From:	Burns, Robert J.
To:	David L. Eaton
Cc:	Assistant Secretary for Health (HHS/OASH); Levine, Rachel (HHS/OASH); NIH Executive Secretariat; Tabak, Lawrence (NIH/OD) [E]; Woychik, Rick (NIH/NIEHS) [E]
Subject:	[EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
Date:	Tuesday, September 20, 2022 5:23:14 PM
Attachments:	220920_niehs_ntp_fluoride_monograph_sig.pdf

Hi, Dr. Eaton. Please find the attached comments to the NIEHS panel reviewing the NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review. We hope the panel will find these comments helpful when evaluating whether NTP adequately responded to outside criticisms, and developing recommendations for whether and how the report should move forward.
Please feel free to contact me if you have any questions. Many thanks.
-Bob

Robert J. Burns
Senior Manager, Strategic Advocacy and Public Policy
Government and Public Affairs
(b) (6) | (b) (6)

American Dental Association 211 E. Chicago Ave. Chicago, IL 60611 www.ada.org

From:	Webster-Cyriaque, Jennifer (NIH/NIDCR) [E]
To:	Tabak, Lawrence (NIH/OD) [E]; Schwetz, Tara (NIH/OD) [E]; D"Souza, Rena (NIH/NIDCR) [E]
Subject:	RE: [EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
Date:	Tuesday, September 20, 2022 3:01:15 PM

Thanks for providing this.
Best,
Jennifer

From: Tabak, Lawrence (NIH/OD) [E] <(b) (6)
Sent: Tuesday, September 20, 2022 12:35 PM
To: Schwetz, Tara (NIH/OD) [E] <(b) (6) D'Souza, Rena (NIH/NIDCR) [E] <(b) (6); Webster-Cyriaque, Jennifer (NIH/NIDCR) [E] (b) (6) >
Subject: FW: [EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
fyi

From: "Burns, Robert J." <(b) (6)
Date: Tuesday, September 20, 2022 at 12:27 PM
To: Kathleen Caron <(b) (6)
Cc: "Assistant Secretary for Health (HHS/OASH)" <(b) (6) "Levine, Rachel (HHS/OASH)" <(b) (6) NIH Executive Secretariat <(b) (6) "Tabak, Lawrence (NIH/OD) [E]" <(b) (6) "Woychik, Rick (NIH/NIEHS) [E]" <(b) (6)
Subject: [EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects

Hi, Dr. Caron. Please find the attached comments to the NIEHS panel reviewing the *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*. We hope the panel will find these comments helpful when evaluating whether NTP adequately responded to outside criticisms, and developing recommendations for whether and how the report should move forward.
Please feel free to contact me if you have any questions. Many thanks.
-Bob

Robert J. Burns
Senior Manager, Strategic Advocacy and Public Policy
Government and Public Affairs
(b) (6) | (b) (6)

American Dental Association 211 E. Chicago Ave. Chicago, IL 60611 www.ada.org

From: D"Souza, Rena (NIH/NIDCR) [E]
To: Tabak, Lawrence (NIH/OD) [E]
c: Schwetz, Tara (NIH/OD) [E]; Webster-Cyriaque, Jennifer (NIH/NIDCR) [E]
Subject: Re: [EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
Date: Tuesday, September 20, 2022 2:1 :0 PM
ttac me t : 220_20_niehs_ntp_fluoride_monograph_sig.pdf

Thanks Larry… recd a courtesy copy earlier

Sent from my iPhone

On Sep 20, 2022, at 6:35 PM, Tabak, Lawrence (NIH/OD) [E] < (b) (6) wrote:

fyi

From: "Burns, Robert J." < (b) (6)
Date: Tuesday, September 20, 2022 at 12:27 PM
To: Kathleen Caron < (b) (6)
Cc: "Assistant Secretary for Health (HHS/OASH)" < (b) (6) "Levine, Rachel (HHS/OASH)" < (b) (6) NIH Executive Secretariat < (b) (6) "Tabak, Lawrence (NIH/OD) [E]" < (b) (6) "Woychik, Rick (NIH/NIEHS) [E]" < (b) (6)
Subject: [EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects

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Please feel free to contact me if you have any questions. Many thanks.

-Bob

Robert J. Burns
Senior Manager, Strategic Advocacy and Public Policy
Government and Public Affairs
(b) (6) | (b) (6)

American Dental Association 211 E. Chicago Ave. Chicago, IL 60611 www.ada.org

From:	Caron, Kathleen M
To:	Burns, Robert J.
Cc:	Assistant Secretary for Health (HHS/OASH); Levine, Rachel (HHS/OASH); NIH Executive Secretariat; Tabak, Lawrence (NIH/OD) [E]; Woychik, Rick (NIH/NIEHS) [E]
Subject:	[EXTERNAL] RE: NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
Date:	Tuesday, September 20, 2022 2:11:49 PM

Dear Mr. Burns,
This past Spring, I completed my 5-year term as Chair of the NIEHS Board of Scientific Counselors. You will likely wish to resend your communication to the new Chair.
Sincerely,
Kathleen
****

Kathleen M. Caron, PhD
Professor & Chair
Dept. Cell Biology & Physiology, UNC-CH
http://caronlab.web.unc.edu/

From: Burns, Robert J. < (b) (6)
Sent: Tuesday, September 20, 2022 12:27 PM
To: Caron, Kathleen M < (b) (6)
Cc: Assistant Secretary for Health (HHS/OASH) < (b) (6) Rachel Levine (HHS/OASH < (b) (6) Office of the NIH Director < (b) (6) Lawrence Tabak (NIH) < (b) (6) Rick Woychik (NIH/NIEHS < (b) (6)
Subject: NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects

Hi, Dr. Caron. Please find the attached comments to the NIEHS panel reviewing the *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*. We hope the panel will find these comments helpful when evaluating whether NTP adequately responded to outside criticisms, and developing recommendations for whether and how the report should move forward.
Please feel free to contact me if you have any questions. Many thanks.
-Bob

Robert J. Burns
Senior Manager, Strategic Advocacy and Public Policy
Government and Public Affairs
(b) (6) | (b) (6)

American Dental Association 211 E. Chicago Ave. Chicago, IL 60611 www.ada.org

From:	urns, Robert J
To:	athleen Caron
c:	Assistant Secretary for Health (HHS/OASH); Levine, Rachel (HHS/OASH); NIH E ecutive Secretariat; Tabak, Lawrence (NIH/OD) [E]; Woychik, Rick (NIH/NIEHS) [E]
Subject:	[EXTERNAL] NTP Monograph on Fluoride and Neurodevelopmental and Cognitive Health Effects
Date:	Tuesday, September 20, 2022 12:2 :5 PM
ttac me t :	220 20 niehs ntp fluoride monograph sig pdf

Hi, Dr. Caron. Please find the attached comments to the NIEHS panel reviewing the *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*. We hope the panel will find these comments helpful when evaluating whether NTP adequately responded to outside criticisms, and developing recommendations for whether and how the report should move forward.

Please feel free to contact me if you have any questions. Many thanks.

-Bob

Robert J. Burns
Senior Manager, Strategic Advocacy and Public Policy
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September 20, 2022

Kathleen M. Caron, Ph.D.
Chair, Board of Scientific Counselors
National Institute of Environmental Health Sciences
c/o University of North Carolina at Chapel Hill
111 Mason Farm Road
5200 Medical Biomolecular Research Building
Chapel Hill, NC 27599-7545

Re: NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review

Dear Dr. Caron:

On behalf of the 162,000 members of the American Dental Association (ADA), we would like to again share our concerns about the National Toxicology Program's May 2022 report, titled *NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review*.

For the last several years, NTP has been examining the literature to determine whether there is a causal relationship between fluoride exposure and neurocognitive health. The NIEHS Board of Scientific Counselors has been asked to evaluate whether NTP adequately responded to outside criticisms. It has also been asked to recommend whether and how the report should move forward, based on its findings.

A number of federal agencies and outside groups—including the National Academies of Sciences, Engineering and Medicine (NASEM); the Centers for Disease Control and Prevention (CDC); the National Institute of Dental and Craniofacial Research (NIDCR); the Food and Drug Administration (FDA); the ADA; and others—have expressed concerns about every version of this report, including the third (and purportedly final) version that was due for publication in May 2020.[1]

Enclosed is an analysis reiterating our concerns about NTP's study evaluation methods, the weight given to certain studies, the rationale for publishing some content separately, the integrity of NTP's peer review process, and the manner in which the findings are being communicated. Our concerns are consistent with those expressed by NASEM.[2-3] We ask that our outstanding concerns be adequately addressed prior to the report's publication.

We are also concerned by the possibility, or perhaps the perception, that NTP's report has not been driven by dispassionate scientific inquiry alone. For example, the NTP director who commissioned the report coauthored an editorial implying that the second draft—*which had yet to survive peer review*—was an indictment of community water fluoridation.[4]

One of NASEM's concerns was that the report might be used in such a way, despite its limitations. In fact, NASEM expressly stated the report "cannot be used to draw any conclusions" about low-level fluoride exposures "including those typically associated with

drinking-water fluoridation."[3]

Further, the former NTP director did not disclose that her coauthors have working relationships with the Fluoride Action Network (FAN), an anti-fluoridation political advocacy group.[5,6,7,8,9] All three report drafts reference FAN and its website at least four times.

Also, there was no mention that FAN had (and still has) an active lawsuit alleging the Environmental Protection Agency did not give full and fair consideration to its petition to "prohibit the purposeful addition of fluoridation chemicals to U.S. water supplies."[10] The judge has repeatedly delayed the case for two years, saying he will not issue a ruling until after NTP's report is released.

We note that NTP proposed commissioning its report in 2015[11-12], which is just prior to when FAN petitioned EPA (2016)[13] and subsequently filed its lawsuit (2017)[10]. We would welcome more transparency about whether and how these events may be connected.

At a time when public mistrust in federally funded research is at an all-time high, we urge you to consider whether this report is consistent with the recommendations of the White House Task Force on Scientific Integrity, which President Biden established just seven days after assuming office.[14]

The Task Force reported in January that violations of scientific integrity are relatively small. However, it also called for greater transparency into research processes and better methods of communicating scientific findings to ensure lay audiences have an accurate understanding of science.[15]

Since there is no compelling scientific or public health reason for rushing the report to publication, we urge that the report not be published until NTP resolves the concerns of NASEM, CDC, NIDCR, and FDA, and perhaps consult the National Institute of Child Health and Human Development. We also urge that NTP adhere to the standard practice of including its meta-analysis in the report instead of publishing it separately on a date to be determined.

Thank you for providing us the opportunity to comment. If you have any questions, please contact Mr. Robert J. Burns at (b) (6) or (b) (6)

Sincerely,

(b) (6)

Cesar R. Sabates, D.D.S.
President

(b) (6)

Raymond A. Cohlmia, D.D.S.
Executive Director

CRS:RAC:rjb
Enclosures (3)

cc: ADM Rachel Levine, Assistant Secretary for Health, U.S. Department of Health and Human Services
Dr. Lawrence Tabak, Acting Director, National Institutes of Health
Dr. Rick Woychik, Director, National Institute of Environmental Health Sciences, and Director, National Toxicology Program

[1] National Toxicology Program. May 2022 [Prepublication Draft]. NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review. Office of Health Assessment and Translation, Division of the NTP, National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services.

[2] National Academies of Sciences, Engineering, and Medicine. 2020. *Review of the Draft NTP Monograph: Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*. Washington, DC: The National Academies Press.

[3] National Academies of Sciences, Engineering, and Medicine. 2021. *Review of the Revised NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*: A Letter Report. Washington, DC: The National Academies Press.

[4] Lanphear B, Tilland C, Birnbaum LS. Op-ed: It is time to protect kids' developing brains from fluoride. *Environ Health News*. Oct 07, 2020. https://www.ehn.org/fluoride-and-childrens-health-2648120286/costs-outweigh-benefits (Accessed August 22, 2022)

[5] Fluoride Action Network (August 6, 2020). TSCA Fluoride Trial Witnesses Spotlight [PSA]. https://fluoridealert.org/articles/tsca-fluoride-trial-witness-spotlight/

[6] Fluoride Action Network (October 7, 2020). Former Director of NIEHS Warns Of Neurotoxic Harm From Water Fluoridation [Blog]. https://fluoridealert.org/articles/little-things-matter-fluoride-brain/

[7] Quackwatch (April 9, 2013). A Critical Look at Paul Connett and his Fluoride Action Network [Blog]. https://quackwatch.org/11ind/connett/

[8] Healthy Debate (April 22, 2020). Fluoridation and the 'sciency' facts of critics [Blog]. https://healthydebate.ca/2020/06/topic/fluoridation-and-facts-of-critics/

[9] Open Parachute (April 22, 2020). Author confirms anti-fluoridation activist misrepresentation of her work [Blog]. https://openparachute.wordpress.com/2020/04/22/author-confirms-anti-fluoridation-activist-misrepresentation-of-her-work/

[10] Food & Water Watch, Inc. et al v. Environmental Protection Agency et al (Docket No. 3:17-cv-02162) (N.D. Cal. filed Apr 18, 2017).

[11] 80 FR 60692 (October 7, 2015).

[12] National Toxicology Program. (2015, December 1-2). *Summary Minutes of the NTP Board of Scientific Counslors: Lisa Peterson presiding*. Research Triangle Park, NC: National Institute of Environmental Health Sciences. https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2015/december/bsc_dec2015_minutes_508.pdf.

[13] 82 FR 11878 (February 27, 2017).

[14] The White House, Memorandum on Restoring Trust in Government Through Scientific Integrity and Evidence-Based Policymaking (January 27, 2021).

[15] Scientific Integrity Fast-Track Action Committee of the National Science and Technology Council, Protecting the integrity of Government Science, (January 2022).

ADA American Dental Association®

Scientific/Technical Comments

on the

NTP Monograph on the State of the Science Concerning Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects: A Systematic Review

May 2022 ersion

NTP claims, This review finds, with moderate confidence, that higher fluoride e posure e.g., represented by populations whose total fluoride e posure appro imates or e ceeds the World Health rgani ation Guidelines for Drinking-water uality of 1.5 mg L of fluoride is consistently associated with lower I in children.

NTP s claim is based on 19 publications it deems to have a low risk of bias. Eighteen reported an association between higher fluoride e posure and lower I in children one did not. The 18 publications that reported an association, which include three prospective cohort studies and 15 cross-sectional studies, were conducted in 6 countries outside the nited States Bra il, Canada, China, India, Iran, and Me ico .

Since there is no compelling scientific or public health reason for rushing the report to publication, we urge the panel to

- ecommend that NTP adhere to the standard practice of including its meta-analysis in the report instead of publishing it separately on a date to be determined.

- ecommend that NTP downgrade or upgrade the studies referenced, based on the findings in this analysis. The rationale for downgrading or upgrading each study s bias rating is provided in Table 1 downgrading and Table 2 upgrading .

- ecommend that the report not be published until NTP fully resolves, to their satisfaction, the concerns of NASEM, CDC, NIDC , and DA, and perhaps consult the National Institute of Child Health and Human Development.

- ecommend that NTP clearly state throughout the report that while it recommends further research in this area, the recommendation is not nor should it be construed as an indictment of community water fluoridation at levels recommended by the .S. Public Health Service and the Centers for Disease Control and Prevention.

- ecommend that any and all references to the ha ard conclusions in previous drafts be accompanied by a conte tual statement e plaining why those ha ard conclusions were withdrawn.

Questionable Omission of Meta-Analysis

It is standard practice for a report of this kind to include a meta-analysis. However, NTP did not perform a meta-analysis prior to submitting its first draft for peer review.

In its peer review of the first draft[1], NASEM wrote, The committee notes that NTP did not conduct a meta-analysis. Given that meta-analysis is a useful tool for aggregating and summari ing data and analy ing comparable studies, the committee strongly recommends that NTP reconsider its decision not to perform one. [2]

At NASEM s urging, NTP performed a meta-analysis and included it in its second draft. NASEM took issue with the meta-analysis, however, writing in its second peer review, NTP should e amine the studies included in the meta-analysis in greater depth to determine whether each study properly accounted for its design because not doing so could invalidate the meta-analysis results... The committee strongly recommends that NTP improve the revised monograph by seriously considering the suggestions that are provided in this letter report to improve its clarity and transparency.

It is unclear whether NTP resolved NASEM s concerns about the meta-analysis because NTP abandoned NASEM s line of peer review. Instead, NTP has said, The meta-analysis conducted in association with this systematic review further informs this issue and will be published separately. [5]

We question why NTP is seeking to publish its meta-analysis separately when it is so interlinked with this report. There is no guarantee that it will survive a ournal s peer review or even that a ournal will accept it for publication. It already failed one peer review by NASEM and, based on our understanding, was not accepted for publication in *JAMA Pediatrics*.

urther, NTP left the door open to publishing the meta-analysis on its own without further peer review or even not at all. The May 2022 version of the report implies that the report can stand on its own without a meta-analysis at all. NTP stated[5]

> This state-of-the-science document does not include the meta-analysis of epidemiological studies or ha ard conclusions found in previous draft monographs however, it provides a comprehensive and current assessment of the scientific literature on fluoride as an important resource to inform safe and appropriate use.

Since there is no compelling scientific or public health reason to publish this report quickly, we ask that both the meta-analysis and response to NASEM be included in the final report. Both will add a level of transparency that is currently lacking.

Questionable Risk Bias Ratings

NTP failed to note that all 19 publications it graded as having a low risk of bias are all based on or are among only 11 foundational studies whose **limitations do not warrant a moderate degree of confidence** in the body of evidence see Table 1 .

Bashash M, Thomas D, Hu H, Martine -Mier EA, Sanche BN, Basu N, Peterson E, Ettinger AS, Wright , hang et al. 2017. Prenatal fluoride e posure and cognitive outcomes in Prepublication Draft - Interagency Deliberative Communication 8 children at and 6-12 years of age in Me ico. Environ Health Perspect. 125 9 1-12. https doi.org 10.1289 ehp655

Choi AL, hang , Sun G, Bellinger DC, Wang , ang , Li S, heng , u , Grand ean P. 2015. Association of lifetime e posure to fluoride and cognitive functions in Chinese children A pilot study. Neuroto icol Teratol. 7 96-101.

Ding , Sun H, Han H, Wang W, i , Liu , 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. Ha ard Mater. 186 19 2-19 6.

Green , Lanphear B, Hornung , lora D, Martine -Mier EA, Neufeld , Ayotte P, Muckle G, Till C. 2019. Association between maternal fluoride e posure during pregnancy and I scores in offspring in Canada. AMA Pediatr.E1-E9.

ocha-Amador D, Navarro ME, Carri ales L, Morales , Calderon . 2007. Decreased intelligence in children and e posure to fluoride and arsenic in drinking water. Cad Saude Publica. 2 Suppl S579-587.

Sa ena S, Sahay A, Goel P. 2012. Effect of fluoride e posure on the intelligence of school children in Madhya Pradesh, India. Neurosci ural Pract. 1 -1 9.

Sera B, Shahrabi M, Shadfar M, Ahmadi , allah adeh M, Eslamlu H , hara ifard M . 2012. Effect of high water fluoride concentration on the intellectual development of children in Makoo, Iran. Dent. 9 221-229.

Soto-Barreras , Escalante- illalobos , Holguin-Loya B, Pere -Aguirre B, Nevare - ascon A, Martine -Martine E, Loyola- odrigue P. 2019. Effect of fluoride in drinking water on dental caries and I in children. luoride. 52 7 - 82.

Sudhir M, Chandu GN, Prashant GM, Subba eddy . 2009. Effect of fluoride e posure on intelligence quotient I among 1 -15 year old school children of known endemic area of fluorosis, Nalgonda District, Andhra Pradesh. Indian Assoc Public Health Dent. 2009 1 88-9 .

Trivedi M, Sangai N, Patel , Payak M, yas S. 2012. Assessment of groundwater quality with special reference to fluoride and its impact on I of schoolchildren in si villages of the Mundra egion, achchh, Gu urat, India. luoride. 5 77- 8 .

u , Chen , Li , Liu H, Hou C, eng , Cui , hao L, Li P, hou et al. 2018. Threshold effects of moderately e cessive fluoride e posure on children s health A potential association between dental fluorosis and loss of e cellent intelligence. Environ Int. 118 116-12 . https doi.org 10.1016 .envint.2018.05.0 2

or one study a pilot study of 51 children Choi, et. al 2015 the sample si e is too small to warrant a low risk of bias rating. Two prospective secondary analysis studies Bashash et al. 2017 and Green et al. 2019, use an invalid biomarker spot maternal urinary fluoride as a pro y for measuring fetal fluoride e posure. sing an invalid biomarker alone warrants a rating of low or no confidence.

Had Green et al. 2019 assessed the validity of this biomarker, they would have found that Thomas et al. 2016 reported lack of association between spot maternal urinary fluoride and maternal plasma fluoride in their multiple regression analysis. The Spearman coefficient was

0.29 in first trimester and -0.2 in third trimester. In fact, Thomas et al. 2016 found maternal plasma fluoride levels to be some 0 times lower than urinary fluoride levels.

Eight of the 11 are cross-sectional studies of endemic fluorosis areas. Cross-sectional study design cannot rule out reverse causality in endemic fluorosis areas. As stated in Guth et al. 2021

> It is possible that parents with higher I read or inform themselves about the possible health ha ards to children, and therefore avoid fluoride e posure. In this case, high maternal parental intelligence which is correlated with children s I would be causally linked to lower fluoride e posure rather than high fluoride e posure causing lower intelligence in children.

E cept for u et al. 2018, these studies also rely on non-probability convenience or purposive sampling of endemic fluorosis areas, as well as statistical operations that rely on randomness for their validity e.g., hypothesis testing or linear regression . These studies, which are based on questionable methods, are of insufficient quality to warrant a low risk of bias rating.

The remaining eight low level of bias publications are various forms of analyses of the 11 foundational studies noted above. nfortunately, the authors made no effort to validate the data in the 11 foundational studies, or to scrutini e the analytical methods used for the findings.

or e ample, the initial confidence is based on comparison of the groups used. Many studies from high fluoride areas do not provide sufficient data to support this key criterion.

Notwithstanding other limitations see Table 1 , these eight publications are **too sufficiently flawed to warrant moderate confidence** in the body of evidence.

Cui , u , hang B, Guo B, Gao T, Liu H. 2020. The relationships between thyroid-stimulating hormone and or dopamine levels in peripheral blood and I in children with different urinary iodine concentrations. Neurosci Lett. 729 1 981. https doi.org 10.1016 .neulet.2020.1 981

Cui , hang B, Ma , Wang , hao L, Hou C, u , hao , hang , Nie et al. 2018. Dopamine receptor D2 gene polymorphism, urine fluoride, and intelligence impairment of children in China A school-based cross-sectional study. Ecoto icol Environ Saf. 165 270-277. https doi.org 10.1016 .ecoenv.2018.09.018

Till C, Green , lora D, Hornung , Martine -Mier EA, Bla er M, armus L, Ayotte P, Muckle G, Lanphear B. 2020. luoride e posure from infant formula and child I in a Canadian birth cohort. Environ Int. 1 105 15. https doi.org 10.1016 .envint.2019.105 15

Wang G, Gao M, hang M, ang M, iang . 2012. Correlation between total fluoride intake and children s I . Southeast niv Med Ed.7 -7 6.

Wang M, Liu L, Li H, Li , Liu H, Hou C, eng , Li P, hao , Dong L et al. 2020b. Thyroid function, intelligence, and low-moderate fluoride e posure among Chinese school-age children. Environ Int. 1 105229. https doi.org 10.1016 .envint.2019.105229

iang , Liang , Chen B, Chen L. 2011. Analysis of children s serum fluoride levels in relation to intelligence scores in a high and low fluoride water village in China. luoride. 191-19

iang , Liang , Chen L, Wang C, Chen B, Chen , hou M. 200 a. Effect of fluoride in drinking water on children s intelligence. luoride. 6 8 -9 .

hang S, hang , Liu H, u W, Guan , eng , iang C, Gao H, hang C, Lei et al. 2015b. Modifying effect of C MT gene polymorphism and a predictive role for proteomics analysis in children s intelligence in endemic fluorosis area in Tian in, China. To icol Sci. 1 2 8-2 5.

Factors for Potential Downgrading

Risk of bias. ut of the ten studies, nine used a non-probability convenience sample. nly one study u et al. 2018 sampled more than ten villages towns cities, which should decrease confidence in the body of evidence. The community-level effect was not adequately addressed in any of the studies. ften, the e posure measure is one or two samples of spot urinary fluoride with or without ad ustment for urinary dilution. This is not a valid measure of long-term fluoride e posure. nly one study Bashash et al. 2017 ad usted for maternal I .

Unexplained inconsistency. Previous meta-analyses have shown substantial une plained heterogeneity. Duan et al. 2018 conducted a meta-analysis of standardi ed mean difference in I scores between higher water fluoride communities Mean .7 mg L and normal fluoride communities Mean 0.6 mg L . The summary results indicated high water fluoride e posure was associated with lower intelligence levels standardi ed mean difference -0.52 95 CI -0.62 to -0. 2 P 0.001 . However, there was substantial heterogeneity I^2 69.1 P 0.001 . The authors were unable to e plain the source of heterogeneity. Studies conducted after 201 show that the effect si es are smaller and not statistically significant, including Green et al. 2019 and Bashash et al. 2017.

There are also inconsistencies within the same study. or e ample, Green et al. 2019 the Maternal-Infant esearch on Environmental Chemicals study, or MI EC reported a differential effect such that the association between maternal urinary fluoride M and I was found only in boys. However, Till et al. 2020 stated that M was not statistically significant either in boys or girls once postnatal fluoride was added to the model. armus et al. 2021 reported that fluoride e posures during any trimester, average across all trimesters, infancy, and childhood was not significantly associated with I outcomes after city was controlled and correction for multiple testing was applied. While Bashash et al. 2017 reported a threshold at 0.8 mg L M ages 6-12 years , Thomas et al. 201 found no evidence of a detectable adverse outcome on offspring ages 1- years neurobehavioral development associated with maternal fluoride e posure during pregnancy.

Imprecision. As NASEM observed in its second review , the standard errors are underestimated.

f most concern are the studies that used fluoride concentration measured at the community level as the e posure see, for e ample, Sera et al. 2012 , Till et al. 2020 , Trivedi et al. 2012 , and Wang et al. 2012 . When everyone in a community is sub ect

> to the same e posure, the standard error of the difference in means between high-e posure and low-e posure groups increases multiplicatively by the square root of a variance inflation factor I equal to 1 n - 1 r , where n is the number of persons in each community and r is the correlation in outcomes such as I score between members of the same community Murray 1998 Donner and lar 2000 eng et al. 2001 . The same phenomenon occurs in randomi ed control trials that assign treatment to groups of persons. Thus, unless within-community clustering is accounted for in the analysis for e ample, through a random effects model standard-error estimates will be too small and confidence intervals CIs too narrow or individual-level e posures, such as urinary fluoride concentration, the I is probably smaller than one would see for community level e posures because some communities might contain people in multiple e posure groups. However, it is still important to account for clustering in the analysis because one would e pect most people in a community to be in the same e posure group.

Please note that when the average cluster si e is large e.g., n 66 in Green et al. 2019 , even an interclass correlation coefficient of 0.2 will greatly impact I .

Publication bias. There is evidence of publication bias. or e ample, the Thomas et al. 201 thesis that showed a beneficial effect of fluoride e posure in the Early Life E posures in Me ico to Environmental To icants ELEMENT is not published. Another e ample is that Green et al. 2019 do not discuss the lack of effect of M on SI in their paper. armus et al. 2021 removed the sentence, However, e posures do not significantly associate with I outcomes once city is controlled and D is applied, which was in a pre-print from the final publication.

Misleading Statements about Lower Level Fluoride Exposures

As a science-based organi ation, the ADA welcomes calls for high quality research into any potential health effects of fluoride e posure, even at the lower levels the Centers for Disease Control and Prevention recommends for community water fluoridation 0.7 mg L . However, we dispute NTP s use of statements whose lack of conte t would leave a lay reader to misinterpret the state of the science on associations between *lower* total fluoride e posure and children s I .

or e ample

> Associations between lower total fluoride e posure e.g., represented by populations whose total fluoride e posure was lower than the WH Guidelines for Drinking-water uality of 1.5 mg L of fluoride WH 2017 and children s I **remain unclear**.
>
> More studies are needed to fully understand **the potential for** lower fluoride e posure to affect children s I .
>
> More studies at lower e posure levels are needed to fully understand **potential associations** in ranges typically found in the nited States i.e., 1.5 mg L in water . However, it should be noted that, as of April 2020, CWS supplying water with ≥1.5 mg/L naturally occurring fluoride served 0.59 of the .S. population 1.9 million people CDC Division of ral Health 2020 .

This state-of-the-science document does not include the meta-analysis of epidemiological studies or **hazard conclusions found in previous draft monographs** however, it provides a comprehensive and current assessment of the scientific literature on fluoride as an important resource to inform safe and appropriate use.

Based on the qualitative review of these studies, the evidence of an association between fluoride e posure below 1.5 mg L and lower I in children appeared less consistent than results of studies at higher e posure levels.

T he ma ority of the available studies in both analyses compare populations with high fluoride e posure to those with lower fluoride e posure with the lower e posure levels frequently in the range of drinking water fluoridation in the nited States . The meta-analysis conducted in association with this systematic review further informs this issue and will be published separately.

This state-of-the-science document does not include the meta-analysis of epidemiological studies or ha ard conclusions found in previous draft monographs however, it provides a comprehensive and current assessment of the scientific literature on fluoride as an important resource to inform safe and appropriate use.

These and other stand-alone statements could lead a lay reader to conclude that no high-quality research on lower level fluoride e posure e ists, or that the e isting literature is too weak for any conclusions to be drawn. That is not accurate. In fact, the following high quality studies actually refute the claim that lower level e posures impact I levels.

Aggeborn L, hman M. The effects of fluoride in drinking water. ournal of Political Economy. 2021 129 2 65- 91. doi 10.1086 711915

Do LG, Spencer A , Sawyer A, et al. Early childhood e posures to fluorides and child behavioural development and e ecutive function A population-based longitudinal study. Accepted for publication in the ournal of Dental esearch.

armus L, Till C, Green , et al. Critical windows of fluoride neuroto icity in Canadian children. *Environmental Research*. Published online 2021 111 15. doi 10.1016 .envres.2021.111 15

Ibarlu ea , Gallastegi M, Santa-Marina L, et al. Prenatal e posure to fluoride and neuropsychological development in early childhood 1-to years old children. Environmental esearch. Published online ctober 2021.

u , An N, Huang H, et al. luoride e posure and intelligence in school-age children evidence from different windows of e posure susceptibility. BMC Public Health. 2020 20 1 1657-166 .

If NTP is intent on making statements about what is known or not known about potential neurodevelopmental and cognitive health effects of low-level fluoride e posures, it should

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The NTP notes, NTP is aware that this study was published after April 2021 Ibarlu ea et al. 2021 and, therefore, is not included in this monograph because it is beyond the dates of the literature search The study will be e amined as part of the NTP meta-analysis, which is being prepared as a separate report for publication.

provide a complete account of the research that has been done to prevent the lay reader from drawing inaccurate conclusions.

NTP should clearly state throughout the document that while it recommends further research on lower level fluoride e posures, which the ADA supports, the recommendations in this report are not nor should they be construed as an indictment of community water fluoridation at levels recommended by the .S. Public Health Service and the Centers for Disease Control and Prevention. NASEM recommended the same in its review of NTP s revised draft monograph

> NTP did not conduct a formal dose-response assessment that could inform a discussion on water fluoridation. NTP needs to state clearly that the monograph is not designed to be informative with respect to decisions about the concentrations of fluoride that are used for water fluoridation. That point should be reiterated at the end of the monograph with some indication that the monograph does not draw any conclusions regarding drinking-water fluoridation or other fluoride sources, such as toothpaste or other dental treatments T he conte t into which the monograph falls calls for much more carefully developed and articulated communication on this issue.

urther, any and all references to ha ard conclusions found in previous draft monographs [5] should be accompanied by a clear follow-up statement indicating why those ha ard conclusions were withdrawn.

Transparency

We are concerned by the possibility, or perhaps the perception, that NTP s report has not been driven by dispassionate scientific inquiry alone. or e ample, the NTP director who commissioned the report coauthored an editorial implying that the unpublished second draft *which had yet to survive peer review* was an indictment of community water fluoridation. She stated, fluoride is to ic to the developing brain at levels routinely found in the general population .[6]

The NTP director s editorial was accompanied by an online video containing unsubstantiated claims that the practice of community water fluoridation lowers population I .[7] It was produced by her coauthor, who was the principal investigator of the Green et al. 2019 . That study is heavily favored in NTP s report. The study s questionable grading is addressed in Table 1

The NTP director s coauthor also has a working relationship with the luoride Action Network AN , an anti-fluoridation political advocacy group.[8,9,10,11,12] He was the first witness to testify on AN s behalf during an active lawsuit alleging the Environmental Protection Agency did not e ercise due diligence when reviewing a petition to ban the practice nationwide.[8,1]

The udge has repeatedly delayed AN s lawsuit for two years, saying he will not issue a ruling until after NTP s report is released.

We note that NTP proposed commissioning its report in 2015[1 -15], which is ust prior to when AN petitioned EPA 2016 [16] and subsequently filed its lawsuit 2017 [1] .

We question whether a desire to influence the AN lawsuit may be driving NTP s timeline. We question whether it compelled NTP to change peer reviewers multiple times. We question whether it led NTP to leave out critical elements, like its meta-analysis. And we question

whether it led NTP to publish its response to the NASEM committee s recommendations in a separate document instead of including it in the report itself.[5]

We would welcome more transparency about whether and how these events may be connected.

CDC hailed community water fluoridation as one of ten great public health achievements of the 20th century.[17-18] The Community Preventive Services Task orce reaffirmed this determination in 201 by updating its recommendation for water fluoridation, based on strong evidence of effectiveness in reducing tooth decay dental caries across populations.[19] It is a safe and ine pensive way to reduce tooth decay by at least 25 percent in the population.[20]

It would be a shame to distract from over 75 years of public health success over a misleading analysis of studies conducted outside the nited States.

Again, the ADA welcomes calls for high quality research into any potential health effects of fluoride e posure, even at the lower levels the Centers for Disease Control and Prevention recommends for community water fluoridation 0.7 mg L . However, we urge NIEHS to be more e plicit about its research design parameters for future studies.

Better design parameters would reinforce the need for investigators to acknowledge the limitations of their analyses e.g., convenience sampling, secondary bio-bank data analysis, e posure and outcome measures without validation, lack of statistical rigor, etc. . It would also reinforce the need for federally funded research to be an ob ective, dispassionate endeavor.

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Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Bashash 2017	NTP rated this study as having a low risk of bias. However, the study relies on spot maternal urinary fluoride—an invalid biomarker—as a proxy for measuring fetal fluoride exposure. Using an invalid biomarker alone warrants a rating of low (or no) confidence. The low risk of bias rating is not justified and the rating should be downgraded. This cohort study is based on a convenience sample drawn from multiple hospitals (clusters) in Mexico. Study results based on convenience sampling cannot be used to draw inferences. Spot maternal urinary fluoride is the proxy for fetal exposure. However, Thomas et al. 2016 showed a weak correlation between urinary F and plasma F. There was no association between urinary fluoride and plasma fluoride in a multiple regression analysis. Not a valid biomarker. The source of F is salt. Therefore, the higher fluoride exposure is confounded by higher salt intake, which is associated unhealthy diet and poor pregnancy outcomes. The authors did not assess whether the lower IQ is due to an unhealthy diet. Cantoral et al. 2021 cited this as a limitation in their analysis of the ELEMENT data. The authors did not account for clustering resulting from samples drawn from hospitals. The study is not compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) research methodology, which is a best practice for studies of this kind. To avoid bias, or even the perception of bias, an independent, STROBE-compliant analysis of the MIREC and ELEMENT data is warranted. Selective reporting: This study should receive a definitely high risk of bias rating for selective reporting because it excluded the positive findings associated with fluoride exposure from the Thomas et al. 2014 dissertation that analyzed the same ELEMENT cohorts.

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Choi 2015	NTP rated this study as having a low risk of bias. However, the sample size is too small to justify a low risk of bias rating. The study also relies on unrelated exposure variables. The low risk of bias rating is not justified and the rating should be downgraded. This is a pilot study of 51 students in China. The authors also used dental fluorosis as an exposure variable, which is a *postnatal* phenomenon. Dental fluorosis of primary teeth is extremely rare, even in endemic fluorosis areas.
Cui 2018 Cui 2020 Zhang 2015 Yu 2018 Wang 2020b	NTP rated these studies as having a low risk of bias. However, the study designs (cross sectional) do not account for reverse causality, which is likely in these cases. The low risk of bias ratings are not justified and the ratings should be downgraded. These publications are from a more extensive study of 2886 resident children, aged 7 to 13 years, randomly from endemic and non-endemic fluorosis areas in Tianjin, China (Yu et al. 2018). Used a complex survey design (stratified sampling of clusters from endemic and non-endemic fluorosis areas). Cui et al. 2018, Cui et al. 2020, and Zhang et al. 2015, selected a subset of schools based on IQ scores and F levels, leading to selection bias. The authors did not account for the complex survey design. Therefore the standard errors are underestimated, and there is a possibility of Type 1 error. Exposure measure is a spot urinary fluoride of unproven validity. NTP highlighted only the statistically significant results but left out the results that did not show statistically significant results. Yu et al. 2018 showed a threshold effect such that there is no effect of fluoride on IQ below 3.4 mg/L fluoride in water (B=−0.04 (−0.33, 0.24)) or below 1.6 mg/L urinary F (B=0.36 (−0.29, 1.01)).

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Ding 2011	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This is a cross-sectional study in Inner Mongolia, China. The authors selected schools from 4 sites in endemic and nonendemic fluorosis areas. The authors did not account for the cluster sampling design. The standard errors are therefore underestimated. NTP rated a high risk of bias for confounding. The regression equation included only age. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias.

Green 2019 Till 2020	NTP rated these studies as having a low risk of bias. However, the studies rely on spot maternal urinary fluoride an invalid biomarker as a pro y for measuring fetal fluoride e posure. NTP also lists this as a prospective cohort study however, there is only one I measurement. There are also inconsistencies in the results of these two studies. The low risk of bias ratings are not ustified and the ratings should be downgraded. ***Green et al. (2019).*** Green et al. 2019, relies on an invalid biomarker spot maternal urinary fluoride as a pro y for measuring fetal fluoride e posure. sing an invalid biomarker alone warrants a rating of low or no confidence. Had Green et al. 2019 assessed the validity of this biomarker, they would have found that Thomas et al. 2016 reported lack of association between spot maternal urinary fluoride and maternal plasma fluoride in their multiple regression analysis. The Spearman coefficient was 0.29 in first trimester and -0.2 in third trimester. In fact, Thomas et al. 2016 found maternal plasma fluoride levels to be some 0 times lower than urinary fluoride levels. Also, the convenience sample in Green et al. 2019 was drawn from seven hospitals in si cities clusters in Canada, creating a hierarchical data structure. The statistical analysis did not adequately take into account the city-level effect. I varied by as much as 8 points between the non-fluoridated cities of ancouver and ingston page 0, Green 2018 Master s Thesis . A single staff person from each study site administered in-person I assessments. Thus, the assessor was matched to the city. This would be considered a fatal flaw in any CT or case-control study. Additionally, the Green et al. 2019 study is not compliant with the Strengthening the eporting of bservational Studies in Epidemiology ST BE research methodology, which is a best practice for studies of this kind. To avoid bias, or even the perception of bias, an independent, ST BE-compliant analysis of the MI EC and ELEMENT data is warranted. In its peer review of NTP s second draft, NASEM reported[1] In the case of Green et al. 2019 , NTP learned from the investigators that accounting for city-level clustering via a random-effects model showed similar results to the main model. More details should be provided regarding the similarity of results because although overall conclusions might not have

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
	changed, the results of the meta-analysis could be affected by incorrect exposure-effect or standard-error estimates. The Canadian Agency for Drug and Technologies in Health—analyzed the Green et al. (2019) study and determined a high risk of bias in the study[2]: The study by Green et al., 2019 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... Between nonfluoridated and fluoridated maternal exposure (assessed by MUF_{SG} or daily fluoride intake), the difference in mean FSIQ in total children (108.07 ± 13.31 versus 108.21 ± 13.72) was minimal. The average FSIQ in boys in the non-fluoridated and fluoridated groups were 106.31 ± 13.60 and 104.78 ± 14.71, respectively, and in girls were 109.86 ± 12.83 and 111.47 ± 11.89, respectively. According to the WPPSI test scoring, these numbers were considered as normal, as a score of 90 to 109 represents average intelligence. Given that these values were available during data collection period, it was unclear about the authors' rationale to further explore the associations between maternal fluoride exposure and children's IQ. Indeed, adjusted estimates with a limited set of covariates showed no statistically significant association between an increase of 1 mg/L in MUFSG and FSIQ, PIQ or VIQ in all children. These were not discussed or considered when formulating the conclusion. Health Canada also evaluated Green et al. (2019) and concluded[3]: The authors identified limitations in the study and where possible implemented measures to reduce their impact. However, a number of uncertainties remain (e.g., estimation of prenatal fluoride exposure, other unmeasured factors affecting child IQ) which limit this study's ability to confirm a causal relationship between prenatal fluoride and deficits in child IQ. The CADTH and Health Canada evaluations are appended to this document. ***Till et al. (2020).*** Till et al. 2020 reported that after postnatal exposure was introduced into the model, maternal urinary fluoride was not associated with FSIQ in boys or girls. The authors found two outliers in the same cohort, and the association became non-significant when two outliers were removed.

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Rocha-Amador 2007	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This cross-sectional study of 132 children of age 6-10 was conducted in areas of Brazil where mean levels of Arsenic in water were 17 and 19 times higher than WHO limits in Salitral (mean F level in water 5.3 mg/L) and 5 de Febrero (9.4 mg/L F), respectively. However, it was not included in the regression model. While height for age was included in the model, age was not. Mothers' education levels differed among the three areas with low fluoride community with the highest level of education. This community-level effect was not controlled. Therefore, NTP noted that the results might still be biased. NTP rated this study as having a probably high risk for bias for selective reporting. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias.
Saxena 2012	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This is a cross-sectional study of 120 children in India from 3 endemic areas, and 50 children from 1 non-endemic area were included in the analysis. The mean urinary fluoride level in the non-endemic areas was 2.25 mg F/L which is about three times higher compared to a fluoridated area. NTP correctly noted that the author's use of linear regression for an ordinal IQ outcome with five levels was inappropriate. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias. Similarly, the authors used ANOVA for socioeconomic status and other variables measured with an ordinal scale. This alone should have received a high risk of bias rating.

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Seraj 2012	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This cross-sectional study of 293 6-11 year-old children in Iran from five selected rural areas. The authors state that these areas were similar in their general demographic and geographic characteristics, with the inhabitants having a comparable socioeconomic status and similar occupations. However, there is no data to support the comparability of areas. NTP somehow found indirect evidence of comparability. NTP rated probably high risk of bias for exposure assessment. The authors did not provide data to indicate that the mean was representative of the fluoride levels over 12 years and throughout the village. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias. The statistical analysis is also difficult to comprehend.
Soto-Barreras 2019	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This is a cross-sectional study of 161 children aged 9 to 10 years of age from Chihuahua, Mexico. NTP rated probably high risk of bias for confounding and water fluoride exposure. There was no adjustment for clustering at the school level or the sampling design. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias. Still, the authors themselves report that they did not find a relationship between fluoride exposure and IQ.

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Sudhir 2019	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This is a cross-sectional study of exactly 1000 children of 13 to 15 years of age from Nalgonda district (Andhra Pradesh), India. NTP rated probably high risk for bias for the outcome because no information was provided to indicate that the methods were reliable and valid in this study population, and lack of blinding. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias. Clustering of children within the four areas was not accounted for in the analysis; About 70% of children in the low exposure group were in the below-average intelligence grade. The authors did not consider a multivariate analysis.
Trivedi 2012	NTP rated this study as having a low risk of bias. However, the study design (cross sectional) does not account for reverse causality, which is likely in this case. The low risk of bias rating is not justified and the rating should be downgraded. This is a cross-sectional study of 84 children from Gujarat, India. NTP noted insufficient information on the sampling methods to determine whether the populations were similar. NTP also noted a probably high risk of bias rating for statistical analysis. "Area-level exposures were used. There was no accounting for the clustering of children within the villages, and comparative analyses did not account for covariates. Urinary fluoride was not considered in the comparative analyses. The lack of individual exposure levels and the lack of accounting for clustering are likely to bias the standard error of the difference in mean IQ levels between the high- and low-fluoride villages and make the differences appear stronger than they actually are." If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias.

Table 1: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Downgrading)

Study	*Rationale for Potential Downgrading*
Xiang 2003 Xiang 2011 Wang 2012	NTP rated these studies as having a low risk of bias. However, the study designs (cross sectional) do not account for reverse causality, which is likely in these cases. The low risk of bias ratings are not justified and the ratings should be downgraded. This is a cross-sectional study of 512 children aged 8-13 years from Wamiao (severe endemic fluorosis) and Xinhua (non-endemic) villages in Sihong County, Jiangsu Province, China. According to the authors, these "villages are situated in isolated low-income areas with less economic development and a relative lack of communication with the outside world, resulting in poor living conditions for the majority of the residents, especially the elderly and children." The two villages are not comparable concerning the education of parents. The proportion of parents with senior high school education was 13.5% in Wamiao and 41.7% in Xinhua. NTP noted that a potential concern raised by the NASEM (2020) committee's review was the lack of accounting for relationships in exposure between persons from the same village. Given only two villages were included and the analyses consisted of village-level comparisons (no use of individual-level covariate data), it is likely that the standard error of the difference in mean IQ between fluoride in water exposure groups will be biased, making differences appear stronger than they actually are. Without controlling for village effects and given the large differences in fluoride concentrations and IQ levels between villages, the apparent dose-response relationship could be due to a village effect in addition to a fluoride effect. If a study is at high risk of bias for one item, then the overall rating should also be high-risk of bias.

Table 2: Concerns about NTP's Assessment of Confidence in the Body of Evidence (Upgrading)

Study	*Rationale for Potential Upgrading*
Broadbent 2015	NTP rated this study as having high risk of bias, citing that the authors did not account for other sources of fluoride in non-fluoridated areas. The high risk of bias rating is questionable, however, because NTP did not seek clarification from the authors in the same matter it did with the authors of other studies. The study should be given full and fair consideration. The oversight led the authors to file their own response in a letter to the editor of the American Journal of Public Health: "In the Dunedin [New Zealand] Study cohort, the majority of children who took fluoride tablet supplements did so intermittently and for only a short period of time. We have now estimated average total fluoride intake in our cohort up to age five years, including tablets, toothpastes, and dietary sources. We identified no differences in IQ in childhood or adulthood by total fluoride intake, but we did identify significantly fewer dental caries in both childhood and adulthood among those with higher estimated fluoride intake up to age five years." [Source: Broadbent JM, W. Thomson WM, Moffitt TE, Poulton R, "Broadbent et al. Respond", American Journal of Public Health 105, no. 4 (April 1, 2015): pp. e3-e4. DOI: 10.2105/AJPH.2015.302647]

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CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Community Water Fluoridation Exposure: A Review of Neurological and Cognitive Effects

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Abbreviations

CI	Confidence interval
CWF	Community water fluoridation
FSIQ	Full Scale IQ
HOME	Home Observation for Measurement of the Environment
HTA	Health technology assessment
IQ	Intelligence quotient
MA	Meta-analysis
MIREC	Maternal-Infant Research on Environment Chemicals
MUF	Maternal urine fluoride
NR	Not reported
PIQ	Performance IQ
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic review
VIQ	Verbal IQ

Context and Policy Issues

In Canada, community water fluoridation (CWF) is the process of monitoring and controlling fluoride levels (by adding or removing fluoride) in the public water supply to reach the optimal level of 0.7 part per million (ppm) and not to exceed the maximum concentration of 1.5 ppm, as recommended in the 2010 *Health Canada Guidelines for Drinking Water Quality*.[1] CWF has been identified as a cost-effective method of delivering fluoride to the population and reducing dental caries in children and adults.[2,3] The Centers for Disease Control and Prevention recognized CWF as one of 10 great public health achievements of the 20th century because of its contribution to the prevention of tooth decay and improvement in oral health over the past 70 years.[4] CWF is endorsed by over 90 national and international governments and health organizations around the world.[5,6]

Despite the endorsement of governments and health organizations, and a large body of empirical evidence on the preventive effect of CWF on dental caries, a number of municipalities across Canada have not implemented or have discontinued water fluoridation.[7] In 2017, 38.7% of the Canadian population were exposed to community water systems having recommended optimal fluoride levels to protect their teeth.[7] Different factors contributed to CWF cessation including concerns about the potential harmful side effects of water fluoride to human health, including fluorosis, skeletal fractures, cancer, reproduction and development, thyroid function, and children's intelligence quotient (IQ).[1]

Multiple studies have been published showing that exposure to higher levels of fluoride in drinking water may be associated with lower intelligence among children.[8-11] However, the generalizability of the findings from those studies to the Canadian context is unlikely given they were conducted in rural areas and areas of low socioeconomic status in countries, such as China, India, Iran, or Mexico, which also include other sources of fluoride such as fluoridated salts or naturally occurring water fluoride levels that are many folds higher than the current Canadian levels.[8-11] Multiple methodological limitations were identified in these studies including the lack of control for important confounding variables such as exposure to known neurotoxicants (e.g., lead, arsenic, or iodine), socioeconomic status, nutritional status, and parental education that could be related to fluoride exposure and also potentially affect children's IQ.[12] The CADTH CWF Review of Dental Caries and Other Health Outcomes reviewed studies from countries with comparable water fluoride levels and socioeconomic parameters, and found no evidence for an association between water fluoridation at recommended Canadian levels and IQ or cognitive function.[12] A study published by a group of researchers in Canada and the US after the CADTH HTA concluded that exposure to higher levels of fluoride during pregnancy is associated with lower IQ scores in children aged 3 to 4 years in Canada.[13] The findings of that study prompted a further review on this topic.
The aim of this report is to review recent evidence on the effects of fluoride exposure through CWF at levels that are relevant to the Canadian context on the neurological or cognitive development in children and adolescents less than 18 years of age.

In this report, gender-neutral language has been used where possible in order to be inclusive of all gender identities. When reporting results from the published manuscript, gender-neutral language was not used in order to be consistent with the terms used in the source material.

Research Question

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Key Findings

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's intelligence quotient scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in mother urine fluoride and Full Scale intelligence quotient score in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in mother urine fluoride and performance intelligence quotient or verbal intelligence quotient in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with a 4.49 point lower intelligence quotient score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's intelligence quotient score. The interaction between child sex and maternal fluoride intake was not statistically significant. 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.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were water fluorination and children (<18 years). No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and September 13, 2019. The search dates were selected to identify information published subsequent to a previous search for the CADTH CWF Review of Dental Caries and Other Health Outcomes.[12]

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Persons less than 18 years of age (including *in utero*)
Intervention	Natural or artificial water fluoridation (range between 0.4 ppm to 1.5 ppm with the optimal level being 0.7 ppm)
Comparator	No water fluoridation, low fluoride level (< 0.4 ppm), or different fluoride levels in drinking water
Outcomes	Neurological (e.g., neurotoxicity) or cognitive outcomes (e.g., Intelligence Quotient)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2017. Primary studies were also excluded if they had been included in the recent CADTH HTA report on CWF.[12]

Critical Appraisal of Individual Studies

The methodological quality (i.e., internal and external validity) of the included non-randomized study was assessed using the National Institute for Health and Care Excellence (NICE) checklist.[14] Summary scores were not calculated for the included study; rather, a review of the strengths and weaknesses were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 302 citations were identified in the literature search. Following screening of titles and abstracts, 294 citations were excluded and eight potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publication was retrieved from the grey literature search. Of the eight potentially relevant articles, seven publications were excluded for various reasons, while one study met the inclusion criteria and was included in this report. **Appendix 1** presents the PRISMA flowchart[15] of the study selection.

Summary of Study Characteristics

The characteristics of the identified study (Table 2) are presented in Appendix 2.

Study Design

The identified study was a prospective, multicentre birth cohort study,[13] which acquired data and frozen urine samples from the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) program. Maternal urine fluoride (MUF) concentrations were measured in urine spot samples collected at each trimester of gestation and adjusted for specific gravity (MUF_{SG}). Information regarding pregnant persons' consumption of tap water and other beverages such as tea and coffee was obtained using a self-reported questionnaire. The water fluoride concentrations in the areas where persons resided during pregnancy were estimated based on the levels of fluoride in the municipal water reported by waste water treatment plants and persons' postal code. Daily fluoride intake was estimated based on a combination of the above measures. IQ of children was assessed once at ages of three to four years.

Country of Origin

The identified study[13] was conducted by authors in Canada and the US.

Population

The MIREC study recruited 2,001 pregnant persons within the first 14 weeks of pregnancy from 10 Canadian cities. A subset of mother-child pairs (n = 610) from six of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were recruited for the measurement of children's IQ. Of 610 children, 601 had complete IQ data. Of 601 mother-child pairs, 369 had complete exposure and covariate data and drink tap water or live in a water treatment zone and were thus included in an analysis of the association between MUF and children's IQ. Further, 400 mother-child pairs had complete data and drink tap water or live in a water treatment zone and were included in a second analysis of the association between daily fluoride intake and children's IQ. Thus, 39.5% and 34.4% of the initial sample (n = 610) were excluded from the first and second analyses, respectively, due to missing data or ineligible exposure.

The mean age of pregnant persons at the time of recruitment was 32.3 years, and mean age of children at IQ testing was 3.4 years. Fifty two percent of children were female. Other characteristics of mothers and children are shown in Table 2 of Appendix 2.

Interventions and Comparators Mean MUF_{SG} value of the total sample of pregnant persons was 0.51 mg/L. The mean MUF_{SG} values of non-fluoridated and fluoridated groups were 0.40 mg/L and 0.69 mg/L, respectively.

Mean daily fluoride intake value of the total sample of pregnant persons was 0.54 mg. The mean daily fluoride intake values of non-fluoridated and fluoridated groups were 0.30 mg and 0.93 mg, respectively.

The average community fluoride level of areas of total sample of pregnant persons was 0.31 ppm. The mean water fluoride levels in the non-fluoridated and fluoridated areas were 0.13 ppm and 0.59 ppm, respectively.

Outcomes

The primary outcome was full scale IQ (FSIQ), a measure of global intellectual functioning, assessed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III).[16] Verbal IQ (VIQ), a measure of verbal reasoning, and performance IQ (PIQ), a measure of non-verbal reasoning, spatial processing and visual-motor skills, were also assessed. The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range. An overall intelligence score between 90 to 109 with a standard deviation of 15 is considered as average.[16,17] The reliability coefficients for WPPSI-III composite scales range from 0.89 to 0.95[16,17] [Reliability coefficient values range from 0.00 (significant error – no reliability) to 1.00 (no error – perfect reliability), and are used to indicate the amount of error in the scores]. The associations between children's IQ and maternal fluoride exposure (e.g., MUF, daily fluoride intake, water fluoride level) were estimated using linear regression analyses.

Summary of Critical Appraisal

The assessment of the methodological quality of the identified study is presented in Table 3 of Appendix 3.

Strengths

The identified study[13] was conducted in Canada with a well described source population.

The study assessed maternal fluoride exposure using a combination of mother urine fluoride, daily fluoride intake, in areas with or without fluoridation.

The study used linear regression analyses with two main measures of fluoride exposure (i.e., maternal fluoride urine and daily fluoride intake) to estimate the association between maternal fluoride exposure and children's IQ. Test statistics and associated *P* values were reported for all analyses.

The study analyzed mother urine fluoride concentration using established methods that were previously published. Children's' IQ (i.e., full scale IQ, verbal IQ and performance IQ) was assessed using a well-established method (i.e., the Wechsler Preschool and Primary Scale of Intelligence, third Edition).

Weaknesses

The recruitment of participants was not defined. It was unclear how 6 of 10 cities (Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax) were chosen. The authors stated that, due to budgetary restraints, those cities were chosen as most participants fell into the age range required. While there was minimal difference between the MIREC sample, the sample of persons included in the analyses and the sample of persons who had incomplete MUF data, the study did not describe the method of selection of participants from the eligible population. There was no report on the percentage of selected individuals who agreed to participate. Thus, there is a potential risk of bias in selection of participants into the study.

The study did not clearly pre-define the level of fluoride exposure that was considered as low or high at start of the study. As participants were not randomly assigned to level of fluoride exposure at the beginning of the study, mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after maternal fluoride exposure was determined by a combination of maternal urine fluoride, daily fluoride intake and community water fluoride concentrations. This approach, together with the knowledge of children's IQ, might have affected the classification of exposure status of the mothers. The study did not report the period of fluoride exposure. Some persons might have a lifetime exposure, while others might just have exposure during pregnancy. This strategy may result in classification of intervention bias.

The study tried to link fluoride exposure through drinking tap water and IQ in children. However, fluoride exposure may not specifically come solely from CWF, but rather from other sources, including food and toothpaste. Other sources of fluoride were not accounted and controlled in the analyses.

Although the study used appropriate statistical analyses (e.g., multiple linear regression) to control for some confounding variables, other potential important confounding factors during pregnancy and after birth, as well as those between birth and children's age of 3 or 4 when IQ was assessed, were not fully addressed. Some

potential important confounders included parental IQ, father's education, socioeconomic status, duration of breast feeding, postnatal exposure to fluoride, postnatal diet and nutrition, and child's health status.[18,19] There is a potential risk of bias due to confounding.

The outcome measures (i.e. FSIQ, PIQ, and VIQ) could have been influenced by the knowledge of intervention received, or fluoride exposure, as the authors were aware of potential correlation and association between higher maternal fluoride exposure and lower children's' IQ from previous studies. Systematic errors might exist in the measurement IQ, MUF and daily fluoride intake. No information was provided regarding IQ measurement, such as the number of times the test was given per child (as a single measure may not capture all cognitive performance),[20] when and where the test took place (different environments and times may give different results),[18] whether the child was comfortable with the examiner before the test,[17] and whether the outcome assessors were blinded (risk of detection bias). For urine fluoride, although the authors corrected for variations in urine dilution (e.g., samples collected in early morning is more concentrated than those collected in later of the day) by adjusting MUF for specific gravity, the accurate measure of true values of MUF that correctly reflect maternal fluoride exposure remains questionable, given the short half life of fluoride (about 5 hours),[21] and only three urine samples, one at each trimester, during the entire pregnancy. The estimation of the maternal daily fluoride intake may inherit inaccuracies due to the fact that the self-reported questionnaire and the estimation/calculation methods of fluoride intake have not been validated. The estimation was subjected to recall bias as it was based on self-reported estimates of the amount of tap water and types of tea (e.g., black tea has more fluoride than green tea) consumed per day, whose data were collected on only two occasions, first and third trimesters, of pregnancy. The daily fluoride intake did not consider other sources of fluoride such as food or swallowing toothpaste after toothbrushing. The accuracy of the estimated fluoride intake levels is questionable given the discrepancies compared with MUF_{SG} values. For example, the difference in values were lower in the non-fluoridated groups (0.30 mg relative to 0.40 mg/L) and higher in the fluoridated groups (0.93 mg relative to 0.69 mg/L).[21] Given the interrelationship between maternal fluoride exposure and IQ in the estimation of the association, any incorrect assessment of fluoride intake, MUF or IQ could have a great impact on the direction of bias due to measurement of outcomes.

The outcome, exposure and covariate data were not available for all, or nearly all, participants. Over one third of initial sample were excluded due to missing data of MUF, water fluoride, and covariates. Of the 601 mother-child pairs, 369 pairs were used for urine fluoride association analysis and 400 pairs for fluoride intake association analysis. There was no information regarding the proportion of participants and reasons for missing data between exposure to higher fluoride level and lower fluoride level. There is a potential risk of bias due to missing data.

The study did not report R-squared values for the regression lines, and *P* values were reported instead, which are known to be misleading.[22] In the first analysis with MUF_{SG}, the *P* value for interaction in boys was 0.02, and the second analysis with daily fluoride intake, the *P* value was 0.04. No sample size calculation was performed. Thus, it is unclear if the study was sufficiently powered to detect a meaningful effect, and whether or not there was a strong association between maternal fluoride exposure and children's IQ.

In summary, multiple methodological weaknesses that potentially affect the internal validity of the study results limit the generalizability of the findings to all pregnant persons in Canada.

Summary of Findings

The main findings and conclusion of the identified study[13] are presented in Table 4 of Appendix 4.

What are the neurological or cognitive effects of community water fluoridation, compared with non-fluoridated or different fluoride levels in drinking water, in individuals less than 18 years of age?

Children's FSIQ

The mean FSIQ score of the total children sample was 107.16 ± 13.26. The mean FSIQ scores of non-fluoridated and fluoridated groups were 108.07 ± 13.31 and 108.21 ± 13.72, respectively.

Boys had mean FSIQ scores of 104.61 ± 14.09 in the total sample, 106.31 ± 13.60 in non-fluoridated group, and 104.78 ± 14.71 in fluoridated group.

Girls had FSIQ scores of 109.56 ± 11.96 in the total sample, 109.86 ± 12.83 in non-fluoridated group, and 111.47 ± 11.89 in fluoridated group.

Associations between MUF_{SG} and FSIQ in children

Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.49 FSIQ score (95% confidence interval [CI] -8.38 to -0.60) after adjusting for covariates (city, Home Observation for Measurement of the Environment [HOME] score, maternal education, race/ethnicity, and child sex interaction). Likewise, an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 0.70 mg/L MUF_{SG} (a value spanning the 80th central range between 10th to 90th percentiles) was associated with a significant reduction of 1.48 (95% CI -2.76 to -0.19) or 3.14 (95% CI -5.86 to -0.42) FSIQ score in boys, respectively.

Sensitivity analyses

Adjusting for maternal blood concentrations of lead, mercury, perfluorooctanoic acid, arsenic, manganese, or maternal secondhand smoke exposure alone did not change the overall estimate for the association between MUF_{SG} and FSIQ in boys or girls. Excluding data from two boys with FSIQ lower than 60 or use of the adjusted MUF for creatinine in the models did not markedly change the regression coefficient in boys.

Associations between maternal daily fluoride intake and FSIQ in children

Both unadjusted and adjusted estimates showed a significant association between daily fluoride intake and FSIQ in the total sample of boys and girls. An increase of 1 mg fluoride intake was associated with a significant reduction of 3.66 FSIQ score (95% CI -7.16 to -0.15) after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). Likewise, an increase of 0.62 mg fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) or an increase of 1.04 mg fluoride intake (a value spanning the 80th central range between 10th to 90th percentiles) was

associated with a significant reduction of 2.26 (95% CI -4.45 to -0.09) or 3.80 (95% CI -7.46 to -0.16) FSIQ score, respectively. A subgroup analysis was not performed here, as the authors stated that the interaction between child sex and maternal fluoride intake was not statistically significant.

Associations between community water fluoride concentration and FSIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 5.29 FSIQ score in the total sample after adjusting for covariates (city, HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg/L MUF_{SG} and PIQ in total sample of boys and girls, or in girls. In boys, an increase of 1 mg/L MUF_{SG} was associated with a significant reduction of 4.63 PIQ score.

Associations between maternal daily fluoride intake and PIQ in children

Adjusted estimates showed no significant association between an increase of 1 mg daily fluoride intake and PIQ in total sample of boys and girls. Subgroups analyses based on child sex was either not performed or reported.

Associations between community water fluoride concentration and PIQ in children

A 1-ppm (or 1-mg/L) increase in fluoride concentration in the community water was associated with a significant reduction of 13.79 PIQ score (95% CI -18.82 to -7.28) in total sample after adjusting for covariates (HOME score, maternal education, race/ethnicity, child sex and parental secondhand smoke exposure). The city covariate was excluded from the model because it was strongly multi-collinear with water fluoride concentration. No subgroup analysis was conducted, or reported, by sex.

Associations between MUF_{SG} and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg/L MUF_{SG} and VIQ in the total sample, in boys, or in girls.

Associations between maternal daily fluoride intake and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 mg daily fluoride intake and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Associations between community water fluoride concentration and VIQ in children

The adjusted estimate showed no significant association between an increase of 1 ppm fluoride concentration in the community water and VIQ in the total sample. A subgroup analysis based on child sex was not performed or reported.

Limitations

The study by Green et al., 2019[13] 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. Between nonfluoridated and fluoridated maternal exposure (assessed by MUF_{SG} or daily fluoride intake), the difference in mean FSIQ in total children (108.07 ± 13.31 versus 108.21 ± 13.72) was minimal. The average FSIQ in boys in the non-fluoridated and fluoridated groups were 106.31 ± 13.60 and 104.78 ± 14.71, respectively, and in girls were 109.86 ± 12.83 and 111.47 ± 11.89, respectively. According to the WPPSI test scoring,[17] these numbers were considered as normal, as a score of 90 to 109 represents average intelligence. Given that these values were available during data collection period, it was unclear about the authors' rationale to further explore the associations between maternal fluoride exposure and children's IQ. Indeed, adjusted estimates with a limited set of covariates showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ, PIQ or VIQ in all children. These were not discussed or considered when formulating the conclusion. The authors performed subgroups analysis based on child sex and found that an increase of 1 mg/L MUF_{SG} was significantly associated with a 4.49 point lower (95% CI -8.38 to -0.60) in FSIQ only in boys. In contrast, there was a non-significant increase in IQ scores in girls associated with increase maternal fluoride exposure. No pre-registered protocol was reported as available, and it is possible that the decision to conduct a subgroup analysis based on sex was made post hoc. As indicated by the authors, further investigation is needed examining differences in boys versus girls regarding their vulnerability to neurocognitive effects associated with fluoride exposure. Further, no rationale is provided to suggest why an increase in daily fluoride intake was significantly associated with lower FSIQ in total children, while no association was seen with MUF_{SG}. For the interaction with child sex, the effect on fluoride exposure was seen in analysis with MUF_{SG} but not in analysis with fluoride intake. These results were inconsistent.

The 1-mg/L increase in MUF_{SG} that was used to examine the association between fluoride exposure and childrens' IQ was far larger than the MUF_{SG} difference between fluoridated and nonfluoridated exposure in reality, which was 0.29 mg/L (difference between 0.69 mg/L and 0.40 mg/L), corresponding with a deficit of 1.53 points in FSIQ in boys (difference between 104.78 and 106.31). This was corroborated with the 1.48 point deficit in FSIQ in boys, corresponding to a MUF_{SG} difference spanning the 25^{th} to 75^{th} percentile range, which was 0.33 mg/L. Given that the reliability coefficients of WPPSI test range from 0.89 to 0.95,[17] the 1.5 points or even 4.5 points deficit is within the range of error (i.e., 5% to 11%).

The estimated level of IQ deficit in boys is likely to be reflected by non-homogeneous distribution of data as relative to fluoride intake, or biases due to uncontrolled confounders. Most of the FSIQ data were concentrated in the lower end of the MUF_{SG} concentrations, with few observations at the extreme level; therefore, an assumption for a linear correlation may not be appropriate. It appears that the effect was not observed at low MUF_{SG} concentrations, and the overall association may be driven by some outliers and few points at the extreme MUF_{SG} concentrations. There were some boys in the sample with extremely low IQ with at least two with FSIQ scores in the 50s and five with FSIQ scores below 75, while all the girls' data points were above 80, as shown in Figure 3 of the study report.[13] Although the authors stated that a sensitivity analysis removing two boys with FSIQ scores in the 50s did not substantially change

the overall estimate, data of boys below 75 were not taken into consideration in the sensitivity analysis. 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.

Conclusions and Implications for Decision or Policy Making

This review identified one prospective birth cohort study[13] examining the association between fluoride exposure of mothers during pregnancy and subsequent children's IQ scores at age 3 to 4 years. Both unadjusted and adjusted estimates showed no significant association between an increase of 1 mg/L in MUF_{SG} and FSIQ in the total sample of boys and girls, or in girls. Adjusted estimates also showed no statistically significant association between an increase of 1 mg/L in MUF_{SG} and PIQ or VIQ in all children. In boys, every 1 mg/L increased in mothers' urine fluoride levels was associated with 4.49 points lower in FSIQ score. Every 1 mg increase in daily fluoride intake of mothers corresponded with 3.66 points lower in total children's FSIQ score. The interaction between child sex and maternal fluoride intake was not statistically significant. Given multiple aforementioned 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), the findings of this study should be interpreted carefully.

A recent CADTH Review of Dental Caries and Other Health Outcomes report on CWF[12] found that water fluoridation levels relevant to the Canadian context is associated with reducing dental caries in children and adults, and there was no evidence that water fluoridation is associated with adverse effects on human health outcomes including cancer, hip fracture, Down syndrome, and IQ and cognitive function. For the IQ and cognitive function, the HTA report[12] identified three studies that were relevant to the Canadian context (a prospective cohort study in New Zealand,[24] an ecological study in Sweden,[25] and a cross-sectional study in Canada).[26] The New Zealand study[24] assessed IQ among participants at age 7 to 13 years, and subsequently at age 38 years, who were residents in areas with CWF (0.7 ppm to 1.0 ppm) and areas without CWF (≤ 0.3 ppm). The study found no clear differences in IQ between fluoridated and non-fluoridated groups and concluded that CWF programs at 0.7 ppm to 1.0 ppm is not neurotoxic. The Swedish study[25] investigated the effect of fluoride exposure through the drinking water throughout life on cognitive and non-cognitive ability, as well as math test scores in participants up to age 18 years. Fluoride in the community water supply in Sweden is naturally occurring and its level is kept at or below 1.5 ppm. The study found that water fluoride levels in Swedish drinking water had no effects on cognitive ability, non-cognitive ability, and math test scores. The Canadian study[26] examined the relationship between fluoride exposure (estimated from urine fluoride levels and tap water samples) and reported diagnosis of learning disability among children aged 3 to 12 years. The study found no association between fluoride exposure and reported learning disability (i.e., attention

deficit disorder and attention deficit hyperactivity disorder) diagnosis among Canadian children.

The findings reported by the identified study[13] in this review provided weak evidence and should be interpreted carefully, given the multiple aforementioned limitations. This, along with other evidence described in the CADTH Review of Dental Caries and Other Health Outcomes on CWF[12] which demonstrated no association with IQ and cognitive function should be considered. The identified study should be viewed as part of the research effort to investigate possible associations between fluoride exposure and neurological development in children. Together with a larger body of evidence on this topic, further well conducted research is needed to reduce uncertainty.

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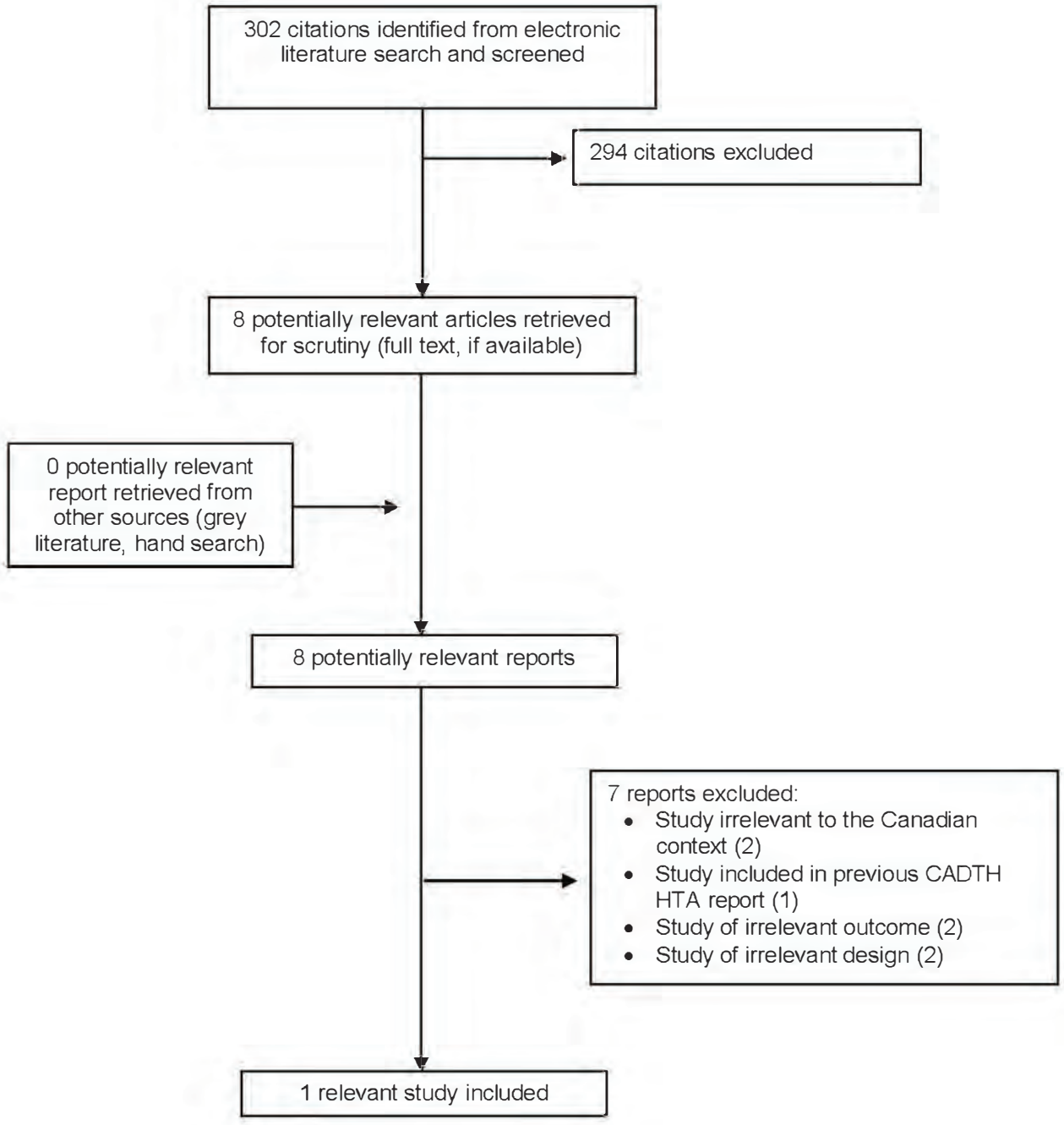
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Primary Study

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Green et al., 2019[13] Canada Funding: Public	Prospective birth cohort study Multicentre Sample size calculation: No Cohort was from the MIREC program that recruited 2,001 pregnant women from 10 cities across Canada A subset of 610 mother-child pairs from 6 out of 10 cities of the MIREC study was selected for neurodevelopment testing of children at ages 3 to 4 years	Mothers: Pregnant women within the first 14 weeks of pregnancy Mean age (SD): 32.33 (5.07) years White: 90 % Married or common law: 97% Bachelor's degree or higher: 68% Employed at time of pregnancy: 88% Net income household > $70,000 CAD: 71%	Exposure to higher levels of fluoride determined by MUF or fluoride intake, and correlated with living area having CWF	Exposure to lower levels of fluoride determined by MUF or fluoride intake, and correlated with living areas having non-CWF	Primary outcome: – FSIQ (measuring global intellectual functioning) Other outcomes: – VIQ (measuring verbal reasoning and comprehension) – PIQ (measuring nonverbal reasoning, spatial processing, and visual-motor skills)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
	Up to 241 mother-child pairs were excluded due to various reasons, leaving 369 mother-child with MUF, IQ, complete covariates and water fluoride data, and 400 mother-child pairs with fluoride intake, IQ, complete covariates and water fluoride data Two sets of measurements: By MUF By fluoride intake Statistical analysis: Multiple linear regression analyses	Smoked in trimester 1: 2% Secondhand smoke at home: 4% Alcohol consumption (drink/month): None: 83% < 1: 8% ≥ 1: 9 Parity (first birth): 46% Children: Female: 52% Mean age (SD) at testing: 3.42 (0.32) years Mean gestation (SD): 39.12 (1.57) weeks Mean birth weight (SD): 3.47 (0.49) kg	Maternal fluoride exposure[a] measurements: Mean MUF_{SG} (SD) – Total sample: 0.51 (0.36) mg/L – Non-fluoridated areas: 0.40 (0.27) mg/L – Fluoridated areas: 0.69 (0.42) mg/L Mean daily fluoride intake (SD) – Total sample: 0.54 (0.44) mg – Non-fluoridated areas: 0.30 (0.26) mg – Fluoridated areas: 0.93 (0.43) mg Mean water fluoride level (SD) – Total sample: 0.31 (0.23) ppm – Non-fluoridated areas: 0.13 (0.06) ppm – Fluoridated areas: 0.59 (0.08) ppm		

CWF = community water fluoridation; FSIQ = Full Scale IQ; IQ = intelligence quotient; MIREC = Maternal-Infant Research on Environment Chemicals; MUF = maternal urine fluoride; PIQ = performance IQ; VIQ = verbal IQ

[a] Fluoride came from any source, not specifically from CWF

Appendix 3: Quality Assessment of Included Study

Table 3: Quality Assessment of Included Prospective Cohort Study

NICE Checklist[14]	Green et al., 2019[13]	
Question	**Answer**	**Comment**
SECTION 1: POPULATION		
1.1 Is the source population or source area well described?	Yes	The Maternal-Infant Research on Environment Chemicals (MIREC) recruited pregnant persons within the first 14 weeks of pregnancy from 10 cities in Canada. A subset of 610 mother-child pairs in the MIREC study were recruited from 6 of 10 cities: Vancouver, Montreal, Kingston, Toronto, Hamilton, and Halifax. Children aged 3 to 4 years.
1.2 Is the eligible population or area representative of the source population or area?	Probably no	The recruitment of individuals, clusters or areas was not defined. It was unclear how 6 of 10 cities were chosen.
1.3 Do the selected participants or areas represent the eligible population or area?	Probably no	The method of selection of participants from the eligible population was not described. There was no report on the percentage of selected individuals or clusters who agreed to participate. Risk of selection bias.
SECTION 2: METHOD OF ALLOCATION TO INTERVENTION (OR COMPARISON)		
2.1 Selection of exposure (and comparison) group. How was selection bias minimized?	Acceptable	Fluoride exposure assessed by areas of fluoridation or non-fluoridation, and by mother urine fluoride and daily fluoride intake. There was no clear pre-defined level of fluoride exposure that was considered as low or high at start of the study. Mother-child pairs were sorted out based on maternal urine fluoride and fluoride intake after mother had been exposed to fluoride, and the knowledge of children's IQ might have affected the classification of exposure status of the mothers.
2.2 Was the selection of explanatory variables based on sound theoretical basis	Probably no	Evidence for the hypothesis that maternal fluoride exposure was associated with lower IQ in children was drawn from studies conducted in countries not applicable to the Canadian context (e.g., use of fluoridated salts, or water fluoride levels many folds higher

NICE Checklist[14]	Green et al., 2019[13]	
		than the current recommended level in Canada)
2.3 Was the contamination acceptable low?	No	Fluoride exposure did not specifically come from CWF; it could be from other sources such as foods or swallowing toothpaste after toothbrushing.
2.4 How well were likely confounding factors identified and controlled?	Partially	Some confounding factors such as city, HOME score, maternal education, race/ethnicity, child sex, and prenatal secondhand smoke exposure were adjusted in the regression analysis.
2.5 Is the setting applicable to the Canadian context?	Yes	The study was conducted in Canada
SECTION 3: OUTCOMES		
3.1 Were the outcome measures and procedures reliable?	Partially	Mother urine fluoride concentration was analyzed using biochemical method previously published. Childrens' IQ was assessed using the Wechsler Preschool and Primary Scale of Intelligence, third Edition. The questionnaire used to collect the information on consumption of tap water and other beverages (tea, coffee) and the methods to estimate and calculate fluoride intake were not validated. Self-reported of dietary intake tends to be an unreliable measure.
3.2 Were the outcome measurements complete?	No	Results form all recruited participants were not reported. Over one third were excluded due to missing data. Unclear if missing IQ data from excluded children could affect the findings.
3.3 Were all the important outcomes assessed?	Yes	Full Scale IQ, verbal IQ and performance IQ were measured.
3.4 Was there a similar follow-up time in exposure and comparison groups?	Probably not	Unclear about the period of fluoride exposure of women. Some women might have a lifetime exposure, while others might just have exposure during pregnancy.
3.5 Was follow-up time meaningful?	Yes	All included children had lived in the areas since birth.
SECTION 4: ANALYSES		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)?	Not reported	The study did not perform any sample calculation to obtain sufficient power to detect an intervention effect.
4.2 Were multiple explanatory variables considered in the analyses?	Yes	Two measures of fluoride exposure (maternal fluoride urine and fluoride intake) were used in the analyses for the association between fluoride exposure and children's IQ.

NICE Checklist[14]	Green et al., 2019[13]	
4.3 Were the analytical methods appropriate?	Probably Yes	Linear regression analyses were adjusted with some confounding factors. Multiple analyses of the intervention-outcome relationship (both unadjusted and adjusted data) were reported.
4.4 Was the precision of association given or calculable? Is association meaningful?	Probably yes	Test statistics and associated *P* values reported for all analyses. R-squared values for linear regression were not reported. Unclear if association was meaningful.
SECTION 5: SUMMARY		
5.1 Are the study results internally valid (i.e., unbiased)?	No	High risk of bias due to selection of participants, classification of intervention, confounding, missing data, and measurement of outcomes
5.2 Are the findings generalizable to the source population (i.e., externally valid)?	Probably not	Although the study was conducted in Canada, there was a risk of selection bias of the participants into the sample. The findings could not be generalizable to the entire Canadian population.

CWF = community water fluoridation; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Primary Study

Main Study Findings	Author's Conclusions
Green et al., 2019[13]	
Children's intellectual ability measurements[a] Mean FSIQ (SD) – Total sample: 107.16 (13.26) Boys: 104.61 (14.09) Girls: 109.56 (11.96) – Non-fluoridated areas: 108.07 (13.31) Boys: 106.31 (13.60) Girls: 109.86 (12.83) – Fluoridated areas: 108.21 (13.72) Boys: 104.78 (14.71) Girls: 111.47 (11.89) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and FSIQ** Measurements with MUF_{SG} Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -2.60 (-5.80 to 0.60) Boys: -5.01 (-9.06 to -0.97) Girls: 2.23 (-2.77 to 7.23) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.95 (-5.19 to 1.28) Boys: -4.49 (-8.38 to -0.60) Girls: 2.40 (-2.53 to 7.33) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.33 mg/L MUF_{SG} (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -0.64 (-1.69 to 0.42) Boys: -1.48 (-2.76 to -0.19) Girls: 0.79 (-0.83 to 2.42) Adjusted[b] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.70 mg/L MUF_{SG} (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -1.36 (-3.58 to 0.90) Boys: -3.14 (-5.86 to -0.42) Girls: 1.68 (-1.77 to 5.13) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.19 (-5.94 to -0.44) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 mg of daily fluoride intake – Total sample: -3.66 (-7.16 to -0.15)	*"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."*[13] p. E1

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 0.62 mg of daily fluoride intake (a value spanning the interquartile range between 25th to 75th percentiles) – Total sample: -2.26 (-4.45 to -0.09) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1.04 mg of daily fluoride intake (a value spanning 80th central range between 10th to 90th percentiles) – Total sample: -3.80 (-7.46 to -0.16) *Measurements with water fluoride concentration* Unadjusted estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.49 (-9.04 to 2.06) Adjusted[c] estimates, regression coefficient *B* (95% CI) of FSIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -5.29 (-10.39 to -0.19) **Sensitivity analyses predicting the associations between an increased of 1 mg/L of MUF_{SG} and FSIQ in boys, regression coefficients *B* (95% CI)** – Model A[d]: -4.49 (-8. 8.38 to -0.60) – Model A adjusting for lead: -4.61 (-8.50 to -0.71) – Model A adjusting for mercury: -5.13 (-9.16 to -1.10) – Model A adjusting for perfluorooctanoic acid: -4.57 (-8.21 to -0.50) – Model A adjusting for arsenic: -4.44 (-8.35 to -0.54) – Model A adjusting for manganese: -4.55 (-8.42 to -0.69) – Model A adjusting for secondhand smoke exposure: -4.18 (-8.06 to -0.30) – Model A excluding two boys with FSIQ lower than 60: -4.11 (-7.89 to -0.33) – Model A adjusting for creatinine: -6.96 (-8.56 to -1.36) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and PIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -5.81 (-9.31 to -2.30) Boys: -8.11 (-13.29 to -4.32) Girls: -0.56 (-6.09 to 4.97) Adjusted[b] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.24 (-4.88 to 2.40) Boys: -4.63 (-9.01 to -0.25) Girls: 4.50 (-1.02 to 10.05) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -5.75 (-8.74 to -2.76) Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 mg daily fluoride intake – Total sample: -2.74 (-6.82 to 1.34) *Measurements with water fluoride concentration*	

Main Study Findings	Author's Conclusions
Adjusted[c] estimates, regression coefficient *B* (95% CI) of PIQ for an increase of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: -13.79 (-18.82 to -7.28) **Associations between fluoride exposure variables (MUF_{SG}, daily fluoride intake, or water fluoride concentration) and VIQ** *Measurements with MUF_{SG}* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: 1.28 (-1.87 to 4.43) Boys: -0.21 (-4.19 to 3.77) Girls: 4.78 (-0.14 to 9.70) Adjusted[b] estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg/L MUF_{SG} – Total sample: -1.60 (-4.74 to 1.55) Boys: -2.82 (-6.62 to 0.98) Girls: 0.50 (-4.32 to 5.33) *Measurements with daily Fluoride Intake* Unadjusted estimates, regression coefficient *B* (95% CI) of VIQ for an increase of 1 mg daily fluoride intake – Total sample: -0.03 (-2.71 to 2.64) Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 mg daily fluoride intake – Total sample: -3.08 (-6.40 to 0.25) *Measurements with water fluoride concentration* Adjusted[c] estimates, regression coefficient *B* (95% CI) of VIQ for an increased of 1 ppm (or 1 mg/L) of water fluoride concentration – Total sample: 3.37 (-1.50 to 8.24)	

CWF = community water fluoridation; FSIQ = full Scale IQ; HOME = Home Observation for Measurement of the Environment; IQ = intelligence quotient; MUF_{SG} = maternal urine fluoride concentration adjusted for specific gravity; ppm = part per million (or mg/L); PIQ = performance IQ; SD = standard deviation; VIQ = verbal IQ

[a] Children intellectual ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)[16] The WPPSI-III contains 14 subtests and two age ranges (from 2 years and 6 months to 3 years and 11 months, and from 4 years and 0 months to 7 years and 3 months). For children in the first age range, FSIQ, VIQ and PIQ scores are obtained from four core subtests. Seven core subtests are for children in the second age range.

[b] Adjusted for city, HOME score, maternal education, race/ethnicity, and child sex interaction.

[c] adjusted for city, HOME score, maternal education, race/ethnicity, child sex interaction, and prenatal secondhand smoke exposure.

Overview of York University Fluoride Study

Prepared by the Water and Air Quality Bureau, Health Canada

(le français suit)

Health Canada's *Guidelines for Drinking Water Quality in Canada* provides parameters to provinces, territories and federal Government Departments for water systems across the country. The Drinking Water Guideline for fluoride establishes a maximum acceptable concentration (MAC) for fluoride at 1.5 mg/L that factors in all sources of exposure to fluoride. The Guideline, published in 2010, was informed by published peer reviewed studies and the recommendations of an expert panel that included the Chief Dental Officer. The expert panel examined both potential adverse health effects of fluoride and the public health benefits of adding fluoride to drinking water through community water fluoridation to prevent dental caries. Since the Drinking Water Guideline for fluoride was established in 2010, Health Canada has regularly reviewed the state of the science on the health effects of fluoride and has concluded the current available science indicates that fluoride at levels below this guideline does not pose a health concern.

A York University study, "Association Between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada", linking maternal fluoridation exposure during pregnancy to lower IQ scores in children aged 3 to 4 was published in JAMA Pediatrics on August 19, 2019. As is the case with all new science, Health Canada has reviewed this study and has considered it in weight of evidence-based decision-making to protect the health and safety of Canadians. It is important to note that when assessing the health risk, Health Canada looks at the available body of science –not one single study— in order to determine whether there is enough evidence to warrant a change in position.

In reviewing this study, Health Canada notes that from analysis of data and banked maternal urine (for fluoride) from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, the authors conclude that "… maternal exposure to higher levels of fluoride during pregnancy was associated with lower IQ scores in children aged 3 to 4 years." The key element of this study is that it is an observational study, which found an association between higher levels of two different measures of fluoride exposure during pregnancy and small decreases in child IQ at 3-4 years of age. This one study is not able to prove that prenatal fluoride exposure causes deficits in child IQ, only that there was an observation of such an association. The study was well designed and analysed. The authors identified limitations in the study and where possible implemented measures to reduce their impact. However, a number of uncertainties remain (e.g., estimation of prenatal fluoride exposure, other unmeasured factors affecting child IQ) which limit this study's ability to confirm a causal relationship between prenatal fluoride and deficits in child IQ.

This study is one of the first linking fluoride and neurological effects, and Health Canada will continue to monitor and evaluate studies as they are published. Based on the current weight of evidence, Health Canada continues to support the existing Drinking Water Guideline for fluoride. As Health Canada continues to keep abreast of scientific developments, the Department will collaborate with the Office of the Chief Dental Officer, provinces and territories and other interested stakeholders.

From: Schwetz, Tara (NIH/OD) [E]
To: Tabak, Lawrence (NIH/OD) [E]
Subject: FW: Fluoride Discussion
Date: Thursday, August 1 , 2022 : 3:3 PM
ttac me t : image001.png
image002.jpg

FYSA—fluoride update.
Best,
Tara

From: "Iademarco, Michael (HHS/OASH)" <(b) (6)
Date: Thursday, August 18, 2022 at 4:40 PM
To: "Woychik, Rick (NIH/NIEHS) [E]" <(b) (6) Tara Schwetz <(b) (6)
Cc: "Simon, Dina (NIH/OD) [C]" <(b) (6) "Calsyn, Maura (HHS/OASH)" <(b) (6) "Oh, Kathy (OS/OASH)" <(b) (6) "Lee, Kinbo (HHS/OASH)" <(b) (6) "Boateng, Sarah (HHS/OASH)" <(b) (6) "States, Leith (HHS/OASH)" <(b) (6) "D'Souza, Rena (NIH/NIDCR) [E]" <(b) (6), "Mitra, Jenny (HHS/OASH)" <(b) (6)
Subject: RE: Fluoride Discussion
This is all good, thank you. And importantly thanks for the clarification between NTP and the NTP BSC. I get it. Best, Michael

---

From: Woychik, Rick (NIH/NIEHS) [E] <(b) (6)
Sent: Thursday, August 18, 2022 10:16 AM
To: Schwetz, Tara (NIH/OD) [E] <(b) (6) Iademarco, Michael (HHS/OASH) <(b) (6)
Cc: Simon, Dina (NIH/OD) [C] <(b) (6) Calsyn, Maura (HHS/OASH) <(b) (6) Oh, Kathy (OS/OASH) <(b) (6) Lee, Kinbo (HHS/OASH) <(b) (6) Boateng, Sarah (HHS/OASH) <(b) (6) States, Leith (HHS/OASH) <(b) (6) D'Souza, Rena (NIH/NIDCR) [E] <(b) (6); Mitra, Jenny (HHS/OASH) <(b) (6)
Subject: RE: Fluoride Discussion
Just a couple additional comments.
The National Toxicology Program is a virtual collaboration with just NCTR (FDA), NIOSH (CDC) and the DNTP (NIEHS). The two manuscripts that are under consideration of products of this virtual collaboration. The NTP has its own Board of Scientific Counselors (BSC), which is a FACA committee charged specifically with overseeing the work and the products of this virtual collaboration.
Let us know if you have other questions.
I apologize for the delay in getting this moving. This is my first time through having to engage the BSC in this type of activity, and it's the first time that the Director of the NTP has ever engaged the BSC in this way. It's also complicated by the fact that Dr. Berridge has announced that he will be stepping down as Scientific Director of our DNTP, which is responsible for generating most of the data for the two publications.
All the best,

Rick

From: Schwetz, Tara (NIH/OD) [E] <(b) (6)
Sent: Thursday, August 18, 2022 9:48 AM
To: Iademarco, Michael (HHS/OASH) <(b) (6) Woychik, Rick (NIH/NIEHS) [E] <(b) (6)
Cc: Simon, Dina (NIH/OD) [C] <(b) (6) Calsyn, Maura (HHS/OASH) <(b) (6) Oh, Kathy (OS/OASH) <(b) (6) Lee, Kinbo (HHS/OASH) <(b) (6) Boateng, Sarah (HHS/OASH) <(b) (6) States, Leith (HHS/OASH) <(b) (6) D'Souza, Rena (NIH/NIDCR) [E] <(b) (6); Mitra, Jenny (HHS/OASH) <(b) (6)
Subject: Re: Fluoride Discussion

Michael,

Please see below (in **purple**) for responses to your questions. Let us know if you have further questions.

Best,

Tara A. Schwetz, PhD *(she/her)*
Acting Principal Deputy Director, NIH
A: Building 1, Room 109
P: (b) (6) | **M:** (b) (6)

From: "Iademarco, Michael (HHS/OASH)" <(b) (6)
Date: Thursday, August 18, 2022 at 9:16 AM
To: "Woychik, Rick (NIH/NIEHS) [E]" <(b) (6) Tara Schwetz <(b) (6) "Woychik, Rick (NIH/NIEHS) [E]" <(b) (6)
Cc: "Simon, Dina (NIH/OD) [C]" <(b) (6) "Calsyn, Maura (HHS/OASH)" <(b) (6) "Oh, Kathy (OS/OASH)" <(b) (6) "Lee, Kinbo (HHS/OASH)" <(b) (6) "Boateng, Sarah (HHS/OASH)" <(b) (6) "States, Leith (HHS/OASH)" <(b) (6) "D'Souza, Rena (NIH/NIDCR) [E]" <(b) (6)>, "Mitra, Jenny (HHS/OASH)" <(b) (6)
Subject: RE: Fluoride Discussion

Thanks everyone. Progress. Two questions...

1. If I recall the NTP is a federal advisory committee. **The NTP itself is an interagency program. The NTP BSC is a FACA committee.**
2. Is this subgroup of experts being formed a workgroup or a subcommittee? **It will be a working group of the NTP BSC, particularly since it will be time-limited. That is, it's not a standing subcommittee.**
3. Will their meetings be open to the public? **The WG meetings will not be public; however, they will report out on their recommendations at a public meeting of the NTP BSC.**

Best, Michael

From: Woychik, Rick (NIH/NIEHS) [E] <(b) (6)
Sent: Wednesday, August 17, 2022 3:14 PM
To: Schwetz, Tara (NIH/OD) [E] <(b) (6) Iademarco, Michael (HHS/OASH) <(b) (6) Woychik, Rick (NIH/NIEHS) [E] <(b) (6)
Cc: Simon, Dina (NIH/OD) [C] <(b) (6) Calsyn, Maura (HHS/OASH) <(b) (6) Oh, Kathy (OS/OASH) <(b) (6) Lee, Kinbo (HHS/OASH)

< (b) (6) Gray, Oneika (HHS/OASH) < (b) (6) Boateng, Sarah (HHS/OASH) < (b) (6) Fisher, Megan (HHS/OASH) < (b) (6) States, Leith (HHS/OASH) < (b) (6) D'Souza, Rena (NIH/NIDCR) [E] < (b) (6) ; Mitra, Jenny (HHS/OASH) < (b) (6)

Subject: RE: Fluoride Discussion

Dear RADM lademarco,

In response to the email you sent to Dr. Schwetz last Tuesday (see below), I am sending you a summary of where we stand relative to the WG to evaluate the two fluoride documents. I am also attaching a copy of the memo that I sent to you and the other key stakeholders across HHS last June which highlighted the "charge" to the WG.

Please let us know if you have any questions.

All the best,

Tara and Rick

Update on NTP Fluoride Study Activities

NIEHS Board of Scientific Counselors (BSC) Working Group Development—Completed Steps

NIEHS worked with Dr. Eaton, NTP BSC Chair, to develop a process to create a working group of the outside experts to review the NTP fluoride documents.

- Initial screening of the 20 Nominees received from stakeholder agencies identified information about each person including affiliation, position, research topics, areas of expertise from websites, LinkedIn, etc.
- Each person was then evaluated for their participation/affiliation with fluoride activities (NASEM panel, fluoride-related publications, webinars/symposia, public comments to NASEM).
- Dr. Eaton identified 6 possible candidates and then conducted an in-depth COI screening via Lexis/Nexis (news articles and networks), SCOPUS (2019-2022, looked at topic, cross-checked collaborators with other potential WG members and persons involved with NTP fluoride project), Google (podcast topics, news articles, opinion pieces, etc.).
- From this group, 5 persons were best qualified without any COIs.

Thus far, Dr. Eaton and NIEHS has held these confidential interviews by zoom with all 5 individuals. WG candidates were told about the WG activity including charge, timeline, SoS and meta-analysis documents, honorarium, expertise areas needed, WG's product, BSC meeting, etc. All 5 are willing to continue with the process.

NIEHS BSC Working Group Development—Ongoing Steps

Dr. Eaton and NIEHS leadership will review all of the details relating to the qualifications and COIs for the nominated candidates during the last week of August in preparation for an HHS stakeholder meeting. NIEHS is scheduling this meeting for early September when the HHS stakeholders are all available.

Following the meeting with the HHS stakeholder group, a COI screening package will be sent to persons who are interested and qualified in participating on the WG. The package will identify the chemical and topic of the systematic review/meta-analysis and will ask for standard information (e.g., CV, COI form, anti-lobbying form) and ask about relationships with listed staff who have been involved in development/review of the two documents.

NIEHS BSC Working Group Development—Next Steps

Materials [e.g., CV, COI form, search results (i.e., Lexis/Nexis, SCOPUS, Google)] will be shared with Dr. Eaton and NIEHS leadership for their approval of the WG membership.

The goal is to have the COI screening and have the proposed BSC WG identified by Aug 31. In early September, at a time when the HHS stakeholders are available, the stakeholder group will be convened to provide detailed reasoning for the choice of the WG members and to confirm the next steps. Then, Dr. Eaton will officially charge the working group (see attached document that Dr. Woychik shared with the stakeholder group last June, which includes the language describing the charge). Of note, this is not meant to be a thorough peer review of both manuscripts, but rather will be a focused effort of the working group dedicated to be: a) primarily an adjudication of the written comments from key stakeholders (e.g., NIDCR, NIH-OD, FDA, CDC, and OASH), b) secondarily to provide any additional insights into the quality of the work, including whether strength of the underlying data was appropriately and thoroughly assessed.

The WG will meet as necessary to consider the elements of the charge, and then will make recommendations to the NTP BSC, which will then conduct a public session to review the recommendations from the WG. The Chair of the NTP BSC will then make recommendations to Dr. Woychik, who will decide how to proceed with the two publications after meeting with the HHS stakeholder group, including the ASH.

From: Schwetz, Tara (NIH/OD) [E] <(b) (6)
Sent: Tuesday, August 9, 2022 11:51 PM
To: Iademarco, Michael (HHS/OASH) <(b) (6)
Cc: Simon, Dina (NIH/OD) [C] <(b) (6) Calsyn, Maura (HHS/OASH) <(b) (6) Oh, Kathy (OS/OASH) <(b) (6) Lee, Kinbo (HHS/OASH) <(b) (6) Gray, Oneika (HHS/OASH) <(b) (6) Boateng, Sarah (HHS/OASH) <(b) (6) Fisher, Megan (HHS/OASH) <(b) (6) Woychik, Rick (NIH/NIEHS) [E] <(b) (6) States, Leith (HHS/OASH) <(b) (6) D'Souza, Rena (NIH/NIDCR) [E] <(b) (6) ; Mitra, Jenny (HHS/OASH) <(b) (6)
Subject: Re: Fluoride Discussion

Michael,

You read my mind! I was actually in NC today, visiting the NIEHS campus, and Rick and I discussed providing an update soon. We'll get something together and get it to you next week.

Best,

Tara A. Schwetz, PhD *(she/her)*
Acting Principal Deputy Director, NIH
A: Building 1, Room 109
P: (b) (6) | **M:** (b) (6)

From: "Iademarco, Michael (HHS/OASH)" <(b) (6)
Date: Tuesday, August 9, 2022 at 2:53 PM
To: Tara Schwetz <(b) (6)
Cc: "Simon, Dina (NIH/OD) [C]" <(b) (6) "Calsyn, Maura (HHS/OASH)" <(b) (6) "Oh, Kathy (OS/OASH)" <(b) (6) "Lee, Kinbo (HHS/OASH)" <(b) (6) "Gray, Oneika (HHS/OASH)" <(b) (6) "Boateng, Sarah (HHS/OASH)" <(b) (6) "Fisher, Megan (HHS/OASH)"

< (b) (6) "Woychik, Rick (NIH/NIEHS) [E]" < (b) (6) "States, Leith (HHS/OASH)" < (b) (6) "D'Souza, Rena (NIH/NIDCR) [E]" < (b) (6), "Mitra, Jenny (HHS/OASH)" < (b) (6)

Subject: RE: Fluoride Discussion

Tara, I'd like to provide a brief update summary to ADM Levine in the next week or so. Could you help facilitate? Best, Michael

---

From: D'Souza, Rena (NIH/NIDCR) [E] < (b) (6)

Sent: Wednesday, June 29, 2022 6:08 AM

To: Levine, Rachel (HHS/OASH) < (b) (6) Iademarco, Michael (HHS/OASH) < (b) (6) Boateng, Sarah (HHS/OASH) < (b) (6)

Cc: Simon, Dina (NIH/OD) [C] < (b) (6) Calsyn, Maura (HHS/OASH) < (b) (6) Handley, Elisabeth (OS/OASH) < (b) (6) Oh, Kathy (OS/OASH) < (b) (6) Lee, Kinbo (HHS/OASH) < (b) (6) Gray, Oneika (HHS/OASH) < (b) (6) Fisher, Megan (HHS/OASH) < (b) (6) Schwetz, Tara (NIH/OD) [E] < (b) (6) Woychik, Rick (NIH/NIEHS) [E] < (b) (6) States, Leith (HHS/OASH) < (b) (6)

Subject: Re: Fluoride Discussion

Thank you for this summary VADM Iademarco.
Minor edits and 2 comments from me for you to consider.
Best, Rena

Rena N. D'Souza, D.D.S., M.S., Ph.D.,
Director,
National Institute of Dental and Craniofacial Research/NIH
31 Center Drive, MSC 2290 Building 31C, Suite 2C39
Chief,
Section on Molecules & Therapies for Craniofacial & Dental Disorders
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Maryland 20892
Email: (b) (6)
Phone: (b) (6)
Cell: (b) (6)

From: Levine, Rachel (HHS/OASH) < (b) (6)

Date: Tuesday, June 28, 2022 at 8:15 PM

To: Iademarco, Michael (HHS/OASH) < (b) (6) Boateng, Sarah (HHS/OASH) < (b) (6)

Cc: Simon, Dina (NIH/OD) [C] < (b) (6) Calsyn, Maura (HHS/OASH) < (b) (6) Handley, Elisabeth (OS/OASH) < (b) (6) Oh, Kathy (OS/OASH) < (b) (6) Lee, Kinbo (HHS/OASH) < (b) (6) Gray, Oneika (HHS/OASH) < (b) (6) Fisher, Megan (HHS/OASH) < (b) (6) Schwetz, Tara (NIH/OD) [E] < (b) (6) D'Souza, Rena (NIH/NIDCR) [E] < (b) (6), Woychik, Rick (NIH/NIEHS) [E]

< (b) (6) States, Leith (HHS/OASH) < (b) (6)
Subject: RE: Fluoride Discussion

RADM Iademarco, Sounds good, Thanks, RLL

Rachel L. Levine, M.D.
ADM, United States Public Health Service

Assistant Secretary for Health
Office of the Assistant Secretary for Health

Email: (b) (6)
hhs.gov/ash

From: Iademarco, Michael (HHS/OASH) < (b) (6)
Sent: Tuesday, June 28, 2022 3:26 PM
To: Levine, Rachel (HHS/OASH) < (b) (6) Boateng, Sarah (HHS/OASH) < (b) (6)
Cc: Simon, Dina (NIH/OD) [C] < (b) (6) Calsyn, Maura (HHS/OASH) < (b) (6) Handley, Elisabeth (OS/OASH) < (b) (6) Oh, Kathy (OS/OASH) < (b) (6) Lee, Kinbo (HHS/OASH) < (b) (6) Gray, Oneika (HHS/OASH) < (b) (6) Fisher, Megan (HHS/OASH) < (b) (6) Schwetz, Tara (NIH/OD) [E] < (b) (6) D'Souza, Rena (NIH/NIDCR) [E] < (b) (6) ; Woychik, Rick (NIH/NIEHS) [E] < (b) (6) States, Leith (HHS/OASH) < (b) (6)
Subject: RE: Fluoride Discussion
ADM Levine, Attached is a meeting summary that Tara and I worked out, just to capture the approach. Anyone copied, should let me know if there are any concerns. Based on communications with the NIH, these steps are underway. V/r, Michael
-----Original Appointment-----
From: Levine, Rachel (HHS/OASH) < (b) (6)
Sent: Thursday, June 2, 2022 8:02 PM
To: Levine, Rachel (HHS/OASH); Levine, Rachel (HHS/OASH); Schwetz, Tara (NIH/OD) [E]; D'Souza, Rena (NIH/NIDCR) [E]; Woychik, Rick (NIH/NIEHS) [E]; Iademarco, Michael (HHS/OASH); Boateng, Sarah (HHS/OASH)
Cc: Simon, Dina (NIH/OD) [C]; Calsyn, Maura (HHS/OASH); Handley, Elisabeth (OS/OASH); Oh, Kathy (OS/OASH); Cure, Kelly (OS/OASH) (CTR); Lee, Kinbo (HHS/OASH); Gray, Oneika (HHS/OASH); Fisher, Megan (HHS/OASH)
Subject: Fluoride Discussion
When: Monday, June 6, 2022 5:30 PM-6:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: (b) (6)

ADM Rachel Levine is inviting you to a scheduled ZoomGov meeting.
Join ZoomGov Meeting
(b) (6)
Meeting ID: (b) (6)
Passcode: (b) (6)

One tap mobile

+(b) (6) US (San Jose)

+(b) (6) US (New York)

Dial by your location

+(b) (6) US (San Jose)

+(b) (6) US (New York)

+(b) (6) US (San Jose)

+(b) (6) US

Meeting ID: (b) (6)

Find your local number: (b) (6)

Join by SIP

(b) (6)

Join by H.323

(b) (6) (US West)

(b) (6) (US East)

Meeting ID: (b) (6)

Passcode: (b) (6)

From: NIH E ecutive Secretariat
To: Matthew rooks
Subject: RE: [EXTERNAL] Potential cures
Date: Monday, July 11, 2022 3: 2: PM
ttac me t : image001 pg

Dear Mr. Brooks,

Thank you for your emails to Dr. Lawrence Tabak, Acting Director of the National Institutes of Health (NIH). Your email has been provided to the appropriate NIH offices for their review and consideration. Due to the press of agency business, it is not possible for NIH to respond to every inquiry. NIH staff may contact you should they wish to discuss further.

Thank you for your continued support of NIH.

NIH Executive Secretariat
www.nih.gov

From: Matthew Brooks <(b) (6)
Sent: Friday, July 8, 2022 9:28 PM
To: Tabak, Lawrence (NIH/OD) [E] <(b) (6)
Subject: [EXTERNAL] Potential cures

Good evening Dr. Tabak,

Thank you for all your hard work at the NIH. I know your schedule keeps you busy, so I'll keep this as short as possible.

My name's Matthew Brooks. I recently discovered what may be a potential cure for cancer: c=sodium hydroxide Fluoride. I also came up with what may be a potential cure to HIV/AIDS (e.g. sodium fluoride), Covid (e.g. sodium benzoate or sodium benzoate pentachloraide phosphide), and Bipolar (e.g. bicadium).

I know this may seem odd to send this to you, but I wanted to let someone of your position know about it before letting it go and thinking little of it. Let me know your thoughts on it when you have a moment.

Thanks again For. Tabak.

Matthew R. Brooks
(b) (6)
(b) (6)
Ph: (b) (6)

From: Matthew Brooks
To: NIH Executive Secretariat
Subject: Re: [EXTERNAL] Potential cures
Date: Friday, July 15, 2022 5:54:43 PM
Attachments: image001.jpg
image001.jpg

Good afternoon,

Thank you for your response. I look forward to hearing from the department soon.

With kind regards,
Matthew R. Brooks
(b) (6)
(b) (6)
Ph: (b) (6)

On Mon, Jul 11, 2022, 2:42 PM NIH Executive Secretariat < (b) (6) wrote:

> Dear Mr. Brooks,
>
> Thank you for your emails to Dr. Lawrence Tabak, Acting Director of the National Institutes of Health (NIH). Your email has been provided to the appropriate NIH offices for their review and consideration. Due to the press of agency business, it is not possible for NIH to respond to every inquiry. NIH staff may contact you should they wish to discuss further.
>
> Thank you for your continued support of NIH.
>
> NIH Executive Secretariat
>
> www.nih.gov
>
> 
>
> **From:** Matthew Brooks < (b) (6)
> **Sent:** Friday, July 8, 2022 9:28 PM
> **To:** Tabak, Lawrence (NIH/OD) [E] < (b) (6)
> **Subject:** [EXTERNAL] Potential cures
>
> Good evening Dr. Tabak,

Thank you for all your hard work at the NIH. I know your schedule keeps you busy, so I'll keep this as short as possible.

My name's Matthew Brooks. I recently discovered what may be a potential cure for cancer: c=sodium hydroxide Fluoride. I also came up with what may be a potential cure to HIV/AIDS (e.g. sodium fluoride), Covid (e.g. sodium benzoate or sodium benzoate pentachloraide phosphide), and Bipolar (e.g. bicadium).

I know this may seem odd to send this to you, but I wanted to let someone of your position know about it before letting it go and thinking little of it. Let me know your thoughts on it when you have a moment.

Thanks again For. Tabak.

Matthew R. Brooks

(b) (6)

(b) (6)

Ph: (b) (6)

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and are confident the content is safe.

From: Matthew rooks
To: Tabak, Lawrence (NIH/OD) [E]
Subject: [EXTERNAL] Potential cures
Date: Friday, July , 2022 :2 :31 PM

Good evening Dr. Tabak,

Thank you for all your hard work at the NIH. I know your schedule keeps you busy, so I'll keep this as short as possible.

My name's Matthew Brooks. I recently discovered what may be a potential cure for cancer: c=sodium hydroxide Fluoride. I also came up with what may be a potential cure to HIV/AIDS (e.g. sodium fluoride), Covid (e.g. sodium benzoate or sodium benzoate pentachloraide phosphide), and Bipolar (e.g. bicadium).

I know this may seem odd to send this to you, but I wanted to let someone of your position know about it before letting it go and thinking little of it. Let me know your thoughts on it when you have a moment.

Thanks again For. Tabak.

Matthew R. Brooks
(b) (6)
Ph: (b) (6)

From: urklow, John (NIH/OD) [E]
To: Tabak, Lawrence (NIH/OD) [E]; Schwetz, Tara (NIH/OD) [E]
Subject: NTP briefing for the ASH
Date: Thursday, June 30, 2022 5:1 :3 PM

Hi, Larry, Tara—
Just to report that the NTP briefing on data sharing with the ASH went very well. Rick's team did a great job. As always, she was fully engaged, asked good questions (about data security and legal aspects), and was very complimentary and supportive.
Best,
John

From:	McManus, Ayanna (NIH/OD) [E]
To:	Tabak, Lawrence (NIH/OD) [E]; Schwetz, Tara (NIH/OD) [E]
c:	Chao, rittany (NIH/OD) [E]; LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	RE: LAT homework June 2
Date:	Monday, June 2 , 2022 3:1 : PM

Comments below in **purple.**
Thanks,
Ayanna

From: Tabak, Lawrence (NIH/OD) [E] <(b) (6)
Sent: Saturday, June 25, 2022 2:08 PM
To: Schwetz, Tara (NIH/OD) [E] <(b) (6)
Cc: Chao, Brittany (NIH/OD) [E] <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6); Aklin, Courtney (NIH/OD) [E] <(b) (6) Burrus-Shaw, Cyndi (NIH/OD) [E] <(b) (6) Dzokoto-Pomenya, Caroline (NIH/OD) [E] <(b) (6) Landis, Erica (NIH/OD) [E] <(b) (6) McManus, Ayanna (NIH/OD) [E] <(b) (6) Simon, Dina (NIH/OD) [C] <(b) (6) Burklow, John (NIH/OD) [E] <(b) (6) Walsh, Elizabeth (NIH/OD) [E] <(b) (6)
Subject: Re: LAT homework June 24
Replies in **orange please**.
Thanks
Larry

From: "Schwetz, Tara (NIH/OD) [E]" <(b) (6)
Date: Saturday, June 25, 2022 at 1:51 PM
To: "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6), "Aklin, Courtney (NIH/OD) [E]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" <(b) (6) "Landis, Erica (NIH/OD) [E]" <(b) (6) "McManus, Ayanna (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burklow, John (NIH/OD) [E]" <(b) (6) "Walsh, Elizabeth (NIH/OD) [E]" <(b) (6)
Subject: Re: LAT homework June 24
See below in bold, underlined, italics.
Best,

Tara A. Schwetz, PhD
National Institutes of Health
(b) (6)
Sent from my iPhone

On Jun 25, 2022, at 1:17 PM, Tabak, Lawrence (NIH/OD) [E]

< (b) (6) wrote:

Thanks for putting everything together. Comments in red.
Please take time to enjoy the weekend.
Larry

From: "Chao, Brittany (NIH/OD) [E]" < (b) (6)
Date: Friday, June 24, 2022 at 9:01 PM
To: LAT-Homework Meeting < (b) (6) "Tabak, Lawrence (NIH/OD) [E]" < (b) (6)
Cc: "Aklin, Courtney (NIH/OD) [E]" < (b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" < (b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" < (b) (6) "Landis, Erica (NIH/OD) [E]" < (b) (6) "McManus, Ayanna (NIH/OD) [E]" < (b) (6) "Simon, Dina (NIH/OD) [C]" < (b) (6) "Burklow, John (NIH/OD) [E]" < (b) (6) "Walsh, Elizabeth (NIH/OD) [E]" < (b) (6) "Chao, Brittany (NIH/OD) [E]" < (b) (6) "Schwetz, Tara (NIH/OD) [E]" < (b) (6)
Subject: LAT homework June 24

Hi Larry – please find your HW attachments/references enclosed (hyperlinked from the Sharepoint folder):

Staff Meeting Agenda

- *6/27 Overdose Prevention Strategy Implementation Update Pre-Brief*

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SC/ICD Meeting At a glance

- Let's discuss at catch up please

COVID-19 Updates

For Review/Action

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    - OIR/NIDDK prepared a draft response that was reviewed by OGC (also attached) in response to an email from Dr. Robert Hanson
    - You indicated that the response should come from you, so Exec Sec wanted to follow up to see if you have sent it or would like them to send it on your behalf.

- Blog packet 476: responded by separate email.

    - **NIDDK-STEP-UP-South Pacific** - Select a headline and tweet. The post has been cleared through NIDDK.
    - **Director's Blog Topics** – Please choose a news post and tweets for next week.

FYI/Admin

- N/A

Best,
Team Tabak

From:	Tabak, Lawrence (NIH/OD) [E]
To:	Schwetz, Tara (NIH/OD) [E]
c:	Chao, rittany (NIH/OD) [E]; LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	Re: LAT homework June 2
Date:	Saturday, June 25, 2022 2:0 :5 PM

Replies in **orange please**.
Thanks
Larry

From: "Schwetz, Tara (NIH/OD) [E]" <(b) (6)
Date: Saturday, June 25, 2022 at 1:51 PM
To: "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6), "Aklin, Courtney (NIH/OD) [E]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" <(b) (6) "Landis, Erica (NIH/OD) [E]" <(b) (6) "McManus, Ayanna (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burklow, John (NIH/OD) [E]" <(b) (6) "Walsh, Elizabeth (NIH/OD) [E]" <(b) (6)
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National Institutes of Health
(b) (6)
Sent from my iPhone

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Date: Friday, June 24, 2022 at 9:01 PM
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[E]" < (b) (6) "Chao, Brittany (NIH/OD) [E]"
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FYI/Admin

- N/A

Best,
Team Tabak

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To:	Tabak, Lawrence (NIH/OD) [E]
c:	Chao, rittany (NIH/OD) [E]; LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	Re: LAT homework June 2
Date:	Saturday, June 25, 2022 1:51: PM

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National Institutes of Health
(b) (6)

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Subject:	Re: LAT homework June 2
Date:	Saturday, June 25, 2022 1:1 :0 PM

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Date: Friday, June 24, 2022 at 9:01 PM
To: LAT-Homework Meeting <(b) (6) "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
Cc: "Aklin, Courtney (NIH/OD) [E]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" <(b) (6) "Landis, Erica (NIH/OD) [E]" <(b) (6) "McManus, Ayanna (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burklow, John (NIH/OD) [E]" <(b) (6) "Walsh, Elizabeth (NIH/OD) [E]" <(b) (6) "Chao, Brittany (NIH/OD) [E]" <(b) (6) "Schwetz, Tara (NIH/OD) [E]" <(b) (6)
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FYI/Admin

- N/A

Best,
Team Tabak

From: Hallett, Adrienne (NIH/OD) [E]
To: Tabak, Lawrence (NIH/OD) [E]
Subject: Flouridation questions
Date: Tuesday, May 1 , 2022 :2 :21 PM

These are the questions we've gotten from two offices now:

1. It is my understanding that the line of peer review for this kind of publication would typically continue with the National Academies of Sciences, Engineering and Medicine. Did NTP run the state-of-science report through NASEM, and if not, why not?

2. Have CDC, NIDCR, and/or NICHD expressed any concerns about the presentation of the findings? Do they agree that the findings are being presented in a responsible and scientifically accurate way? If concerns have been raised, what are they and what has NTP done to address those concerns?

3. What are NTP's plans to make it clear, even to a lay person, that this report will not be an indictment of community water fluoridation and should not be used to influence debates about the practice?

4. How many individuals in the U.S., including pregnant women and young children, are consistently exposed to unusually high fluoride concentrations (≥1.5 mg/L) for prolonged periods every year? How does the report clearly distinguish the potential risk to those individuals from those receiving community water fluoridation?

From:	Chao, rittany (NIH/OD) [E]
To:	Schwetz, Tara (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]
c:	LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	Re: LAT homework May 2
Date:	Tuesday, May 31, 2022 :05:02 AM
ttac me t :	image001 png

Hi all,
Please see comments in blue.
Best.
Brittany

From: "Schwetz, Tara (NIH/OD) [E]" <(b) (6)
Date: Monday, May 30, 2022 at 10:45 PM
To: "Tabak, Lawrence (NIH/OD) [E]" <(b) (6) "McManus, Ayanna (NIH/OD) [E]" <(b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6), "Aklin, Courtney (NIH/OD) [E]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" <(b) (6) "Landis, Erica (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burklow, John (NIH/OD) [E]" <(b) (6) "Walsh, Elizabeth (NIH/OD) [E]" <(b) (6)
Subject: Re: LAT homework May 27
Larry,
I think the NTP thing is OK for now, but I'm still going back and forth on this with Rick and also still going through my email.
Best,

Tara A. Schwetz, PhD *(she/her)*
Acting Principal Deputy Director, NIH
A: Building 1, Room 109
P: (b) (6)

Executive Assistant: Caroline Dzokoto-Pomenya (b) (6)
Scheduler: Dina Simon (b) (6)

From: Larry Tabak <(b) (6)
Date: Monday, May 30, 2022 at 6:50 AM
To: "McManus, Ayanna (NIH/OD) [E]" <(b) (6) Tara Schwetz <(b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6), "Aklin, Courtney (NIH/OD) [E]" <(b) (6) Cyndi Burrus-Shaw <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]"

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< (b) (6) "Walsh, Elizabeth (NIH/OD) [E]" < (b) (6)
Subject: Re: LAT homework May 27
comments in orange.
thanks
Larry

From: "McManus, Ayanna (NIH/OD) [E]" < (b) (6)
Date: Sunday, May 29, 2022 at 9:23 PM
To: "Schwetz, Tara (NIH/OD) [E]" < (b) (6) "Tabak, Lawrence (NIH/OD) [E]"
< (b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" < (b) (6) LAT-Homework Meeting < (b) (6)
(b) (6), "Aklin, Courtney (NIH/OD) [E]" < (b) (6)
"Burrus-Shaw, Cyndi (NIH/OD) [E]" < (b) (6) "Dzokoto-Pomenya,
Caroline (NIH/OD) [E]" < (b) (6) "Landis, Erica (NIH/OD) [E]"
< (b) (6) "Simon, Dina (NIH/OD) [C]" < (b) (6) "Burklow, John
(NIH/OD) [E]" < (b) (6) "Walsh, Elizabeth (NIH/OD) [E]"
< (b) (6)
Subject: RE: LAT homework May 27
Comments in **purple.**
Thanks,
Ayanna

From: Schwetz, Tara (NIH/OD) [E] < (b) (6)
Sent: Sunday, May 29, 2022 5:01 PM
To: Tabak, Lawrence (NIH/OD) [E] < (b) (6)
Cc: Chao, Brittany (NIH/OD) [E] < (b) (6) LAT-Homework Meeting < (b) (6)
(b) (6) Aklin, Courtney (NIH/OD) [E] < (b) (6) Burrus-
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< (b) (6) Landis, Erica (NIH/OD) [E] < (b) (6)
McManus, Ayanna (NIH/OD) [E] < (b) (6) Simon, Dina (NIH/OD) [C]
< (b) (6) Burklow, John (NIH/OD) [E] < (b) (6) Walsh, Elizabeth
(NIH/OD) [E] < (b) (6)
Subject: Re: LAT homework May 27
All,
See below in ***bold italics***.
Best,

Tara A. Schwetz, PhD
National Institutes of Health
(b) (6)
Sent from my iPad

On May 28, 2022, at 2:03 PM, Tabak, Lawrence (NIH/OD) [E]

< (b) (6) wrote:

Thanks for assembling this. Comments in red.
Hope you are all enjoying the holiday weekend.
Larry

From: "Chao, Brittany (NIH/OD) [E]" < (b) (6)
Date: Friday, May 27, 2022 at 5:58 PM
To: LAT-Homework Meeting < (b) (6) "Tabak, Lawrence (NIH/OD) [E]" < (b) (6)
Cc: "Aklin, Courtney (NIH/OD) [E]" < (b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" < (b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" < (b) (6) "Landis, Erica (NIH/OD) [E]" < (b) (6) "McManus, Ayanna (NIH/OD) [E]" < (b) (6) "Simon, Dina (NIH/OD) [C]" < (b) (6) "Burklow, John (NIH/OD) [E]" < (b) (6) "Walsh, Elizabeth (NIH/OD) [E]" < (b) (6) "Chao, Brittany (NIH/OD) [E]" < (b) (6) "Schwetz, Tara (NIH/OD) [E]" < (b) (6)
Subject: LAT homework May 27

Hi Larry – please find your HW attachments/references enclosed (hyperlinked from the Sharepoint folder):

Staff Meeting Agenda

- Topics for our meeting with DepSec (5/31)
    - March In
    - Timing on WIV termination//reinstatement
    - Royalties
    - Fluoride – is this still needed?

- Is the ASH briefing on Fluoride on 6/1 – Tara, should I join or do you prefer that I do not since you have been working directly with Rick? ***There's a slide set and some emails that I haven't had a chance to really look at yet. Will do so later this evening (once we get back) or tomorrow and will let you know.*** **ok, thanks – let me know.**
- What am I doing at OD Return to Work Town Hall? ***Based on a previous discussion, we hadn't slotted you in for a role. If you would like to participate (opening remarks?), let us know.*** **no, not necessary. thanks.**
- Wednesday 6/8 – Nina Schor is certainly welcome to join when the Taiwan delegation visits. Brittany will also join. **Ok, thanks**
- Unless the new NIH director has just arrived (not likely given the timing) I plan to be on annual leave from August 23rd through Friday August 26th (but will be reachable throughout – we will be driving to Cleveland to visit the Melvins) ***FYI—looking like I will be in South Korea for a presentation on 8/31 and a meeting on 9/1. Because of timing and duration of flights, it pretty much knocks out***

the whole week for me. **ok, since we are driving I can remain in contact the entire time**

- No ICD/SC meeting on Thur August 25th (most people will be on leave) Ok

- TFC would like to plan a 30-minute virtual meeting to further discuss T42(f) workforce diversity positions. Who should participate? LAT or TAS?

  - Sorry, who/what is TFC? ***Is this supposed to be ETFC?*** **Yes, this should have been ETFC I will participate. Tara is welcome to join if she wishes to.**

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FYI/Admin

- N/A

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Best,
Team Tabak

From:	Tabak, Lawrence (NIH/OD) [E]
To:	McManus, Ayanna (NIH/OD) [E]; Schwetz, Tara (NIH/OD) [E]
c:	Chao, rittany (NIH/OD) [E]; LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	Re: LAT homework May 2
Date:	Monday, May 30, 2022 :50:2 AM

comments in orange.
thanks
Larry

From: "McManus, Ayanna (NIH/OD) [E]" <(b) (6)
Date: Sunday, May 29, 2022 at 9:23 PM
To: "Schwetz, Tara (NIH/OD) [E]" <(b) (6) "Tabak, Lawrence (NIH/OD) [E]" <(b) (6)
Cc: "Chao, Brittany (NIH/OD) [E]" <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6), "Aklin, Courtney (NIH/OD) [E]" <(b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" <(b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" <(b) (6) "Landis, Erica (NIH/OD) [E]" <(b) (6) "Simon, Dina (NIH/OD) [C]" <(b) (6) "Burklow, John (NIH/OD) [E]" <(b) (6) "Walsh, Elizabeth (NIH/OD) [E]" <(b) (6)
Subject: RE: LAT homework May 27
Comments in **purple.**
Thanks,
Ayanna

From: Schwetz, Tara (NIH/OD) [E] <(b) (6)
Sent: Sunday, May 29, 2022 5:01 PM
To: Tabak, Lawrence (NIH/OD) [E] <(b) (6)
Cc: Chao, Brittany (NIH/OD) [E] <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6); Aklin, Courtney (NIH/OD) [E] <(b) (6) Burrus-Shaw, Cyndi (NIH/OD) [E] <(b) (6) Dzokoto-Pomenya, Caroline (NIH/OD) [E] <(b) (6) Landis, Erica (NIH/OD) [E] <(b) (6) McManus, Ayanna (NIH/OD) [E] <(b) (6) Simon, Dina (NIH/OD) [C] <(b) (6) Burklow, John (NIH/OD) [E] <(b) (6) Walsh, Elizabeth (NIH/OD) [E] <(b) (6)
Subject: Re: LAT homework May 27
All,
See below in ***bold italics***.
Best,

Tara A. Schwetz, PhD
National Institutes of Health
(b) (6)
Sent from my iPad

On May 28, 2022, at 2:03 PM, Tabak, Lawrence (NIH/OD) [E] < (b) (6) wrote:

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Larry

From: "Chao, Brittany (NIH/OD) [E]" < (b) (6)
Date: Friday, May 27, 2022 at 5:58 PM
To: LAT-Homework Meeting < (b) (6) "Tabak, Lawrence (NIH/OD) [E]" < (b) (6)
Cc: "Aklin, Courtney (NIH/OD) [E]" < (b) (6) "Burrus-Shaw, Cyndi (NIH/OD) [E]" < (b) (6) "Dzokoto-Pomenya, Caroline (NIH/OD) [E]" < (b) (6) "Landis, Erica (NIH/OD) [E]" < (b) (6) "McManus, Ayanna (NIH/OD) [E]" < (b) (6) "Simon, Dina (NIH/OD) [C]" < (b) (6) "Burklow, John (NIH/OD) [E]" < (b) (6) "Walsh, Elizabeth (NIH/OD) [E]" < (b) (6) "Chao, Brittany (NIH/OD) [E]" < (b) (6) "Schwetz, Tara (NIH/OD) [E]" < (b) (6)
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looking like I will be in South Korea for a presentation on 8/31 and a meeting on 9/1. Because of timing and duration of flights, it pretty much knocks out the whole week for me. **ok, since we are driving I can remain in contact the entire time**

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Best,
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c:	Chao, rittany (NIH/OD) [E]; LAT-Homework Meeting; Aklin, Courtney (NIH/OD) [E]; urrus-Shaw, Cyndi (NIH/OD) [E]; Dzokoto-Pomenya, Caroline (NIH/OD) [E]; Landis, Erica (NIH/OD) [E]; Simon, Dina (NIH/OD) [C]; urklow, John (NIH/OD) [E]; Walsh, Elizabeth (NIH/OD) [E]
Subject:	RE: LAT homework May 2
Date:	Sunday, May 2 , 2022 :2 :00 PM

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Sent: Sunday, May 29, 2022 5:01 PM
To: Tabak, Lawrence (NIH/OD) [E] <(b) (6)
Cc: Chao, Brittany (NIH/OD) [E] <(b) (6) LAT-Homework Meeting <(b) (6) (b) (6); Aklin, Courtney (NIH/OD) [E] <(b) (6) Burrus-Shaw, Cyndi (NIH/OD) [E] <(b) (6) Dzokoto-Pomenya, Caroline (NIH/OD) [E] <(b) (6) Landis, Erica (NIH/OD) [E] <(b) (6) McManus, Ayanna (NIH/OD) [E] <(b) (6) Simon, Dina (NIH/OD) [C] <(b) (6) Burklow, John (NIH/OD) [E] <(b) (6) Walsh, Elizabeth (NIH/OD) [E] <(b) (6)
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Subject:	Re: LAT homework May 2
Date:	Sunday, May 2 , 2022 5:02:5 PM
ttac me t :	CCRH 2022 0 01 Meeting Summary pdated 05 2 22[1] pdf H C TPs doc H C funding trends ppt

---

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