. Consultant (Joseph Braun, PI). Early Life Perfluoroalkyl Substance Exposure and Obesity: Mechanisms and Phenotyping. 02/01/2016-01/31/2021. National Institutes of Health, \$523,725 (5% effort). The purpose of this award is to study the impact of exposure to perfluoroalkyl chemicals on the development of child obesity, adverse cardiometabolic markers and gene regulation. (2.5% effort)
2. Co-Applicant (Linda Booij, Maryse Bouchard PI). In utero exposure to Bisphenol-A and the developing brain in humans: A longitudinal study of epigenetic mechanisms. 03/01-2016 – 03/31/2019. Canadian Institutes of Health Research (CIHR), \$344,025. (2.5% effort).
3. Principal Investigator (Multiple PI Award with Christine Till). “Impact of early life fluoride exposure on cognitive and behavioural outcomes in children”. NIEHS, 09/30/16 – 05/01/19, \$296,683 (10% effort).
4. Consultant (Aimin Chen, Principal Investigator). Developmental neurotoxicity of organophosphate and novel brominated flame retardants in children. National Institute for Environmental Health Sciences. 1RO1ES028277. 09/30/2017-06/30/22 (10% effort).
5. Mentor (Cynthia Curl, Principal Investigator). Measurement of Agricultural and Dietary Glyphosate Exposure among Pregnant Women. National Institutes of Environmental Health Sciences. 1KO1ES028745-01A1. 09/01/2018-08/31/2022 (5% effort).

Past Grant Awards

1. Principal Investigator, "Dust-Lead and Blood Lead Levels among Urban Children". The National Center for Lead-Safe Housing, \$561,619, 06/15/93 to 08/31/94. Department of Housing and Urban Development Contract MDLPT0001-93. (25% effort).
2. Principal Investigator, "Determinants of Lead Exposure among Children in Monroe County, NY", NIEHS Pilot Grant, University of Rochester School of Medicine and Dentistry, Department of Environmental Medicine. \$7,600, 06/15/93 to 12/31/95. (0% effort)
3. Principal Investigator, "The Effectiveness of Dust Control in Reducing Children's Blood Lead Levels" U.S. Department of Housing and Urban Development, \$128,394, 04/01/94 to 05/30/95. (25% effort).
4. Principal Investigator, "Primary Prevention of Exposure to Lead". Centers for Disease Control and Prevention, \$832,228, 09/30/94 to 10/01/98. (25% effort)
5. Principal Investigator, "Lead-Contaminated House Dust and Children's Blood Lead Levels". National Center for Lead-Safe Housing, \$43,260, 10/01/96 to 03/30/96. (25% effort).
6. Co-investigator (Christy, PI), "Tuberculosis Screening in Children". New York Department of Health, \$15,000, 01/01/95 to 12/31/96. (0% effort)
7. Co-investigator (Weitzman, PI), "Fellowship Training in General Pediatrics" (Grant # D28PE50008). Bureau of Health Professions, HRSA, U.S. Public Health Service, \$1,752,816, 06/01/96 to 05/30/97. (10% effort).
8. Principal Investigator, "Neurobehavioral Effects of Low-Level Childhood Lead Exposure". University of Rochester School of Medicine & Dentistry, \$8,560, 06/01/96 to 05/30/97. (0% effort)
9. Principal Investigator, "Neurobehavioral Effects of low-level Lead Exposure in Children". NIEHS Pilot Grant, University of Rochester Department of Environmental Medicine, \$20,035, 09/01/97 to 08/30/97. (0% effort).
10. Co-investigator (Howard, PI), "Effect on Breastfeeding of Pacifiers and Bottle Feeding". Bureau of Maternal and Child Health, \$420,333, 10/01/96 to 09/30/00. (2.5% effort)
11. Co-investigator (Canfield, PI) "Lead and Children's Cognitive Functioning", Research Grants Program, Cornell University. \$17,000, 10/01/96 to 09/31/97 (0% effort).

12. Principal Investigator, "Neurobehavioral Effects of Low-Level Lead Exposure in Children" (RO1-ES 08338). National Institute of Environmental Health Sciences, 12/01/96 to 11/31/01, \$1,946,848. (25% effort).
13. Co-investigator, (Aligne, PI). "Reduction in Passive Smoking among Children with Asthma: A Randomized Trial of HEPA Air Filtration." 10/01/96 to 09/31/97, \$6,000. KIDD Grant, Rochester General Hospital (0% effort).
14. Co-investigator, (DeWitt, PI). "Faculty Development in General Pediatrics". Bureau of Health Professions, Health, Department of Health and Human Services 07/01/97 to 06/30/00, \$338,000. (15% effort).
15. Principal Investigator, "A Side-by-Side Comparison of Allergen Sampling Methods", U.S. Department of Housing and Urban Development, 01/02/98 to 12/31/98, \$163,065. (15% effort).
16. Principal Investigator, "National Research Service Award - Fellowship Training in General Pediatrics and Adolescent Medicine" (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/03. \$634,408. (0% effort).
17. Co-investigator, (Steiner, PI) "Survey of Directors and Graduates of NRSA Fellowship Training Programs", Health Resources and Services Administration, Department of Health and Human Services. 06/01/98 to 06/30/99.
18. Principal Investigator, "Effect of Soil Remediation on Children's Blood Lead Levels in Midvale, Utah". U.S. Environmental Protection Agency, 08/01/98 to 07/30/99. \$62,550. (15% effort).
19. Co-investigator, (Phelan, PI) Trends and Patterns in Playground Injuries among U.S. Children." Ambulatory Pediatric Association, 05/05/99 to 05/04/00. \$9,000 (0% effort).
20. Principal Investigator, "Risk Assessment for Residential Lead Hazards". U.S. Department of Housing and Urban Development, 09/01/99 to 08/30/00. \$102,435. (25% effort).
21. Principal Investigator, "Residential Exposures associated with Asthma in U.S. Children and Adolescents" U.S. Department of Housing and Urban Development, 07/16/99 to 03/15/00. \$30,400. (20% effort).
22. Principal Investigator, "Effectiveness of Lead Hazard Control Interventions – A Systematic Review" National Center for Lead-Safe Housing, 10/01/99 to 06/01/00. \$22,500 (10% effort).
23. Principal Investigator, "Racial Disparity in Blood Lead Levels due to Genetic Variation in Calcium Absorption". NIEHS Pilot Grant, Center for Environmental Genetics, University of Cincinnati, 04/01/00 to 03/31/01. \$28,130 (0% effort).
24. Principal Investigator, "International Pooled Analysis of Prospective, Lead-Exposed Cohorts". National Institute of Environmental Health Sciences, National Institutes of Health, 08/15/00 to 09/14/01, \$16,000. (2.5% effort).

25. Principal Investigator, "A Randomized Trial to Reduce ETS in Children with Asthma" (RO1-HL/ES65731). National Heart, Lung and Blood Institute, National Institutes of Health, 09/29/00 to 09/28/04, \$1,546,848. (25% effort).
26. Co-investigator, (Geraghty, PI) "Breastfeeding Practices of Mothers of Multiples". Ambulatory Pediatric Association, 05/01/01 to 04/30/02. \$5,000 (0% effort).
27. Principal Investigator (Subcontract), "A Longitudinal Study of Lead Exposure and Dental Caries". National Institute of Dental and Craniofacial Research, National Institutes of Health, 08/01/01 to 07/30/04. \$300,000 (10% effort).
28. Co-investigator (Phelan, PI), "Fatal and Non-Fatal Residential Injuries in U.S. Children and Adolescents" U.S. Department of Housing and Urban Development, 03/01/01 to 11/31/01. \$40,700. (5% effort).
29. Principal Investigator, "Prevalent Neurotoxicants in Children" (PO1-ES11261). National Institute for Environmental Health Sciences and U.S. Environmental Protection Agency, 09/01/01 to 09/31/06, \$5,000,000. (30% effort).
30. Principal Investigator, "International Pooled Analysis of Lead-Exposed Cohorts". Centers for Disease Control (RO1/CCR 521049). Centers for Disease Control, 09/15/01 to 09/14/02, \$28,473. (3% effort).
31. Principal Investigator, supplement to "Prevalent Neurotoxicants in Children" (PO1-ES11261). NIEHS, 09/01/02 to 09/31/07, \$1,800,000. (10% effort).
32. Co-Investigator, "ADHD Phenotype Network: Animal Model to Clinical Trial". National Institute of Neurologic Diseases, 09/15/02 to 06/30/05 (15% effort).
33. Principal Investigator, "Linkage of ADHD and Lead Exposure", Springfield, Ohio Department of Health, 02/01/03 to 06/01/04, \$25,000. (0% effort).
34. Co-investigator (Yolton, PI) "Explorations of ETS Exposure on Child Behavior and Sleep" NIEHS, 04/01/04 to 03/30/06, \$300,000. (5% effort).
35. Co-investigator (Haynes, PI) "MRI as a Biomarker of Manganese Exposure". NIEHS, 09/01/04 to 08/30/06, \$300,000. (5% effort).
36. Co-investigator (National Center for Healthy Housing, PI) "Development of a Standardized Housing Assessment for Asthma", U.S. Department of Housing and Urban Development, 11/01/05 to 10/31/07, \$50,000. (5% effort).
37. Co-Investigator (Hershey, PI) "Epithelial Genes in Allergic Inflammation" National Institutes of Allergy and Infectious Diseases", 07/01/06 to 06/30/07, \$4,787,541. (3% effort).

38. Co-Investigator and Mentor (Wilson, PI), "Racial Difference in DNA Adducts in Tobacco-Exposed Children". Dean's Scholar Award, University of Cincinnati, 02/22/06 to 01/21/09, \$150,000 (5% effort).
39. Principal Investigator, "National Research Service Award - Fellowship Training in Primary Care Research," (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/08. \$1,600,000. (0% effort).
40. Co-Investigator and Mentor (Kahn, PI). "Childhood Asthma in an Era of Genomics: Will the Generalist's Role be Recast?" Robert Wood Johnson Generalist Physician Faculty Scholars Program" 06/01/04 to 05/30/08, \$300,000.
41. Co-Investigator and Mentor (Spanier, PI), "Exhaled Nitric Oxide to Manage Childhood Asthma". National Heart, Lung and Blood Institute, 07/01/06 to 06/31/08, \$200,000 (10% effort).
42. Co-investigator (Sub-Contract PI), BYPL Vanguard Center (Specker, Principal Investigator), "National Children's Study", National Institute for Child Health and Development, 11/01/05 to 10/31/10, \$500,000. (20% effort). [Relinquished with relocation to SFU].
43. Associate Director and Co-Investigator, (Ho, PI). "Center for Environmental Genetics," NIEHS, 04/01/08 to 3/31/13, \$1,000,000 (10% effort). [Relinquished with relocation to SFU.]
44. Co-Investigator (Yolton, PI). "Tobacco Smoke and Early Human Behavior". Clinical Innovator Award, Flight Attendant Medical Research Institute", 07/01/07 to 06/30/10, \$300,000. (3% effort).
45. Co-Investigator (Spanier, PI). "Low Level Prenatal Tobacco Exposure and Infant Wheeze." Young Clinical Scientist Award, Flight Attendant Medical Research Institute, 07/01/07 to 06/30/12, \$300,000. (5% effort).
46. Co-Investigator and Mentor (Spanier, PI). K23, "Prenatal Low Level Tobacco & Phthalate Exposure and Childhood Respiratory Health". National Institute for Environmental Health Sciences, 12/1/07 to 11/30/12, \$623,679 (0% funded effort).
47. Co-investigator (Yolton, PI). "Neurobehavioral effects of insecticide exposure in pregnancy and early childhood." NIEHS, 09/01/09 to 08/31/12.
48. Principal Investigator (Bruce Lanphear, PI), "A Community-Based Trial to Prevent Lead Poisoning and Injuries," National Institute for Environmental Health Sciences, 04/01/07 to 03/30/13, \$2,000,000. (25% effort).
49. Co-Investigator (Kim N. Dietrich, PI). "Early Lead Exposure, ADHD & Persistent Criminality: Role of Genes & Environment," National Institute for Environmental Health Sciences, 04/01/07 to 3/31/2013, \$1,250,000. (2.5% funded effort).

50. Co-Investigator and Sub-Contract PI (Brenda Eskenazi, PI). This supplemental award was to conduct a pooled analysis of prenatal organophosphate pesticide exposures with birth outcomes and neurodevelopment in children using 4 US birth cohorts. NIEHS, 09/01/2009 to 08/31/2013, \$96,000 (0% effort).
51. Mentor and Supervisor (Glenys Webster, PI). Michael Smith Foundation for Health Research Postdoctoral Training Award, 03/01/12 to 02/28/15, \$134,500 (5% effort).
52. Co-Principal Investigator (Tye Arbuckle, PI). Maternal-Infant Research on Environmental Chemicals: Effects on Child Development (MIREC-CD). 06/26/11 to 5/25/14, Health Canada Chemical Management Program, \$283,000 (10% effort).
53. Co-Investigator (Patti Dods and Amanda Wheeler, co-PIs). Phthalate Exposure and the development of asthma in the CHILD Study. 06/01/11 to 05/30/14, Health Canada Chemical Management Program, \$204,000 (5% effort). Consultant (Stephanie Engel, PI). A pooled investigation of prenatal phthalate exposure and childhood obesity. 11/01/2012 – 10/31/15, NIEHS. \$275,000. (5% effort).
54. Co-Investigator (Ryan Allen, PI). A randomized air filter intervention study of air pollution and fetal growth in a highly polluted community. 06/08/2012 – 05/30/15, CIHR \$348,000 (10% effort).
55. Co-Investigator (William Fraser and Tye Arbuckle, co-PIs). MIREC-CD Biomonitoring Study in Vancouver. 09/01/2013 – 08/30/2014. Health Canada, \$120,138 (10% effort).
56. Principal Investigator. Knowledge translation tools for capacity building for an online Canadian Environmental Health Atlas. 03/01/12 – 02/28/13, Canadian Institutes of Health Research, \$98,974 (10% effort).
57. Principal Investigator (with Lawrence McCandless). Prenatal exposure to environmental contaminants and fetal growth: How to account for multiplicity when testing multiple statistical hypotheses?. 07/01/2015-06/30/2016. Canadian Institutes of Health Research (CIHR), \$12,000 (5% effort).
58. Principal Investigator, Canadian Environmental Health Atlas Knowledge Translation to produce videos and interactive tools. 06/01/2015-07/30/2016. Canadian Internet Registration Authority, \$50,000 (10% effort).
59. Co-Investigator (Kieran Phelan, PI). “Injury Prevention in a Home Visitation Population”. NICHD, 09/28/10 to 07/31/16, \$2,000,000 (total direct costs over 5 years) (10% effort).
60. Co-applicant (Timothy F. Oberlander, PI). Developmental origins of autism: A population level linked data study of prenatal antidepressant medication exposure. 09/01/2013 – 09/31/2016, Canadian Institutes of Health Research (CIHR), \$285,768.

61. Principal Investigator (Multiple PI Award with Aimin Chen and Kimberly Yoltan).
“Longitudinal study of exposures to PBDEs and PFCs and child behavior”. NIEHS,
04/30/11 – 05/01/17, \$2,150,000 (total direct costs over 5 years) (20% effort).
62. Principal Applicants (McCandless and Lanphear). Biostatistical methods for estimating the
cumulative impact of environmental contaminant exposures on preterm birth. Canadian
Institute for Human Development, Child and Youth Health. 12/06/16-12/05/18, \$200,000
(10% effort).
63. Co-investigator (Ryan Allen, PI). Randomized Interventions to Evaluate the Effects of Air
Pollution Exposure on Children's Health and Development. 03/01/2015 – 03/31/2019,
Canadian Institutes of Health Research (CIHR), \$720,535. (10% effort)
64. Co-investigator (Joseph Braun, PI). Endocrine Disrupting Chemicals, Thyroid Hormones
and Child Neurobehavior. 06/01/2015-03/31/2019. National Institutes of Health, \$471,241
(5% effort). The purpose of this study is test if and when early life exposures to phthalates,
triclosan, or bisphenol A adversely impacts children’s cognition and behavior.
- 65.

Ethics Training for Research

CITI (Collaborative Institutional Training Initiative) (Reference# 7159023). Academic and Regional
Health Centers Curriculum Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 7160515), Canada GCP Curriculum
Course, completed on December 16th, 2011.

CITI (Collaborative Institutional Training Initiative) (Reference# 8316270), Human Subjects Core
Curriculum, completed on August 17th, 2012.

CITI (Collaborative Institutional Training Initiative) (Reference# 13561457), Academic and Regional
Health Centers Core Curriculum, completed on September 1st, 2014.

CITI (Collaborative Institutional Training Initiative) (Reference# 16954900), Human Subjects Research
Core Curriculum, completed on October 31st, 2015.



PERSPECTIVE

Controversy: The evolving science of fluoride: when new evidence doesn't conform with existing beliefs

Christine Till¹ and Rivka Green¹

Over the past 75 years, health authorities have declared that community water fluoridation—a practice that reaches over 400 million worldwide—is safe. Yet, studies conducted in North America examining the safety of fluoride exposure in pregnancy were nonexistent. When a Canadian study reported that higher fluoride exposure in pregnant women was associated with lower IQ scores in young children, critics attacked the methodology of the study and discounted the significance of the results. Health authorities continued to conclude that fluoride is unequivocally safe, despite four well-conducted studies over the last 3 years consistently linking fluoride exposure in pregnancy with adverse neurodevelopmental effects in offspring. We describe the challenges of conducting fluoride research and the overt cognitive biases we have witnessed in the polarized fluoride debate. The tendency to ignore new evidence that does not conform to widespread beliefs impedes the response to early warnings about fluoride as a potential developmental neurotoxin. Evolving evidence should inspire scientists and health authorities to re-evaluate claims about the safety of fluoride, especially for the fetus and infant for whom there is no benefit.

Pediatric Research _#####_; <https://doi.org/10.1038/s41390-020-0973-8>

Do not avoid difficult areas of investigation. Take risks. If scientists exclusively choose the safe routes, avoid controversial research problems and play only minor variations of someone else's themes, they voluntarily turn themselves into technicians. Our craft will indeed be in peril.¹ Herbert Needleman, MD

Most people assume that community water fluoridation (CWF)—adding fluoride to public drinking water supplies—is a safe and effective way to prevent cavities. After all, it has been endorsed by public health, dental and medical organizations since it was introduced 75 years ago.^{2,3} Today, about three-fourths of people in the United States and one-third of Canadians have fluoride added to their drinking water.

After reviewing the scientific literature, it became clear that there were growing concerns about fluoride as a developmental neurotoxin.^{4,5} In 2006, a report by the National Research Council (NRC)⁶ acknowledged that fluoride exposure may be associated with adverse cognitive and endocrine outcomes, and recommended further study, especially for vulnerable populations. One NRC panel member, Dr. Isaacson, said the report “should be a wake-up call”. Yet, nearly 10 years later, not a single study had directly examined fetal exposure to fluoride in humans.

In many academic circles, it is a taboo to study fluoride. Dr. Phyllis Mullenix,⁷ former Head of the Toxicology Department at the Forsyth Dental Centre in Boston, was heavily criticized for publishing her study showing that sodium fluoride was neurotoxic to developing rats. People who questioned the safety of water fluoridation are quickly dismissed as zealots or anti-science fanatics. Indeed, some scientists dismissed our funding application with comments such as, “This study is not needed. We know that

fluoride is safe”. But we forged ahead; shouldn't claims about safety be based on evidence?

In 2015, we sought funding to investigate the safety of fluoride exposure in pregnancy. We assembled an interdisciplinary team of scientists from complementary fields including epidemiology, environmental health, neuropsychology, and dentistry—knowing that diverse perspectives would be critical for minimizing conscious or unconscious biases in our investigative process. We naively expected that the public health and medical community would trust the scientific process.

THE SCIENTIFIC PROCESS

We studied 512 mother–child pairs enrolled in the MIREC (Maternal Infant Research on Environmental Contaminants) study. The families lived in six Canadian cities; 40% lived in cities with CWF. To our astonishment, we found that higher levels of fluoride in pregnant women and water concentrations were associated with a 3- to 5-point lower IQ score in their 3- to 4-year-old children.⁸ We thought there may be other factors at play, but this association held up after accounting for important characteristics of the study population and looking at the relationship in many different ways.

In August 2018, we presented our findings at an international meeting held in Ottawa. We were nervous how the results would be received by the audience, which included members from Health Canada and other public health agencies. Afterwards, someone approached me and said, “Congratulations – you have just sabotaged your career before it even started”. Rivka Green

As part of our agreement, our manuscript required approval by the MIREC Biobank before we submitted it for publication.

¹Department of Psychology, York University, 4700 Keele St., Toronto, ON, Canada
Correspondence: Christine Till (ctill@yorku.ca)

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Considering the sensitive nature of the topic, the manuscript was sent to reviewers from various divisions of public health. In over 60 pages, we responded to over 200 specific critiques. The upshot of addressing each critique was that we were able to do better science by refining our methods.

We submitted the manuscript to three top medical journals; two did not send it for peer review because it was “of low research relevance”. As we waited, we hired an independent data analyst to rerun all of the analyses for the third time. In April 2019, *JAMA Pediatrics* accepted our paper. We responded to several additional rounds of review by the *JAMA* editors until we eventually reached a compromise that reflected the strength of the evidence, as well as their implications for public health.

One year after that conference in Ottawa, our article was published on August 19, 2019. In only 2 months, it was viewed over 100,000 times and ranked among the top 0.0005% of research output scored by Altmetric. We expected our study would reignite the debate about the safety of fluoridation, but we didn't expect we would be at the crossfire of this political and polarized debate.

THE BACKLASH

Outside of our colleagues in environmental epidemiology, who were initially skeptical, the results were met with resistance. Attempts to debunk the data were especially apparent from “experts” who held strong beliefs about the benefits and safety of fluoridation.

There are thousands of articles pointing to the safety of community water fluoridation ... this study doesn't change the benefits of optimally fluoridated water and exposure to fluoride.⁹ Dr. Braun, chair of the AAP Section on Oral Health Executive Committee

Yet, there are no other prospective studies with biomarkers of fluoride in pregnant women living in regions with CWF. Canada's national newspaper rang with the headline, “Fluoride won't make you dumber, but the ‘debate’ about its safety might”.¹⁰ Didn't the NRC deliberately call for more studies to address this “debate”?⁶

Vitriolic comments and claims with little scientific basis, such as the results are driven by outliers, were made by the American Council on Science and Health¹¹ and the UK-based Science Media Centre,¹² both heavily funded by the pharmaceutical and food and beverage industries. In reality, we presented our models with and without outliers and the effect remained. These types of vacuous claims exemplify attempts to manipulate the scientific evidence and manufacture doubt.

So what this study found was just an association. And we know from other areas ... they are inherently problematic and inherently complex.¹³ Timothy Caulfield, University of Alberta

This was not a scholarly debate on the neurotoxicity of fluoride; it was an attack on IQ scores, statistical methodology, and observational studies. Ironically, the evidence showing that CWF protects against tooth decay was largely based on observational or “association” studies, most of which were conducted prior to the introduction of fluoridated toothpaste in the early 1970s.¹⁴ Moreover, most landmark studies in public health—including those linking smoking with lung cancer, air pollution with coronary heart disease, and asbestos with mesothelioma—were observational. Indeed, this design is optimal to study many important public health problems, usually in conjunction with toxicological studies.

There is no sensible biochemical reason why fluoride would harm the brains of boys but not those of girls. So, are the authors wrong? Probably.¹⁵ Alex Berezow, Ph.D., Vice President of Scientific Affairs, American Council on Science and Health

Our paper continued to be attacked in scientific and public arenas, many of them drawing upon critiques made by the industry-funded groups. Accusations that our data did not support our conclusions spread quickly and were propagated by social media. “Experts” wrote that the association between maternal urinary fluoride and lower IQ in males, but not females, defied plausibility. However, as we noted in our original proposal, males are often more susceptible to toxicants and failure to examine sex-specific effects of fluoride exposure may result in missing a potentially vulnerable group. Further, the NTP in 2016 specifically called for more studies on fluoride exposure with an emphasis on sex-specific associations.¹⁶

I'm confused as to why the authors would want to withhold the data.¹⁷ Stuart Ritchey, Ph.D.

On October 23, 2019, a letter signed by 30 health-care professionals and scientists from six countries was sent to the Acting Director and Acting Deputy Director of the NIEHS. The letter cited concerns about the replicability of scientific research in general and the need for transparency. Our research team was accused of “refusing to release data”, but we had not refused to release the data. The policies that govern access to the MIREC Biobank and procedures to access it are sent to anyone who requests the data.

RISK AND BENEFITS

Some critics maintained that our conclusion—that pregnant women should reduce their fluoride intake—overstated the implication of the findings and was “dangerous”. Other critics said that we should not change our actions based on “one study”. We agree that no one study is definitive; we should carefully evaluate the collective evidence from multiple studies, as well as the risks and benefits of fluoridation.

Four high-quality, prospective birth cohort studies^{5,8,18,19} show that fetal exposure to fluoride is associated with diminished cognitive abilities. In November 2019, the National Toxicology Program released a draft report on fluoride concluding that fluoride is presumed to be a cognitive neurodevelopmental hazard. This report was largely ignored by the critics of our study.^{17,20}

Fluoride offers no benefits to the fetus. The beneficial effects of fluoride predominantly occur at the tooth surface, after the teeth have erupted.^{21–23} Accordingly, the Canadian Pediatric Society and the American Academy of Pediatrics advise against fluoride supplements during the first 6 months of life.²⁴

Exposure to fluoride comes from a variety of sources, but for people who live in cities with fluoridated water, the main source of ingestion is drinking water. Importantly, pregnant women and formula-fed babies may not be able to access nonfluoridated water.

CONCLUSION

Did our article shift the needle? Perhaps for those who are willing to integrate new knowledge with their existing beliefs. To understand why many questions about the safety of CWF are still not settled after 75 years, we need to recognize how entrenched beliefs can lead to biases and blind spots, even among highly trained clinicians and scientists. Science advances by continuously challenging old ideas and adjusting our beliefs as new knowledge emerges, even if this new evidence conflicts with conventional wisdom or is inconvenient.

Dr. Lanphear, a senior scientist on our team who conducted many of the pivotal lead toxicity studies that helped confirm Dr. Needleman's work, reminded us that it took two decades of research before the CDC declared, “there is no safe level of lead in children's blood”. Dr. Lanphear wrote, “The critics—who were often paid by industry or simply ignorant about lead toxicity but

still willing to offer their 'expert' opinion—delayed efforts to prevent lead poisoning by decades”.

We typically fret about subtle biases, like recall bias and unmeasured confounding, but confirmation bias, the tendency to ignore or debunk data that does not conform to what we believe, is arguably a much larger problem. Failure to act on consistent evidence that indicates safety risks could amount to enormous costs at the population level.

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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C. ANDREW WATERS, ESQ., CA Bar No. 147259
MICHAEL CONNETT, ESQ., CA Bar No. 300314
WATERS, KRAUS & PAUL
222 N. Pacific Coast Hwy, Suite 1900
El Segundo, CA 90245
310-414-8146 Telephone
310-414-8156 Facsimile

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA
AT SAN FRANCISCO

FOOD & WATER WATCH, et al.,

Plaintiffs,

vs.

U.S. ENVIRONMENTAL PROTECTION
AGENCY, et al.

Defendants.

Civ. No. 17-CV-02162-EMC

**DECLARATION OF
HOWARD HU, MD, MPH, ScD**

TABLE OF CONTENTS

I. SUMMARY OF QUALIFICATIONS1

II. SUMMARY OF OPINIONS3

III. BASIS FOR OPINIONS.....3

 A. The Methodological Strengths of the ELEMENT Studies3

 B. Prenatal Fluoride Exposure Is Associated with Substantial and
Significant Adverse Effects on IQ and ADHD-Behaviors in the
ELEMENT Cohort.....7

 C. The Limitations of Our Studies Do Not Provide Plausible
Alternative Explanations for the Results12

 D. Implications of Our Findings to the General Population in Water-
Fluoridated Areas.....15

IV. REFERENCES18

I, Howard Hu, MD, MPH, ScD, declare that:

1. I am a physician-scientist trained in internal medicine, occupational/environmental medicine, epidemiology and general public health who has held leadership positions in science and academia for over 2 decades.

2. I am also the Principal Investigator of ongoing research that is examining the impact of early-life exposures to fluoride on neurobehavioral development in the offspring participating in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project.

I. SUMMARY OF QUALIFICATIONS

3. A complete summary of my qualifications and publications can be found in my Curriculum Vitae, which has been marked as Plaintiffs' Exhibit 5 and attached herein.

4. As relevant to my testimony here, I am an epidemiologist with decades of research experience investigating the impact of environmental toxicants on human health. In 1990, I received a Doctor of Science degree in Epidemiology from the Harvard School of Public Health, and since that time have taught epidemiology at Harvard, University of Michigan, and University of Toronto, where I served as Dean of the School of Public Health.

5. I hold editorial positions on leading environmental and occupational health journals, including the *American Journal of Industrial Medicine*, *Current Environmental Health Reports* and *Environmental Health Perspectives*, and serve as a peer reviewer for the *American Journal of Epidemiology*, *Epidemiology*, *Journal of the American Medical Association*, *Lancet*, *New England Journal of Medicine*, and *Pediatrics*, amongst others.

6. My own epidemiological research has resulted in hundreds of peer-reviewed publications in leading scientific journals. For the past 29 years, this research has been continuously funded by the National Institutes of Health (NIH) through a number of competitive R01 grants.

1 7. The Environmental Protection Agency (EPA) has funded several of my epidemiological
2 studies, including a \$7.8 million research grant to study the effects of metals mixtures on children's
3 health. I have also served as an expert advisor to the EPA, including as a member of EPA's Science
4 Advisory Board on Relative Risk Reduction Strategies and as an expert reviewer of EPA's recent draft
5 report on the concentration-response functions between lead exposure and cardiovascular disease.

6 8. In 1993, I co-founded the ELEMENT research project, a pregnancy and birth cohort that
7 has been funded by both the EPA and NIH. Since its inception, ELEMENT has evolved into a highly
8 successful, award-winning project involving collaborators at the University of Michigan, Harvard, and
9 other academic institutions in the U.S., Canada, and Mexico.

10 9. Through the ELEMENT cohort, we have studied how prenatal exposure to environmental
11 toxicants—including lead, mercury, and fluoride—affect children's health, including their
12 neurodevelopment. Thus far, the ELEMENT cohort has generated over 80 high-impact publications and
13 provided evidence contributing towards environmental health policies around the world, including the
14 EPA's national air standard for lead and the CDC's "Guidelines for the Identification and Management
15 of Lead Exposure in Pregnant and Lactating Women."

16 10. In 2012, following the National Research Council's (NRC) call for more research to
17 investigate the neurobehavioral risks of fluoride exposure, the team I lead successfully competed for a
18 peer-reviewed NIH RO1 grant to study the neurodevelopmental effects of pre- and post-natal fluoride
19 exposures. This research was funded with an understanding that it would provide a major contribution to
20 fluoride risk assessment and policy decision-making on the neurotoxicity concerns identified by the
21 NRC.

22 11. To date, my team has published five peer-reviewed studies on fluoride, including two
23 prospective studies on fluoride and neurodevelopment that were published in the world's two most
24
25
26
27

1 prominent environmental health journals: *Environmental Health Perspectives* and *Environment*
2 *International* (Bashash 2017, Bashash 2018, Cantoral 2019, Liu 2019, Thomas 2016). As with our own
3 research, the journal *Environmental Health Perspectives* is funded by the NIH.

4 **II. SUMMARY OF OPINIONS**

5 12. The ELEMENT prospective cohort studies of fluoride's neurodevelopmental effects are
6 methodologically rigorous studies that provide scientifically reliable and robust results.

7 13. The results of the ELEMENT prospective cohort studies are consistent with and support
8 the conclusion that fluoride is a developmental neurotoxicant at levels of exposure seen in the general
9 population in water-fluoridated communities.
10

11 **III. BASIS FOR OPINIONS**

12 **A. The Methodological Strengths of the ELEMENT Studies**

13 14. ***Prospective Birth Cohort Study Design:*** One of the key strengths of our ELEMENT
14 research is that it has utilized a prospective birth cohort design. Prospective studies (aka longitudinal
15 cohort studies designed at the outset to enable research on the topics of interest and that follow a defined
16 group of individuals) are recognized by epidemiologists as the ideal study design for investigating the
17 impact of environmental toxicants on human health, in part, because the measurement of exposure
18 precedes the development of disease/dysfunction. This is important because it permits greater
19 confidence in the causal relationship of an association since the requirement of temporality is satisfied
20 i.e., the exposure precedes the effect, which, in turn, is one of the components of the Bradford Hill
21 criteria. Where there is suspicion that a chemical may exert a toxic effect *in utero*, a birth cohort study
22 design is critical because it allows an assessment of exposure during the prenatal period.
23

24 15. ***Effective Control for Other Factors that Influence IQ:*** Our ELEMENT studies have
25 considered and controlled for a large number of factors known to affect neurodevelopment, which
26
27

1 increases the rigor of the results. First, we excluded women from the study who had characteristics
2 known to affect neurodevelopment, including gestational diabetes, renal disease, hypertension,
3 circulatory diseases, use of illicit drugs, and alcohol consumption. Second, our analyses of fluoride and
4 neurodevelopment controlled for a large number of potential confounders, including maternal age,
5 maternal education, maternal IQ, birth weight, gestational age at time of delivery, sex of child, birth
6 order, maternal smoking, and marital status. Third, we performed sensitivity analyses which controlled
7 for the quality of the child's home environment (i.e., HOME),¹ as well as prenatal lead and mercury
8 exposures.
9

10 16. **Blinded Assessments:** Our studies employed a "blinded" study design where neither the
11 examiners nor the subjects were aware of the subject's fluoride exposure status at the time of the
12 neurodevelopmental exams. A blinded study design is superior to a non-blinded study because it helps
13 protect against bias, including unconscious bias, in the assessment.

14 17. **Individual Biomarkers of Both Prenatal and Postnatal Exposure:** As cohort studies, our
15 investigations have collected and utilized individual measurements of fluoride exposure, covariates, and
16 the outcomes of interest. Cohort studies with individual measurements of exposure, covariates and
17 outcomes are considered much more robust than studies with group-level metrics (otherwise known as
18 "ecological studies") because the accuracy and precision of individual-level measures are far superior to
19 the estimates of these parameters that are associated with ecological studies. In our studies, we measured
20 prenatal fluoride exposure by testing archived samples of the mother's urine that were collected during
21 pregnancy. Urine fluoride is a well-accepted biomarker of total fluoride exposure. As the EPA has
22
23

24 ¹ The HOME Score is a rating that is performed by a research observer who gains permission to
25 enter the home and observe the interactions between the offspring and other family members, as well as
26 other characteristics of the home environment. It is intended to try to capture the ability of the home to
27 enrich a child's educational development and skill development. It is often highly correlated with socio-
28 economic status, but it also has some independent value of its own in determining a child's
neurodevelopmental trajectory.

1 recognized, “archives of biological samples from birth cohort studies . . . provide critical information on
2 the prenatal and childhood determinants of adult disease” (EPA-NIEHS 2017, p. 9). The archived urine
3 samples in our studies were tested under the oversight and direction of Dr. Angeles Martinez-Mier, a
4 leading authority on the measurement of fluoride in urine and plasma.

5 18. As I acknowledge and discuss further below, there are some limitations with our urine-
6 based exposure estimates. These limitations, however, do not provide a plausible explanation for the
7 results we have observed as they create *non-differential* imprecision in the exposure variable (in this
8 case, the non-differential exposure misclassification is sometimes referred to as “random” or “classical”
9 measurement error associated with exposure). It is a basic epidemiologic axiom that non-differential
10 errors, such as non-differential exposure misclassification, bias the results towards the null (i.e., no
11 association exists), rather than create spurious associations where none otherwise exist. I discuss this
12 further below.
13

14 19. ***Large Cohort Sizes:*** Our studies have involved a sufficiently large number of mother-
15 offspring pairs to permit statistical analyses that are stable and robust. In our 2017 study (“Bashash
16 2017”), we investigated fluoride’s relationship with intelligence among 299 mother-offspring pairs. This
17 included 287 mother-offspring pairs for the analysis of intelligence at age 4, and 211 mother-offspring
18 pairs for an analysis of intelligence at ages 6-12. In our 2018 study (“Bashash 2018”), we investigated
19 the relationship between fluoride and symptoms of Attention-Deficit Hyperactivity Disorder (ADHD)
20 among a total of 213 mother-offspring pairs, with the ADHD assessment conducted between the ages of
21 6 and 12.
22

23 20. ***Reliable Neurocognitive Tests:*** Our 2017 study on intelligence used validated,
24 standardized neurocognitive tests that were administered by a team of psychologists. For the 4-year old
25 children, we used the McCarthy Scales of Children’s Abilities (MSCA), and focused on the General
26
27
28

Cognitive Index (GCI) score. For the 6-12 year old children, we used the Spanish version of the Wechsler Abbreviated Scale of Intelligence (WASI)² to assess Full-Scale IQ. All raw scores were standardized for age and sex. The examining psychologists were trained and supervised by an experienced developmental psychologist, and independent testing confirmed a very high correlation (0.99) in the scoring, thus confirming a high degree of inter-examiner reliability.

21. ***Reliable Neurobehavioral Tests:*** Behaviors associated with ADHD were assessed using the Spanish version of the Conners' Rating Scales-Revised (CRS-R)³ and Conners' Continuous Performance Test (CPT-II, 2nd Edition).⁴ All measures of ADHD-behaviors were standardized for age- and sex. Higher T-scores (mean of 50, SD of 10) indicate poorer performance. All psychometric tests were applied under the supervision of an experienced psychologist.

22. ***Appropriate Statistical Analyses that Did Not Assume Linearity:*** We used the same standard statistical analyses for our fluoride studies as we have used for our other ELEMENT studies. These included regression analyses that appropriately adjusted for potential confounders, as well as Generalized Additive Models (GAM) that visualized adjusted associations between fluoride and neurodevelopment for purposes of assessing the linearity of the relationship. We did *not* assume

² The WASI shows strong criterion validity with the full-length Wechsler Intelligence Scale for Children (WISC-III; ages 6-16 yrs), and the Wechsler Adult Intelligence Scale (WAIS; ages 16+ yrs). The correlation coefficient between the Full Scale IQ of the WASI and WISC-III is 0.81 (Wechsler, 1991), and 0.92 between the WASI and the WAIS-III (Wechsler, 1999), indicating a high covariance between the abbreviated and full-length measures of intellectual ability. The WASI is also correlated with another abbreviated IQ test, the Kaufman Brief Intelligence Test ($r = 0.89$), providing evidence for convergent validity (Hays et al., 2002). Finally, the WASI demonstrates excellent internal consistency (reliability=0.976) (based on data from Tables 5.1 and 5.8 of the WASI manual).

³ The CRS-R contains three ADHD scales that correspond with the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) criteria for ADHD: 1) DSM-IV Inattention Index, 2) DSM-IV Hyperactive-Impulsive Index, and 3) DSM-IV Total Index (inattentive and hyperactive-impulsive behaviors combined). It also examines seven types of behavior problems that were derived through factor analysis, including: Oppositional, Anxious-Shy, Cognitive Problem/Inattention, Hyperactivity, Perfectionism, Psychosomatic, and Social Problems. For our study, we examined the three DSM-IV ADHD scales as our primary outcomes because these scales are intended to screen for ADHD, and are commonly used to study the association between diverse environmental contaminants and ADHD- behavior problems.

⁴ The CPT-II is a computer-administered signal detection paradigm. Using the CPT-II, we measured errors of omission and commission, and hit reaction time (response latency).

linearity in the dose-response relationship. Additionally, we took appropriate steps to eliminate the influence of outliers and influential points.

B. Prenatal Fluoride Exposure Is Associated with Substantial and Significant Adverse Effects on IQ and ADHD-Behaviors in the ELEMENT Cohort

23. In the ELEMENT cohort, we found that prenatal fluoride exposure has a linear, dose-response relationship with reduced IQ among both 4-year old and 6-12 year old children (Bashash 2017).⁵ In our main model that adjusted for potential confounders, we found that each 0.5 mg/L increase in maternal urinary fluoride (which approximates the interquartile range, i.e., the difference between the 25th v. 75th percentile) was significantly associated with a loss of 3.15 GCI points among the 4-year-olds, and a loss of 2.5 IQ points among the 6-to-12 year olds. These are substantial reductions in intelligence that rival the effect sizes associated with lead exposure. As one measure of practical impact developed and published in 2009 by an expert from the Economics Policy Institute, each IQ point lost due to lead exposure was estimated to represent a loss of \$17,815 in present discounted value of lifetime earnings (in 2006 USD) (Gould 2009).

24. Visual assessment of the adjusted associations between fluoride and intelligence confirmed the monotonic, mostly linear nature of the relationships (see Figures A and B). Notably, there was no evidence of a threshold among the 4-year olds, although there was some suggestion of a threshold at approximately 0.8 mg/L among the 6-12 year olds.

⁵ We have subsequently reported an analysis, in abstract form, of neurocognitive outcomes at ages 1 to 3, as measured through the Mental Development Index (Thomas 2018). These results are consistent with the age 4 and age 6-12 analyses in that they show significant adverse associations with maternal urinary fluoride. I do not rely on these results here, however, since they have not yet been published in full

Figure A: Visual Association Between Maternal Urinary Fluoride and Intelligence at Age 4

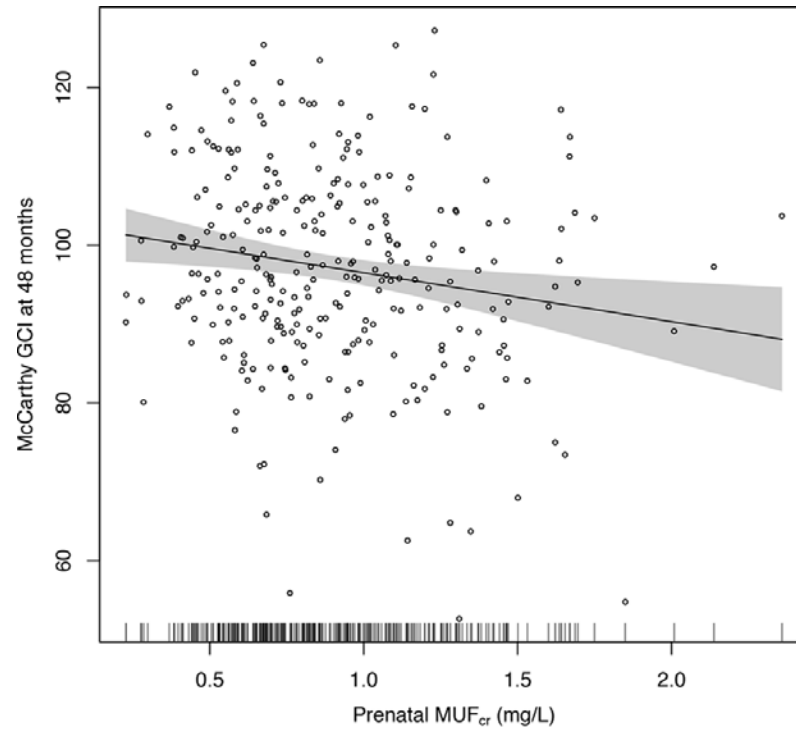
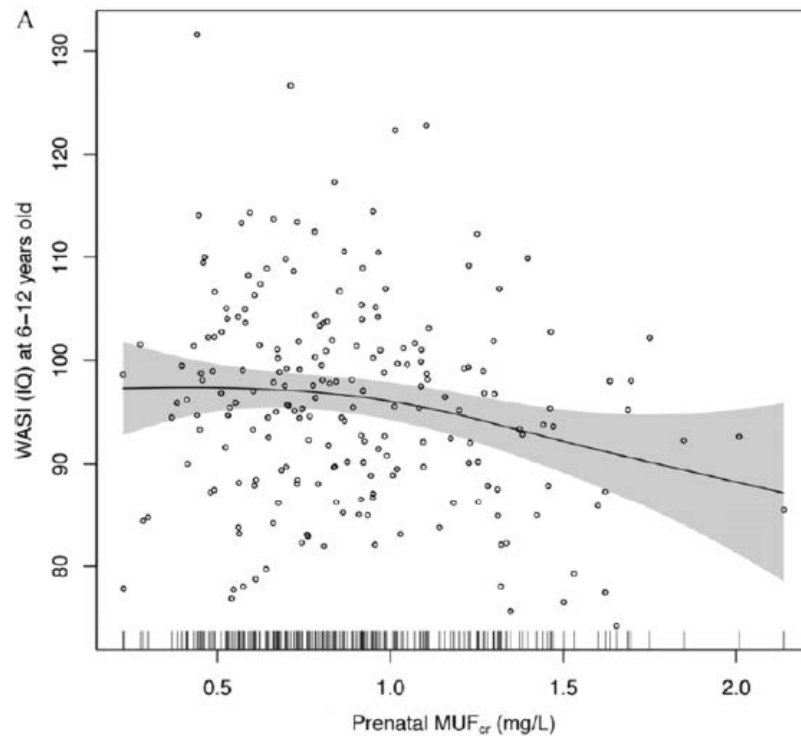


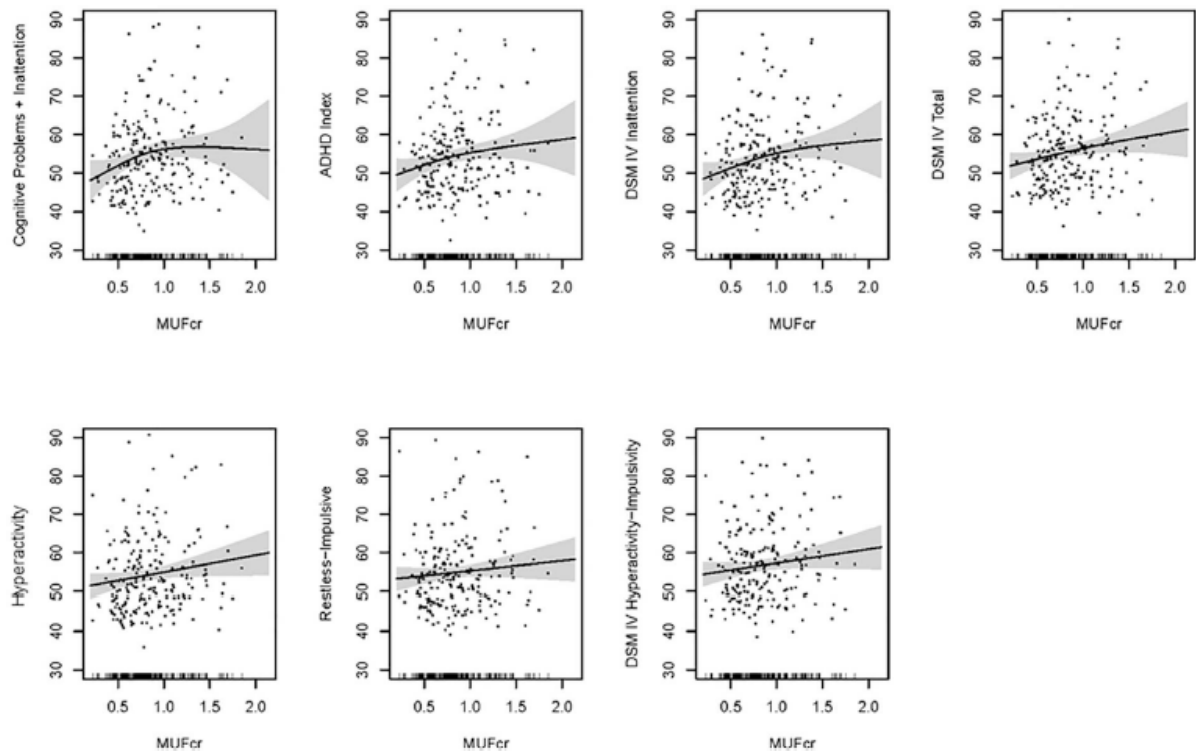
Figure B: Visual Association Between Maternal Urinary Fluoride and Intelligence at Ages 6-12



1 25. In contrast with prenatal exposures, we did not find statistically significant associations
2 between IQ and childhood urinary fluoride levels at ages 6 to 12, although there was some suggestion of
3 an adverse effect. This suggests that the timing of fluoride exposure is an important determinant of
4 fluoride's neurodevelopmental effects, and is consistent with exposures occurring prenatally being more
5 detrimental than those occurring during school-aged years. This is plausible given fluoride's passage
6 through the placental barrier, and the known enhanced vulnerability of the developing brain to
7 neurotoxins during the *in utero* period.

8
9 26. In addition to IQ, we have also found a significant association between prenatal fluoride
10 exposure and some attention deficit hyperactivity disorder (ADHD)-like behaviors on the CRS-R test,
11 including cognitive problems and inattention (Bashash 2018). As with our IQ analyses, the associations
12 were linear, although—as we have found for lead (Huang 2016)—there was some indication in some of
13 the analyses of a ceiling effect at higher doses (i.e., the dose-response curve for cognitive problems and
14 inattention began to flatten above 1 mg/L).

15
16 27. The effect sizes between prenatal fluoride and ADHD behaviors in our cohort were
17 substantial. For those effects which reached statistical significance, increases of 0.5 mg/L in maternal
18 urinary fluoride were associated with 2.4 to 2.8-point higher scores (higher scores reflect indicate poorer
19 performance). Whereas IQ is standardized to a mean of 100, the ADHD behavior scales are standardized
20 to a scale of 50. The effect sizes that we found for prenatal fluoride are similar to what we have found
21 for childhood blood lead levels (Huang 2016).
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Figure C: Association Between Maternal Urinary Fluoride & ADHD Behaviors

28. We did not find statistically significant associations between fluoride and ADHD-behaviors on the CPT-II test. Other studies of environmental chemicals have reported similar discrepancies between the two tests, suggesting that they are assessing different constructs. The stronger association that we found between fluoride and ADHD behaviors on the CRS-R scale may be explained by the CRS-R's focus on constructs that rely on attention (e.g., new learning, ability to hold information and complete tasks, organizational skills, etc).

29. The relationship we observed between fluoride and inattention is consistent with some animal research that has reported a relationship between prenatal fluoride exposure and hypoactive behavioral patterns (Mullenix 1995), as well as prior epidemiological research associating fluoride with impaired working memory (Choi 2015). Working memory is linked with the ability to control attention and it is common for youth with ADHD to have weaknesses in working memory (Kasper 2012).

Fluoride's effect on working memory may relate to an effect on the dopamine system, which fluoride has been found to alter in animal studies (Pal & Sarkar 2014). Dopamine is an important modulatory neurotransmitter in planning and initiation of motor responses, activation, switching, reaction to novelty and processing of reward (Fararone 2015).

30. Some have suggested that the “scatter” in the above scatterplots is a basis to doubt the relation between fluoride and the neurodevelopmental outcomes. Such scatter, however, is typical in epidemiological studies of neurotoxicants, as can be seen in the following figure from our study on lead and neurocognitive effects which the EPA relied upon as evidence of low-level lead neurotoxicity when the Agency set the national air standard for lead (Tellez-Rojos 2006, Fig 1, reproduced as Figure D below). We also found similar scatter in our analysis of blood lead and ADHD behaviors, as measured by CRS-R (Huang 2016, Fig. 1, reproduced as Figure E below). The scatter relates to the fact that there are multiple factors that impact on intelligence and behavior; however, unless they are confounders (which we controlled for), they do not preclude the ability to focus on the specific effect of fluoride.

Figure D: Association Between Childhood Blood Lead Levels and Mental Development Index

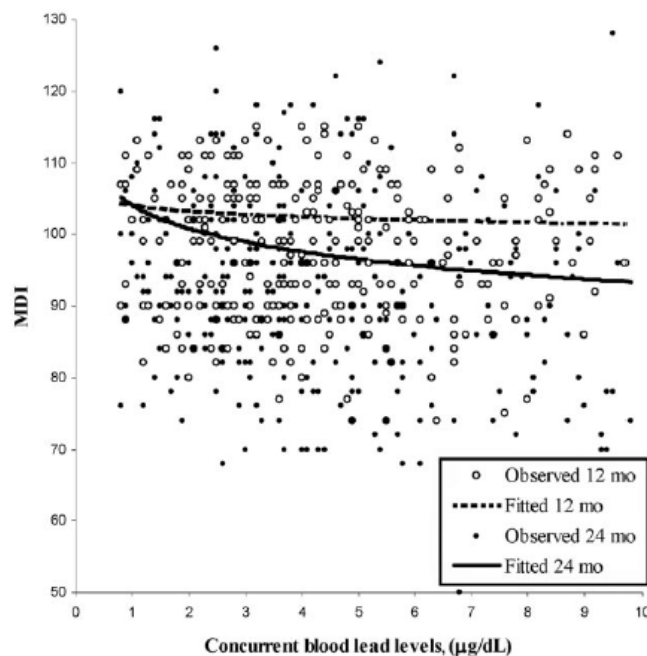
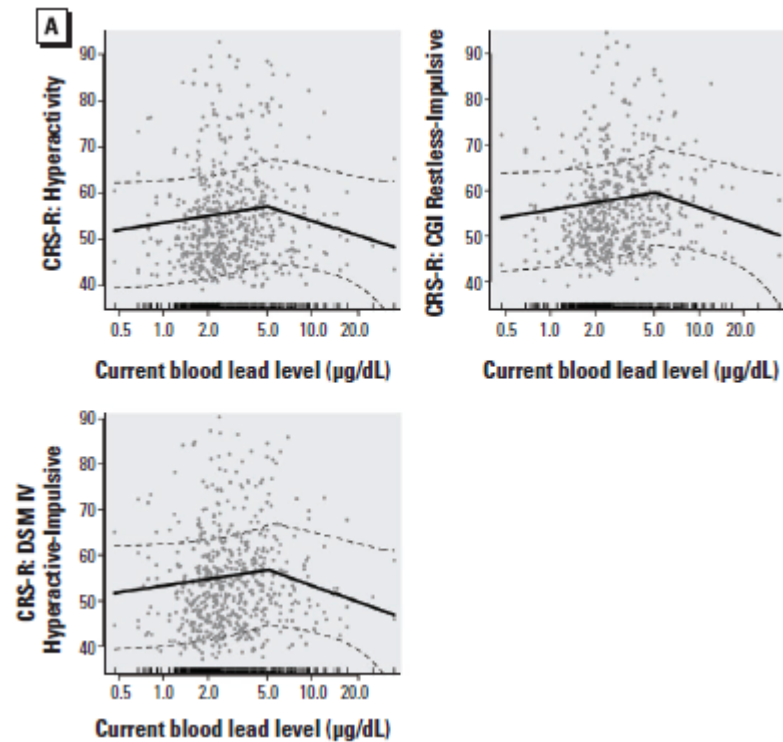


Figure E: Association Between Childhood Blood Lead Levels and ADHD Behaviors



C. The Limitations of Our Studies Do Not Provide Plausible Alternative Explanations for the Results

31. Every epidemiological study, including our studies on fluoride and neurodevelopment, has its limitations. Some of these limitations could theoretically be avoided through the use of human experiments where the toxicant is delivered to the study participants in a controlled and randomized manner. Human experimentation on neurotoxicants, however, is strictly prohibited for obvious ethical reasons. We are thus left with “observational” studies to investigate the impact of environmental toxicants on human health, with prospective cohort studies being the study design best suited for this purpose.

32. As is often the case with epidemiological studies of environmental toxicants, there are limitations in the exposure measurements that we have used in the ELEMENT studies. Our use of spot samples to collect the urine introduces some imprecision into the exposure measurement because urinary

1 fluoride concentrations can fluctuate somewhat throughout the day. This imprecision would have been
2 reduced through the use of 24-hour urine collection samples, and, to a lesser extent, fasting first-morning
3 voids, which are both considered more rigorous measures of fluoride exposure. We compensated for this
4 limitation by using “timed” samples (i.e., second void in the morning) and adjusting for urinary
5 creatinine. Urinary fluoride concentrations fluctuate during the day in large part because fluctuations in
6 an individual’s hydration during the day result in fluctuations in urinary dilution (and therefore, urinary
7 concentrations). Adjusting for urinary creatinine is particularly important because the resulting measure
8 adjusts for urinary dilution. As a result, measures of fluoride in spot urine samples adjusted for
9 creatinine have been found to have excellent agreement with 24-hour samples (Zohouri 2006). Timed
10 spot samples also have an important advantage over 24-hour samples in that they are less imposing on
11 study participants. This is an important consideration when designing cohort studies because the
12 imposition of difficult tasks like collecting 24-hour urines serve to reduce participation, which, in turn,
13 reduces the study’s sample size and statistical power.⁶
14

15 33. Another limitation in our exposure measurements is that, for most of the mothers, we did
16 not have urine samples for every trimester. In our age 4 IQ analysis, 49%, 42%, and 9% of the mother-
17 offspring pairs had urine samples for one, two, and all three trimesters, respectively. In the age 6-12
18 analysis, the respective percentages were 56%, 39%, and 5%; while in the ADHD study, the respective
19 numbers were 57%, 36.4%, and 6.5%. It is common for prospective cohort studies to only have one or
20 two exposure measurements during the prenatal period, but this does not introduce undue imprecision in
21 the exposure estimate, as exposures to a toxicant have limited variation during pregnancy.
22

23 34. Importantly, the imprecision in our exposure measurements does not explain the large
24 and significant associations we observed between maternal urinary fluoride and neurodevelopmental
25

26 ⁶ To put it in simple terms, less people will volunteer to participate in a study if it requires them to
27 collect all of their urine throughout the entire day, including while they are in public spaces, such as
28 their work environment and restaurants, etc.

1 effects. Imprecision in exposure measurements (of the classical or random type, as noted above) is a
2 type of non-differential error that introduces scatter into the analysis which has a generally expected
3 effect of biasing the results towards the null hypothesis. To put it another way, imprecisions in exposure
4 measurements make it *harder*, not easier, to detect an association between an exposure and outcome,
5 much like background noise makes it harder to hear a sound or signal of interest. Imprecision in the
6 exposure measurement is thus anticipated to *obscure* an association, rather than create spurious
7 associations where none otherwise exist. Because of this, improvement in the measurement of a
8 particular exposure tends to reveal and strengthen associations associated with that exposure, not
9 eliminate them.
10

11 35. Another limitation with our studies is, as with most observational studies, we could not
12 rule out the potential for uncontrolled confounding from factors that we did not measure. For example,
13 we did not have data on arsenic which is a neurotoxicant that has been associated with fluoride in certain
14 rural drinking water supplies. While it is always preferable to have more data than less, it is unlikely that
15 arsenic is a meaningful confounder in our cohort. To be a confounder, a covariate must be associated
16 with *both* the outcome *and* exposure. In our cohort, the main source of fluoride is from *salt*, not water.⁷
17 Accordingly, even if arsenic is correlated with fluoride in rural water supplies in Mexico, this
18 association is unlikely to be materially associated with fluoride exposures in our cohort.
19

20 36. Finally, an additional limitation in our studies is that we did not have information on the
21 iodine status of our cohort. Iodine has been theorized to be a potential effect-modifier for fluoride's
22 nervous system effects, i.e., deficiencies of iodine may magnify fluoride's effects, and vice versa (NRC
23 2006). However, failure to control for an effect modifier is unlikely to produce an association between
24 exposure and outcome that does not otherwise exist. Moreover, in Mexico, salt is required by law to be
25

26 ⁷ The water in Mexico City has low levels of fluoride (i.e., 0.16 mg/L) and thus does not present a
27 meaningful exposure in our cohort (Cantoral et al. 2019).

1 iodized. Fluoride levels in our cohort are thus likely correlated with *increased* iodine. To the extent that
2 iodine modifies the effect of fluoride in our population, it is more likely to be in the direction of
3 *reducing* toxicity rather than magnifying it.

4 **D. Implications of Our Findings to the General Population in Water-Fluoridated**
5 **Areas**

6 37. In 2016, we published the largest characterization to date of urinary and plasma fluoride
7 levels throughout pregnancy (Thomas, et al. 2016). At the time we published this study, there had yet to
8 be a population-based study of fluoride exposures among pregnant women in North America, although
9 there were two small-scale studies available from Israel and Poland. The lack of data from North
10 America prevented us, at that time, from comparing the urinary fluoride levels in our cohort with
11 populations from Canada or the United States.

12 38. Urine and plasma fluoride are metrics of the total absorbed dose of fluoride, sometimes
13 referred to as the “internalized” or “bioavailable” dose. These internalized doses do not currently permit
14 one to directly estimate the amount of fluoride that is ingested (i.e., the “external” exposure), nor do they
15 permit the determination of source apportionment of the fluoride exposures. Internalized doses,
16 however, are more relevant than external intake in predicting toxic effects, since they reflect the
17 concentration of toxics that are being delivered to target organs in the body.

18 39. Our 2016 study presented the urinary and plasma fluoride levels from 825 and 330
19 pregnant women from our cohort, respectively. The urine samples were collected and measured using
20 the procedures discussed above for our neurodevelopmental papers (i.e., early morning 2nd voids that
21 were adjusted for creatinine), and both the urine and plasma samples were tested under the direction of
22 Dr. Angeles Martinez-Mier from Indiana University, a world leader in the measurement of fluoride in
23 biological samples.

24 40. The average creatinine-adjusted urinary fluoride level across all three trimesters in the
25
26
27
28

1 ELEMENT cohort was 0.91 mg/L, with a standard deviation of 0.4 mg/L.⁸ The average plasma fluoride
 2 level across all three trimesters was 0.0221 mg/L, with a standard deviation of 0.0164 mg/L.⁹

3 41. By the time we published our 2018 study on ADHD behaviors, general population data
 4 had become available on maternal urinary fluoride levels in pregnancy (Till 2018). As we noted in our
 5 2018 study, the maternal fluoride levels in the Canadian study are similar to the levels in our cohort
 6 (Bashash 2018). The mean (creatinine-adjusted) maternal urinary fluoride level among pregnant women
 7 living in the water-fluoridated areas of Canada was 0.87 mg/L, with a standard deviation of 0.50 mg/L,
 8 which is clearly in the same range as our cohort (i.e., mean = 0.91 mg/L, SD = 0.4 mg/L). The urine
 9 samples in the Canadian study were tested by Dr. Martinez-Mier using the same creatinine-adjustment
 10 method, which increases the comparability of the data.
 11

12 42. The similarity in maternal urinary fluoride levels between pregnant women in the
 13 ELEMENT cohort and water-fluoridated areas of the Canadian cohort is consistent with the fact that
 14 both populations are receiving so-called “optimal” levels of fluoride through fluoridation programs (i.e.,
 15 salt fluoridation in Mexico, and water fluoridation in Canada). Since salt fluoridation programs are
 16 designed to replicate the doses provided by fluoridated water, it is a reasonable, first-order expectation
 17 that populations living in salt-fluoridated and water-fluoridated areas will receive similar doses of
 18 fluoride.
 19

20 43. The maternal urinary fluoride data from the ELEMENT cohort and water-fluoridated
 21 areas of Canada support the conclusions that the two populations have essentially the same *internalized*
 22 doses of fluoride. The internalized doses in water-fluoridated areas are thus in the range that we have
 23

24 ⁸ The 75th and 90th percentile values were 1.09 mg/L and 1.37 mg/L, respectively.

25 ⁹ We tested for and found no correlation between creatinine-adjusted urinary fluoride and
 26 sociodemographic variables, including maternal age, maternal education, child sex, smoking status, birth
 27 order, and cohort. Although we found a trend towards increasing urinary fluoride levels through the first
 28 22-23 weeks of pregnancy, and a reduction thereafter, these trends were not statistically significant
 (Thomas 2016).

1 found to be associated with substantial and significant neurodevelopmental harms in the ELEMENT
2 cohort.

3 44. Although direct comparisons of *external* fluoride intake cannot yet be made, such
4 information is not necessary to generalize the neurodevelopmental results from the ELEMENT cohort to
5 water-fluoridated areas.

6 45. There is no identified reason to believe that the neurodevelopmental effects of fluoride
7 will differ by the source of exposure, be it fluoridated salt or fluoridated water; once inside the body the
8 source of fluoride is immaterial.

9 46. For the reasons stated, it is my opinion to a reasonable degree of scientific certainty that
10 the results of the ELEMENT studies support the conclusion that fluoride is a developmental
11 neurotoxicant at levels of internalized exposure seen in water-fluoridated communities.
12

13
14 I declare under penalty of perjury, under the laws of the United States, that the foregoing
15 is true and correct to the best of my knowledge and belief.

16 Executed on May 20, 2020, in Seattle Washington.

17
18
19 

20 HOWARD HU, MD, MPH, ScD

IV. REFERENCES

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9 Mercado-Garcia A, Bashash M et al: Urinary and plasma fluoride levels in pregnant women from
10 Mexico City. *Environ Res* 2016, 150:489-495.
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13 1-3 years of age in Mexico. *British Medical Journal* 2018; 75(Suppl 1):A10.
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**CURRICULUM VITAE OF
HOWARD HU, MD, MPH, ScD**

CURRICULUM VITAE

Date Prepared: May, 2019

NAME: Howard Hu

PRIMARY AFFILIATION: School of Public Health, University of Washington

SECONDARY AFFILIATION: School of Public Health, University of Michigan

CONTACT: Howard Hu, M.D, M.P.H., Sc.D.

Email: hhu5@uw.eduLINKS: https://deohs.washington.edu/faculty/hu_howard
<https://www.linkedin.com/in/howard-hu-059703a/?trk=public-profile-join-page>

TABLE OF CONTENTS

SUBJECT	PAGE
EDUCATION	2
POSTDOCTORAL TRAINING	2
CERTIFICATION AND LICENSURE	2
ACADEMIC APPOINTMENTS	2
ADMINISTRATIVE APPOINTMENTS	3
CLINICAL APPOINTMENTS	4
OTHER ACADEMIC POSITION/VISITING APPOINTMENTS	4
MAJOR RESEARCH INTERESTS	5
GRANTS	5
HONORS AND AWARDS	9
MEMBERSHIPS	10
EDITORIAL POSITIONS AND BOARDS	10
PEER REVIEW SERVICE	11
TEACHING	11
COMMITTEE, ORGANIZATIONAL, VOLUNTEER SERVICE	17
OTHER PUBLIC SERVICE	22
CONSULTING POSITIONS	22
VISITING PROFESSORSHIPS	23
SEMINARS AND EXTRAMURAL INVITED PRESENTATIONS	23
BIBLIOGRAPHY	31

EDUCATION:

9/1973-6/1976	Biology	B.Sc.	Brown University
9/1977-6/1982	Medicine	M.D.	Albert Einstein College of Medicine
9/1979-6/1980 (degree in 6/1982*)		M.P.H. (Occ Hlth)	Harvard School of Public Health
9/1985-6/1986	Epidemiology	M.S.	Harvard School of Public Health
7/1986-6/1990	Epidemiology	Sc.D.	Harvard School of Public Health

* Awarding of the Harvard M.P.H. to medical students is delayed until the M.D. degree is conferred

POSTDOCTORAL TRAINING:

Research Fellowships

7/1987-6/1988 Occupational Health Research Fellow, Dept. of Environmental Health
Harvard School of Public Health

Internship and Residencies

7/1982-6/1983	Intern in Medicine	Boston City Hospital
7/1983-6/1984	Junior Assistant Resident, Internal Medicine	Boston City Hospital
7/1984-6/1985	Senior Assistant Resident, Internal Medicine	Boston City Hospital
7/1985-6/1987	Resident, Occupational Medicine	Harvard School of Public Health

CERTIFICATION AND LICENSURE:

1984	Massachusetts Medical License Registration
1985	American Board of Internal Medicine, Diplomate
1987	American Board of Preventive Medicine, Diplomate (Occupational Medicine)
2006	Michigan Medical License Registration
2013	College of Physicians & Surgeons of Ontario
2018	Washington State Medical License Registration

ACADEMIC APPOINTMENTS:

9/1988-6/1992	Instructor in Medicine Department of Medicine, Harvard Medical School
9/1988-6/2006	Associate Physician (Clinical and Research), Channing Laboratory, Department of Medicine, Brigham & Women's Hospital
9/1990-6/1994	Assistant Professor of Occupational Medicine Department of Environmental Health, Harvard School of Public Health

CV: Howard Hu, M.D., M.P.H., Sc.D.

7/1992-6/1997 Assistant Professor of Medicine
Department of Medicine, Harvard Medical School

7/1994-6/2002 Associate Professor of Occupational Medicine
Department of Environmental Health, Harvard School of Public Health

7/1997-8/2006 Associate Professor of Medicine
Department of Medicine, Harvard Medical School

7/2002-8/2006 Professor of Occupational and Environmental Medicine (tenured)
Department of Environmental Health, Harvard School of Public Health

9/2006-6/2012 Chair and Professor of Environmental Health Sciences (tenured), Department of
Environmental Health Sciences, University of Michigan School of Public Health

9/2006-8/2009 Adjunct Professor of Occupational and Environmental Medicine
Department of Environmental Health, Harvard School of Public Health

9/2006-6/2012 Research Associate Physician, Channing Laboratory, Department of
Medicine, Brigham & Women's Hospital

5/2007-2012 Professor of Epidemiology, University of Michigan School of Public Health

5/2007-2012 Professor of Internal Medicine, University of Michigan Medical School

1/2009-2012 NSF International Endowed Department Chair, University of Michigan School of
Public Health, Department of Environmental Health Sciences

7/2012-2018 Professor of Environmental Health, Epidemiology and Global Health (tenured)
Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario,
Canada (on sabbatical/administrative leave, 2017-2018)

7/2012-2018 Professor, School of Medicine, University of Toronto, Toronto, Ontario, Canada

7/2012- Adjunct Professor, Department of Environmental Health Sciences, University of
Michigan School of Public Health

7/2012-2013 Director, Dalla Lana School of Public Health, University of Toronto, Toronto,
Ontario, Canada

7/2013-6/2017 Founding Dean, Dalla Lana School of Public Health, a Faculty of the University
of Toronto, Toronto, Ontario, Canada

7/2017- Affiliate Professor (started as Visiting Scholar until December, 2017),
Department of Occupational and Environmental Health Sciences, University of
Washington School of Public Health, Seattle, WA

ADMINISTRATIVE APPOINTMENTS:

7/1991-6/2006 (Founding) Director, Metals Epidemiology Research Group, Channing Laboratory,
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and
Department of Environmental Health, Harvard School of Public Health

7/1992-6/1995 Director, Commission to Investigate the Health and Environmental Effects of Nuclear
Weapons Production, International Physicians for the Prevention of Nuclear War

7/1996-6/2006 Director, Residency Program in Occupational and Environmental Medicine, Harvard
School of Public Health

7/1996-8/2006 Director, Occupational and Environmental Medicine Core, National Institute for
Occupational Safety and Health Educational Resource Center at the Harvard School of

CV: Howard Hu, M.D., M.P.H., Sc.D.

Public Health

- 7/1998-6/2004 (Founding) Medical Editor, Environmental Health Perspectives (official journal of NIEHS)
- 7/2000-8/2006 Associate Director, the Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health
- 7/2004-6/2009 (Founding) Principal Investigator and Director, Harvard Center for Children's Environmental Health and Disease Prevention Research (co-PI and co-Director after 9/1/08)
- 9/2006-6/2012 Chair, Department of Environmental Health Sciences, University of Michigan School of Public Health
- 9/2006-2012 Director, Occupational Epidemiology Core, NIOSH Education and Research Center, University of Michigan
- 9/2006-2012 Co-Director, Michigan-Harvard/Harvard-Michigan Metals Epidemiology Research Group
- 7/2009-2011 Director, NIA T32 Training Grant in Aging and Public Health, University of Michigan School of Public Health
- 1/2010-2012 Chair, Faculty Steering Committee on Global Health, University of Michigan School of Public Health
- 4/2011-2012 (Founding PI) and Director, University of Michigan NIEHS P30 Core Center.
- 7/2012-2013 Director, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
- 7/2013-6/2017 Founding Dean, Dalla Lana School of Public Health, a Faculty of the University of Toronto, Toronto, Ontario, Canada

CLINICAL APPOINTMENTS:

- 7/1985-6/1987 Attending Physician, Emergency Department, Whidden Memorial Hospital
- 7/1985-6/1988 Assistant Visiting Physician, Department of Medicine, Boston City Hospital
- 1/1985-6/2006 Consultant in Occupational and Environmental Medicine, Center for Occupational and Environmental Medicine, Northeast Specialty Hospital (formerly known as the Olympus Specialty Hospital, the Massachusetts Respiratory Hospital, and Norfolk County Hospital).
- 3/1987-9/1987 Attending Physician, Occupational Health Program, University Hospital/Boston University Medical Center
- 7/1988-9/2006 Associate Physician, Brigham and Women's Hospital
- 7/1990-6/1995 Occupational/Environmental Medicine Consultant, Brigham and Women's Hospital Employee Health Services
- 7/2007-2012 Associate Physician, Division of General Medicine, Department of Medicine, University of Michigan Health System
- 1/2019-present Staff Physician, RotaClinic-Lake City, Seattle, WA

OTHER ACADEMIC POSITIONS and MAJOR VISITING APPOINTMENTS:

CV: Howard Hu, M.D., M.P.H., Sc.D.

7/1987-6/1990 Visiting Physician, South Cove Health Center, Boston (Chinatown)
 7/1996-8/2006 Associate, Center for Health and the Global Environment, Harvard Medical School
 2/1997 Alice Hamilton Visiting Professor, Division of Occupational and Environmental
 Medicine, Department of Medicine, University of California at San Francisco
 11/2000- Visiting Scientist, Sri Ramachandra Medical College and Research Institute
 7/2010- Senior Consultant, Tianjin Centers for Disease Control and Prevention, Tianjin,
 China
 10/2012- Visiting Professor, Shanghai Key Laboratory of Children's Environmental Health,
 Xinhua Hospital, Shanghai Jiao-Tung University, China
 7/2013-6/2016 Visiting Professor, Shanghai Jiao Tong School of Medicine, China
 5/2015- Affiliate Scientist to the Li Ka Shing Knowledge Institute, St. Michael's Hospital,
 Toronto, Canada

MAJOR RESEARCH INTERESTS:

1. Environmental and molecular epidemiologic research related to heavy metals, potential endocrine disruptors, other neurotoxicants, carcinogens, etc.
2. Gene-environment interactions; epigenetic dysregulation
3. Fetal/early life exposures and long-term effects
4. Aging-environment interactions
5. Environmental health, health inequities and health disparities, human rights
6. Health and the global environment
7. "Big Data" for population health
8. Environmental sensitivities/Multiple chemical sensitivities

GRANTS (as PI, Co-PI, or primary mentor only):

Past Funding:

1980 (summer) Montefiore Hospital, Bronx NY, PI; \$2,000 (approx)
 A study of rural and occupational health in Tulua, Colombia, South America
 1982 (summer) Albert Einstein College of Medicine, PI; \$3,000 (approx)
 A study of occupational/environmental health in Shanghai, China
 7/1987-6/1989 NIEHS Center Grant ES00002 Pilot Project, PI; \$12,000
 The Long-term Renal and Neurologic Effects of Childhood Plumbism
 7/1989-6/1990 NIEHS subcontract 7083-1, PI; \$50,000 (approx)
 The Use of X-Ray Fluorescence to Measure Lead Burden and Childhood Lead
 Exposure
 7/1990-6/1992 Agency for Toxic Substances and Disease Registry, PI; \$150,000 (approx)
 "Clinical Environmental/ Occupational Medicine Research Fellowship Award",
 7/1990-6/1991 NIEHS Center Grant ES00002 Pilot Project, PI; \$12,000
 The Metabolic Effects of Pregnancy and Lactation on Lead Burden

CV: Howard Hu, M.D., M.P.H., Sc.D.

7/1990-6/1991 Harvard School of Public Health Basic, PI
Research Support Grant; \$10,000
K-X-Ray Fluorescence Measured Lead Burden

10/1991-11/1991 NIOSH Special Grants, PI; \$50,000 (approx)
The Carpenters Lead Project

4/1991-3/1996 NIEHS/R01, PI; \$2,200,000 (approx)
The Epidemiology of Lead, Diet and Blood Pressure

7/1991-6/1996 NIEHS/R01 supplement, PI; \$240,000 (approx)
The Epidemiology of Lead, Diet and Blood
Pressure--Research Supplement for Minority Investigator

7/1992-6/1995 NIEHS/R01 (Office of Research on Women), PI; \$200,000 (approx)
Lead and Hypertension in Women

7/1993-6/1996 NIEHS/subcontract, PI; \$150,000 (approx)
Exposure to Neurotoxins as Risk Factors for Amyotrophic Lateral Sclerosis

7/1995-6/1998 State of Washington, Department of Labor, PI; \$350,000 (approx)
SPECT Imaging of the Brain in Patients with Multiple Chemical Sensitivity
Syndrome and Controls

7/1996-6/1997 NIEHS Center Grant ES00002 Pilot Project, PI; \$15,000
Electrocardiographic abnormalities in association with low-level lead exposure
among middle-aged to elderly men: the Normative Aging Study

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); \$1,800,000 (approx)
Lead Exposure, Accumulation in Bone, and Reproductive Toxicity Among Men and
Women In Mexico

4/1995-3/2000 NIEHS Project PI (Program Project PI: Richard Monson); \$1,900,000 (approx)
Lead Exposure, Accumulation in Bone, and Cognitive Toxicity Among Elderly Men
and Women

6/1997-5/2002 NIEHS/R01 ES05257 PI; \$2,312,274
Lead Biomarkers, Aging, and Chronic Disease

7/1997-6/1999 NIEHS Center Grant ES00002 Pilot Project, PI; \$10,000
The effect of genetic polymorphisms of metallothionein-IIA on mRNA levels in
middle-aged to elderly men: the Normative Aging Study

7/1998-6/2003 NIEHS/R01 PI (with no-cost extension; 5R01ES007821); \$2,291,833
Lead Dose Biomarkers, Reproduction, and Infant Outcomes

7/1999-6/2000 NIEHS Center Grant ES00002 Pilot Project, co-PI; \$14,000
Magnetic Resonance Spectroscopy in the Evaluation of Lead Neurotoxicity: the
Normative Aging Study

7/2000-6/2001 MAVERIC (Massachusetts Area Veterans Epidemiology Resource and Institute
Center) Pilot Project PI (with Dr. Robert Wright, co-PI); \$10,000
The Use of Magnetic Resonance Spectroscopy in Lead Poisoning

7/2000-6/2001 NIOSH Center Grant Pilot Project, PI (with Dr. Robert Wright, co-PI); \$12,000
Interaction between ApoE Genotype and Lead Exposure in the Development of
Cognitive Impairment

7/2002-6/2004 The Rasmussen Foundation/Health Care Without Harm; \$50,000

CV: Howard Hu, M.D., M.P.H., Sc.D.

CV: Howard Hu

7

- Medical Use of Phthalate Containing Products in the Neonatal Intensive Care Unit and Biomarkers of Neonatal Phthalate Metabolites
7/2002-6/2003 NIEHS Center Grant Pilot Project, PI; \$8,000
Vitamin D Receptor Gene and Bone Lead in Reproduction
- 3/2004-2/2005 The Critelli Family Foundation; \$10,000
Review of Environmental Cadmium Exposure and Toxicity
- 4/2000-3/2007 NIEHS Project Leader (Program Project PI: Richard Monson; 5P01ES05947); \$2,472,677; Controlled Trial in Pregnancy of Dietary Supplements for the Suppression of Bone Resorption and Mobilization of Lead into Plasma (no cost extension)
- 4/2000-3/2007 NIEHS Project co-Leader (Program Project PI: Richard Monson; 5P01ES05947); \$1,210,000 (approx); A Community-Based Study of Lead Exposure Pathways, Biomarkers of Dose, Health Effects, and Phytoremediation Strategies at the Tar Creek Superfund Site (no cost extension)
- 4/2002-9/2007 NIEHS/R01 PI (5R01ES010798); \$3,011,295
Gene-Metal Interactions and Parkinson's Disease
- 10/2003-9/2007 NCMHI/P20 Project Leader (MD000501-01; Hughes Harris, PI); \$828,781 (Project)
"FAMU and Harvard Center for Health and Health Care Disparities"
- 8/2003-7/2008 NIEHS/R01 PI (2R01ES05257-11A2); \$3,357,424 (became co-PI in 2007 after move to University of Michigan)
Lead-Gene Interactions and Cognition
- 6/2004-3/2009 NIEHS/P01 PI (5 P01ES012874-01); \$6,662,670 (became co-PI in 2006 after move to University of Michigan)
Metals Mixtures and Children's Health (Center for Children's Environmental Health and Disease Prevention Research)
- 7/2002-12/2009 NIH/R03 PI (1R03TW005914; no cost ext through 2008); \$192,000 (approx)
Lead, Genes, and Cognition in Children in Chennai, India
- 9/2006-7/2011 NIEHS/R01 PI (R01ES0007821); \$3,116,831
Fetal Origins of Neurobehavior: Lead and Cholesterol Metabolism Interactions
- 7/2006-6/2011 NIEHS/R01 co-PI (R01ES013744; PI Wright), \$3,200,000
Stress, Lead, Iron Deficiency and Neurodevelopment
- 7/2006-6/2011 NIEHS/R01 co-PI (R01ES014930; PI Wright), \$2,800,000
Metal Mixtures and Neurodevelopment
- 2/2008-2/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; \$26,000 (no cost extension)
Epigenetics of Early Life Events and Environmental Toxicants
- 4/2009-4/2010 Michigan Alzheimer's Disease Research Center Pilot Project PI, \$25,000
Environment, Epigenetics and Alzheimer's Disease (no cost extension)
- 12/2009-12/2010 University of Michigan Center for Global Health Pilot Project PI, \$25,000
Climate Variability and Impacts on Mortality and Morbidity in Chennai, India: A Pilot Project Stemming from the 2009 U.S.-India Workshop on Climate Change and Public Health, Goa India (no cost extension)

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8

9/2009-9/2010 Michigan Institute for Clinical and Health Research (MICHR; home of the UM CTSA; UL1RR024986) Pilot Project PI; \$26,000 (no cost extension)
Epigenetics and Epigenomics in the Etiology of Alzheimer Disease

7/2008-6/2011 NIA/T32 PI (T32AG027708); \$450,000
Interdisciplinary Training Program in Aging and Public Health

4/2010-3/2015 NIEHS P42 Superfund Co-Inv, Project 2, Co-investigator (P42ES017198; PI: Alshawabkeh, Project 2 Leader: Meeker) Puerto Rico Testsite For Exploring Contaminant Threats, \$12,000,000

4/1/2011-6/2015 NIEHS Core Environmental Health Sciences Center, Founding PI and Director (until 2012; now consultant; P30 ES017885), \$ 4,620,100;
“Lifestage Exposures and Adult Disease”

4/2010-3/2014 NIEHS/EPA P20 Co-PI and Clin Health Specialist (P20 ES018171; PI Peterson) Formative Children’s Environmental Health and Disease Prevention Center, \$1,959,960; "Perinatal Exposures, Epigenetics, Child Obesity & Sexual Maturation"

7/1/2013-6/30/2014 CIHR, Canadian Institute for Health Services and Policy Research; Planning Grants-Priority Announcement:Partnerships for Health System Improvement; PI, \$24,992
“The Surviving Opioid Overdose with Naloxone (SOON) Project and Roundtable”

07/1/11-06/30/16 NIEHS K01 ES019909 (co-mentor; PI: Somers)
“Immune dysfunction associated with early life heavy metal exposure”

4/1/12-3/30/17 NIEHS R01ES013744 (consultant; PI: Wright; Mt Sinai School of Medicine)
“Stress-Lead Interactions and Child Development”

7/1/2012-7/1/2017 European Commission (EC), Funded under FP7-Health, Project 304925, co-Investigator; PI, epidemiologic studies, \$6,000,000 E
“A novel micronutrient-based strategy to prevent hearing impairments: test and road to market for age-related hearing loss and preservation of residual hearing”

Current Funding

6/1/2012-7/1/2019 1R01ES021446-01, PI, \$4,140,000 (parent + supplement awards);
“Prenatal and Childhood Exposure to Fluoride and Neurodevelopment”

5/15/2015-5/15/2019 Health Canada; PI, \$200,000 (Phase 1); \$1,400,000 (proposed Phase 2)
“A Community-based First Nation Study of Cancer and the Environment in Northern Ontario”

4/1/13-3/31/23NIEHS/EPA P01ES022844 (co-inv; PI: Peterson at the University of Michigan)
“Lifecourse Exposures & Diet: Epigenetics, Maturation & Metabolic Syndrome.”

7/1/16-6/30/21 CIHR (co-PI; Director; PI: Jeffrey Brook at the Dalla Lana School of Public Health) \$4,700,000 CDN
“CANadian Urban Environmental (CANUE) Health Research Consortium”

9/1/16-8/31/21 NIH 5R01ES026033-02, (consultant; PI: Arora at Mt. Sinai School of Medicine) \$648,000 “Novel Biomarker to Identify Critical Windows of Susceptibility to Metal Mixture”

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9

Applications Under Review

Wellcome Trust, co-investigator (PI: P Landrigan)

“Quantifying the Cognitive and Economic Benefits of Reducing Air Pollution to Achieve Climate Change Mitigation”

Competitive Renewal Application In Progress

R01ES021446-01, PI, \$4,140,000

A Prospective Study of Early Life Exposure to Fluoride, Thyroid Function, and Neurobehavioral Outcomes

Amended Application In Progress

R01ES007821-11, PI, \$4,800,000;

Early Life Toxicants and Cardiovascular Outcomes” (priority score 27 by CASE Study section; 25th percentile)New Application in Progress

Wellcome Trust, xxx, multiple-PI

Addressing Two Critical Gaps in Understanding the Impacts of Lead Exposure on the Global Burden of Disease: (a) Impacts on Cardiovascular Disease; (b) Exposures and Sources in Low and Middle-Income Countries

HONORS AND AWARDS:

1978-1982 National Health Service Corps Scholarship

1985-1988 National Research Service Award

1990-1992 Agency for Toxic Substances and Disease Registry Clinical Environmental Medicine Award

1994 Will Solimene Award of Excellence, American Medical Writers Association, for: Chivian E, McCally M, Hu H, Haines H, eds. *Critical Condition: Human Health and the Environment*. Cambridge: The MIT Press, 1993.

1997 Alice Hamilton Lecturer, University of California at San Francisco

1998 First Prize for Best Infant Nutrition Research, Instituto Danone, Mexico (for González-Cossío T, Peterson KE, Sanín L, Fishbein SE, Palazuelos E, Aro A, Hernández-Avila M, Hu H. “Decrease in birth weight in relation to maternal bone lead burden.” Published in *Pediatrics*)

1999 National Institute for Environmental Health Sciences “Progress and Achievement of the

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10

- Year Award", 1998-1999
- 1999 True Memorial Lecturer, Maine Medical Center, Portland ME.
- 2000-2001 Faculty Sabbatical Award, Harvard School of Public Health
- 2000-2001 Senior Fulbright Scholar in India
- 2001 Hoopes Prize, Faculty Mentorship (for Senior Thesis of Charles Lin, "More than Black and White: Lead Poisoning as an Environmental Justice Issue in Boston")
- 2003 Best Paper in Preventive Medicine by a Medical Student (for Senior Thesis of Vanitha Janakiraman; Janakiraman V, Hu H, Mercado-Garcia A, Hernandez-Avila M. A randomized crossover trial of nocturnal calcium supplements to suppress bone resorption during pregnancy. *Am J Prev Med* 2003;24:260-4.). American College of Preventive Medicine, Ulrich and Ruth Frank Foundation for International Health.
- 2004 Das Travel Grant Award, The South Asia Initiative, Harvard University (for Travel in India)
- 2005 Adolph G. Kammer Merit in Authorship Award, the American College of Occupational and Environmental Medicine (for Rhodes D, Spiro A, Aro A, Hu H "Relationship of Bone and Blood Lead Levels to Psychiatric Symptoms: The Normative Aging Study", Published in the *Journal of Occupational and Environmental Medicine*)
- 2006 Teacher of the Year Award, Occupational/Environmental Medicine Residents, Harvard School of Public Health
- 2006 Harriett Hardy Award, the New England College of Occupational and Environmental Medicine
- 2009 Linus Pauling Award for Lifetime Achievements, American College for the Advancement of Medicine
- 2011 Award for Excellence, American Public Health Association
- 2015 John R. Goldsmith Award for Outstanding Contributions to Environmental Epidemiology, International Society for Environmental Epidemiology
- 2016 Election to Fellowship, Canadian Academy of Health Sciences

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

Memberships

- 1981- American Public Health Association (APHA)
- 1982-2006 Massachusetts Coalition for Occupational Safety and Health
- 1983-1989 American College of Physicians
- 1985- Physicians for Social Responsibility
- 1987- Physicians for Human Rights
- 1990- International Society for Environmental Epidemiology (ISEE)
- 1990-2000 American Association for the Advancement of Science
- 1990-2006 Association of Occupational and Environmental Clinics (AOEC)
- 1991- International Physicians for the Prevention of Nuclear War (IPPNW)

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11

1994-1996 Society for Occupational and Environmental Health (SOEH)
2000-2012 American College of Occupational and Environmental Medicine (ACOEM)
2009-2012 Society of Toxicology
2012- Canadian Public Health Association (CPHA)

Committee Assignments

1981-1982 Program Committee, Occupational Safety and Health Section, APHA
1987-1988 Program Committee, Asian-American Caucus, APHA
1992-1998 Membership Committee, ISEE
1995-1998 Quality Assurance Committee, AOEC
1997-1998 Program Committee, 1998 Superfund Basic Research Program, Annual National Meeting
2001-2006 Program Committee, New England College of Occupational and Environmental Medicine
Annual Meetings

EDITORIAL POSITIONS AND BOARDS:

1977-1982 Einstein Community Health Newsletter
1988-1992 Bookreview Co-Editor, Section on Occupational Safety and Health, Am Public Health
Assoc.
1993- Journal of Health and Human Rights
1998- Environmental Health Perspectives (Founding Medical Editor, 1998-2004; Associated
Editor, 2004-)
2004- American Journal of Industrial Medicine
2007-2009 Faculty of 1000 Medicine
2017- Current Environmental Health Reports
2017- Faculty of 1000 Medicine

PEER REVIEW SERVICE

American Journal of Epidemiology
American Journal of Industrial Medicine
Archives of Environmental and Occupational Health
Biomed Central
Circulation
Environmental Health
Environmental Health Perspectives
Environment International
Environmental Research
Epidemiology

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12

Indian Journal of Medical Research
 Journal of Health and Human Rights
 Journal of the American Medical Association
 Kidney International
 Lancet
 New England Journal of Medicine
 Pediatrics
 PLOS One
 Science of the Total Environment

TEACHING:

1. LOCAL CONTRIBUTIONS (at the Harvard School of Public Health, 1985-2006)

1985-	“Toxicology of the Kidney and Urinary Tract” Guest Lecturer for TOX204a,b
1988-	“Occupational Health” Guest Lecturer for EH201a,b
1989-1992	“Lead Toxicology” Guest Lecturer for TOX204a,b
1990-	<u>Grand Rounds in Occupational/Environmental Medicine</u> Director
1990-2000	<u>Introduction to Occupational and Environmental Medicine (EH232c,d)</u> Course director, lecturer
1990-	“The Epidemiology of Lead Exposure, Dose, and Toxicity” Guest Lecturer for EPE215c,d and EPE215t
1990-	“Solvent toxicity” Fundamentals of Industrial Hygiene, Continuing Education Department
1992	"Current Research on Lead", Metals Epidemiology Research Group Seminar Presenter
1992	"Lead Poisoning Without a Known Source in a Hyperthyroid Patient" Case discussant, Grand Rounds in Occupational and Environmental Medicine
1992-	“Biological Markers of Lead Dose” Guest Lecturer, EHE280c,d
1994-	“Screening for Lead Toxicity” Guest lecturer, EPI227d
1994-	“Lead Exposure and Biological Monitoring” Guest Lecturer, ID263b
1994-	“Case Study: Lead” Guest Lecturer and Case Discussant, EH202d
1996-	<u>Introduction to Environmental Health (EH201b)</u>

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13

- 1997- Course director and lecturer
Human Health and Global Environment Change (EH278a,b)
 Course Co-developer, Co-director, and lecturer

Hospital courses and Invited Teaching Presentations (Harvard-affiliated Hospitals)

- 1990 Guest Lecturer on Occupational Medicine
 Residency Program, Department of Medicine, Brigham and Women's Hospital
- 1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
 Department of Obstetrics and Gynecology, Brigham and Women's Hospital
- 1994 Speaker, Grand Rounds; "Is Lead a Ticking Time Bomb?"
 Department of Medicine, Brockton V.A. Hospital
- 1994 Speaker, Symposium on Preventive Medicine and Clinical Epidemiology,; "Is Lead a Ticking Time Bomb"; Brigham and Women's Hospital
- 1995 Discussant, "Multiple Chemical Sensitivity", Occupational/Environmental Medicine
 Grand Rounds, Occupational Health Program, Harvard School of Public Health
- 1996 Guest lecturer, "Lead Toxicity as a Paradigm for a Regional and Global Health Hazard", Environmental Health Student Group, Holmes Society, Harvard Medical School
- 1997 Speaker, "Mobilization of maternal bone lead as a hazard to the fetus", Grand Rounds, Dept. of Neonatology, Beth Israel Hospital, Boston, MA
- 2000 Guest lecturer, "Update on Lead Toxicity Research", Program in Pediatric Toxicology, Children's Hospital
- 2000 Discussant, "Adult Lead Toxicity", Weekly Case Round, Department of Medicine, Brigham and Women's Hospital, Boston.
- 2000 Lecturer, "Update on Lead Toxicity, Hypertension, and Chronic Renal Failure", Renal Rounds, Division of Nephrology, Department of Medicine, Brigham and Women's Hospital, Boston.
- 2002 Lecturer, "Maternal Bone Lead as a Threat to Fetal Development", Program in Neonatology, Beth Israel-Deaconness Hospital, Boston, MA

Doctoral student committees

Chair and member:

- | | |
|-----------------------|---|
| Dr. Rokho Kim | Dr.P.H. Occupational Health and Epidemiology, '96 |
| Dr. Yawen Cheng | Sc.D. Epidemiology, '98 |
| Dr. Sharon Tsaih | Sc.D. Epidemiology, '99 |
| Dr. Hung Yi Chuang | Sc.D. Occupational Health, '99 |
| Dr. Adrienne Ettinger | Sc.D. Environmental Health, '03 |
| Dr. Florence Wang | Sc.D. Environmental Health, '05 |
| Dr. Sung K. Park | Sc.D. Environmental Health, '05 |
| Dr. Pradeep Rajan, | Sc.D. Occupational Health, '06 |

Member/Advisor:

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14

Dr. How Ran Guo	Sc.D. Occupational Health, '94
Dr. Joshua Cohen	Sc.D. Health Policy and Management, '94
Dr. Jane Hoppin	Sc.D. Environmental Health, '95
Dr. Salma Elreedy	Sc.D. Environmental Health, '97
Dr. Mary Jean Brown	Sc.D. Maternal and Child Health, '00
Dr. Brisa Sanchez	Sc.D. Biostatistics, '06
Dr. Ami Zota	Sc.D. Environmental Health, '07
Dr. Ananya Roy	Sc.D. Environmental Health, '08
Dr. Elissa Wilker	Sc.D. Environmental Health, '09

Post-doctoral fellow mentor:

Dr. Marinelle Payton (Channing Lab), Dr. Susan Korrick (Channing Lab), Dr. Rokho Kim (Channing Lab), Dr. Viji Potula (HSPH Research Fellow), Dr. Barbara Nowak (Visiting Scientist from Silesian University School of Medicine, Poland), Dr. Robert Wright (Channing Lab), Dr. Ming Tsuang Wu (HSPH Research Fellow), Dr. Yawen Cheng (Channing Lab), Dr. Geeta Mathur (neonatology fellow at the Brigham and Women's Hospital), Dr. Sri Hari Bojja (HSPH Research Fellow), Dr. Hae-Kwan Cheong (Visiting Scientist from Dongguk University School of Medicine, S. Korea), Dr. Sahar Elmarsafawy (HSPH Research Fellow), Dr. Jing Lu (Visiting Scientist from the Chinese Academy of Preventive Medicine), Dr. Dieter Affeln (Occ/Env Med Fellow), Dr. Ahmed Gomaa (Occ/Env Med Fellow), Dr. Chris Leffler (Occ/Env Med Fellow), Dr. Ronald Dykeman (Occ/Env Med Fellow), Dr. Uma Dhanabalan (Occ/Env Med Fellow), Dr. Hsien-Wen Hsu (Occ/Env Med Fellow), Dr. Betty Ann Cohen (Occ/Env Med Fellow), Dr. Arvin Chin (Occ/Env Med Fellow), Dr. Daniel Rhodes (Occ/Env Med Fellow), Dr. Richard Wittman (Occ/Env Med Fellow), Dr. Sun-Dong Lee (Visiting Scientist from Sangji University, Korea), Dr. Ronald Green (Occ/Env Med Fellow), Dr. Erma Lawson (Environmental Health Fellow), Dr. Marc Weisskopf (Environmental Health Fellow), Dr. Bridget Bagert (Occ/Env Med Fellow), Dr. John Jarrell (Visiting Scientist from University of Calgary), Dr. Jennifer Weuve (Environmental Health Fellow), Dr. Karen Chou (Visiting Scientist from Michigan State), Dr. Nitin Jain (Channing Laboratory Fellow), Dr. Adrienne Ettinger (Children's Center Scientist), Dr. Sam Myers (Fellow in Alternative and Complementary Medicine), Dr. Marcelo Targino (Occ/Env Med Fellow), Dr. Manish Arora (Post-doctoral fellow from University of Sydney), Dr. Huiling Nie (Post-doctoral fellow from McMaster University).

Other faculty mentorship:

Elizabeth Rubinstein (HMS Summer research), Alicia Marier (HMS Summer research), Vanitha Janakiraman (HMS Summer research), Young-Sook Lim (Harvard College Summer research), Charles Lin (Harvard College Senior thesis research), Ed Hsieh (Harvard College Summer research), Naveen Thomas (Emory University Medical School Senior thesis research), Shreekrishna Akilesh (Harvard Dental School summer research), Christine Pace (HMS Summer research)

Advisory and supervisory responsibilities

1985-1987 Attending Physician, outpatient general medicine clinic, Boston City Hospital; weekly precepting for housestaff and medical students

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15

- 1990-2006 Preceptor, Residency in Occupational and Environmental Medicine, Harvard School of Public Health at the Mass Respiratory Hospital
- 1990-2006 Advisor to general M.P.H. students, Harvard School of Public Health.

2. LOCAL CONTRIBUTIONS (at the University of Michigan, 2006-2012)

- 2006- Principles of Environmental Health (EHS-500)
Course director and lecturer
- 2006- Environmental Epidemiology (EHS-608)
Guest lecturer on birth cohorts and environmental epidemiology
- 2006- Occupational and Environmental Disease (EHS-501)
Guest lecturer on metals exposure and health effects; Course Director (2009-)
- 2007- Metals Exposure, Biomarkers and Toxicity: A Multi-disciplinary Environmental Epidemiology Approach (EHS-698 reading course)
Course director and lecturer
- 2008-2009, Topics in Environmental Health Sciences (EHS-688)
2010-2011 Course director and lecturer
- 2009 Occupational and Environmental Disease (EHS-501)
Course director and lecturer
- 2009- On-line (Long-distance Foundations in Public Health Certificate Program): Principles of Environmental Health (EHS-500-801)
Course director and lecturer
- 2009 Introduction to Public Health (HMP-200)
Guest lecturer on environmental health
- 2009- Seminars in Aging and Public Health (EPID 813)
Course director and lecturer
- 2011 Seminar on Public Health in China (HMP-xxx)
Guest lecturer on "Environmental Health in China"

Post-doctoral fellow mentor:

Dr. Sung Kyun Park (Environmental Health Sciences Fellow, now Research Assistant Professor), Dr. Brisa Sanchez (Biostatistics Research Assistant Professor, now Assistant Professor), Dr. Richard Pilsner (Robert Wood Johnson Health & Society Fellow), Dr. Aimin Zhang (Environmental Health Sciences Fellow, Toxicology Training Grant), Dr. Ananya Roy (Environmental Health Sciences Fellow), Dr. David Cantonwine (Reproductive Sciences Fellow).

Doctoral Student Advisor (principal)

- | | |
|------------------|---|
| David Cantonwine | Ph.D. Environmental Health Sciences (2009) |
| Myriam Afeiche | Ph.D. Environmental Health Sciences (co-mentor with Karen Peterson; 2010) |
| Yoon-Hyeong Choi | Ph.D. Environmental Health Sciences (co-mentor with Sung Kyun Park; 2011) |

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16

Katie F. Bush	Ph.D. Environmental Health Sciences (co-mentor with Marie O'Neill; 2011)
Kelly Bakulski	Ph.D. Environmental Health Sciences (2012)
Gamola Fortenberry	Ph.D. Environmental Health Sciences (co-mentor with John Meeker; 2013)
Siyang Huang	Ph.D. Environmental Health Sciences (2013)
Deena Thomas	Ph.D. Environmental Health Sciences (2014)
Rebecca Tutino	Ph.D. Environmental Health Sciences (2015)
Zishaan Farooqui	Ph.D. MD-PhD Medical Scientist Training Program (2015)

Masters Student Thesis Advisor

Bradley Lampe (OEE), Troy Meissner (OEE), Pheba Alexander (OEE), Brian Davis (OEE & HBHE), Aaron Leftwich (OJOC program), Suengwon Lee (Nutrition), Allen Zhong (OEE), Graham Newman (OEE), Jacqueline Barkoski (OEE)

Undergraduate Thesis Advisor

Lauren Schwartz (Neuroscience, LSA)

3. LOCAL CONTRIBUTIONS (at the University of Toronto, 2012-present)

2012	Determinants of Community Health (Faculty of Medicine) Guest lecturer on 'The Future of Medicine & Public Health in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World'.
2012-	CHL5004H Introduction to Public Health Guest lecturer on "The Future of Public Health (and Your Role !) in a Hot, Flat, Crowded...and Diverse, Aging, Stratified, Urbanized, Polluted, Thirsty, Hungry, Debt-Ridden World". "What is Public Health?", "Climate Change and Health"
2012-	CHL 5912F Industrial Toxicology. Guest lecturer on the "Toxicology of Metals".
2013-2014	Department of Family & Community Medicine "Building Blocks" (short course for International post-graduate primary care trainees); Guest lecturer on "Public Health & Primary Care"
2013-	CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health Guest lecturer on "The Challenges of Environmental Health in a Rapidly-Changing World, from the Molecular to the Global".
2014	JCR1000 "Interdisciplinary Approach to Global Challenges" Guest lecturer on "Global Environmental Health"
2014-	PHS100H1 "Grand Opportunities in Global Health"; Guest lecturer on "Urban Environments"
2015	Public Health & Preventive Medicine Residency Rounds "Physicians, Climate, and other Global Environmental Changes: Our Role"
2016	<u>CHL5004H Introduction to Public Health, Course Co-Director (with Professor Erica</u>

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17

- 2016 DiRuggiero)
CHL 7001H F6 Environmental-Molecular Epidemiology, Course Co-Moderator (with Professor Morteza Bashash)
- 2016 CHL5701H Doctoral Seminar, Collaborative Doctoral Program in Global Health, Course Co-Director (with Professors Erica DiRuggiero and Abdallah Daar)
- 2016 Joint Seminar, “The Impact on Intelligence, Behaviour, and Society of Lead Exposure: A Case Study of a Global Pollutant and On-going Research”; Collaborative Program in Neurosciences and Collaborative Global Health Doctoral Program, University of Toronto
- 2016 CHL5420H “Global Health Research Methods”
 Guest lecturer on “The Early Life Exposures in Mexico to Environmental Toxicants Project (ELEMENT): A Global Health Collaboration Case Study”

Masters student research advisor

Maele Marchand

Doctoral student advisor

Adele Carty

Doctoral student thesis committee member

Laura Bogaert

Doctoral student thesis examination committee member

Claudie CY Wong (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)

Zilong Zhang (doctoral student in epidemiology, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong)

Post-doctoral fellow mentor:

Siyang Huang, Ph.D.; Morteza Bashash, Ph.D.; Roman Pabayo, Sc.D. (Harvard School of Public Health); Tripler Pell, M.D., M.P.H.

4. LOCAL CONTRIBUTIONS (at the University of Washington, 2017-present)

Doctoral student thesis research mentor

Megan Suter

Doctoral student special projects advisor

Rachel Shaffer

Joey Frostad

Rebecca De Buen

5. NIH K-grant mentorship:

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18

Robert Wright, M.D., M.P.H. (K-23 ES000381, “*Neurochemical and Genetic Markers of Lead Toxicity*”), 2000-2005; Dr. Wright is now Prof of Pediatrics, Mt. Sinai School of Medicine
 Marc Weisskopf, Ph.D. (K-01 ES012653, “*New Biomarkers of Neurotoxicity*”), 2004-2009; Dr. Weisskopf is now Associate Prof of Occup Health, Harvard Sch Public Health
 Sung Kyun Park, Sc.D. (K-01 ES016587; “*Environment, Novel Aging Outcomes, and Genetics*”), 2009-2014; Dr. Park is now Assistant Prof, Department of Epidemiology, University of Michigan Sch Public Health
 Emily Somers, Ph.D. (K-01 ES019909; “*Immune Dysfunction Associated with Early Life Heavy Metals Exposure*”), 2011-2016; Dr. Somers is now Associate Prof, Division of Rheumatology, Department of Internal Medicine, University of Michigan Medical School

COMMITTEE, ORGANIZATIONAL, AND VOLUNTEER SERVICE

National/International

1978-1982 Taskforce on Occupational and Environmental Health, Co-coordinator, Am Med Stu Assoc
 1989 Ad Hoc Study Committee, National Institute for Environmental Health Sciences Council
 1989-2006 Association of Occupational and Environmental Medicine Clinics (AOEC)-- (through the Northeast Specialty Hospital Center for Occupational and Environmental Medicine)
 1989-1990 Member, Relative Risk Reduction Strategies Committee, Science Advisory Board, U.S. Environmental Protection Agency
 1989-1992 Member, Board of Directors, Physicians for Human Rights, Boston, MA
 1991 National Institutes of Health, General Clinical Research Center Program, Site Visit Team
 1992- Member, National Advisory Committee, Physicians for Human Rights, Boston, MA
 1992 Special Study Section member (R3/S1/B3), National Institutes of Health
 1994 Ad Hoc Reviewer, National Institutes of Health, General Dental Research Center Program
 1994- Advisory Board, Institute for Energy and Environmental Research
 1994-1996 Associate, Project on Global Environmental Change and Health, Physicians for Social Responsibility
 1995 Ad Hoc Reviewer, National Institutes of Health, Diagnostic Radiology Study Section
 1996- Membor, Editorial Board, Health and Human Rights—an International Journal
 1995-1998 Advisory Committee, Consortium for Environmental Education in Medicine, Cambridge, MA.
 1996-1997 Reviewer, Agency for Toxic Substances and Disease Registry
 1997-1998 Program Committee, Annual Mtg, NIEHS Superfund Basic Research Group Centers
 1998-2013 (Founding) Medical Editor (1998-2004); Associated Medical Editor (2004-), Environmental Health Perspectives (official journal of NIEHS)
 2001 Ad Hoc Reviewer, National Institutes of Health, R-13 applications

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19

- 2002-2006 External Advisory Committee, Program Project on Lead and Osteoporosis, University of Rochester
- 2003-2005 Member, Ad-Hoc Expert Panel to Form Medical Management Guidelines for Lead-Exposed Adults, (supported by NIOSH and AOEC)
- 2003-2009 Member, Working Group on Lead and Pregnancy, Advisory Committee on Childhood Lead Poisoning Prevention, U.S. Centers for Disease Control and Prevention
- 2004 Ad Hoc Reviewer, National Institutes of Health, K-23 applications
- 2004 Ad Hoc Reviewer, Draft of "Immunization Safety Review: Vaccines and Autism" Immunization Safety Review Committee, Institute of Medicine, National Academies of Science
- 2004 Finalist (one of 8), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
- 2005 Member, Strategic Planning Conference, National Institute for Environmental Health Sciences, Research Triangle Park, NC
- 2006 Ad Hoc Reviewer, Draft of "Preterm Birth: Causes, Consequence, and Prevention" Committee on Understanding Premature Birth and Assuring Health Outcomes, Institute of Medicine, National Academies of Science
- 2006 Member, External Advisory Committee, NIEHS Center, University of Rochester
- 2007 Member, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2007/05 ZES1 JAB-C (DI) (NIEHS Discover Centers)
- 2007-2010 Member, Board on Population Health and Public Health Practice, Institute of Medicine, National Academies, Washington DC.
- 2007 Member, Ad Hoc Review Panel, Centers of Excellence Program, Swedish Council for Working Life and Social Research.
- 2007-2008 Member, Search Committee for Director of Extramural Research, NIEHS
- 2007 Special Consultant, Ad Hoc Study Section, Special Emphasis Panel/Scientific Review Group 2008/01 ZAR1 CHW-G (NIAMS Arthritis Centers)
- 2008 Report Reviewer, Draft National Research Council Report, "The National Children's Study Research Plan: A Review", National Academies
- 2008 Report Reviewer, Draft National Research Council Report, "Gulf War and Health: Updated Literature Review of Depleted Uranium", Institute of Medicine, National Academies
- 2008-2009 Data Safety Monitoring Board, "d-Penicillamine Chelation in lead-poisoned Children—A Phase II/III Trial" (R01FD003361; PI: Michael Shannon)
- 2008 Subcommittee to review Draft Report on Bisphenol A, Science Board, Food and Drug Administration
- 2008 Planning Committee, International Symposium on the Environmental and Health Consequences of Metal Mining and Smelting
- 2008-2009 Co-Chair, Planning Committee, "Climate Change Impacts on Public Health in India", Workshop that took place in Goa, India in Aug-Sept 2009 co-sponsored by UM Center for Global Health, the US Centers for Disease Control and Prevention and the Indian Council for Medical Research

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20

- 2008 Finalist (one of 2), Search for Director, National Institute for Environmental Health Sciences, U.S. National Institutes of Health
- 2009-2012 Member, Board on Environmental Studies and Toxicology, National Research Council
- 2009 Reviewer, NIH Challenge Grants, Special Emphasis Panel/Scientific Review Group 2009/10 ZRG1 GGG-F
- 2009-2010 External Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health
- 2010-2012 Member, External Advisory Committee, University of Rochester NIEHS P30 Core Center
- 2010 Member, Ad-hoc review committee, National Health Research Institutes of Taiwan, Special Emphasis Panel—NHRI-Kaoshiung Medical College Program Project on “: “Gene Environment Interaction in the Genesis of Asthma and Allergic Diseases”
- 2010-2012 Member, Advisory Board, Institute of Public Health, Florida Agricultural & Mechanical University, Tallahassee, FL
- 2011 Reviewer, NIEHS Career Development Awards, Special Emphasis Panel/Scientific Review Group 2011/05 ZES1 LKB-J (K9)
- 2011-2016 Member, NIEHS National Advisory Environmental Health Sciences Council
- 2012 Member, Editorial Board, Journal of Alzheimer’s Disease
- 2015 Member and External Reviewer, School of Population and Public Health Review Committee, University of British Columbia, Vancouver, B.C.
- 2016- Chair, Board of Directors, Canadian Urban Environmental Health Research Consortium, (National Consortium based out of the Dalla Lana School of Public Health)
- 2017- Member, Energy Research Committee, Health Effects Institute, Boston, MA
- 2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative, March 1-2, 2018, Institute for Health Metrics and Evaluation, Seattle, WA
- 2017- Executive Co-Leader, Global Burden of Disease-Pollution and Health Initiative
- 2019- Member, Research Advisory Committee, Centre of Environmental Health, The Public Health Foundation of India and the Tata Institute of Social Sciences, New Delhi, India
- 2019- Reviewer, draft report on trace metals levels in pregnancy women, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta

Regional

- 1988-1990 Health Facilities Appeals Board, Member, Dept. Public Health, Comm. Of Mass.
- 1988-2006 Advisory Board, Massachusetts Department of Public Health, Sentinel Event Notification System for Occupational Risks (SENSOR) Project
- 1989-1995 Advisory Board, Massachusetts Division of Occupational Hygiene, Lead Registry Project
- 1990-1992 Board of Directors, Member, Health Care for All, Boston, Massachusetts
- 1993-1995 Faculty Council, Member, Harvard School of Public Health
- 1995-2006 Faculty Advisory Committee, Public Health Practice Program, Harvard School of Public Health

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CV: Howard Hu

21

1996-2006 Advisory Board, Boston VA Environmental Hazards Center, Boston

1997-2001 Faculty Steering Committee, Center for Children's Health, Harvard School of Public Health

1996-2006 Senior Epidemiology Consultant, Massachusetts Veterans Epidemiology Research and Information Center, Boston.

1996-2006 Associate, Center for Health and the Global Environment, Harvard Medical School

1997-2002 Faculty Advisory Committee on Continuing Professional Education, Harvard School of Public Health

1998-2006 Faculty Steering Committee, Masters of Public Health program, Harvard School of Public Health

2001-2003 Board of Directors, New England College of Occupational and Environmental Medicine

2001-2006 Associate Director, Harvard NIEHS Environmental Sciences Center, Harvard School of Public Health

2001-2006 Senior Advisory Council Member, Lowell Center for Sustainable Production, University of Massachusetts, Lowell, MA

2003-2006 Member, Human Subjects Committee, Harvard School of Public Health

2003-2006 Advisory Committee, Occupational Health Services Research Program, Harvard School of Public Health

2006 Study Section Review Committee, Pilot Project Program, Graham Environmental Sustainability Institute, School of Natural Resources and Environment, University of Michigan

2006-2007 Chair, Planning Committee, Health Sector, May 8-10, 2007 National Summit on Coping with Climate Change, University of Michigan

2007-2009 Member, Advisory Committee, SPH Practice Committee, University of Michigan School of Public Health

2007-2012 Member, Residency Advisory Committee, General Preventive Medicine Residency, University of Michigan School of Public Health

2008-2009 Member, Steering Committee, NIA T32 Training Grant on Aging Research (PI: Mary Haan), University of Michigan School of Public Health

2008-2013 Member, Advisory Committee, Outstanding New Environmental Scientist Awardee (Marie O'Neill), NIEHS

2008-2009 Member, Search Committee for Director of the Risk Science Center, University of Michigan School of Public Health

2009 Co-Chair, Planning Committee, Workshop on Predicting and Preventing Climate Change Impacts on Public Health, Goa, India (Collaboration with the UM Center for Global Health, the US Centers for Disease Control and Prevention, and the Indian Council for Medical Research)

2009-2011 Director and PI, NIA T32 Training Grant on Aging Research, University of Michigan School of Public Health

2009-2010 Member, Planning Committee, University Research Corridor (U of M, Michigan State, Wayne State) symposium on environmental health sciences in January 2010

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22

2009-2012 Faculty Associate, Center for Global Health, University of Michigan
 2009-2012 Member, Internal Advisory Board, Cancer Epidemiology Education in Special Populations Program, University of Michigan School of Public Health
 2009-2011 Chair, Steering Committee on Global Health, University of Michigan School of Public Health
 2010-2012 Member, Executive Committee, Graham Environmental Sustainability Institute, University Of Michigan
 2010-2012 Member, Committee on Diversity, University of Michigan School of Public Health
 2012-2017 Chair, Executive Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Tenure Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Decanal Promotions Committee, Dalla Lana School of Public Health, University of Toronto
 2012-2017 Chair, Executive Advisory Committee, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
 2013-2015 Interim Director, Institute for Global Health Equity & Innovation, Dalla Lana School of Public Health, University of Toronto
 2013-2014 Co-Chair, Research Committee, Dalla Lana School of Public Health, University of Toronto
 2014-2017 Chair, Executive Advisory Committee, Institute for Health Policy Management and Evaluation, University of Toronto
 2014 Chair, Ad-hoc Committee to create an Institute for Indigenous Health (based on a \$10 million endowment gift made to DLSPH), Dalla Lana School of Public Health, University of Toronto; Chair, Executive Advisory Committee beginning 2015
 2015-2017 Chair, Executive Advisory Committee, Joint Centre for Bioethics, University of Toronto
 2015- Chair (2015-2017); Member (2017-present), Taskforce on Environmental Health, Ministry of Health and Longterm Care, Province of Ontario
 2016-2017 Chair, Executive Advisory Committee, Centre for Critical Qualitative Health Research, University of Toronto
 2017-2018 Executive Co-Chair, Workshop on the Global Burden of Disease-Pollution and Health Initiative (a collaboration between the Global Alliance on Health and Pollution and the Institute for Health Metrics), Seattle, WA

Hospital

1982-1985 Occupational Safety and Health Committee, Member, Boston City Hospital, Boston
 1983-1984 House Officers Association, Treasurer, Boston City Hospital
 1984-1985 House Officers Association, Co-President, Boston City Hospital

OTHER PUBLIC SERVICE

1987 Member, Fact-finding tour on "The Health Effects of Massive Exposure to Tear Gas",

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23

- Seoul, South Korea, July 11-18 (Sponsored by Physicians for Human Rights, American College of Physicians)
- 1988 Member, Fact-finding tour on "Chemical Weapons and the Iraqi Kurdish refugees", Turkey Oct 6-16 (Sponsored by Physician for Human Rights and the MacArthur Foundation)
- 1990 Leader, Fact-finding tour on "Health and Human Rights in Burma (Myanmar)", Thailand-Burma Dec. 26-Jan 6 (Sponsored by Physician for Human Rights and the MacArthur Foundation)
- 2009 Consultant and senior advisor, Fact-finding tour on "Mining and Potential Exposures and Health Effects in Guatemala", August 2009 (Sponsored by Physicians for Human Rights)

CONSULTING POSITIONS

- 1987-1989 Consultant, "In-Vivo Total Body Lead Analysis by X-Ray Fluorescence", NIH/SBIR Grant 2R44ES03918-02
- 1988-1989 Consultant, "Boston Area Health Coalition Demonstration Project", DHHS/MP000003-A1
- 1993-1995 Consultant, Employee Health Services, Brigham and Women's Hospital
- 1994 Consultant, Public Welfare Foundation, Washington, DC (review of Environmental Programs)
- 1997-2006 Consultant, Pediatric Environmental Health Center, Children's Hospital, Boston, MA
- 2000 Consultant, Doris Duke Foundation, New York, NY (review of potential Environment and Medicine programs)
- 2009-2010 Consultant and Member, Academic Program Review Site Visit Committee, Department of Environmental and Occupational Health Sciences, University of Washington School of Public Health, Seattle, WA
- 2011 Consultant, JPB Foundation, New York, NY (review of Environmental Health programs)
- 2014- Advisor, Hearing Health Sciences, Ann Arbor MI and Amsterdam, Netherlands

VISITING PROFESSORSHIPS

- 1997 Alice Hamilton Visiting Professor, University of California at San Francisco
- 2000-2001 Visiting Professor, Sri Ramachandra Medical College & Research Institute, Chennai, India
- 2004 Visiting Professor, Department of Environmental Medicine, University of Rochester
- 2013 Visiting Professor, Shanghai Key Laboratory, Shanghai Jiao-Tung University

SEMINARS AND EXTRAMURAL INVITED PRESENTATIONS (last 15 years, since 2003; prior presentations upon request)

CV: Howard Hu, M.D., M.P.H., Sc.D.

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24

- 2003 Guest lecturer, "Lead as a trans-generational toxin", Seminar series, Department of OB/GYN, Brigham and Women's Hospital
- 2003 Plenary speaker, "Clinical opportunities in environmental health", Annual Leadership Retreat, National Institute for Environmental Health Sciences, Greensboro, NC.
- 2003 Discussant, "Uncontrolled Hypertension in a Painter", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2003 Discussant, "A 53-Year Old Teacher with Chemical Sensitivities", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2003 Lecturer, "Pestilence and Progress: The Future of Public Health through the Lens of Blood", Center for Blood Research Symposium, Museum of Science, Boston, MA.
- 2003 Speaker, "Bones, Genes, Plasma, and Lead: New Frontiers in Understanding the Toxicity of an Old Hazard", Distinguished Lecture Series. National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta GA.
- 2003 Plenary speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Superfund Basic Research Program Annual Meeting, Dartmouth University, Hanover, NH.
- 2003 Special Lecturer, "Lead Exposure and Chronic Disease: Recent Research on Susceptible Sub-populations", Florida Agricultural and Mechanical University, Tallahassee, FL.
- 2004 Speaker, "New Frontiers in Understanding the Toxicity of Lead", Department of Environmental Medicine, University of Rochester, Rochester, NY.
- 2004 Presenter, "Lead Exposure During Pregnancy: Mobilization of Maternal Bone Lead Stores and Their Threat to the Fetus", Semi-annual meeting of the Childhood Lead Poisoning Prevention Branch, Centers for Disease Control and Prevention, Baltimore, MD
- 2004 Presenter, "Environmental Medicine", Annual meeting of the Editorial Board, *Environmental Health Perspectives*, Baltimore MD
- 2004 Plenary speaker, "Metals, Genes, and Neurodegeneration: the Approach of the Metals Epidemiology Research Group at the Harvard School of Public Health", National Institute for Environmental Health Sciences Conference on Neurodegeneration.
- 2004 Discussant, "Suspected Lead Toxicity" Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2004 Discussant, "Mercury Exposure in a Metal Worker", Grand Rounds in Occupational/Environmental Medicine, Harvard School of Public Health
- 2004 Presenter, "Effects of Our Environment on Intellect, Behavior, Life and Death," Leadership Council meeting, Harvard School of Public Health
- 2004 Guest Speaker, "Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard", Department of Environmental Health, University of Michigan School of Public Health
- 2004 Guest Speaker, "Medicine, Public Health, and the Great American Melting Pot: A Second-Generation Chinese-American Reflects on His Personal Odyssey", Sponsored by the Asian Student Association, Harvard School of Public Health
- 2004 Speaker, "Aging, the Environment and Genetics: Recent Insights from

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25

- Epidemiologic Studies of Environmental Lead Exposure”, Annual Leadership Retreat, National Institute for Environmental Health Sciences, Pinehurst, NC.
- 2004 Plenary Speaker, “Guidelines for the Management of Lead-Exposed Adults: Recommendations by a National Expert Panel Based on Recent Research”, New England College of Occupational and Environmental Medicine Annual Meeting
- 2005 Lecturer, “Biomarkers, Genes, Interactions and Lead: New Insights from Research on an Old Hazard”, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India
- 2005 Lecturer, “Your Child's IQ, Behavior and Neuropathology: Genes or Environment?”, the Harvard Club of Boston, Boston, MA
- 2005 Guest Speaker, “Metals, Neurodevelopment, and Neurodegeneration: The Work of the Metals Epidemiology Research Group at HSPH”, Neurostatistics Working Group, Harvard School of Public Health, Boston, MA.
- 2005 Plenary Speaker, “Aging, the Environment and Genetics: Recent Insights from Epidemiologic Cohort Studies of Environmental Lead Exposure”, NIEHS Symposium on Aging and the Environment, Duke University, Durham, NC.
- 2005 Plenary Speaker, “SPECT Imaging and Chemical Intolerance”, NIEHS/NIAA symposium on “Chemical Intolerance and Addiction: a Shared Etiology?”, Research Triangle Park, NC
- 2005 Workshop Presenter, “Social and Environmental Threats: the Unnecessary Epidemics”, Harvard School of Public Health Leadership Council Annual Conference, Boston, MA
- 2005 Keynote Speaker, “Our Food, Our Water, Our Homes: Toxic Metals”, The Boston Foundation, Boston, MA.
- 2006 Invited Speaker (invited by David Schwartz, NIEHS Director), “Goal IV: Improve and Expand Community-Linked Research”, Roundtable on Environmental Health Sciences, Research, and Medicine; Institute of Medicine, National Academy of Sciences, Wash DC.
- 2006 Speaker, “The Future of Environmental Health Sciences at the University of Michigan”, Dean’s Advisory Board, University of Michigan School of Public Health, Ann Arbor, MI
- 2006 Keynote Speaker and Harriett Hardy Annual Lecturer, “The ‘E’ in Occupational/Environmental Medicine: the Present and the Future”, New England College of Occupational Medicine Annual Meeting, New Bedford, MA
- 2007 Speaker, “The Future of Environmental Health Sciences at the University of Michigan”, Meetings of the UMSPH Alumni Council and the EHS Emeritus Faculty, Ann Arbor, MI
- 2007 Moderator and Speaker, “The Normative Aging Study: Health Effects of Lead”, Symposium on the Health Effects of Lead, 2007 Annual Meeting of the International Society for Environmental Epidemiology, Mexico City, Sept 8, 2007
- 2007 Guest Lecture, “Uncovering the Impact of the Environment on Disease: Big Opportunities for Physician-Scientists”, Medical Scientist Training Program, University of Michigan Medical School
- 2007 Guest Lecture, “Industrialization, Pollution and Public Health in India: Can India Survive Modernization?”, Osher Institute, Ann Arbor, MI
- 2007 Plenary Speaker, “Environmental Equity: Local and Global Challenges and the Balance Between Research and Advocacy”, Michigan’s Premier Public Health Conference,

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CV: Howard Hu

26

- October 16, 2007, Dearborn, MI
- 2007 Board Member Lecture, "Metals, Genes, Health and Human Rights: from the Molecular to the Global", Fall Meeting of the Board of Population Health and Public Health Practice, Institute of Medicine, National Academies of Science, Washington DC, Dec 13, 2007.
- 2008 Speaker, "MDs as Leaders for Change in Environmentalism", 2008 Annual Regional Political Leadership Institute, American Medical Student Association, University of Michigan Medical School, February 16, 2008
- 2008 Speaker, Grand Rounds, "The Impact of Environmental Pollutants on Disease: New Insights and Implications for Research and Medical Practice" Department of Medicine, University of Michigan Health System.
- 2008 Guest Lecture, "Emerging Insights into the Pervasive Influence of Environment Toxicants on Reproductive Outcomes and Offspring Development: Lead as a Case Study", Reproductive Sciences Program, University of Michigan
- 2008 Panelist, "Environmental Health in China", Public Health Grand Rounds, Division of Health Practice, University of Michigan School of Public Health
- 2008 Keynote Speaker, "Human Health and the Role of Water", Symposium on Water, Health & The Environment, Graham Environmental Sustainability Institute, University of Michigan
- 2008 Guest Speaker, "Lead Exposure and Toxicity: New Insights Using Molecular Epidemiology" Wadsworth Laboratories and SUNY-Albany
- 2008 Speaker: "Impact of Climate Change on Human Health: Vulnerability" 5th AKKA World Kannada Conference, Chicago IL
- 2008 Speaker, "The 'E' in Occupational/Environmental Medicine: the Present and the Future", Michigan Occupational/Environmental Medicine Annual Meeting, Mackinac Island, MI
- 2008 Speaker, "Impact of Climate Change on Human Health", University of Michigan Chapter of the American Medical Student Association, Ann Arbor, MI
- 2008 Speaker, "Early Life Origins of Adult Chronic Disease: Environmental Health and Toxicology at a Crossroads" Michigan Chapter of the Society for Toxicology, Ann Arbor, MI
- 2009 Speaker, "Evidence for Lead as an Environmental Stressor of Alzheimer's Disease and the Role of Epigenetics", Symposium Panel, Annual Meeting of the Society for Toxicology, Baltimore, MD
- 2009 Keynote Speaker, "Lead, Late-Life and Early Life Effects, and the Emerging Field of Environmental Epigenetics: Looking Ahead", Annual Meeting of the American College for the Advancement of Medicine, San Diego, CA
- 2009 Speaker, "Lead Toxicity and Mechanistically-Oriented Molecular Epidemiology: Targeting the Epigenetics of Alzheimer's Disease", Seminar Series, Institute for Environmental Health Sciences, Wayne State University, Detroit, MI
- 2009 Speaker, "Climate Change Impacts on Health in the Developing World", Research Discussion Series, University of Michigan Center for Global Health
- 2009 Speaker, "Autism, Aggressive Behavior, Anxiety, and Alzheimer's: are Environmental Toxicants Playing a Major Etiologic Role?", Department of Psychology, University of Michigan
- 2009 Speaker, "Early Life Exposures and Endocrine Disruption: Evidence from Molecular

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CV: Howard Hu

27

- Epidemiology”, Pediatric Endocrine Seminar, University of Michigan Medical School
- 2009 Distinguished Speaker, “Lead Toxicity: Twenty Years of Research On The Poison That Keeps on Poisoning” 10th Anniversary of the Department of Microbiology and Environmental Toxicology, University of California at Santa Cruz
- 2010 Speaker, “The Centers for Disease Control and Prevention & the Environmental Protection Agency: Potential Funding Opportunities for Regional Collaboration in Michigan”, University Research Corridor Symposium on Environmental Health, Detroit, MI.
- 2010 Speaker, “The Future of Public Health”, University of Washington School of Public Health
- 2010 Speaker, “The Environment Meets the Epigenome: Is This Where Autoimmunity Begins?” Symposium on Autoimmunity and Epigenetics, University of Michigan
- 2010 Keynote Speaker, “A New Twist to an Old Story: The Evidence for Early Life Lead Exposure as a Risk Factor for Alzheimer's Disease through Epigenetic Programming”, NIEHS Environmental Health Sciences Center and Toxicology Training Program Retreat, University of Rochester, NY
- 2010 Speaker, “Lead Toxicity: Twenty Years of Research on The Poison That Keeps on Poisoning” and “Environmental Health Sciences at the University of Michigan”, Tianjin Centers for Disease Control, Tianjin, China
- 2010 Speaker, “Pediatric Lead Toxicity”, Xinhua Hospital and the Shanghai Jiao-Tung Medical University Department of Pediatrics, Shanghai, China
- 2010 Speaker, “Environmental Health Sciences at the University of Michigan”, Fudan University, Shanghai, China
- 2010 Speaker, “Alzheimer’s Disease, Epigenetics and the Environment”, Symposium Update, Alzheimer’s Disease Association, Ann Arbor, MI
- 2010 Speaker, “Environmental Justice, Progress (and the Lack Thereof) and the Role of Research”, Roundtable on Environmental Health Sciences, Research and Medicine, Institute of Medicine, National Academies, Washington DC.
- 2010 Speaker, “White Coats, Population Science and Poison Gas: A Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights”, Robert Wood Johnson Clinical Fellows Program, University of Michigan Medical School, Ann Arbor, MI
- 2011 Speaker, “The Three Most Difficult Challenges to Molecular Epidemiologic Research on Gene-Environment Interactions: Lead Toxicity as a Case Study.” Department of Human Genetics, University of Michigan Medical School, Ann Arbor, MI
- 2011 Speaker, “The Integration of Data on Environmental Carcinogens with Population and Genetic Resources”, “Opportunities & Challenges for Translational Research on Cancer Prevention”, Translational Cancer Prevention & Biomarkers Workshop, Mazamdur-Shaw Cancer Center, Bangalore, India.
- 2011 Speaker, “Success in the Academy”, Faculty Panel, Students of Color of Rackham, Rackham Graduate School, University of Michigan
- 2011 Speaker, “White Coats, Population Science and Poison Gas: Fact-Finding Missions by Health Professionals for Human Rights”, Sujal Parikh Memorial Symposium, University of Michigan Medical School.
- 2011 Speaker, “The Analysis of Biomarker Data to Ascertain the Contribution of Environmental

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28

- Exposures to the Etiology of Disease: Lead Exposure and Toxicity as a Case Study”, Department of Computational Medicine and Bioinformatics, University of Michigan Medical School.
- 2012 Speaker, “Research and Analysis Linking Upstream and Downstream Disparities Work”, Webinar hosted by the Health & Environmental Funders Network, Bethesda, MD, with 52 Foundations related Health.
- 2012 Keynote Speaker, “The Future of Public Health & Medicine in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World”. E.J. Van Liere Memorial Convocation and Health Sciences Center Research Day, West Virginia University, Morgantown, West Virginia
- 2012 Plenary Speaker, “Transgenerational Impacts of Pollutants on Offspring: Recent Insights and Case Studies”, Connaught Global Challenge International Symposium, University of Toronto.
- 2012 Speaker, “Environmental Impacts on Aging (+ an update on the Dalla Lana School of Public Health)”, Community Medicine Rounds, University of Toronto
- 2012 Speaker, “The Environment & Public Health in a Research-Intensive University: Opportunities for Scholarship in a Crowded, Diverse, Stratified, Hot, Urbanized, Polluted, Thirsty, Hungry and Debt-Ridden World”, School for the Environment, University of Toronto
- 2012 Speaker, “Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, External Advisory Meeting, Public Health Ontario, Toronto
- 2012 Speaker, “Canadian Public Health Schools (in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World): The View from Toronto, External Advisory Board Meeting, Institute for Population and Public Health, Canadian Institutes for Health Research, Toronto
- 2012 Speaker, “Sustainable Development and Health: The Global Mining Industry”, Canadian Society for International Health Annual Meeting, Ottawa
- 2012 Speaker, “Big Public Health Challenges (& Opportunities) in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Xinhua Hospital/Shanghai Jiao-Tung University, Shanghai, China.
- 2012 Speaker, “The Impact of Population-Wide Lead Exposure and Gene-Lead Interactions on Chronic Disease”, Genetic Grand Rounds, Sick Kids Hospital, Toronto.
- 2012 Speaker, “Looking behind the curtain: Lead Toxicity as a Case Study of Methodologic Challenges in Gene-Environment Interactions Research”, Strategic Training in Advanced Genetic Epidemiology (STAGE), Dalla Lana School of Public Health, University of Toronto.
- 2012 Keynote speaker: “Public Health—the Next Frontier in Health Professions Education”. Council of Health Sciences annual retreat, University of Toronto.
- 2013 Speaker, “White Coats, Population Science and Poison Gas: Lessons from a Life Spent at the Intersection of Academic Medicine, Global Health & Human Rights”, Joint Center for Bioethics, University of Toronto
- 2013 Speaker, “Gauging environmental impact on the development of chronic inflammation”,

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CV: Howard Hu

29

- Connaught Global Challenge Workshop, University of Toronto.
- 2013 Speaker, “The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Grand Rounds, Department of Medicine, University of Toronto.
- 2013 Speaker, “Metals, Mega-trends, and Me: Reflections on Research and the Vision for the Dalla Lana SPH”, Occupational and Environmental Medicine Grand Rounds, St. Michael’s Hospital, Toronto, ON.
- 2013 Speaker, “Air pollution and Cardiovascular Disease: Health Impacts, Mechanisms, and Research Opportunities”, University of Toronto & FMUSP-InCor Symposium on Cardiology, Sao Paulo, Brazil.
- 2013 Speaker: “Lead Exposure’s Impact on Health and Policy: A History of Neglect and Missed Opportunities”, Public Health Policy Rounds, CIHR Strategic Training Program in Public Health Policy, University of Toronto.
- 2013 Speaker: “Lead Toxicity: The Long Tail of Health Impacts (and On-going Research Opportunities!) From an Historical Environmental Air Pollutant”, Southern Ontario Centre for Air Pollution and Aerosol Research, University of Toronto.
- 2013 Speaker: “Water and Sanitation”, Water, Sanitation and Hygiene (WASH) Canada, Toronto, Ontario, Canada
- 2014 Speaker: “Conflict and Public Health”, Ontario Medical Association, Toronto, Canada
- 2014 Panelist: “Judging Evidence: Finding a Place for Variation in an Evidence-Based World”, Health Quality Ontario, Toronto, Canada
- 2014 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, Special meeting of the Canadian Chamber of Commerce in Shanghai
- 2014 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, Jockey School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China
- 2015 Speaker: “The Grand Convergence: Creating Health in a Globalized World”, School of Public Health and the ASEAN Institute, Mahidol University, Bangkok, Thailand
- 2015 Speaker: “Gene-environment Interactions and the Role of Big Data in Environmental Health” Seminar series, School of the Environment, University of Toronto, Toronto, Canada
- 2015 Speaker: “Global Health Security”, Ill with Illness—Economic, Social & Security Barriers to the Provision of Global Health, Munk School of Global Affairs, University of Toronto, Toronto, Canada
- 2015 Speaker: “The Dalla Lana School of Public Health: Big Ideas and Initiatives for Creating Health in a Globalized World”, Speaker Series, University of Toronto Alumni of Toronto.
- 2015 Speaker: “Unique Scientific Opportunities for the Precision Medicine Initiative National Research Cohort: Exposomics, Data Linkage, and Global Collaborations”. Working group on President Obama’s Precision Medicine Initiative (Chaired by Francis Collins, Director, NIH)
- 2015 Speaker: “What is the Role of Schools of Public Health in the 21st Century?” 50th Anniversary Celebration of the Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec.
- 2015 Welcoming Address: “Global Public Health and Mental Health”, Going Global for Mental Health conference, Centre for Addictions and Mental Health/Department of Psychiatry/Dalla

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30

- Lana School of Public Health, Toronto, ON
- 2015 John Goldsmith Memorial Lecture: “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Opening Plenary Session, International Society for Environmental Epidemiology Annual Meeting, Sao Paulo, Brazil
- 2015 Inaugural Speaker: “The Future of Public Health and Medicine in a Crowded and Complex World”, Global Health Leadership Series, PSG Medical School & the Shanti Ashram Foundation, Coimbatore, Tamil Nadu, India
- 2016 Speaker “The Future of Public Health & Medicine in a Crowded, Diverse, Aging, Stratified, Urbanized, Polluted, Hot, Thirsty, Hungry, Debt-Ridden World”, Indian Institutes of Public Health—Hyderabad, Hyderabad, India
- 2016 Speaker: “Integration of Public Health & Health Care: The Unmet Agenda for a Truly Sustainable Health System”, Board of Directors Retreat, Toronto East General Hospital, Toronto
- 2016 Plenary speaker: “Health Promotion, Prevention and Health Protection: Innovative Initiatives”, 6th Asia-Pacific Conference on Public Health | 1st ASEAN Health Promotion Conference Bangkok, August
- 2016 Speaker: “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Mount Sinai School of Medicine, New York, NY
- 2016 Plenary Speaker: “The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances”, International College of Integrative Medicine Annual Meeting, Toronto, ON
- 2016 Plenary Speaker: “Big Data and Implications for Environmental Health”, 15th Anniversary Conference, Jockey Club School of Public Health & Primary Care, Chinese University of Hong Kong, Hong Kong
- 2016 Plenary Speaker: “Innovations in Assessing Lead Poisoning and Child Health: Policy & Clinical Implications”, Chinese University of Hong Kong-Fudan-Oxford International Symposium on Health Impacts of Environmental Exposures”, Hong Kong
- 2016 Speaker: “Addressing a Changing Environment (and Impacts on Health, AKA Can India Survive Modernization?)”, Indian Institutes of Technology Alumni, Canada, International Conference 2016, Toronto.
- 2016 Plenary Speaker, “Hidradenitis Suppurativa: Research Directions from a Population Health Perspective”, Symposium on Hidradenitis Suppurativa Advances, Toronto.
- 2016 Plenary Speaker, “Children’s Environmental Health”, The 2016 Annual National Conference on Children’s Healthcare, Shanghai, China
- 2016 Special Guest Speaker, “Big Data, Environmental (and Social) Epidemiology, Power and Politics”, Shanghai Municipal Center for Disease Control, Shanghai, China
- 2016 Lecturer, “Lead and Human Health: Recent Research and Associated Lessons for Science & Policy”, Fudan University School of Public Health, Shanghai, China
- 2017 Lecturer, “The Impact of Environmental Toxicants on Health: Recent Epidemiologic Approaches & Advances”, Saw Swee Hock School of Public Health, National University of Singapore, Singapore
- 2017 Lecturer, “The Future of Academic Public Health”, Saw Swee Hock School of Public Health,

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CV: Howard Hu

31

- National University of Singapore, Singapore
- 2017 Lecturer, “Recent Advances in Understanding, Preventing, and Reversing the Impact of Environmental Factors on Health”, Society of Chinese Bioscientists in America, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, ON
- 2017 Lecturer, “Environmental Epidemiology in the Era of Exposomics, Lifecourse Epidemiology, Big Data and Big Science”, Department of Environmental Health, Harvard School of Public Health, Boston, MA
- 2017 Speaker, “The Role of a Re-emergent Canadian School of Public Health in a Hot, Hungry, Polluted, Aging, Polarized World Prone to Pandemics, Chronic Disease, and Unsustainable Health Systems”, Royal Canadian Institute for Science, Toronto, ON
- 2017 Speaker, “The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment”, Seminar Series in Environmental Epidemiology, University of Washington School of Public Health, Seattle, WA
- 2017 Plenary Speaker: “New realities arising from the extractive industries and agri-business: the Pollution and health perspective,” Hong Kong Summit of Global Health Leaders. University of Hong Kong, Hong Kong
- 2018 Plenary Speaker: “The GBD-Pollution and Health Initiative: Challenges & Opportunities”, Workshop on the Global Burden of Disease-Pollution and Health Initiative, Institute for Health Metrics, University of Washington, Seattle, WA
- 2018 Guest Lecturer: “Partnerships, Local Responsiveness, National and Global Impacts”, University of Iowa College of Public Health, Iowa City, IA
- 2018 Plenary Speaker: “Current Research on Fluoride and Neurodevelopment: The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study”, Annual meeting of the International Academy of Oral Medicine and Toxicology, Denver, CO
- 2018 Speaker, “Recent Epidemiologic Research on Lead Toxicity: New Surprises regarding an Old Global Pollutant”, Department of Environmental and Occupational Health Sciences Seminar Series, University of Washington School of Public Health, Seattle, WA
- 2018 Speaker: “The Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Birth Cohort Study: Current Research on Fluoride and Neurodevelopment”, Symposium on Fluoride research, Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON
- 2018 Panelist, “The Fluoridation Decision: Considering the Evidence for Benefits, Possible Risks as well as Ethical World Views”, Annual meeting of the International Society for Environmental Epidemiology/International Society for Exposure Science, Ottawa, ON
- 2018 Speaker: “Grand Opportunities”, The UC-Irvine School of Population Health and the Samueli College of Health Sciences, Irvine, CA
- 2018 Speaker, “The Global Burden of Disease-Pollution and Health Initiative”, Office of the Director and the Global Environmental Health Program, U.S. National Institute for Environmental Health Sciences, Research Triangle Park, NC
- 2019 Speaker, “Evaluating, treating and managing disabilities of patients with chemical intolerance”, Symposium on Chemical Intolerance—A Way Forward, Marilyn Brachman

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CV: Howard Hu

32

Hoffman Foundation and the Hoffman Program on Chemicals and Health at the Harvard T.H. Chan School of Public Health, Dallas, TX

2019 Guest Lecturer: “The Global Burden of Disease-Pollution and Health Initiative”, Center for Population Health Sciences, Stanford University, Palo Alto, CA

INVENTIONS/PATENTS: n/a

BIBLIOGRAPHY: (H-index, as of April, 2019, Google Scholar: 83)

Peer-reviewed journals

1. Hu H, Markowitz SB. A case-study of industrial bladder cancer. *Einstein Quarterly Review of Biology and Medicine* 1982;1:29-35.
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52

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67

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70

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73

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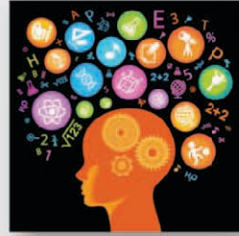
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The Scientific Evidence for **Fluoride's** Developmental Neurotoxicity



February 10, 2020

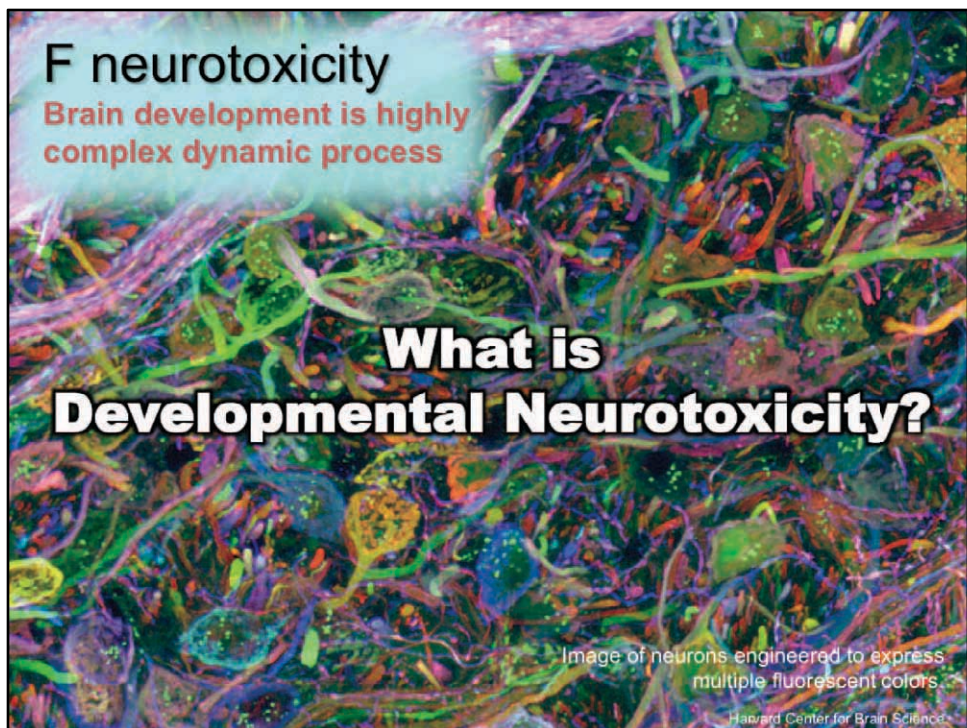


American **Environmental** Health **Studies** Project

 **FLUORIDEALERT.ORG**
Fluoride Action Network

1

I'm Chris Neurath and I'm the Research Director for the American Environmental Health Studies Project. I'm going to give an overview of the scientific evidence for fluoride's developmental neurotoxicity.



I'm going to start with some amazing and beautiful pictures ... and the question: What exactly is developmental neurotoxicity ... and why is it such a focus of current research on fluoride?

F neurotoxicity

Brain development is highly
complex dynamic process

Brain Development

“The wiring of brains is *staggeringly complex*. Our own brains have tens of billions of neurons connected through perhaps one hundred trillion synapses. *This circuitry is the result of our development and experience*”

Harvard Center for Brain Science

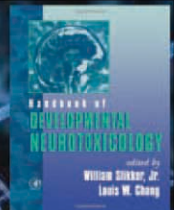
Image of neurons engineered to express
multiple fluorescent colors

Harvard Center for Brain Science

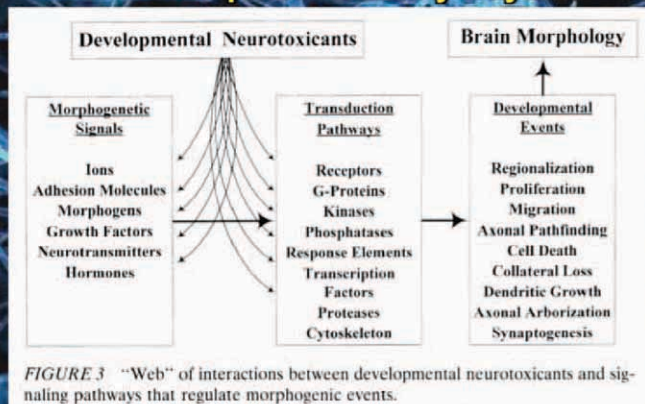
Brain development starts with a few cells in the early fetus and continues rapidly in a highly complex dynamic process through infancy. Indeed the rate of neurodevelopment in humans is extremely rapid in utero, but is even faster in the first months after birth. This formation of the wiring of our brains is “staggeringly complex” as described by the Harvard Center for Brain Science. “Our own brains have tens of billions of neurons connected through perhaps one hundred trillion synapses.”

F neurotoxicity

Brain development is highly complex dynamic process



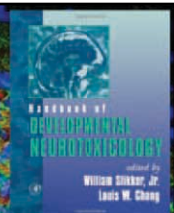
Neurotoxicants can disrupt brain development in many ways



There are many critical processes during neurodevelopment, which all have to take place with precise timing and coordination with the other processes. A disruption from a toxic chemical to any process, even during a brief window of time, can cause permanent harm. Reduced IQ is one symptom of such harm.

F neurotoxicity

Brain development is highly complex dynamic process



The fetal and infant brain is more susceptible than the adult to permanent harm from neurotoxic chemicals.

- The complex precisely timed neurodevelopment process offers many opportunities for disruption.
- The blood brain barrier is not well developed during the fetal period and the first 6 months of life.
- Disruption during even a short window of neurodevelopment can cause life-long permanent harm.

The fetal brain and the infant brain is more susceptible to disruption than the adult brain because of this complex neurodevelopment process but also because the blood-brain barrier, which can limit access of toxic chemicals to the brain in adults, is not well developed until after age 6 months. Disruptions to neurodevelopment can cause life-long harm which often can not be repaired.



**National Toxicology Program (NTP)
draft systematic review and health assessment
of the neurotoxicity of fluoride:**

“Conclusions: NTP concludes that **fluoride is presumed to be a cognitive neurodevelopmental hazard to humans.** This conclusion is based on a **consistent pattern of findings in human studies** across several different populations showing that higher fluoride exposure is associated with **decreased IQ or other cognitive impairments in children.**”

The best place to start is with the recently released National Toxicology Program, or NTP, a systematic review of fluoride’s neurotoxicity. This was a very thorough review that has been 5 years in the making. They concluded that fluoride is a presumed neurotoxin.

F neurotoxicity

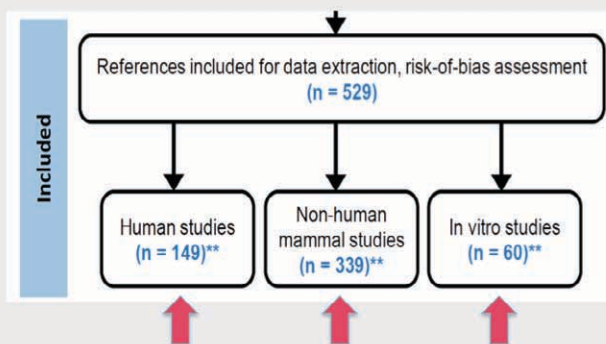
Large number
of studies



National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

Figure 4. Study Selection Diagram



Their conclusion is based on a very large amount of evidence that would probably surprise most people who have not studied fluoride's adverse effects. The NTP identified 149 human studies and 339 laboratory animal studies.

F neurotoxicity

Large number
of studies



National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and
Neurodevelopmental and
Cognitive Health Effects

Figure 5. Number of Epidemiological Studies by Outcome and Age Categories*

Outcome Category	Age Category					
	Child	Adult	Child/Adult Combined	Infant	Fetus	
Intelligence (IQ)	60	3				
Learning/Memory	4	3		1		
Cognitive Development	2			1		
Cognitive Impairment		5				
Attention/Hyperactivity/Behavioral Issues	5					
Motor/Sensory Function or Development	2	4		1		
Mood/Affect		1				
Visual-Spatial/Visual-Motor Function	2	2				
Brain Activity		1				
Brain Structure					2	
Neurological Biochemical	2	1	1		1	
Neurological Complications of Fluorosis		3				
Neurological Symptoms	1	3				
Birth Defects				3		
Thyroid Gland Function	12	5	2			
Thyroid Disease		2				

Of the human studies, there was a wide variety of developmental neurotoxic endpoints, with the largest number being studies of IQ in children with 60 such studies.

F neurotoxicity

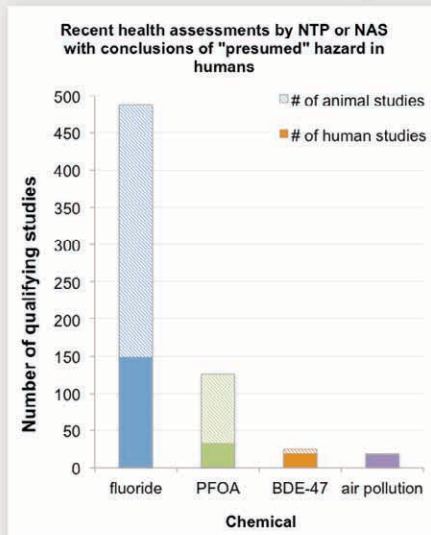
**Large number
of studies**

**NTP found many
more studies of F
neurotoxicity
compared to
what it has found
for other toxins
in its recent
reviews**



National Toxicology Program
U.S. Department of Health and Human Services

Systematic Review of Fluoride Exposure and
Neurodevelopmental and
Cognitive Health Effects



It is worth comparing this NTP review of fluoride neurotoxicity to NTP reviews of other toxic chemicals. The NTP's main purpose is to assess the toxicity of chemicals and they have issued several recent reports on other chemicals that concluded they were "presumed" hazards. But fluoride turns out to have many more studies than any of these other chemicals. The other chemicals shown are PFOA which is a perfluorinated chemical, BDE-47 is a brominated fire retardant, and "air pollution" which includes PM 2.5.

The graphic is from the NTP report but I have added the colored arrows that are **blue**, **purple**, and **black**. They indicate the exposure levels at which harm was found and are related to the exposure levels found in the USA, due largely to artificially fluoridated water. The **blue arrows** indicate studies that found adverse effects at 0.7 mg/L water fluoride concentrations or the equivalent in urine fluoride. 0.7 mg/L is currently the most common level of fluoridation in the USA. The NTP also considered that levels below 1.5 mg/L are relevant to exposures in the USA. I've marked those in **purple**. Half of the high quality studies found that exposures common in the USA were associated with harm, mostly lowered IQ.

F neurotoxicity Pre-conceptions

JAMA Pediatrics | Original Investigation
Association Between Maternal Fluoride Exposure
During Pregnancy and IQ Scores in Offspring in Canada

Frederick P. Rivara, MD, MPH, Robert Henning, PhD, David Hertz, PhD, D. Angeline Barbeau, MD, PhD,
Rachael Neufeld, MD, Harris Smith, PhD, Lisa M. Mulla, PhD, Christine M. Poth

JAMA Editor's Podcast excerpts, on Green 2019:

**Pre-conceptions that people who claimed that
fluoridation is harmful were “nuts”.**



Frederick P. Rivara, MD, MPH
Editor, *JAMA Networks Open*



Dimitri A. Christakis, MD, MPH
Editor, *JAMA Pediatrics*

11

I now want to discuss the reaction to the rapidly emerging evidence that fluoride is neurotoxic and can lower IQ of children. The single study which has received by far the most attention is the Green 2019 study published in *JAMA Pediatrics* in August 2019. You've probably heard about it and may have read it. I found the *JAMA* editors reactions to it to be very revealing of where most people, including health professionals, beliefs about fluoride have been ... and where they can move to when they have an open mind. I'm going to give excerpts from their Podcast discussion of the paper.

F neurotoxicity

Pre-conceptions



Dr Rivara- “The paper is about fluoride, and maternal fluoride exposure during pregnancy, and its effects upon IQ scores of children at ages 3 and 4, which in itself is like a shocking title, because I had never known that there was even any concern that maternal fluoride use might affect children’s IQ.”



Dr Christakis- “... the traditional teaching when I was going through residency in my early professional career was that fluoride was completely safe, all these people that are trying to take it out of the water are nuts, its the best thing that’s ever happened for children’s dental health, and we just need to push back and get it into every water system.”
“So when I first saw this title my initial inclination was **‘What the hell?’**”

12

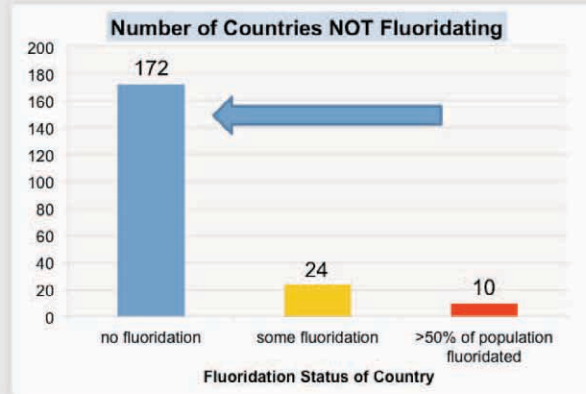
Excerpts from their Podcast: audio clip A.

[Open "JAMAPed clip A" to play](#)

F neurotoxicity

“in Europe only 3% of municipal water supplies are fluoridated”

Editors surprised by just how much of the world does *NOT* fluoridate.



13

The editors were surprised at how many cities and countries do not fluoridate their water. In fact, the large majority of the world does not fluoridate.

F neurotoxicity

“in Europe only 3% of municipal water supplies are fluoridated”



Editors surprised by just how much of the world does *NOT* fluoridate.



Dr Rivara- “... this was from Canada and they picked some large cities in Canada; these were Montreal, Vancouver, Kingston, Toronto, Hamilton and Halifax; so I’m a little surprised that those places did not [all] have fluoridated water supplies.”

Dr Rivara- “And the other interesting thing that came out, like in the editorial and in this paper, was that in Europe only 3% of municipal water supplies are fluoridated.”



Dr Christakis- “Right, so again this was to me sort of eye-opening, that you known, I sort-of thought that ‘everyone did it’; certainly all developed countries, everyone that was at any level of sophistication was putting fluoride in the water.”

14

Excerpts from Podcast: audio clip B.

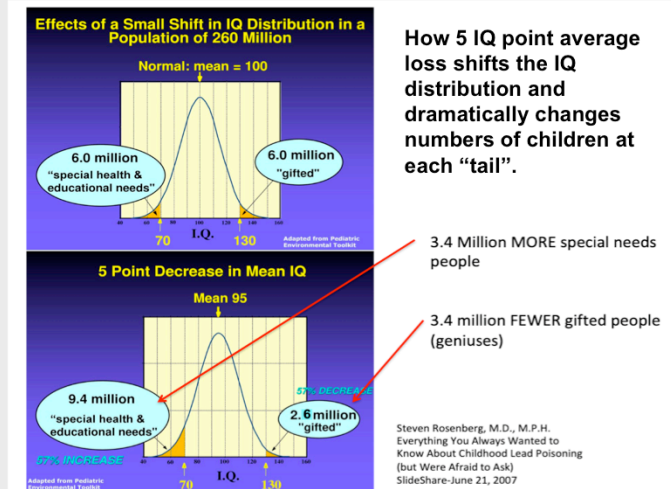
[Open "JAMAPed clip B" to play](#)

F neurotoxicity

A sizable effect “on par with lead”
“that’s a real concern”

Editors “really startled” at size of effect.

For an increase of 1 mg/L in maternal urine fluoride concentration, boys lost 5 IQ points.



The editors noted with concern that the loss of IQ from fluoridation is “on par with lead”. They also point out that even a small average drop of IQ of a few points, can produce a large increase in those on the lower tail of the distribution who need special education, and a halving of the number of gifted children on the high end distribution tail.

F neurotoxicity

**A sizable effect “on par with lead”
“that’s a real concern”**



Dr Rivara- “... a 1 mg/L increase in the maternal urinary fluoride concentration was associated with a 5 point lower score on the boys’ IQ.”

Dr Christakis- “Right. An effect size which is sizable, on a par with lead”

Dr Rivara- “Right, it is.”

Dr Rivara- “The effect size is really quite large, because when you think about it really in terms of not the individual child so much as the shift in the curve ... the shift in the curve, now, being shifted to the left, for boys, that’s a real concern”

Dr Rivara- “the results are really startling”



Dr Christakis- “... there have been other observational studies that have shown this, and there have been animal models as well, that have shown this idea that fluoride could be a neurotoxin; which again was totally news to me because I thought it was junk science, anyone would ever say such a thing.”

16

Excerpts from Podcast: audio clip C.

[Open "JAMAPed clip C" to play](#)

F neurotoxicity

Editor's advice: Pregnant mothers should avoid fluoridated water



The editors concluded with the advice that pregnant mothers should not drink fluoridated water.

F neurotoxicity

Editor's advice: Pregnant mothers should avoid fluoridated water



Dr Rivara- “So, if mothers now come into their doctor’s offices and ask the pediatrician what to do, what are you going to say?”

Dr Christakis- “I think I would advise them to drink bottled water, or filtered water, because its not a particularly odious thing to do, and potentially does reduce the risk.”

Dr Rivara- “Yea, you know the other thing is that some people may not be able to afford bottled water, it could be a financial burden to some low-income families, and we need to think about that as well.”

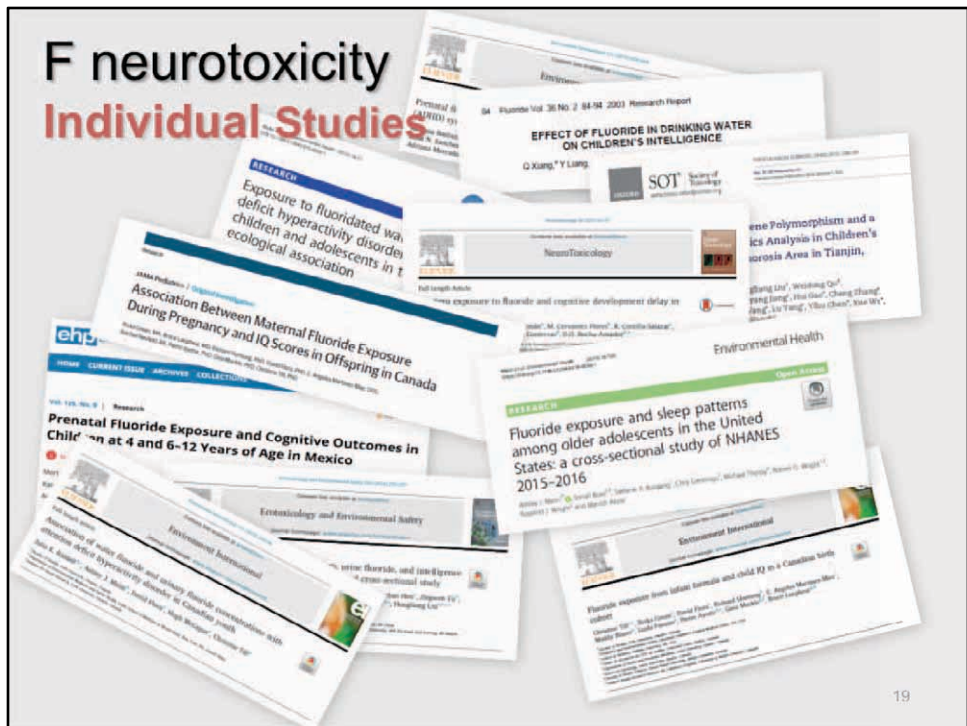
“Well, its going to get a lot of attention, and I’m very proud that you published it.” 18

Excerpts from Podcast: audio clip D.

[Open "JAMAPed clip D" to play](#)

F neurotoxicity

Individual Studies



19

I'm now going to briefly go over some of the most important individual studies. These will just be ones that the NTP rates high quality and low risk of bias.

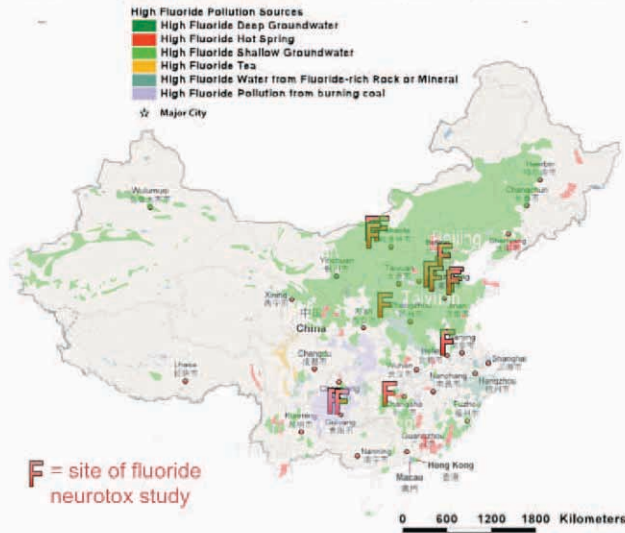
F neurotoxicity

First studies from China

In the 1980s China started investigating F neurotoxicity because it had 100 million people living in endemic fluorosis areas due to natural F in groundwater.

No artificial fluoridation in China.

High Fluoride Pollution Sources in the People's Republic of China



20

Studies of fluoride's developmental neurotoxicity started in China in the 1980s. That's because large areas of China with a population of about 100 million used groundwater for drinking that had elevated fluoride levels. China and WHO consider water fluoride concentrations above 1.5 mg/L elevated. The map shows the large areas with elevated groundwater fluoride as light green. It shows other sources of fluoride exposure in other colors. Purple shaded areas are a special localized situation where people cook indoors using coal briquettes that are made from a mix of clay and coal. The clay is the source of the high indoor fluoride levels. Normal coal combustion, such as from power plants, is not a significant source of fluoride exposure. The large red "F" markers show the locations of neurotox studies, which are spread throughout China in many different populations. Almost all of the studies found reduced IQ in the children with higher fluoride exposure.

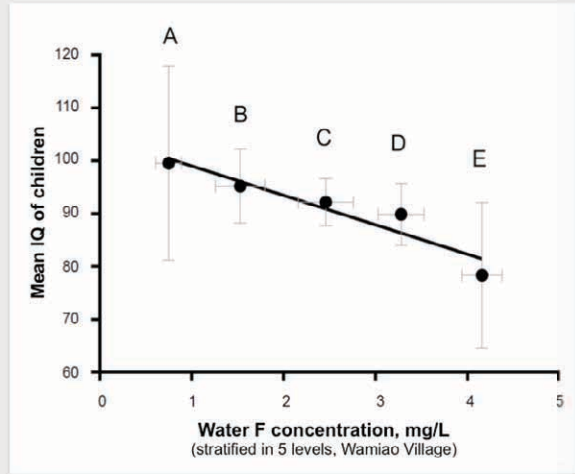
F neurotoxicity

Xiang 2003

High quality
study with
individual level
data; China.

Figure adapted
from Hirzy
2016 based on
data reported
in Xiang 2003.

F and IQ



21

The earliest studies in China were often of relatively unsophisticated design, but by about 2000, stronger study designs were being used. The Xiang 2003 study is the earliest study to be rated high quality in NTP's review. As shown in the graph, as the water fluoride increased, IQ steadily decreased. Loss of IQ is even apparent at concentrations below 1.5 mg/L.

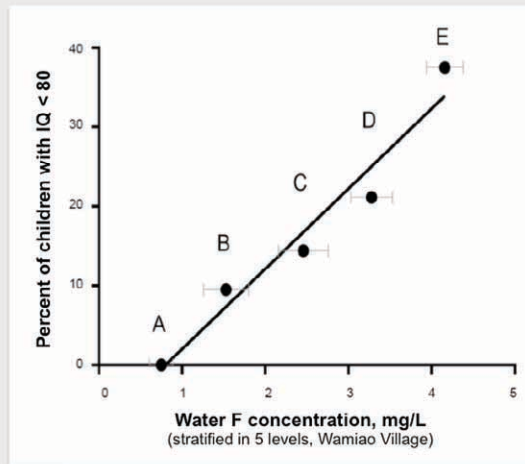
F neurotoxicity

Xiang 2003

High quality
study with
individual level
data; China.

F and % IQ below 80

Figure adapted
from Hirzy
2016 based on
data reported
in Xiang 2003.



22

But Xiang 2003 also found an even more worrying effect by looking at the percentage of children with IQ below 80, as shown in this graph. At the lowest water fluoride level of about 0.8 mg/L, shown as group “A”, no children had IQ below 80. At the next higher level, group “B”, at about 1.5 mg/L, 10% of children had IQs below 80, and at the highest exposure level almost 40% of children had IQ below 80.

F neurotoxicity

Zhang 2015

High quality study; first
with gene-F interaction;
China.

**Found 5x greater
loss of IQ for those
with specific
genotype**

Genotype	N	IQ points lost per 1 mg/L urine F	p- value
combined	108	-2.42	0.030
val/val	28	-9.67	0.003

F and IQ
all genotypes combined

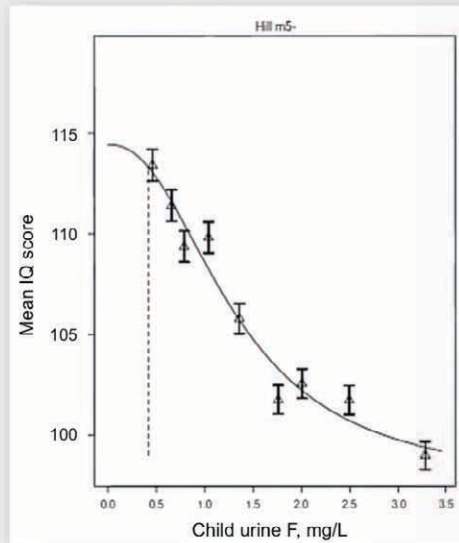


Figure based on Zhang 2015, Figure 1, with Benchmark
Dose analysis using PROAST method.

23

Of the 18 studies in children that NTP considers to be of high quality, I'm only going to discuss those that have some special feature. All 18 found statistically significant adverse effects. The Zhang 2015 study shown here was the first study to look at interactions between fluoride and genes. That is, it looked to see whether individuals with particular genetic variants were more susceptible to loss of IQ from fluoride than more common genetic variants. It found a 5-fold greater loss of IQ for a specific gene variant. The table on the lower left shows that for all children with all variants the loss of IQ was 2.42 points per 1 mg/L increase in urine fluoride, but for the val/val variant, the loss was 9.67 IQ points. About a quarter of the population had the val/val variant. The figure on the right shows how IQ drops in the susceptible group as urine fluoride increases. There is a substantial drop in IQ even at the lowest urine fluoride levels which are well below 1.5 mg/L.

F neurotoxicity

Valdez-Jimenez 2017

High quality study; first mother-offspring longitudinal cohort; Mexico.

F and IQ

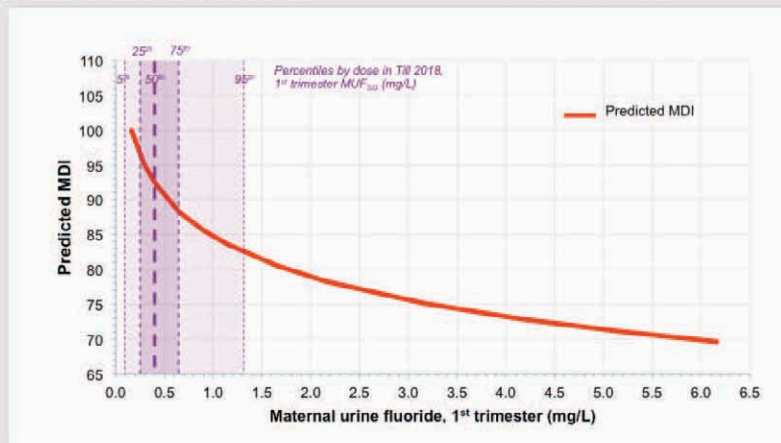


Figure based on Valdez-Jimenez 2017, Table 4, with overlay of Till 2018 exposure levels in Canada.

24

This study is noteworthy because it is the first mother-offspring longitudinal cohort study. It measured fluoride in the mothers during pregnancy and then assessed the neurodevelopment of the infants. There was a steep drop in infant's neurodevelopment score, especially in the range of maternal urine fluoride below 1.5 mg/L. This study was in Mexico, but the exposure levels can be related to those in Canadian pregnant women or pregnant women in the USA, for that matter. The purple shading indicates urine fluoride levels found in a Canadian study. Much of the loss of IQ occurs within the shaded purple range.

F neurotoxicity

Bashash 2017

**High quality, mother-offspring
longitudinal cohort study;
Mexico City.**

**First NIH-funded study of
F developmental
neurotoxicity.**

**Found large, statistically
significant effects on IQ.**

**Average IQ losses of 4-6
points for each 1 mg/L
increase in mother's
urine F.**

F and IQ

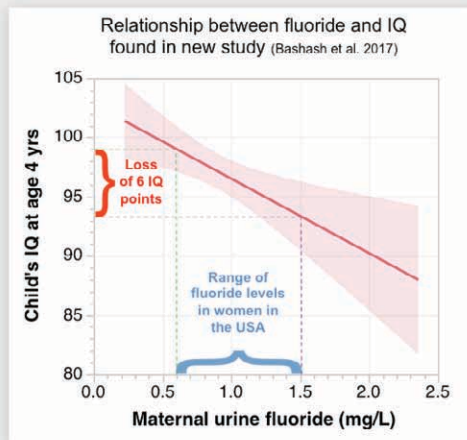


Figure based on Bashash 2017, Figure 2.

25

This study, Bashash 2017, was the first funded by the US National Institutes of Health, or NIH, with a grants totaling about \$3 million. It is a very high quality study and found a large, statistically significant effect of fluoride on IQ. The average loss was 4 to 6 IQ points for each 1 mg/L increase in mother's urine fluoride. The graph shows the dose-response relationship found for children tested at age 4 years. It also shows in the blue bracketed region the range of fluoride levels expected in the USA and the resulting loss of IQ of 6 IQ points is shown in the red bracketed region.

To date, there have not been any published studies of maternal urine fluoride levels in the USA so the range shown here is based on studies in artificially fluoridated areas of Canada and New Zealand.

F neurotoxicity

Bashash 2017



Many potential confounders considered and/or adjusted for:

Child characteristics:

1. gestational age
2. weight at birth
3. sex
4. parity (being the first child)
5. age at outcome measurement

Maternal characteristics:

6. smoking history (ever smoked vs. nonsmoker)
7. marital status (married vs. others)
8. age at delivery
9. maternal IQ
10. education,
11. cohort (Cohort 3-Ca, Cohort 3-placebo and Cohort 2A)
12. HOME score (Home Observation for the Measurement of the Environment)
13. child's urine F at outcome assessment
14. SES (Socio-Economic Status)
15. maternal bone lead
16. maternal blood mercury
17. calcium supplement

Excluded from study if:

18. history of psychiatric disorders
19. high-risk pregnancies
20. gestational diabetes

or reported current use of:

21. daily alcohol
22. illegal drugs
23. continuous prescription drugs

or were diagnosed with:

24. preeclampsia
25. renal disease
26. circulatory diseases
27. hypertension
28. seizures during the index pregnancy

As just one indication of the high quality and rigor of the Bashash 2017 study, this is a listing of all the potential confounders that were considered and adjusted for if necessary.

F neurotoxicity

Bashash 2017

**High quality, mother-offspring
longitudinal cohort study;
Mexico City.**



“Conclusion

In this study, higher levels of maternal urinary fluoride during pregnancy (a proxy for prenatal fluoride exposure) that are in the range of levels of exposure in other general population samples of pregnant women as well as nonpregnant adults were associated with lower scores on tests of cognitive function in the offspring at 4 and 6-12 y old.”

The study concluded: “higher levels of maternal urinary fluoride during pregnancy ... in the range of levels of exposure in other general populations ... were associated with lower scores on tests of cognitive function ... in offspring”. The phrase “in the range of levels of exposure in other general populations” is important, because it means this study in Mexico had fluoride exposures in the same range that women experience in the USA from artificially fluoridated drinking water. There is no artificial water fluoridation in Mexico, and instead salt is fluoridated, but the total intake of fluoride covers the same range as in the USA.

F neurotoxicity

Cui 2018

High quality study; with
gene-F interaction; China.

F and IQ

- Second study to ever look at gene-F interaction. Also found much greater susceptibility to IQ loss for those children with a gene variant:

10 IQ point loss for 1 mg/L increase in urine F.

- 4x greater loss than for all children combined.
- 14% of children had susceptible TT gene variant.

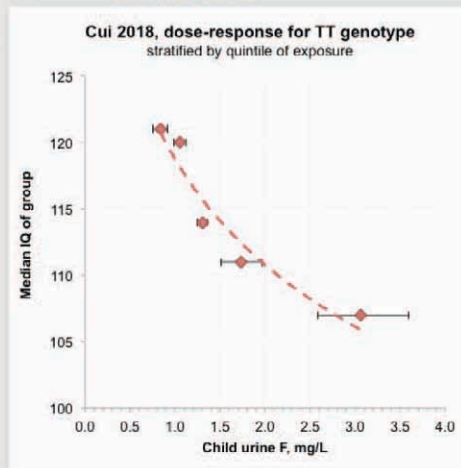


Figure based on
Cui 2018, Table
1 and Table 4.

28

This study, Cui 2018, is noteworthy because it is the second to examine gene-fluoride interactions. Just as the first such study by Zhang 2015, it found a much greater loss of IQ in those children with a particular gene variant, although in this study they looked at a different gene. For the genetically susceptible children, this study found a 10 IQ point loss for each 1 mg/L increase in urine fluoride. This was a 4-fold greater loss than in all children combined. 14% of the children had this susceptible gene variant. The graph shows that this large loss of IQ was found even below 1.5 mg/L urine fluoride.

F neurotoxicity

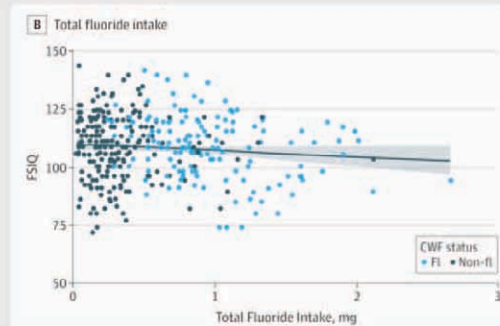
Green 2019

High quality, mother-offspring longitudinal cohort study; Canada.

- Second NIH-funded study of F developmental neurotoxicity.
- Found large, statistically significant effects on IQ.
- Average IQ loss of 4.5 points in boys for each 1 mg/L increase in mother's urine.
- Average IQ loss of 3.7 points for each 1 mg/day increase in mother's F ingestion.

JAMA Pediatrics | Original Investigation
Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada
Hodgeshaw JA, Brown L, et al. *JAMA Pediatrics*. 2019;173(12):e190000. doi:10.1093/pediatrics/kiz123

F and IQ



29

The Green 2019 paper is the highly cited study in *JAMA Pediatrics*, which the editors commented about in their Podcast that I gave excerpts from earlier. This study was also NIH funded, and is important not just because of its very high quality, but because it was done in Canada. Canada is about as similar to the USA in socioeconomic and fluoride exposure conditions as anywhere. Fluoride exposure in both countries comes mainly from artificial water fluoridation, with the average level in Canada being about 0.6 mg/L and in the USA, somewhat higher, at 0.7 mg/L. Although no study of fluoride and IQ has yet been done in the USA, this study in Canada can be considered very applicable to the USA.

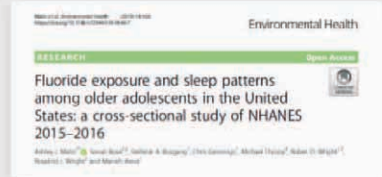
It found large statistically significant effects on IQ. For boys, the average IQ loss was 4.5 points for each 1 mg/L increase in mother's urine. The study also estimated total daily fluoride intake in the mothers and found an average 3.7 IQ points loss for both boys and girls for each 1 mg/day increase in mother's fluoride ingestion.

Defenders of water fluoridation have tried to criticize this Green 2019 study. I won't get into a detailed discussion of this, other than to point out that the authors themselves have rebutted virtually all the criticisms in a letter published in *JAMA Pediatrics* in December 2019. If you are interested in the discussions about the validity and relevance of the Green 2019 study that response letter is a good place to start.

F neurotoxicity

Malin 2019

1st study of F and sleep patterns; adolescents in USA.



- **Altered sleep patterns in adolescents** linked to levels of fluoride in the drinking water in the USA.
- Study used nationally representative NHANES data collected by CDC.
- Animal studies suggest F may impair melatonin production in pineal gland.



30

The NTP review of fluoride neurotoxicity studies only included studies published up until August 2019. There have been 3 more high quality studies published in just the last 6 months, and they both reinforce and extend the evidence compiled in the NTP review. This study, Malin 2019, was the first to ever examine sleep patterns in relationship to fluoride exposure. Furthermore, it used data from the USA in the nationally representative sample of the NHANES survey conducted by the CDC. It found altered sleep patterns in adolescents with higher drinking water fluoride levels. Altered sleep patterns can be considered a neurologic effect. Animal studies suggest fluoride may impair melatonin production in the pineal gland, so that might be the mechanism for altering sleep patterns.

F neurotoxicity

Till 2020

High quality, mother-offspring
longitudinal cohort study;
F in infant formula;
Canada.

Dramatic lowering of IQ

NEW STUDY:
FLUORIDATION LOWERS IQ OF FORMULA-FED BABIES

FLUORIDE & IQ
NEW STUDY
PUBLISHED 2019

Fluoride exposure from infant formula and child IQ in a Canadian birth cohort
Grieson, D.L., Ruka-Green, David Plouffe, Richard Hertzberg, E. Angela Martinez-Morales, Marky Shiner, Linda Fawcett, Phyllis Aynard, Gina Macklin, Brian Langlois

NIH

31

This is the most recently published study, and in my opinion, is the most concerning study yet. It was done in the same Canadian cohort as the Green 2019 paper in *JAMA Pediatrics*. But, instead of estimating prenatal exposure to fluoride it measured exposure to the infants between birth and age 6 months, with comes largely through infant formula when it is made up with fluoridated water.

F neurotoxicity

Till 2020

High quality, mother-offspring
longitudinal cohort study;
F in infant formula;
Canada.

*Children who were formula-fed and lived in
fluoridated areas as babies have dramatically
lower IQ compared to those who lived in non-
fluoridated areas.*



The composite image includes a photograph of a baby's face and a bottle of formula. Overlaid on the image is a circular stamp with the text 'FLUORIDE & IQ' around the top, 'NEW STUDY' in the center, and 'PUBLISHED 2019' around the bottom. To the right, a portion of a news article is visible, with the title 'Fluoride exposure from infant formula and child IQ in a Canadian birth cohort' and a list of authors including Christine Tuff, Rasha Ghossein, David Ploner, Richard Harrison, E. Angelika Martinez-Morales, Madeline Blaney, Linda Fawcett, Phyllis Ayres, and Gail Macdonald. The NIH logo is also present in the bottom right corner of the image.

32

The study found that children who were formula-fed and lived in fluoridated areas as babies have dramatically lower IQ compared to those who lived in non-fluoridated areas.

F neurotoxicity

Till 2020

High quality, mother-offspring
longitudinal cohort study;
F in infant formula;
Canada.

F and IQ

Very large loss of IQ with increasing tap
water F for *formula-fed infants*:

**-9 IQ points (Full Scale IQ) for each 1 mg/L increase in
tap water F.**

based on Till 2020, Table 2

33



Children given formula as infants **lost 9 IQ points** for each 1 mg/L increase in tap water fluoride. For the so-called Performance Scale IQ score, also known as “non-verbal IQ score”, **the children lost 19 points** for each 1 mg/L increase in tap water fluoride. These are dramatic and very concerning reductions in IQ that are even larger than the losses from prenatal exposure.

Two possible factors may explain this greater loss from infant period exposure than from prenatal. First: Brain development is actually more rapid during early infancy than prenatally, so may be more sensitive to disruption by neurotoxic agents. Second: Infant exposures to fluoride are much simpler and are less subject to random error than are maternal urine fluoride measurements. Maternal urine fluoride can vary by whether the mother ingested any fluoride in the hour or so before the urine sample was taken. Random error in estimating the prenatal exposures can lead to what is called “bias toward the null” which is an underestimate of the true effect. Therefore, the studies of prenatal fluoride exposure may be underestimating the size of the effect. In contrast, this study of fluoride from infant formula is not underestimating the effect, so this larger effect may be closer to the true effect.

F neurotoxicity

Till 2020

High quality, mother-offspring
longitudinal cohort study;
F in infant formula;
Canada.

**Recommendation: no fluoridated
water for infants**



**NEW STUDY:
FLUORIDATION LOWERS IQ OF FORMULA-FED BABIES**

“After adjusting for fetal exposure, we found that fluoride exposure during infancy predicts diminished non-verbal intelligence in children. In the absence of any [dental] benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water or water with lower fluoride content as a formula diluent.”



The authors conclude that for infants: **“in the absence of any [dental] benefit from fluoride consumption in the first six months, it is prudent to limit fluoride exposure by using non-fluoridated water”** to make formula.

F neurotoxicity

Fluoride and ADHD

Three studies of Fluoride and ADHD



35

While most studies of fluoride neurotoxicity have looked at IQ loss, there have also been several that have looked at the association with ADHD, or Attention Deficit Hyperactivity Disorder. I'll discuss three such studies.

F neurotoxicity

Malin 2015

F and ADHD

Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association

1st study of F and ADHD; ecological; USA.

Dramatic rise in ADHD prevalence as percent of state fluoridated increased.

About 50% higher ADHD rate in states with most fluoridation compared to those with least.

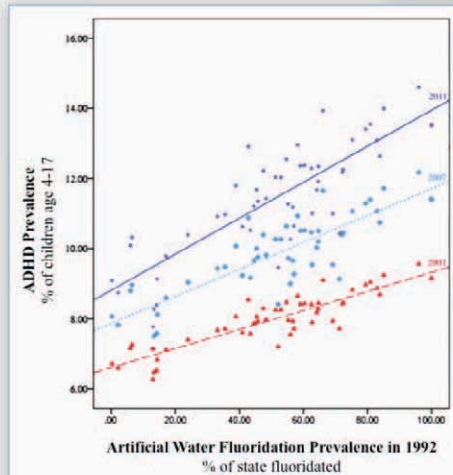


Figure 1. Artificial fluoridation prevalence predicting ADHD prevalence after adjusting for 1992 median household income, by state. For three survey years: 2003, 2007, 2011.

36

The first study to ever look at fluoride and ADHD was by Malin in 2015. It found a dramatic increase of ADHD prevalence with increasing percent of state-level fluoridation. States with high proportions of their population fluoridated had significantly higher rates of ADHD than states with less fluoridation. The effect is large, with the most fluoridated states having about 50% higher rates of ADHD than the least fluoridated states.

The study also looked at secular trends in ADHD rates by comparing surveys conducted in three different years: 2003, 2007, and 2011. In the graph, the red is the earliest survey in 2003, the light blue is the middle survey in 2007, and the most recent survey in 2011 is shown in dark blue. ADHD diagnoses have been increasing over time, and the association between fluoridation and ADHD has continued and even grown between 2003 and 2011.

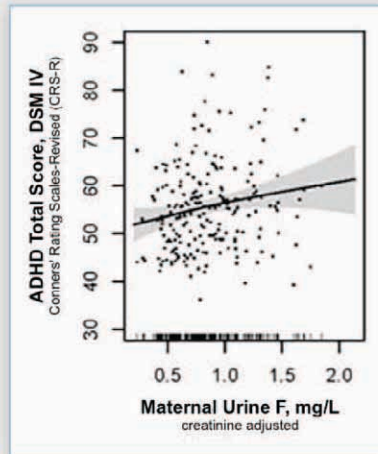
F neurotoxicity

Bashash 2018

**1st high quality
study of F and
ADHD; Mexico.**

**Statistically
significant increase in
ADHD Total Score
(inattentive and
hyperactive-impulsive
behaviors combined)
with higher maternal
urine F.**

F and ADHD



The next study of fluoride and ADHD was the first using a high quality longitudinal mother-child cohort design. It found a statistically significant increase in child ADHD score with increasing prenatal exposure, as estimated by the maternal urine fluoride level.

F neurotoxicity

Riddell 2019

High quality study of F
and ADHD; Canada.



F and ADHD

Found almost **300% higher risk of ADHD** for those living in fluoridated areas in national sample of Canadian children.

Found **600% higher risk of ADHD** for every 1 mg/L increase in tap water F.

“In conclusion, we found that higher tap water fluoride levels and fluoridation of municipal water supplies were associated with a higher risk of an ADHD diagnosis as well as increased symptoms of hyperactivity and inattention, especially among adolescents.”

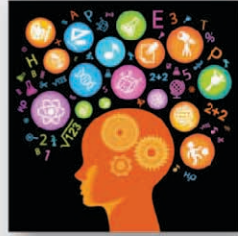
38

The latest fluoride ADHD study was published just a few months ago, and found a dramatically higher risk of ADHD in children living in fluoridated areas of Canada compared to those living in unfluoridated areas. The risk of having a diagnosis of ADHD was **300% higher** in fluoridated areas. The study used a sample of children from throughout Canada from the CHMS survey or Canadian Health Measures Survey. This survey is conducted by Health Canada and is similar to the NHANES survey in the USA.

The increased risk of ADHD, when stated in terms of a 1 mg/L increase in the tap water fluoride concentration, was **600% higher**.

An implication of these findings is that the majority of ADHD cases may be attributable to water fluoridation.

The Scientific Evidence for Fluoride's Developmental Neurotoxicity . . .



is Overwhelming



39

Summarizing the overall body of evidence, with particular focus on the strong studies discussed here, the scientific evidence for Fluoride's developmental neurotoxicity ...

is Overwhelming.

F neurotoxicity

Should we care?

What are the implications of a few IQ points lost per person?

Should we care?



40

But what are the implications of a few IQ points lost per person, on average? Should we care?

F neurotoxicity

Population-wide IQ loss

Estimate of total IQ points lost in the USA due to fluoridated water

Using similar methods as Bellinger 2012 used for other risk factors.
Assume steady-state conditions of exposure.

Loss of IQ for infants fed formula made up with fluoridated tap water:

8.8 IQ points loss per 1.0 mg/L increase in tap water F (Till 2020)

0.46 mg/L difference in water F between fluoridated and non-fluoridated areas (Till 2020)

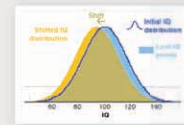
$8.8 \times 0.46 = 4.1$ IQ point average loss in fluoridated areas

50% of infants formula-fed in first 6 months (Till 2020)

70% of USA has fluoridated tap water

$50\% \times 70\% = 35\%$ formula-fed and have fluoridated water

3.8 million children born in USA each year



$3.8 \text{ million children} \times 35\% \text{ who are formula-fed and have fluoridated tap water} \times 4.1 \text{ IQ points loss} =$

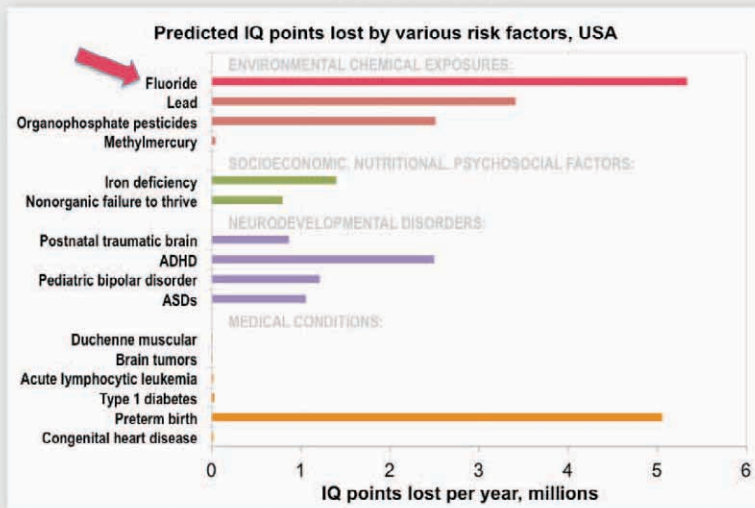
**5.4 million IQ points lost per year in the USA
due to water fluoridation**



As the *JAMA Pediatrics* editors noted in their Podcast, even a small shift downward in the distribution of IQ scores can represent a large population-wide loss of IQ. In order to compare the total harm to the population of the USA from fluoridation to that from other causes of IQ loss, we have calculated the total IQ points lost per year. Since infant formula made with fluoridated water appears to represent the greatest effect on IQ, we used the results from the Till 2020 study in Canada to estimate the total number of IQ points lost in the USA, assuming the same dose-response and infant feeding practices as in Canada but accounting for the much larger population of the USA with fluoridated water. We estimated that 5.4 million IQ points are lost per year. It is likely that a certain fraction of the population who are genetically more susceptible will bear the majority of the burden, although considering the large magnitude of the effect found in the Till 2020 study amongst all children, it is plausible that even those who are genetically less susceptible will suffer loss of IQ.

F neurotoxicity Comparison

*Water fluoridation
causes greater loss of IQ
in the USA than any
other risk factor*



All risk factors except fluoride based on Bellinger 2012, Table 2.

42

A loss of 5.4 million IQ points per year can be put into context by comparing it to the estimated losses from a variety of other risk factors, including the best known developmental neurotoxic chemicals lead, mercury, and organophosphate pesticides. Bellinger 2012 estimated the total USA-wide IQ loss for 16 other well-established risk factors and I have graphed them here. My estimate shows that fluoridated water is responsible for a greater total IQ points loss than any of the other risk factors, including lead, organophosphate pesticides, and preterm birth.

F neurotoxicity

Population-wide
economic cost

\$\$\$ cost of
Fluoridation?

Estimate of total dollar cost due to IQ loss from fluoridated water and
subsequent lower lifetime incomes, in the USA.



43

It may seem crass, but there are standard methods for estimating the total economic cost to society from IQ loss. The main economic harm arises from the reduced lifetime earnings which have been found associated with lowered IQ.

F neurotoxicity

Population-wide economic cost

\$\$\$ cost of Fluoridation?

**Estimate of total dollar cost due to population-wide IQ loss from
fluoridated water and subsequent lower lifetime incomes, in the USA.**

\$20,000	lifetime earnings lost per 1 IQ point reduction per person
79 years	average life expectancy
\$254	earnings lost per year per person per 1 IQ point reduction
327 million	population of USA
50%	percent of infants who drink formula
70%	percent living in fluoridated area as infants
35%	percent of persons who had formula and lived in fluoridated areas as infants
114 million	number of persons in USA who had formula and lived in fluoridated areas as infants
-4.1	average IQ point loss for formula-fed infants in fluoridated areas compared to non-fluoridated
-\$117 billion	annual earnings loss for USA (assuming steady state exposure and costs)

Over \$100 billion per year in USA

44

We have calculated the annual dollar cost of water fluoridation, from earnings lost due to lower IQ. We have used standard methods of health economists that have been applied to other developmental neurotoxins, like mercury. It is worth noting that the US EPA considers that a population-wide average loss of just 1 IQ point is an adverse effect to be avoided.

A standard estimate for lifetime earnings lost per person for a 1 IQ point lowering is about \$20,000. When applied to the population of the USA who are formula-fed as infants and live in fluoridated areas, it works out to a cost of over \$100 billion a year. This assumes steady-state exposure and costs. This is a huge economic cost.

F neurotoxicity

Should we care?



• **4.5 million IQ points lost per year; more than any other risk factor.** Fluoridation is causing more economic harm due to lowered intelligence and achievement than any other IQ risk factor, including lead, mercury, and preterm birth.



• **\$100 billion per year; much more harm than good.** Water fluoridation is causing much more economic harm from IQ loss than any dental benefit it might provide.



• **Easier to solve than any other environmental problem.** Water fluoridation can be stopped immediately at virtually no cost. No other environmental harm is so easily solved.

Pregnant mothers and children should be protected from the risks posed by fluoride.

45

So, should we care about the scientific evidence showing water fluoridation lowers IQ by a few points? **Absolutely!** Fluoridation is doing much more economic harm than good.

- The dollar cost of IQ loss far exceeds any dental benefit water fluoridation may provide. Furthermore, there is no dental benefit from fluoride prenatally and in infancy. It is well established that the dominant dental benefit of fluoride comes from topical contact on the teeth and not from swallowing the fluoride.
- Fluoride may be causing more neurocognitive harm than any other risk factor, including lead, mercury, and preterm birth.
- The environmental health harm from fluoridation is easier to solve than any other environmental problem. Simply stop adding fluoridation chemicals to public drinking water. I'm not aware of any other environmental harm that is so easily and inexpensively solved.
- **Pregnant mothers and children should be protected from the risks posed by fluoride.**

F neurotoxicity

Should we care?



So ... Should we care?

I'd be happy to answer any questions about the science and individual studies.

Jaime Fuge

From: Brenda Staudenmaier <thelovelybrenda@gmail.com>
Sent: Tuesday, July 7, 2020 1:39 PM
To: District Ten
Cc: District Six; District Five; District Eleven; ClerkInquiries
Subject: Fluoride studies since the 2017 council meeting
Attachments: tsca-trial.closing.june2020.pdf; EPA-trial-Grandjean-Declaration.pdf; EPA-trial-Thiessen-Declaration.pdf; EPA-trial-Lanphear-declaration.pdf; neurath-ppt.w-notes.pdf; Till_Green_EvolvingScience.pdf; EPA-trial-Hu-Declaration.pdf

Hello Mark,

Thanks for the phone call today. I look forward to Monday's Protection and Policy meeting! I am copying the other board members and clerk so they have these important documents.

Below are the highlighted studies from the ELEMENT and MIREC projects which were studying toxins in our environment. They just happened to study fluoride as part of the broad range of toxins.

I highlighted the contact for Bruce, one of the world's leading researchers on toxins in the environment and their effects on children's health. Please reach out to him. I met him at UW Madison a few years ago.

The bottom line is that fluoride is harmful to the developing fetus and during the first 6 months of life. During both time periods, fluoride is completely unnecessary and should be avoided. Adding fluoride to public water is an unreasonable risk during the most critical time period of development. Exposure during this time increases learning disabilities and ADHD. Green Bay children and the public school system do not need the burden of increased learning disabilities. Learning disabilities can lead to behavioural issues, crimes, and substance abuse.

WI Utilities Discontinued Fluoridation of Public Water Supplies Since 2016.	
1.	Potosi Waterworks
2.	Fond Du Lac Waterworks
3.	Coloma Waterworks
4.	Blue Mounds Waterworks
5.	South Wayne Waterworks
6.	Luck Waterworks
7.	Windsor Water utility North
8.	Plymouth Utilities
9.	Saukville Waterworks
10.	Lake Delton Waterworks
11.	St Croix Falls Waterworks
12.	Mellen Water Utility
13.	Bonduel Waterworks
14.	Berlin Waterworks
15.	Oconto Falls Waterworks

In July 2020 The Journal of Pediatrics published, Translating Best Evidence into Best Care, stating, "...since the beneficial effects of fluoride predominantly occur at the tooth surface after teeth have erupted, whereas fluoride is not essential for growth and development, a cautious step could be avoidance of fluoridated products and water by women during pregnancy and by infants during the first 6 months of life." [https://www.jpeds.com/article/S0022-3476\(20\)30467-4/fulltext#secsectitle0045](https://www.jpeds.com/article/S0022-3476(20)30467-4/fulltext#secsectitle0045)

Maternal and fetal exposures to fluoride during mid-gestation among pregnant women in northern California <https://ehjournal.biomedcentral.com/articles/10.1186/s12940-020-00581-2?eType=EmailBlastContent&eId=5e4bf31d-32d9-49e1-a78a-8fc83cf8cab7>

Maternal-Infant Research on Environmental Chemicals (**MIREC**): ^[L]_{SEP} <http://www.mirec-canada.ca/en/>

1. [Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada. Rivka Green, Bruce Lanphear, Richard Hornung, et al. JAMA Pediatrics. August 19, 2019 \[online ahead of print\].](#)
2. [Fluoride exposure from infant formula and child IQ in a Canadian birth cohort. Till C, Green R, Flora D, Hornung R, Martinez-Miller EA, Blazer M, Farmus L, Ayotte P, Muckle G, Lanphear B. Environment International. Nov, 18, 2019.](#)
3. [Fluoride exposure and thyroid function among adults living in Canada: Effect modification by iodine status. Ashley J. Malin, Julia Riddell, Hugh McCague, Christine Till. Environment International. Volume 121, Part 1, December 2018, Pages 667-674.](#)
4. [Community Water Fluoridation and Urinary Fluoride Concentrations in a National Sample of Pregnant Women in Canada. Christine Till, Rivka Green, John G. Grundy, et al. Environmental Health Perspectives. 2018.](#)
5. [Association of water fluoride and urinary fluoride concentrations with attention deficit hyperactivity disorder in Canadian youth. Julia K. Riddell, Ashley J. Malin, David Flora, Hugh McCague, Christine Till. Environment International. Volume 133, Part B, 2019](#)

Early Life Exposures in Mexico to Environmental Toxicants (**ELEMENT**): ^[L]_{SEP} <https://sph.umich.edu/cehc/element/index.html>

1. [Prenatal Fluoride Exposure and Cognitive Outcomes in Children at 4 and 6-12 Years of Age in Mexico. Morteza Bashash, Deena Thomas, Howard Hu, et al. Environ Health Perspect. Sept 2017. Vol 125, Issue 9.](#)
2. [OP V - 2 Prenatal fluoride exposure and neurobehavior among children 1-3 years of age in Mexico. Deena Thomas, Brisa Sanchez, Karen Peterson, et al. Occup Environ Med. 2018;75:A10.](#)
3. [Prenatal fluoride exposure and attention deficit hyperactivity disorder \(ADHD\) symptoms in children at 6-12 years of age in Mexico City. Morteza Bashash, Maelle Marchand, Howard Hu, et al. Environment International. Volume 121, Part 1, December 2018, Pages 658-666.](#)
4. [Fluoride exposure and pubertal development in children living in Mexico City. Yun Liu, Martha Téllez-Rojo, Howard Hu, et al. Environ Health. 2019 Mar 29;18\(1\):26.](#)

If you have questions on the issue of fluoride chemicals added to the public drinking water supply please reach out to:

Dr. Bruce Landphear a researcher from BC Children's Hospital and Professor at Simon Fraser University
1 778 782-8650
blanphear@sfu.ca
<https://www.sfu.ca/fhs/about/people/profiles/bruce-landphear.html>

Dr. Phillip Grandjean from Harvard T.H. Chan School of Public Health pgrand@hsph.harvard.edu
<https://www.hsph.harvard.edu/philippe-grandjean/>

Dr. Bruce Landphear a researcher from BC Children's Hospital and Professor at Simon Fraser University, "Our study of prenatal fluoride and IQ in the MIREC cohort (Green 2019) further enhances the quality of data related to the neurotoxicity of fluoride. As with the ELEMENT cohort, we employed a prospective cohort design, had extensive control for potential confounders, and had multiple measures of fluoride exposure during pregnancy, including three types of urinary fluoride measurements for each trimester of pregnancy. The maternal urinary fluoride levels in the MIREC cohort were significantly associated with lower intellectual abilities in 3-4-year-old children. These associations remain large and significant when controlling for relevant covariates. Converging results from the MIREC and ELEMENT cohorts indicate that exposure to "optimal" levels of fluoride during fetal development is associated with diminished intelligence in childhood. In the MIREC cohort, exposure to fluoridated water in infancy, particularly among formula-fed infants, was also associated with diminished intelligence (Till 2020). This association remains significant after controlling for fetal fluoride exposure and other relevant covariates, suggesting that susceptibility to fluoride's adverse neurological effects may extend into infancy."

Dr. Grandjean from Harvard T.H. Chan School of Public Health, "The weight of epidemiological evidence leaves no reasonable doubt that developmental neurotoxicity is a serious human health risk associated with elevated fluoride exposure, including those occurring at the levels added to drinking water in fluoridated areas. The IQ losses associated with community water fluoridation are substantial and of significant public health concern."

Dr. Hu, "The ELEMENT prospective cohort studies of fluoride's neurodevelopmental effects are methodologically rigorous studies that provide scientifically reliable and robust results. The results of the ELEMENT prospective cohort studies are consistent with and support the conclusion that fluoride is a developmental neurotoxicant at levels of exposure seen in the general population in water-fluoridated communities."

I am attaching the closing arguments from our trial. A powerpoint of the studies we used in our suit. Also, some of the declarations from leading experts in child development and environmental chemical exposures.

Thanks,
Brenda Staudenmaier
920.634.8657

thelovelybrenda@gmail.com

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MINUTES
PROTECTION & WELFARE COMMITTEE
Monday, January 30, 2017
City Hall, Room 207
5:00 p.m.

MEMBERS PRESENT: Chairperson Ald. Scannell, Vice Chairperson Ald. Dorff,
Ald. Galvin, Ald. Zima

MEMBERS EXCUSED: None

MEMBERS ABSENT: None

OTHERS PRESENT: Asst. City Atty Joe Faulds, Captain John Laux; Chief of Staff
Celestine Jeffreys; General Manager Nancy Quirk of Green Bay
Water Utility, Water Quality Manager Russ Hardwick, Ald. David
Nennig and other interested parties

1. Roll Call. Ald. Scannell, Ald. Dorff and Ald. Galvin were present. Ald. Zima arrived later.

The meeting was called to order by Chairman Scannell at 5 p.m.

2. Approval of the Agenda.

Motion made by Ald. Scannell to take agenda item #11 before item #10 on the agenda.

Motion to approve the amended agenda made by Ald. Dorff; seconded by Ald. Galvin. Motion carried.

3. Approval of the minutes from the January 9, 2017 meeting.

Motion to approve the minutes made by Ald. Dorff; seconded by Ald. Galvin.

Motion carried.

4. Consideration with possible action a request by Green Bay Sportservice, Inc. to amend their "Class B" Combination License at 1265 Lombardi Ave. to include the Johnsonville Tailgate Village with attached deck.

The Law and Police departments had no objections.

Motion by Ald. Dorff; seconded by Ald. Galvin to approve a request by Green Bay Sportservice, Inc. to amend their "Class B" Combination License at 1265 Lombardi Ave. to include the Johnsonville Tailgate Village with attached deck.
Motion carried.

5. Consideration with possible action on an application for a “Class A” Cider License by Kwik Trip, Inc. at 515 W. Walnut St. (currently has beer license).

The Law Department had no objections.

Approved by Ald. Dorff; seconded by Ald. Galvin to approve a “Class A” Cider License by Kwik Trip, Inc. at 515 W. Walnut St. (Currently has beer license approved).

6. Consideration with possible action on an application for an available “Class B” Combination License by Copper State Brewery, LLC at 313 Dousman St. The Law and Police departments had no objections.

Ald. Scannell mentioned the outdoor beer garden would be fenced in with shrubbery.

Motion by Ald. Galvin; seconded by Ald. Dorff to approve an application for an available “Class B” Combination License by Copper State Brewery, LLC at 313 Dousman St.

7. Consideration with possible action on an application for a “Class B” Combination License by Timothy J. Rueckl at 704 Bellevue St. (Currently Greger’s Bad Habit Saloon).

Cpt. Laux mentioned there were some reservations. Cpt. Laux said the license stipulations were agreed to minus one item, which states: “The Licensee or any employee of a license establishment is prohibited from being under the influence of an intoxicant, or a controlled substance or an combination of an intoxicant and a controlled substance, while performing services or job duties on the licensed premises.” During the meeting with the Police Department, Mr. Rueckl made mention he would like to be able to enjoy a beverage with a patron. He assured the Police Department he was not planning on being intoxicated. Cpt. Florence approved the business plan, however, wanted the Council to be aware this item was not signed off on.

Ald. Galvin asked if this item on the license stipulation could be reworded.

Cpt. Laux said the license stipulation is a bit outdated and plans to work with the Law Department to reword this portion.

The Law Department had no objections to approve the application.

Motion by Ald. Dorff; seconded by Ald. Galvin to approve an application for a “Class B” Combination License by Timothy J. Rueckl at 704 Bellevue St. (Currently Greger’s Bad Habit Saloon).

Ald. Zima arrived to the meeting.

8. Consideration with possible action on an application for a "Class B" Combination License by Chanmina, LLC at 1423-1425 S. Broadway Ave. (Currently the Last Drop).

The Police and Law departments had no objections.

Motion by Ald. Zima; seconded by Ald. Dorff to approve an application for a "Class B" Combination License by Chanmina, LLC at 1423-1425 S. Broadway Ave. (Currently the Last Drop).

9. Consideration with possible action on an appeal by Amber Piette to the denial of her Operator License application.

The Law and Police departments recommended denial based on her record.

Motion made by Ald. Dorff; seconded by Ald. Scannell to open the floor. Motion carried.

Amber Piette - 1504 Plymouth Ln
Piette handed character witness letters to the committee.

Ald. Dorff asked what treatment programs Piette has went through and how it has changed her.

Piette said went through AODA class and assessment. She is clean. She has two small children, two jobs and works hard. She was 17 years old when she received her felony.

Piette wants to obtain the license to work at Lambeau Field and Tundra Lodge. Ald. Zima asked how long she has lived in Green Bay.

She moved to Green Bay eight months ago. She previously lived in Shawano County. She moved closer for her position at Lambeau Field, which she has worked at for 2 years.

Ald. Zima asked Piette to obtain a letter from their employer stating they are aware of her past and would like Piette to have a license. Piette said she would ask.

Motion made by Ald. Dorff; seconded by Ald. Galvin to close the floor. Motion carried.

Ald. Zima agrees that Piette has shown a change in her life. She has children and now leads a more responsible lifestyle.

Motion by Ald. Zima; seconded by Ald. Dorff to approve an appeal by Amber Piette to the denial of her Operation License application, contingent upon receipt of a letter of recommendation from her employer.

11. Consideration with possible action on the amendment to GBMC § 6.215 relating to Commercial Quadricycles.

The ordinance was approved in 2016 and is in regards to Quadricycles, also known as pedal pubs.

Asst Cty Atty Faulds discussed the changes.

One change made was the date an operator's license would expire. It was changed to Dec. 31 instead of May 31 as pedal pubs are a seasonal operation. Another change was in Section 3B regarding route approval. The permanent routes are to be approved/denied/amended through the Protection & Welfare Committee.

Ald. Zima suggested a member from the traffic department review permanent routes as well. Asst Cty Atty Faulds said this could happen internally. Changes were made in section 5 about temporary routes. These will now go through the police department to have a faster turnaround time. Temporary routes could be submitted up to three days before the event.

Ald. Zima asked why temporary routes would need such a short turnaround time. Ald. Scannell said special events could be a private event, such as weddings, birthdays and graduations. These might have not been planned as far in advance.

Ald. Galvin mentioned street closures. Also, the committee only meets once a month in the summer. This allows an avenue for operator's to prevent problems.

Ald. Dorff moved to approve, with a replacement of a sentence in section 5. She wanted it to read: "No licensee shall operate a Commercial Quadricycle on a street closed off to public traffic, regardless of whether the street is included an approved route."

Motion by Ald. Dorff; seconded by Ald. Zima to approve the amendment to GBMC § 6.215 relating to Commercial Quadricycles with revisions. Motion carried.

10. A request by Brenda Staudenmaier to rescind the resolution authorizing fluoride chemicals in public drinking water.

The police department had no position on the topic. Cpt. Laux was excused for the remainder of the meeting.

Motion made by Ald. Galvin, seconded by Ald. Dorff to open the floor. Motion carried.

Ald. Scannell mentioned this is a heated topic and asked everyone to remain civil and focus on the ideas and science.

Brenda Staudenmaier-423 S. Van Buren St.

Staudenmaier is a resident of Green Bay. She is also a certified WI Dept. of Natural Resources Drinking Water Operator and Waste Water Operator. She is a Certified Hazard Walker through OSHA. Her continued education is in Environmental Engineer Water technology with a focus on human health and water solutions. She was recognized in 2016 by the White House for her work.

Staudenmaier said fluoride was introduced to Green Bay's water system in 1957. She said it is a chemical that does not occur naturally. It has been sold as something that is good for our teeth, but it is a contaminate that can promote disease.

She submitted 196 studies with a petition to the EPA showing fluoride is a developmental neuro-toxin that can cause learning disabilities.

Staudenmaier noted a city in Maine recently removed fluoride in their water. Their reasoning was that 40 percent of American adolescents are exhibiting some degree of dental fluoresce. Too many people are getting too much fluoride.

Staudenmaier recognized this is a controversial topic and people lean towards the side of caution. The science being used to defend the claims are outdated and biased.

She further presented arguments regarding removing fluoride in Green Bay's Water System.

Lacey Kuehl at 1002 Estes Dr. in De Pere spoke against fluoride in the water. She grew up in Green Bay on Crooks St.

Ald. Zima asked Staudenmaier if water filters take fluoride out of water. Staudenmaier said there are expensive ones that do, but water filters like Brita do not.

Nancy Miller, a Dental Hygienist, spoke in favor of fluoride in the water. Mat Cresipin, Associate Director at Childrens Health Alliance of WI, spoke in favor of fluoride in the water. He had a PowerPoint presentation.

Martin Zahariev, a Green Bay resident at 560 Fair Winds Ln., spoke against fluoride in the water.

Dr. Paula Krum a Periodontist and an Ashwaubenon resident at 2456 Ingold Ct., spoke in favor of fluoride in the water.

Andrew, a Certified Water Operator from Marinette, spoke against fluoride in the water.

Keith Decker, a Green Bay resident at 2821 Bristol Mountain Trl., spoke against fluoride in the water.

Nhia Yang, a Green Bay resident at 1022 Pine St., spoke against fluoride in the water.

Jenna Linden, 9 Cherry Ct. Appleton, WI, spoke in favor of fluoride in Green Bay. She is a Dental Hygienist in Green Bay and currently a Clinical Director at the Brown County Oral Health Partnership.

Lisa Hanson, a Green Bay resident at 708 Kellogg St., spoke against fluoride in the water.

Michael Schwartz-Oscar, a Green Bay resident at 322 S. Van Buren St. and Executive Director of Oral Health Partnership, spoke in favor of fluoride in the water.

Nancy Quirk, General Manager of Green Bay Water Utility, spoke in favor of fluoride in the water. She is an engineer and has been in the drinking water industry for 30 years. She said state Water Utilities follow the DNR codes and are regulated by EPA and the Public Service Commission. Green Bay's Water Utility follows the Safe Drinking Water Act recommendations. Green Bay's Water Utility adds fluoride based on section NR809.74 as regulated by state statutes.

The standard for buying our fluoride is the AWWA standard B703. This on file and information is available to view at the Green Bay Water Utility.

The amount of fluoride found naturally in the water is .1 to .2 mg per liter. Green Bay does add fluoride to a level of .7 mg per liter. Quirk said this is the lowest level the CDC recommends a city can go to ensure that we are protecting our teeth. Fluoresce can occur if more than 2 mg per liter is added to the water.

Quirk stated the pumps are set to eject .7 ppm. If the pumps release too much fluoride, it shuts off. The fluoride content is monitored 24 hours a day.

Fluoride in water is recommended by public health, medical and dental organizations. The US Surgeon General said water fluoridation was the best thing that has happened in the country.

Quirk serves on the National Committee for the Water Utility Council of American Water Works, which stays closely in touch with science and perform studies to regulate the standards.

Ald. Scannell asked if the amount of water you drink can have an effect.

Quirk said the amount was based on normal drinking habits. Some do drink more and some less. This is why the amount added into the water system was lowered due to exposure people have to other fluoride.

Ald. Scannell asked how a fluoride spill would be handled.

Water Quality Manager Hardwick said a spill would be contained in the dosage room and the local fire department would be contacted for proper disposal.

Chuck Decker responded stating he has seen a spill and it had to be addressed with hazmat suits and gas masks.

Quirk said the amount of fluoride is a meniscal amount, amounting to 42 seconds over the course of two years. Quirk said her decision is based on the best health advice available. However, if the Common Council makes a decision to take it out she will follow.

Ald. Galvin asked if the Water Utility monitors for lead and arsenic. Quirk said it is monitored.

Ald. Zima asked if she has looked into the communities that have removed fluoride in the water.

Quirk has not been in contact with them, but will research.

Chuck Decker, a Green Bay resident at 2821 Bristol Mountain Trl., spoke against fluoride in the water.

Keyundray Schultz, a Green Bay resident at 3647 Glenhaven Ln, spoke against fluoride in the water.

Dawn Craft, a Green Bay resident at 2040 Farlin Ave. and a WPS Service Analysis, spoke against fluoride in the water.

Carrie Stempski at 2829 E. Pennwood Cir., a hygienist who is now in management, spoke in favor of fluoride in the water.

Dean Pigeon, a Green Bay resident at 428 Menlo Park Rd, spoke against fluoride in the water.

Anna Destree at 3616 Stanford Dr. New Franken, Interim Health Officer of the Brown County Health Department, spoke in favor of fluoride in the water.

Miriam Owen, a Green Bay resident at 1320 E. Walnut St., spoke against of fluoride in the water.

Staudenmaier, who brought this forward to the committee, reiterated fluoride is a pesticide and an enzyme inhibitor. Staudenmaier asked on behalf of the citizens of Green Bay to have it removed from our water.

Motion made by Ald. Dorff; seconded by Ald. Galvin to close the floor. Motion carried.

Motion by Ald. Scannell; seconded by Ald. Dorff to take a ten minute recess. Motion carried.

Meeting resumed 10 minutes later.

Ald. Zima said those who spoke were speaking from the heart and with intelligence. Ald. Zima wants to respect individuals rights, however, cannot think of a way to offer both choices to citizens. He would not be able to make a decision at this time. In his personal experience, he has not been hurt by fluoride. He was taught to brush and take care of his teeth and not sure if the fluoride helped or not. He was open-minded and wanted more time to review the information.

Ald. Dorff had great respect for those who spoke tonight. She wished one person could come up to the podium and said well there is this, but also this. There were both sides of the spectrum. She would now have to look and decide for herself and be responsible and make a good decision for the community. She was not ready to make the decision that night. She has been a child advocate for the last 38 years and helped bring oral health into the Green Bay Public Schools. In a perfect world, it would be ideal to allow a choice of fluoridated and non-fluoridated taps, however, it would not be feasible. She sees both sides of the debate and would look further into the information to make an informed decision.

Ald. Galvin appreciated the passion of those who spoke and self-educated themselves on the subject. If it was just about tooth decay, it would be an easy answer. However, there are other factors to take into consideration. Ald. Galvin would like more time to review the studies further.

Ald. Scannell said he was leaning a particular way. As an alderman, Ald. Scannell relies on the staff to make an informed decision. He felt the expertise in this case is the established community. However, he will study the information left a door open to change his mind.

Motion made by Ald. Dorff; seconded by Ald. Galvin to hold until the Feb. 27 Protection & Welfare Meeting a request by Brenda Staudenmaier to rescind the resolution authorizing fluoride chemicals in public drink water. Motion carried.

Motion made by Ald. Galvin; seconded by Ald. Dorff to adjourn meeting. Motion carried.

Meeting adjourned at 8:15 p.m.

MINUTES
PROTECTION & WELFARE COMMITTEE
Monday, February 27, 2017
City Hall, Room 207
5:00 p.m.

MEMBERS PRESENT: Chairperson Ald. Scannell, Vice Chairperson Ald. Dorff, Ald. Galvin, Ald. Zima

MEMBERS EXCUSED: None

MEMBERS ABSENT: None

OTHERS PRESENT: Asst. City Atty Joe Faulds, Captain Todd LePine, Ald. Christopher Wery; General Manager Nancy Quirk of Green Bay Water Utility, Water Quality Manager Russ Hardwick of Green Bay Water Utility, Animal Control Officer Mallory Meves, and others

1. Roll Call. All present.
The meeting was called to order by Chairman Scannell at 5 p.m.
2. Approval of the Agenda.
A motion was made by Ald. Dorff, seconded by Ald. Galvin to approve the agenda. Motion carried.
3. Approval of the minutes from the February 13, 2017 meeting.
A motion was made by Ald. Dorff; seconded by Ald. Zima to approve the minutes from the February 13, 2017 meeting. Motion carried.
4. Consideration with possible action on an appeal by Jillian Stitman to the denial of her Operator License application.

Jillian Stitman was not present at this time. Motion made by Ald. Zima; seconded by Ald. Galvin to deny an appeal by Jillian Stitman to the denial of her Operator License application and to reapply if she is still interested in obtaining one.

5. Consideration with possible action on an application for a "Class B" Combination License by Catch-22 Enterprises, LLC at 1699 E. Mason St. (Currently Main & Mason, LLC).

The Law and Police departments had no objections.

A motion was made by Ald. Dorff; seconded by Ald. Galvin to approve an application for a "Class B" Combination License by Catch-22 Enterprises, LLC at 1699 E. Mason St. (Currently Fitzgerald's)

6. Consideration with possible action on an application for a “Class A” Liquor and a Class “A” Beer License by Tikapur Petroleum, LLC at 2056 Main St. (Currently Main & Mason, LLC)

The Law and Police departments had no objections.

Ald. Zima asked if this was in a residential area.

Ald. Galvin said the business is across the street from an apartment complex.

Ald. Zima addressed concerns of its location.

Ald. Scannell said the Committee could seek feedback from the alder on the Council floor at next Tuesday’s City Council meeting.

Motion made by Ald. Dorff; seconded by Ald. Galvin to approve an application for a “Class A” Liquor and a Class “A” Beer License by Tikapur Petroleum, LLC at 2056 Main St. (Currently Main & Mason, LLC). There were no objections and motion carried.

7. Consideration with possible action on an application for a Class “A” Beer License by Tikapur Petroleum, LLC at 2115 Main St. (Currently Main & Mason, LLC)

The Law and Police departments had no objections.

Motion made by Ald. Dorff; seconded by Ald. Galvin to approve an application for a Class “A” Beer License by Tikapur Petroleum, LLC at 2115 Main St. (Currently Main & Mason, LLC). There were no objections and motion carried.

8. Consideration with possible action on an appeal by Christopher Daley regarding his dog, previously discussed at the Feb. 13 P&W meeting and placed on hold.

Asst Cty Atty Faulds recapped from the Feb. 13 meeting. As stated at last meeting, the dog has been declared dangerous by Officer Meves, and the owner Christopher Daley appealed the decision. Feb. 13 was the hearing where the facts were presented to the Committee. New information has come forward since the last meeting. Asst Cty Atty Faulds presented an e-mail sent to the Committee members and entered it into the record.

The e-mail from the Green Bay Police Department stated on Feb. 18, Daley’s dog was loose in his yard when it attacked another dog that was on a leash, as it was being walked by its owner on the sidewalk. The Police Department learned of the attack on Feb. 21 and Animal Control Officer Meves issued a citation and seized Daley’s dog, which is now secured at the Bay Area Humane Society.

Asst Cty Atty Faulds noted Mr. Daley was not present at meeting.

Ald. Dorff and Ald. Galvin moved to denied.

Ald. Zima said he felt very uncomfortable last meeting and said the only reason it went unanimous was that the dog was to leave the city during the decision. The decision was placed on hold so the owner had an opportunity to make an area for the dog to keep her confined. Ald. Zima was in full support of the motion of denial.

Asst Cty Atty Faulds said the Committee has to put into the record the findings of fact on why it is or is not declared dangerous, and the motion one way or another to ensure the record is clear.

Ald. Zima suggested: "In light of the fact the dog has been in four biting incidents in the past year and the owner did not take the necessary precautions, we are declaring the dog dangerous."

Ald. Dorff asked Officer Meves how this has happened and a possible explanation.

Officer Meves said the dog Reba was running loose when the incident happened. A gentleman was walking a leashed dog by the residence. It was a little morkie, a Maltese Yorkie mix, which is a small dog. Reba was running loose and ended up pinning the dog down. Reba caused two pretty big bites to her. The owner of the morkie went to open the dog's mouth and at that point has sustained some scraps. He wasn't sure if it came from the dog during that or while he was down on the ground wrestling the dog. It was a struggle to get the dogs away as he had to hit and kick Reba to get the dog off his. There was no fence made at the time of the incident and the incident happened on the sidewalk. Mr. Daley had given a gift card to the gentleman and asked him to not call the Police.

Officer Meves said she was informed of the situation on a Schmitt Park neighborhood blog. His wife posted a blog that read beware of dog. She posted this blog and everyone said you needed to contact Animal Control. Officer Meves said she reached out to the owners. She confirmed it and met with them and assessed the situation.

Officer Meves then immediately seized the dog, who is now at the Bay Area Humane Society on hold.

Ald. Dorff asked what happens to the dog now.

Officer Meves said based on the Committee's decision tonight, if the dog is declared dangerous it cannot remain in the city. But during this decision process, the dog was not supposed to be in the city. Officer Meves said Daley did

construct a 4x4 makeshift fence, which Officer Meves was able to lift up the bottom of the fence.

If he doesn't reclaim the dog within seven days, Reba would have to be put down. Officer Meves said Daley was considering having the dog stay with his brother in California.

Ald. Zima asked if Daley was cited.

Officer Meves said yes, he was recited for "Animal not attended within five-feet of right away."

Asst Cty Atty Faulds added the findings of fact should meet the elements of section 8.105.

Ald. Dorff asked if the fourth incident was off the owner's property. Officer Meves replied it happened on the sidewalk.

Ald. Zima thought there was a more serious violation as he did not have the dog leave the city and defied the Committee's ruling. It was Ald. Zima's understanding that the dog would leave the City while proper confinements were put in place and the Committee was to review the area.

Ald. Dorff said the Committee couldn't make the owner do it, but the Committee thought he would have.

Asst Cty Atty Faulds clarified that the dog did have to be outside of the city during the pending hearing. However, the Committee could not put stipulations like building a fence.

Ald. Dorff asked to do another finding of fact.

Asst Cty Atty Faulds said if the dog is considered a dangerous dog, then it would also have to be qualified as a menacing dog.

Ald. Scannell suggested starting with Ald. Zima's motion that the animal has four incidents of injuring animals and people while not on the owner's property.

The final motion became: The animal has four incidents of injuring animals and people while not on the owner's property, we declare the animal a dangerous dog that causes injury in a menacing fashion. Therefore, it meets the definition of a dangerous dog and therefore, needs to leave the city.

Motion by Ald. Zima; seconded by Ald. Galvin To deny the appeal of Christopher Daley, 2747 Humboldt Rd., to the declaration of his dog being labeled as a dangerous dog under the City of Green Bay Municipal Code 8.105, Sec., (1), (2),

& (3), based on the adopted findings of facts and conclusions of law announced at the meeting. Motion carried.

9. Consideration with possible action a request by Brenda Staudenmaier to rescind the resolution authorizing fluoride chemicals in public drinking water, previously discussed at the Jan. 30 P&W meeting and placed on hold.

Captain LePine was excused for the remainder of the meeting.

Ald. Zima said he did watch a film that was suggested at last meeting. After watching, Ald. Zima asked if fluoride was good for teeth, then why was it being ingested into the whole system. He previously thought fluoride was good, but was no longer convinced it was. He thought fluoride can be found in other ways.

Ald. Scannell asked if the staff had items to provide.

Nancy Quirk, General Manager of Green Bay Water Utility, addressed the committee.

Quirk spoke with a person from the Water Department of Montello, a community that no longer has fluoride in their water supply. The gentleman said money was the reason why fluoride was given up. They had other things they had to take care of in their water.

Ald. Zima recalled when smoking was a positive thing. Ald. Zima said those against fluoride made a very compelling argument.
Motion made by Ald. Dorff; seconded by Ald. Galvin to open the floor.

Ald. Scannell said this is City Business. The goal is to give the Committee answers and input. Since there was already an open forum, if the information is repetitive, he would let them know. The goal is take the public's information, discuss amongst ourselves and make a decision.

Jillian Stitman addressed the Committee and if would be able to speak on behalf of her Operator License denial.

Motion made by Ald. Zima; seconded by Ald. Dorff to reconsider an appeal by Jillian Stitman to the denial of her Operator License application.

4. Consideration with possible action on an appeal by Jillian Stitman to the denial of her Operator License application.

Motion by Ald. Dorff; seconded by Ald. Galvin to open the floor.

Jillian Stitman
2185 King James

Stitman said she wanted to appeal the denial since she was denied on a felony that occurred 10 years ago. She is almost 35 years old and has changed since then. She has not had a record since that occurrence. Since then, she graduated from college twice.

In August 2013, she was hit by a train. It took a year to recover. She had a brain injury, which has placed limitations on the jobs she can do. Currently, she is a server. The promotion would mean a better income.

Stitman said she made a mistake 10 years and it is unfair to use something she did one time against her. She is completely different now.

Ald. Dorff clarified that if the law states if a person has a felony, it is required that the operator license be denied. However, the Committee can overrule that.

Ald. Dorff asked where Stitman works.

Stitman said she works at Applebee's.

Motion made by Ald. Dorff; seconded by Ald. Galvin to close the floor.

Motion made by Ald. Dorff to approve the appeal by Jillian Stitamn to the denial of her Operator License application, contingent on a receiving a letter from her employer.

Ald. Scannell suggested amending the motion and asked that the Committee not require an employer's letter.

Motion made by Ald. Dorff; seconded by Ald. Galvin to approve an appeal by Jillian Stitman to the denial of her Operator License application. There were no objections and the motion carried.

The Committee returned to Agenda Item #9.

Motion made by Ald. Dorff; seconded by Ald. Galvin to open the floor.

Brenda Staudenmaier: 423 S. Van Buren St.
Staudenmaier spoke to the Committee regarding an update on her petition to the EPA requesting fluoride to be removed in the water on a national level.

Staudenmaier said the EPA denied their petition. She said the EPA was not ready to let go of the outdated assumptions on fluoride.

The petition presented evidence demonstrating that fluoride is a neurotoxin being ingested by children and vulnerable populations. They also presented that fluoride has little benefit when swallowed. Any risks from exposing fluoride chemicals are unnecessary.

She believes that an impartial judge will agree. She will challenge the EPA's denial in court and is confident on the merits of the petition.

Staudenmaier said fluoride is a neurotoxin. The question therefore, is not if fluoride damages the brain, but at what level does it do the damage.

Staudenmaier said the 2006 National Research Council said fluoride can lead to renal, endocrine and gastrointestinal disease. She also noted that it is immoral to be mass medicated and is contradictory to modern principals of pharmacology. Ald. Zima clarified that the communities are allowed to make a decision on fluoride and the petition was based on a national level.

Staudenmaier asked Quirk about the NSF regulations and Green Bay's compliance of water quality.

Quirk discussed the numeric formula used to come to the value. Quirk said Green Bay's water does meet the standards of NSF and AWWA Standard B703.

David Dunlop at 410 N. Ashland:

He said a number of municipalities have abandoned the standard of fluoride. He asked if we are following the leaders or behind the curve. The public policy should be looked at and the scientific evidence be reviewed. He asked the Committee to look at those who took fluoride out of the water and look at their reasoning. He also asked the Committee to review if the municipalities have been cited.

Michael Finney, 2428 Bay Settlement Road, spoke against fluoride in our water. He mentioned the 2006 study that showed there was a concern on fluoride. Fluoride is an endocrine destructor, meaning it is having an effect.

Ald. Dorff asked more for information on the 2006 statements from the National Academy.

Finney said it was a 507 page study done by 12 leading experts in the National Academy of Science that is unbiased. The study stated fluoride has the ability to effect function of the brain and the body by direct and indirect means. He said fluoride is an endocrine destructor. Fluoride can also cause decreased thyroid function and kidney disease.

Keith Decker, 2421 Mountain Trail, spoke against fluoride in Green Bay's water.

He handed an e-mail to the committee regarding the studies to show the cause of concern of fluoride. He believes a mass medication of water is fundamentally wrong.

David VanderLeest 146 Alpine Dr.

He said there is a difference in putting fluoride on topical versus drinking it. He suggested putting the decision to a referendum to place the decision in the hands of the community.

Nicole La Forge at 4481 Nicolet Drive spoke against fluoride in our water and mass medication. She noted eight different cities in Wisconsin have abandoned fluoride in the water.

Robbyn Kuester, Fluoridation Program Coordinator WI Department of Public Health spoke in favor of fluoride in our water. She said fluoridation of water is safe and effective.

Kuester said expert panels have considered the available evidence and found a lifetime of drinking fluoridated water at the optimal level results in no adverse condition for any groups of individuals or individuals.

She addressed the denial of Staudenmaier's petition and read from the EPA's 40-page response as to why it was denied.

She said 90 percent of the population in Wisconsin has access to fluoridated water. The decision is a decision made on the local level. Those who have stopped using fluoride are typically smaller communities with outdated infrastructure and the cost to update the infrastructure and cost of fluoride is too much.

She also noted fluoridation water programs are growing and not decreasing.

Ald. Zima asked if Kuester could elaborate about communities that don't have fluoridation in their water and the dangers these communities have subjected themselves to.

Kuester said there is a health and economic impact.

Mary Rosner, a resident at 1868 Dousman St., spoke in favor of fluoride in our water.

Dr. Rick Vander Heyden, a dentist in Allouez, spoke in against of fluoride in our water. He asked himself as a dentist if he should do the fluoride treatments or not. He found the little bit people could benefit from was not worth the risk. The risk to reward was just not there.

Ald. Zima asked if the amount of fluoride in our water is doing any good or if it is the brushing and flossing and care.

He said it is the proper teeth care that helps and not the water.

Dr. Mark Moss, the State Dental Director, spoke in favor of fluoride in our water.

He said it is good to be skeptical, however, look at the best evidence out there.

Ald. Galvin asked Moss's opinion on the studies presented by those against fluoride in water.

Dr. Moss stated that it is important to look at the different variables like biasness, measurement, selection and confounding, and noted there is no perfect study.

Ald. Zima asked Moss to elaborate on the study of the fluoride and osteosarcoma.

Dr. Moss mentioned there was an animal study that raised a lot of concerns. The study was based on just male rats. There were questions if the study on if it was a fluke or solid evidence. The research community found it to no be evidential.

Ald. Zima asked if they need fluoride all the time or if it could be something that just once a week would be fine. He expressed concerns of drinking it.

Dr. Moss said that in his mind it is safe.

Jenna Linden, Clinical Director of Oral Health Partnership, spoke in favor of fluoride in our water.

She said fluoride can help tooth decay by 25 percent. One way of reaching children and the population is by fluoridating water. We cannot guarantee compliance and fluoridation in water can help.

Chris Le Roy, 2760 Humboldt Rd., spoke against fluoride in our water. He brought a tube of common toothpaste and read the warning label. He said he does not use the toothpaste with the fluoride anymore. He mentioned he buys bottled water, but does like to take a bath nightly. Fluoride is going into the body through our skin. He does not like it in the water supply.

Dave Thompson, a practicing dentist in Green Bay, spoke in favor of fluoride in our water. He said it is the most positive and impactful public health measure that has taken on this country in the last 50 years.

Ald. Scannell asked if anyone would like to speak on the issue.

Keith Decker-

Decker spoke in regards to Moss's information. He said that there are large professional prestigious groups that are against fluoride as well. There are authorities before and against and asked the committee to see the reasonable cause of concern.

Staudenmaier asked if it is worth it to expose your whole body to a neurotoxic substance to save a ½ or one cavity.

Tom Nockerts, a Green Bay Dentist, spoke in favor of fluoride in our water. Fluoride is geared towards the segment of the population that does not get to the dentist.

Ald. Wery spoke to the Committee and asked the information be passed to the rest of the Council to help make an informed decision.

Vander Leest of Alpine Drive spoke before the committee. He asked if there are any studies in the advances of dental health. He recommended having a referendum to let citizens decide.

Motion made by Ald. Dorff; seconded by Ald. Galvin to close the floor. Motion carried.

Motion made by Ald. Galvin; seconded by Ald. Dorff to take a recess. Motion carried.

Motion by Ald. Galvin; seconded by Ald. Dorff to return to regular order. Motion carried.

Ald. Scannell said he did not support taking fluoride out of Green Bay's water at this time. He said there are a lot of studies available, but the most prominent scientific establishments support fluoridating water.

He noted science is a community and not an individual exercise. As more research is presented his decision could change at a later time. At this time, he felt it is the wrong move to remove fluoride.

Ald. Scannell mentioned that chlorine is added to our water to prevent cholera and typhoid, which is for the greater good. He noted it is a balancing act between respecting individual rights and helping the community. Until there are other options, it is in the benefit of the community to keep fluoride in the water.

Ald. Zima said there are an increasing number of professionals questioning the established view that fluoride is good. He said he took a community member's challenge of watching at least five minutes of a video. He ended up listening to the whole video. He felt there are questions that are credible on the opposite side of fluoridation.

He said previously, he did drink the tap water because it comes from Lake Michigan and thought it was probably good for him. He didn't feel it did any serious harm that he knew of, but can't explain all of his aches and pains.

He hoped for an ongoing discussion about fluoride. He noted all the professionals are not on one side, but rather both.

Ald. Zima made a motion to review again in a month and have a debate and acknowledge if there is something to this or not. There was no second. Motion failed.

Ald. Dorff said the full Council will want to weigh in on the decision to remove fluoride. Council is where the decision is to be made and asked people to attend the Council meeting to express their opinion.

Ald. Dorff didn't like the idea of having a referendum to make the decision. She said the community would not have the advantage of listening to expert witnesses. She felt the people with the most money would have the most commercials and advantage.

Ald. Dorff didn't like the idea that keeping fluoride in our water is a conspiracy theory. She watched one of the videos and found there were some leaps in their conclusions.

Ald. Dorff quoted Dr. Moss stating "It's good to be skeptical." She said more research needs to be done and a risk/benefit analysis be reviewed. Ald. Dorff suggested to keep doing what you are doing, but never stop questioning.

Ald. Dorff noted how tobacco was once thought to be helpful. Her mother was smoking while pregnant and that was considered okay. She said obviously, society has come a long way.

Ald. Dorff is not convinced she wanted to move away from the resolution currently in place. However, she is willing to listen and continue studying.

Ald. Galvin said the other three alders expressed how he feels. He noted there are passionate people on both sides. Ald. Galvin referenced issues with windfarms in Brown County. He noted the County has struggled on what to do with that.

Ald. Galvin said he was not in support of eliminating fluoride in our drinking water at this time. It appears to be a benefit throughout the community. He said he saw the effect of tooth decay in his job. He said he can't support removing it, but the City needs to keep doing research and moving forward so we are doing what's best for the citizens.

Ald. Zima suggested an ongoing discussion for the next couple of years, like the County has done with windmills.

Motion made by Ald. Galvin; seconded by Ald. Dorff to receive and place on file a request by Brenda Staudenmaier to rescind the resolution authorizing fluoride chemicals in public drinking water. Alders Galvin, Dorff and Scannell voted yes to receive and place on file. Ald. Zima voted no.

Motion to adjourn made by Ald. Dorff; seconded by Ald. Galvin. Motion carried.

Meeting adjourned at 8:08 p.m.