waterskrauspaul

May 24, 2023

(Sent via Email)

Richard Woychik, Ph.D.
National Institute of Environmental Health Sciences
111 TW Alexander Drive
Durham, NC 27709

Dear Dr. Woychik –

Thank you for the vital work that the National Toxicology Program (NTP) is performing under your leadership on the subject of fluoride's neurodevelopmental toxicity.

I write today as an attorney for plaintiffs in a federal lawsuit on fluoride's neurotoxicity because I have come into possession of information that may be relevant to your ongoing fluoride assessment.

At the May 4, 2023 meeting of the Board of Scientific Counselors (BSC), one of the BSC members recommended that NTP's meta-analysis on fluoride/IQ include a discussion of other recently published meta-analyses, including the paper by Jayanth Kumar, et al., titled "Association between low fluoride exposure and children's intelligence: a meta-analysis relevant to community water fluoridation."

I agree it would be helpful for NTP to explain how and why its meta-analysis differs from these other assessments, including on the risk-of-bias determinations. Towards this end, I am providing you information about the Kumar meta-analysis that is not available in the published manuscript; including documents obtained through Public Records Act requests to the California Department of Public Health; depositions of both Dr. Kumar and his colleague Chris Wood;[1] and documents generated during the course of the federal court proceedings.

Dr. Kumar Has a Conflict of Interest

As an initial matter, Dr. Kumar has a conflict of interest on the fluoride issue that, as with all conflicts of interest, should be given due consideration. Dr. Kumar is California's State Dental Director and serves on the American Dental Association's

[1] Due to their large file size, I have not included the depositions in the Appendices to this letter. Instead, I have posted complete copies of these depositions, including all of the deposition exhibits, to Dropbox at the following link: https://tinyurl.com/depositions-and-video

(ADA) National Fluoridation Advisory Committee.[2] I discussed the biases that Dr. Kumar may have on the fluoride issue at his deposition on March 31, 2023. At the deposition, Dr. Kumar agreed that his "job is to promote fluoridation" and that he "is literally being paid to promote fluoridation." (Kumar Transcript at 38:5-12 & 230:16-21). Dr. Kumar testified he works closely with a public relations professional to promote fluoridation, including "coming up with messaging and strategies for how to best promote fluoridation." (*Id.* at 50:23-51:22). Dr. Kumar further testified he has received awards for his fluoridation advocacy, including an award from the ADA and others which recognized his "longstanding dedication and service to the public for his work to promote water fluoridation." (*Id.* at 41:2-19). Another award recognized Dr. Kumar for his "instrumental" work in "implementing community water fluoridation in many communities." (*Id.* at 42:2-13).

Dr. Kumar Had a Preconceived Conclusion for His Meta-Analysis

By his own statements, it appears that Dr. Kumar had an agenda in mind when he wrote the meta-analysis. In a presentation to colleagues in February 2021, Dr. Kumar announced he was going to write a meta-analysis to "preempt" the NTP and that his paper would show that fluoride has no significant effect on IQ at the levels used to fluoridate drinking water.[3] In the presentation, Dr. Kumar expressed hope that a "friendly editor" would publish his analysis, and in later emails he discussed the "urgency" of getting the paper published. (Appx. 1, at 1.) At his deposition, Dr. Kumar agreed it was his "goal" to publish the meta-analysis before the NTP and that this goal was "important" to him. (Kumar Transcript at 231:8-12).

Dr. Kumar's Biases Influenced His Analyses of the Data

Emails between Dr. Kumar and his co-authors confirm that biases influenced the team's analysis of the data. Perhaps most notably, when Dr. Kumar's team did a dose-response analysis of endemic fluorosis studies, they found a significant adverse association between fluoride and IQ ***below*** 1.5 mg/L. (Appx. 2, at 4.) On March 5, 2022, Kumar's biostatistician Honghu Liu reported "we have done analyses trying to identify a threshold (e.g., around 1.5 mg/L) in hope to see a non-significant fluctuation

[2] The ADA is an organization that aggressively lobbies to promote water fluoridation, restrict the public's access to low-cost dental therapists, and other oral health policies. As noted by the *Washington Post*, "Among the general public, dentists tend to have a Norman Rockwell appeal — solo practitioners who clean your teeth, tell your kids to cut down on the candy, and put their seal of approval on a range of minty toothpastes and mouthwashes. But lawmakers from Maine to Alaska see a different side of dentists and their lobby, the American Dental Association, describing a political force so unified, so relentless and so thoroughly woven into American communities that its clout rivals that of the gun lobby." Mary Jordan, *The Unexpected Political Power of Dentists*, WASH. POST., July 1, 2017, available online at https://tinyurl.com/washpost-ada.

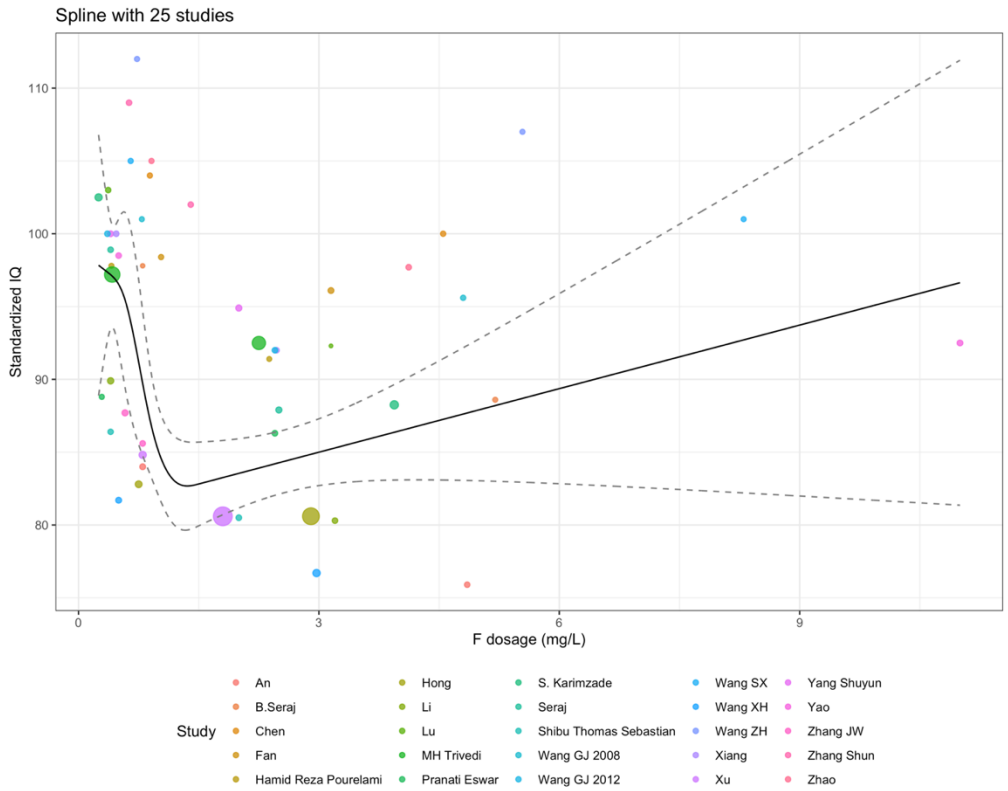
[3] I have posted the relevant excerpt from Dr. Kumar's presentation to the aforementioned Dropbox link (https://tinyurl.com/depositions-and-video).

in IQ before the threshold and significant drop in IQ after the threshold value." (Appx. 2, at 4.) The results, Dr. Liu reported, "are opposite to what we hoped for: the line below the threshold of 1.5 mg/L is significant, but the line after the threshold is not significant." (*Id.* at 4.)

Since these results did not support their hypothesis, Dr. Liu suggested using different models to see if the results would change. (*Id.* at 4.) As he noted, "although hard, we can test more models to try to identify a threshold that can lead to a non-significant fluctuation in IQ before the threshold and a significant drop in IQ after the threshold." (*Id.* at 4.)

The figure below reflects a further analysis that the team conducted, which was included in a March 19, 2022 draft of the paper. This figure shows a steep decline in IQ in endemic fluorosis areas as the water fluoride levels increase from 0 to 1.5 mg F/L.

This analysis, which contradicts Dr. Kumar's conclusion, was omitted from the manuscript that he submitted for publication.



Dr. Kumar Failed to Incorporate Previous Peer Review Recommendations

Dr. Kumar's meta-analysis had been rejected four times prior to the journal *Public Health* accepting it for publication. (Kumar Transcript, at 236:11-13). The *Journal of the American Dental Association* (*JADA*) had rejected two versions of Kumar's meta-analysis, and the journal *Pediatrics* rejected Kumar's meta-analysis after both an initial, and (at the authors' request) second, round of peer review. (Kumar Transcript at 214:3-13; 216:15-217:22; & 225:18-226:13).

While the peer reviewers for *JADA* and *Pediatrics* did not have access to the undisclosed analysis discussed above, they still found many problems with the manuscript. Reviewer No. 1 for *JADA* described the paper as "superficial," "unbalanced," and "misleading," and cautioned, "I'm afraid that the misinformation in this manuscript will fuel more controversy rather than stimulate prudent science-based decisions." (Appx. 3, at 2; Appx. 4, at 5).

Reviewer No. 2 for *JADA* took exception to Dr. Kumar's dismissive approach to observational studies, noting "Observational studies are the optimal study design to address some of the most important questions in public health. For example, observational studies were the key studies used to infer a causal association between tobacco smoke and lung cancer, asbestos and mesothelioma, and lead and IQ deficits. The reduction of tooth decay from fluoride exposure was predominantly based on observational studies." (Appx. 3, at 3-4). This *JADA* reviewer also took exception to Dr. Kumar's claim (which remains in the published manuscript) that there is "no cogent explanation" for fluoride's neurotoxicity. (*Id.* at 4.) The reviewer noted, "Thyroid disruption is one possible explanation for fluoride's toxicity on fetal brain development. The evidence indicating that thyroid disruption is an underlying mechanism - or the key mechanism - for fluoride neurotoxicity is not definitive, but it is a cogent hypothesis supported by considerable evidence." (*Id.*)

The peer reviewers for *Pediatrics* were similarly critical of Kumar's paper. One peer reviewer called Kumar's basis for dismissing the results from endemic fluorosis areas "fallacious." (Appx. 5, at 3). This reviewer also took exception to Kumar's dismissal of observational studies, noting that "the problems in interpreting F studies are not unique, and many topics, especially in environmental epidemiology, are not amenable to RCTs." (*Id.*) This reviewer explained (as did a *JADA* reviewer) that the exposure misclassification issues that Kumar discusses would tend to bias results toward the null, rather than towards spurious associations. (*Id.* at 2.) Kumar's published manuscript fails to acknowledge this concern.

Another repeated criticism in the *JADA* and *Pediatrics* peer reviews is that Kumar's conclusion is not supported by his analysis. A peer reviewer for *Pediatrics* called Kumar's conclusion "internally inconsistent," explaining that "In spite of the authors'

list of the weaknesses in the quality of the data, a very strong, unqualified conclusion is drawn, i.e., 'These meta-analyses show that fluoride concentration used in community water fluoridation is not associated with lower IQ scores.'" (Appx. 5, at 3-4). A *JADA* peer reviewer called this definitive conclusion an "unashamed exaggeration," while another *Pediatrics* peer reviewer called it a "stretch." (Appx. 3, at 2; Appx. 7, at 3). Despite this concern being repeatedly expressed by peer reviewers, Dr. Kumar retained the unqualified conclusion in the published manuscript.

Kumar's Conclusory Risk-of-Bias Assessment Is at Odds with EPA's Assessment

The supplemental materials to Kumar's analysis include a risk-of-bias assessment, wherein Kumar ranks the Broadbent study as a higher quality study than the NIH-funded ELEMENT and MIREC studies. In fact, Kumar ranks the Broadbent study as the highest quality study to date on fluoride/IQ. This is not only at odds with NTP's assessment, it is at odds with the assessment of the Environmental Protection Agency (EPA).

In the federal court case on fluoride's neurodevelopmental toxicity, the EPA agreed that it was an "undisputed fact" that the fluoride/IQ studies from the ELEMENT and MIREC cohorts ***"are the most methodologically reliable human studies to date on the impact of fluoride on neurodevelopment."*** (Appx. 7, at 2-3, emphasis added).

The epidemiologist that EPA retained for the case (Dr. Ellen Chang) agreed with EPA's assessment. Dr. Chang explained that the ELEMENT and MIREC studies are "better conducted," "more rigorous" and "more informative" than the Broadbent study because they include individual biomarkers of exposure during the prenatal period. (Appx. 8, Chang Trial Testimony, at 883-86).

In contrast to the ELEMENT and MIREC studies, the Broadbent study used an ecological measure of waterborne-fluoride exposure, and made no attempt to ascertain fluoride exposures during the critical prenatal period.

As Dr. Philippe Grandjean explained in the federal court case, Broadbent's failure to ascertain prenatal exposures "is an important limitation given the high rate of tea consumption in New Zealand." (Appx. 9, Grandjean Trial Declaration, at 27). In his declaration for the federal court case, Dr. Grandjean explained:

> Tea contains elevated levels of fluoride, and tea consumption can be a major source of fluoride intake among adults (Waugh 2017). During the time that the children in [the Broadbent] study were born (1972-1973), New Zealanders consumed as much as 2.6 kg of tea per capita per year (corresponding to 3-4 teabags per day), as compared to the

> consumption of 0.5 kg in Canada in the approximate time the MIREC cohort was recruited (Grigg 2002). The failure of [the Broadbent study] to consider maternal tea consumption may have introduced substantial imprecision into the exposure classification.

(*Id.*) "An additional concern" with the Broadbent study, according to Dr. Grandjean, "is that the 10% of cohort subjects who had not lived in fluoridated areas very likely received fluoride supplements, which would eliminate much of the (postnatal) difference in exposure between the fluoridated and non-fluoridated areas." (*Id.*)

Further Evidence of Dr. Kumar's Bias

A rigorous debate is to be welcomed as part of scientific inquiry. A rigorous debate, however, is not advanced by spreading false assertions or retaliating against scientists who publish unwelcome findings. Dr. Kumar appears to have been involved in the latter type of conduct, which further evinces a bias in his work.

Dr. Kumar Has Made False Claims About the MIREC Scientists

Dr. Kumar has repeatedly insinuated that the MIREC scientists are refusing to release their data for reanalysis. In a letter that Dr. Kumar asked the Association of State & Territorial Dental Directors (ASTDD) to send to the Directors of the NTP, NIDCR, and NIH, Kumar wrote: "The authors of these studies have not released the data to confirm their findings." (Wood Transcript at 121:8-122:10). When he wrote this, Dr. Kumar was aware that the MIREC study authors expressly *supported* a re-analysis of their data, but omitted this fact from the letter to NIH leadership. (Kumar Transcript, at 173:14-174:5; Appx. 10, at 1). Dr. Kumar also omitted the fact that the authority to release the data rested not with the study authors, but with the MIREC Biobank Committee. (Wood Transcript at 128:22-129:21). Dr. Kumar further omitted that the MIREC Biobank Committee *will* release the data to any *qualified* team that complies with Biobank's *established policies*. (Appx. 10, at 5). Dr. Kumar also omitted the fact that the research team he assembled to analyze the MIREC data failed to meet the Biobank criteria due to ideological bias, lack of qualifications, failure to identify clear limitations in the MIREC team's analyses, and failure to identify any "recognizable and significant methodological improvements to the analysis that Green et al conducted." (Appx 11; Kumar Transcript at 174:17-24 & 184:7-190:23).

Later, in July 2021, Dr. Kumar repeated his claim that "the [MIREC] authors are not releasing the data" as justification for the ASTDD signing onto a complaint of scientific misconduct against the MIREC team. (Appx. 12, at 2). Dr. Kumar encouraged ASTDD to add its name to the complaint (A) despite not having read the full complaint, and (B) despite being told that the complaint had been determined by

legal advisors to be "defamatory." (Appx. 12, at 4; Kumar Transcript, at 236:20-24 & 247:14-23; *see also* Wood Transcript at 161:2-181:4).

The misconduct complaint alleged that the MIREC scientists committed "falsification" by failing to give sufficient emphasis to the *unadjusted* average IQs in the fluoridated and non-fluoridated areas, which the complaint characterized as the "main effect" of the study.[4] (Kumar Transcript at 269:21-273:3). Each of the seven institutions[5] that received the complaint found it to be meritless (Kumar Transcript at 327:1-8), but the process of investigating the claims caused substantial disruption to the research being conducted by the MIREC scientists. (Kumar Transcript at 245:4-249:4.)

The unanimous refutation of the misconduct complaint has not dissuaded Dr. Kumar from making additional claims of improper conduct against the MIREC scientists. In 2022, Dr. Kumar tried to get the journal *Environmental Research* to issue an "Expression of Concern" about another paper from the MIREC team (i.e., Farmus, et. al. 2021), on the purported grounds that the authors hid data that contradicted their conclusions.[6] (Kumar Transcript at 296:11-301:21). After the authors explained, in a published addendum, that the data in question had no bearing on the conclusions and was removed at the suggestion of a peer reviewer, Dr. Kumar recruited others to submit letters to the editor criticizing the MIREC scientists for removing the data. (Kumar Transcript at 301:19-313:6; Wood Transcript at 194:18-200:14.)

Dr. Kumar Has Made False Claims About the NTP

Finally, there are claims that Dr. Kumar has made about the NTP which are clearly false. I only mention them here because they highlight the severity of Dr. Kumar's bias on the fluoride issue.

Dr. Kumar, along with his colleagues at the ADA, have repeatedly claimed and/or insinuated that NTP's scientists are acting in bad faith, including secretly collaborating with the Fluoride Action Network (FAN).

---

[4] This assertion of "falsification" is at stark odds with a previous document that Dr. Kumar drafted for ASTDD, where he suggested that focusing on unadjusted data, when adjusted data is available, is "a violation of the standard codes of scholarly conduct and ethical behavior in professional scientific research." (Kumar Transcript at 278:16-295:24).

[5] The complaint was sent to the five universities that employ the MIREC scientists, as well as *JAMA Pediatrics* and the HHS's Office of Research Integrity. (Appx. 10, at 4).

[6] Dr. Kumar also asked the ASTDD to send a letter to the Directors of NTP, NIH, and NIDCR (which Kumar drafted) stating that the omission of the information was "inexplicable." The ASTDD never provided a follow-up letter to NTP/NIH/NIDCR when ASTDD learned that the information was omitted at the suggestion of a peer reviewer due to its irrelevancy. (Wood Transcript at 152:7-153:12 & 156:6-157:2).

In a March 1, 2021 email, Dr. Kumar told fluoridation lobbyists and advocates that "FAN is not interested in a finding above 1.5 mg/L. So, NTP slanted the report to give the impression that it is a hazard even below 1.5 mg/L." (Appx. 13 at 1).

In a May 2, 2022 email, Dr. Kumar told leaders of the International Association for Dental Research that "We conducted multiple meta-analyses and there is no effect of fluoride on IQ at levels below 1.5 mg/L F. NTP authors also noticed this but didn't want to state it." (Appx. 14).

In a September 20, 2022 letter that Dr. Kumar asked the ADA to submit to the BSC,[7] the ADA wrote: "We note that NTP proposed commissioning its report in 2015, which is just prior to when FAN petitioned EPA (2016) and subsequently filed its lawsuit (2017). We would welcome more transparency about whether and how these events may be connected." (Appx. 15, at 3).

As with the defamatory complaint of scientific misconduct that went to seven institutions, the ADA's letter was circulated far and wide, including to top leadership at HHS.

Concluding Remarks

The public counts on NTP to provide the best available science on the chemicals that impact their lives. I recognize this is a challenging task, particularly for chemicals with significant political interests at stake, but it is vital nonetheless. With this in mind, I am hopeful that the information presented in this letter will be helpful to NTP's assessment of the recent meta-analysis by Kumar *et al.*

Sincerely,

Michael Connett, Esq.

CC: Milene Brownlow
Andrew Rooney
Robert Sills
Kyla Taylor
Mary Wolfe

[7] In the summer of 2022, Dr. Kumar asked the ADA to submit criticism of the NTP's May 2022 monograph to the BSC, and helped draft ADA's comments. (Kumar Transcript at 103:4-105:22).

Appendix 1

From: Kumar, Jayanth@CDPH
To: Moss, Mark Eric
Subject: RE: Next steps - Manuscript
Date: Tuesday, July 19, 2022 2:25:00 PM
Attachments: Lam. PBDEand IQEHP1632.pdf

I think so. I thought of EHP, but I think we run into the same problem. I wanted to publish the paper before the NTP report. There is some urgency.

Juleen Lam, who is considered an expert on systematic review and meta-analysis, published a paper in EHP with only four studies! She served on the NTP review committee. Our analysis is much more robust.

Your thoughts?

From: Moss, Mark Eric <MOSSM17@ECU.EDU>
Sent: Tuesday, July 19, 2022 2:14 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Subject: Next steps - Manuscript

This Message Is From an External Sender
This message came from outside your organization.
Report Suspicious

So is CDOE our choice now?
Should I review and use track changes as we discussed?
-Mark

From: "Fisher-Owens, Susan" <Susan.Fisher-Owens@ucsf.edu>
Date: Tuesday, July 19, 2022 at 12:52 PM
To: "Kumar, Jayanth@CDPH" <Jayanth.Kumar@cdph.ca.gov>, "Liu, Honghu, Ph.D." <hhliu@dentistry.ucla.edu>, "Moss, Mark Eric" <MOSSM17@ECU.EDU>
Subject: RE: PEDIATRICS/2022/058047 - Manuscript Decision

This email originated from outside ECU.

CDOE IF: 3.383

Guidelines for authors:
https://onlinelibrary.wiley.com/page/journal/16000528/homepage/forauthors.html

I do think CDOE will be easier to get this in than JAMAPeds. It's a different audience, though. It is really not going to hit many pediatricians/physicians, but I can work on that.

I wouldn't do an op-ed in same journal, either way.

S

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Tuesday, July 19, 2022 12:39 PM
To: Fisher-Owens, Susan <Susan.Fisher-Owens@ucsf.edu>; Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: PEDIATRICS/2022/058047 - Manuscript Decision

Susan,

Thanks for the insight. I reached out to Luisa Borrell, Associate Editor of AJPH. She didn't think AJPH is a good fit – "However, if you look at systematic review in AJPH they are mostly published as part of a Special Issue or supplement."

She encouraged us to submit the manuscript to Community Dentistry and Oral Epidemiology, a popular journal worldwide. She is also an associate editor of this journal. If we can get it published in this journal, you can write an op-ed.

CDOE accepts free formatting. We can submit the manuscript as is, and the journal will reformat it.

From: Fisher-Owens, Susan <Susan.Fisher-Owens@ucsf.edu>
Sent: Tuesday, July 19, 2022 9:25 AM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: PEDIATRICS/2022/058047 - Manuscript Decision

Hi,

This is disappointing, but not unsurmountable.

Jay had asked me earlier about other pediatrics journals. For the US, I would say JAMA Peds (IF 26.8) or Ambulatory Pediatrics ("a peer-reviewed publication whose purpose is to strengthen the research and educational base of academic general **pediatrics**"; IF 3.107). The former has a higher IF (even than AJPH), but it is more "sciency". The latter is a better fit but lower IF.

Still, I think AJPH will get to more readers in PH, and I can do op-ed pieces in the Peds "throwaways", which still a lot of people read to get the headlines.

Here's the link to formatting for AJPH: https://ajph.aphapublications.org/page/authors.html

Susan

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Monday, July 18, 2022 12:55 PM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>; Fisher-Owens, Susan <Susan.Fisher-Owens@ucsf.edu>
Subject: RE: PEDIATRICS/2022/058047 - Manuscript Decision

In preparation for submission to APHA, I had reached out to former editor Mary Northridge. She was very supportive.

I will reach out to Luisa N. Borrell, DDS, PhD, City University of New York, Graduate School of Public Health, NY. She is an associate editor. She is a former resident of our program.

Jay

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Monday, July 18, 2022 9:07 AM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Moss, Mark Eric <MOSSM17@ECU.EDU>; Susan.Fisher-Owens@ucsf.edu
Subject: Re: PEDIATRICS/2022/058047 - Manuscript Decision

This a disappointing but happens a lot in journal review process...

Appendix 2

From: Liu, Honghu, Ph.D.
To: Kumar, Jayanth@CDPH
Cc: Moss, Mark Eric
Subject: Re: Fluoride-IQ manuscript
Date: Monday, March 7, 2022 12:18:57 PM

I have the similar feeling---if we do identify one, it will be preliminary with exploratory nature as we do not have enough data from rigorously designed trials.
Best,
H

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Monday, March 7, 2022 11:49 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Cc: Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

Grandjean calaculated a dose. According to him, there is no safe dose. But he did not consider the Ibarluzea study from Spain. The NAS committee wanted NTP to focus on hazard identification. Based on the unsophisticated quality of the studies, they were skeptical of a dose-response analysis. But one explanation for the heterogeneity in the effect size is dose.

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Monday, March 7, 2022 11:10 AM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Cc: Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

Hi Jay,
Yes, I agree that using 9 studies will be consistent with our notion of examining low/normal F level (and the results are in favor of our hypothesis--we can show both the non-linear modeling with restricted cubic spline and the linear approximation).
Zhang Shun is indeed an outlier (it provides among the worst point estimates against our hypothesis with IQ=102 when F is high, but IQ=109 when F is low); given his F high=1.4 and F low=0.63, we will still include his study in analyses; the good thing is his data is not strong enough to turn the hypothesis testing around.

We are in very good shape for the analyses and results for F dosage of low/normal.

I am now working on the next part of the analyses---trying to identify a threshold, if all possible. Given the heterogeneity of the studies available to use and the limited quality for quite some of them, this will be challenging. I think that if we do can identify one, it will unlikely be exactly 1.5 mg/L---it will be somewhere around 1.5. I will let you know the results.

I will do my best to join on Wed.

Have a nice and safe trip.
Best,
Honghu

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Monday, March 7, 2022 5:29 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Cc: Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

CAUTION - EXTERNAL EMAIL:Do not click links or open attachments unless you recognize the sender.
Honghue,

I agree with Mark. This is excellent work. Overall, all the models below 1.5 mg/L are not significant. It makes sense to use 9 studies from non-endemic areas. Figures 2 (SMD- 2. Meta-analysis (linear) -- see Meta_lr_N9.png Wald test: p-value = 0.87); and 3 Absolute IQ (restricted cubic spline) -- see StdIQ_N9.png (Standardized score).

This aligns with our SMD analysis (Normal to lower). Zhang Shun (2015) is an outlier. It changes the heterogeneity from 0% to 69%.

I will send the Zoom link. If possible, please attend.

Jay

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Saturday, March 5, 2022 8:45 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Cc: Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

EXTERNAL EMAIL. Links/attachments may not be safe. To report suspicious emails, click “Report Phish” button.

hi Jay,

Here are the summarized results. I put them in the attached word file for your convenience. Let me explain how the analyses were done and their implication here below in the email.

(I) <u>low/normal F dosage modeling with the selected 13 studies.</u>

First, let's look at the 13 studies you recommended with Diff in F dosage no more than 1.5 mg/L. Here are a few issues I like to mention:

(1) Among the 13 studies, Xu 2020 used very high IQ value >120 which is significantly higher than most, if not all, other studies so we did analyses with (N=13) and without (N=12) Xu 2020 in the analyses; Also, to evaluate the relationship between absolute F dosage and IQ level, we also looked at the sub-set of studies that have absolute F dosage <1.5mg/L (N=9 studies). Thus, we have analyses results for N=12, 9, and 13 studies, all having Diff in F dosage no more than 1.5 mg/L.

(2) We have done both non-linear modeling with restricted cubic spline (RCS) and linear modeling (piece-wide modeling when necessary) for both SMD IQ and absolute IQ, recognizing that for modeling with absolute values, the two data points within a study are not completely independent, even though the estimates were calculated by different subjects. However, all point estimates of IQ are valid, and the potential non-independence could only lead to an over-estimate of significance to some degree which is not a problem for us here since we are seeking for non-significant impact of F dosage on IQ when F dosage is low/normal (if we do not see significant result with our analyses, it will be even more non-significant, if the data were completely independent.)

(3) For non-linear modeling with RCS, the parameter estimates from regular non-linear modeling with RCS (e.g., using R programming language) are relatively more detail and easier to interpreter than parameter estimates provided from meta analyses with RCS procedure.

For RCS through regular non-linear modeling, the number of cubic terms will equal to the number of knots one selects with two ends being restricted to linear (that is why it is called RCS). The R package generates a truncated power basis for a RCS, which means, the spline is the linear addition of the basis functions across the entire domain. For example, with the spline with absolute IQ and 12 studies (N=12, see page 3 of the word file), each term is called a basis function and together they make up the estimated restricted cubic spline function. There are four cubic terms, in which the values 0.15, 0.63, 1.02, 1.5 are the four knots we specified. Also in the above function, notice that

- when F < 0.15, the fitted function is 98.9959 - 12.38035*Dose
- when F = 1.5, the sum of the coefficients of cubic terms is 14.35524-33.42762+20.21344-1.141062 = -2e-06, approximately equals to zero. So it will be 98.9959 - 12.38035*Dose again as when F<0.15. This will be also true for the quadratic terms (if we expand the fitted model and write out the quadratic terms, we will see this results). This confirms that two ends of the spline are linear. See References about truncated power basis:

https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-019-0666-3
https://bookdown.org/alecri/thesis/A-sec-rcs-app.html).

For meta analyses for non-linear modeling with RCS, the outputs provided by the software procedure are limited to some degree. For example, for fixed-effects coefficients, it only provides two summarized parameters. These parameters are called regression coefficients for spline. They have some mathematical relationship with the coefficients in the full formula/equation of spline results shown in the regular RCS modeling above. Specifically, the first parameter rcs(dose, knots)dose is associated with linear term in the full formula/equation, and the second parameter rcs(dose, knots)dose' is associated with non-linear terms. Usually people don't interpret these parameters as there is no detailed descriptions available in the software package (even for regular RCS, we normally do not interpret much of the parameter estimates themselves from RCS).

(4) We have obtained p_values for both RCS and linear modeling. For linear modeling, the p-value is simple and associated each line (for its slope; if piece-wide, one p-value for each piece of line); For non-linear with RCS, the p-value is the significance testing result of overall modeling across the multiple spline terms through Wald test that has a Chi-Square distribution. Looking through the p-values across N=12, 9 and 13, we can see that all modeling results both from SMD and absolute IQ are non-significant which support our hypothesis that when F dosage is in normal/low range, there is no significant impact on IQ development among children.

(5) Although not ideal/optimal, the modeling results of both SMD and absolute for F in the low/normal range have each own merit and limitations. For SMD, it uses one summarized data point from each study and standardized the difference in means, and shows the relation between the differences in F dosages in high and low, and the SMD. However, unless we restrict the range of high F dosage to 1.5 mg/L (N=9), even the axis (diff in F) is limited to 1.5mg/L, it is the difference in F dosage between high/low and a little hard to interpret in the context of low/normal range of F (e.g., a low diff in F dosages doesn't necessarily mean low F dosages were used in each arm, and so is true vice versa), since we include studies that use F dosages beyond 1.5 mg/L. For absolute F dosage and IQ, it shows in a straight and bare relationship between levels of F dosage and IQ levels, and easier to understand, but there is a potential non-independent issue which we need to clarify. Although the trends of non-linear curves between SMD (down trend) and absolute F dosage/IQ /F (convex-up) modeling are different, they do not contradict each other, rather they reflect the different ways we use to describe the relationship between F dosage levels and IQ levels. The good news is that no matter which way we analyze the data, we do not see a significant fluctuation in levels of IQ when F dosage is in low/normal range which clearly support our hypothesis----it is safe to drink fluoridated water when F dosage is in low/normal range.

(II) Low/normal and high F dosage modeling with more studies

Second, although we do not have good data when F dosage is high (partially due to low quality of studies in endemic areas with high F dosage), we have done analyses trying to identify a threshold (e.g., around 1.5 mg/L) in hope to see a non-significant fluctuation in IQ before the threshold and significant drop in IQ after the threshold value. Since there is so much variation in IQ metric, F dosage, and study conditions, the analyses are complicated. We have done two modeling with N=33 studies and N=32 studies with *D. Mondal 2015 being excluded* which we cannot standardize its IQ values. Although the results are very sensitive to some single studies (e.g., the N=33 and N=32 piece-wide linear regression results are quite different), the N=33 piece-wide linear regression show some promise (both linear line have down-trend, but the results are opposite to what we hoped for: the line before the threshold of 1.5 mg/L is significant, but the line after the threshold is not significant). There still some more work for this part. Although hard, we can test more models to try to identify a threshold that can lead to a non-significant fluctuation in IQ before the threshold and a significant drop in IQ after the threshold.

I will also write out the statistical methods/approaches for these analyses and modeling.

Questions, let me know.

Best,
Honghu

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Friday, March 4, 2022 4:44 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Cc: Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

Hi Jay,
I am organizing and summarizing the model parameter estimates, significance testing, and the smoothed figures using the 13 studies with different sub-sets. I should be able to send you the summary tomorrow Saturday or Sunday.
Talk soon.
Best,
Honghu

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Thursday, February 17, 2022 10:48 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

Honghu,

I was able to find two more studies <1.5 mg/L range. I will check with Mark and send it you by Monday.

Jay

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Sunday, February 13, 2022 1:16 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

Agreed. Specific fitted non-linear models with parameter estimates, statistical tests, and p-values, as well as smoothed figures for visual display will make the paper strong.
Best,
H

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Sunday, February 13, 2022 10:13 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

Thanks. We need to include parameter estimates and test results.

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Saturday, February 12, 2022 1:53 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

Thanks, Jay, for the list of 10 studies.

I checked against my list (see first excel file that was sent to you last Wed 9:52pm and grouped studies into Group 1, Group 1, Group 3) and your 10 listed studies are all in my list. I put group affiliation in the first column in your excel file (second attached excel file) so you can see (G1 (Group 1) or G2 (Group 2)) . I might have used a slightly different calculated F dose for Xu 2020, but will check and re-fit models.

I have thought through more this morning. I will explore further modeling. For example, in addition to the normal range (around <1.5mg/L) modeling, I will try to come up with a parametric test, if possible, to show its fluctuation in IQ is not significant, when F dose is within range of low/normal; Since for high F dose, the quality of studies are not comparable with those with normal/range range, I will try to fit them separately; if possible to come up with another parametric test.

It will be solid/strong and we will get there.

Best,
Honghu

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Saturday, February 12, 2022 9:51 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

I forgot to add the file.

From: Kumar, Jayanth@CDPH
Sent: Saturday, February 12, 2022 9:50 AM
To: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: RE: Fluoride-IQ manuscript

Honghu,

Thank you for that excellent presentation. Regarding more studies <1.5 F difference, I created a separate sheet with 10 studies.

1. Xu 1994 has data comparing normal (control group) vs. low.
2. Bashah 2007. The authors provide the range of CUF (0.18 to 2.8). Then they provide the 25^{th} and 75^{th} percentile values (0.54, 1.01). I used these for lower and higher values.
3. Xu 2020 has average CUF. The difference is 1.19.

From: Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Sent: Wednesday, February 9, 2022 9:52 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Moss, Mark Eric <MOSSM17@ECU.EDU>
Subject: Re: Fluoride-IQ manuscript

Hi Jay,

I summarize here the nonlinear modeling with restricted cubic spline results examining the relationship between fluoride dosage and IQ level through meta-analyses using SMD and through our own meta-analyses with regular spline procedure using observed IQ scores under varying conditions of weighted/unweighted for precisions, standardize/non-standardized IQ, absolute/difference in F dose on x-axis, etc.

First, the excel file summarizes the 7 studies we use in the current draft paper, and the 26 studies used in Duan's paper, including the year of the study, country, and intelligence assessment methods each one used. I divide all studies into Group 1-3:

- Group 1: the 7 studies in our draft
- Group 2: studies from Duan's paper with F dosage<= 5.2
- Group 3: studies from Duan's paper with F dosage > 5.2

1. Standardization of the IQ score.

One of the issues is to try to standardize the IQ scores, if possible, which has been challenging due to limited information available, but we have tried and standardized for most of them except two studies so far.

We found that most of the IQ scales yield standard scores, i.e.,
- Wechsler test: Mean = 100, SD = 15
- Stanford-Binet test: Mean = 100, SD = 16
- Catell test: Mean = 100, SD = 24
- McCarthy Scales of Children's Abilities: Mean = 100, SD = 16.

Besides, the Raven test and Chinese standardized Raven test use the same methodology as the Wechsler Intelligence Scale.
So we converted IQ scores from other tests to the Wechsler test (Mean = 100, SD = 15):
NewIQ = ((OldIQ - 100) / OldTestSD) * 15 + 100.

However, there are two studies we cannot standardize so far (still searching ways to do so):

1. No.8 (Zhang JW et al.) used the Draw-a-Person test standardized by a Japanese researcher. We couldn't find detailed information about this test.
2. No.25 (D. Mondal et al.) reported the raw Raven score. We need the corresponding distribution in Wechsler scale for raw Raven score conversion, but it is not available.

We are still looking, and hope can find a solution.

(II)non-linear cubic spline results: the attached zipped file contains 14 fitted restricted cubic spline models with figures:

1. SMD_Meta figures. These 6 figures were fitted using R language meta nonlinear cubic spline procedure with SMD or log SMD as the y-axis. The SMD_Meta 4, SMD_Meta 5, and SMD_Spline yield pretty good results.
2. AbsoluteIQ_Spline. These 3 figures were fitted with absolute IQ values (for each study, the two arms contribute two data points in the figure). We can see that the Spline 2 which is weighted by precision of point estimates (the size of the circles is proportional to the level of precision), gives quite good results.
3. StandardizedIQ_Spline3. These 5 figures were fitted with standardized IQ using Wechsler metric as the norm. The StandardizedIQ_All Data gives pretty good results except ((i)an initial acute drop, (ii)two studies are not standardized yet.)

You can tell which is which by checking the labels/legend/title of each figure, but I will walk you through when we meet on Friday.

It is very reasonable to hypothesize that the change in IQ with early low F dose is ignorable (decrease/increase/near flat), and then it is possible to drop once the F dose exceeds certain threshold. Our results are getting closer to support this, and some additional work is still

needed to reach that conclusion. I have some ideas on the next step and will explain to you when we meet.

Regards,
Honghu

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Monday, February 7, 2022 3:12 PM
To: Moss, Mark Eric <MOSSM17@ECU.EDU>; Liu, Honghu, Ph.D. <hhliu@dentistry.ucla.edu>
Subject: Fluoride-IQ manuscript

Mark,

I am virtually introducing you to Dr. Honghu Liu, Professor of Statistics at UCLA. I scheduled a Zoom meeting this Friday at 2 PM PST to discuss the population dose-response analysis to explain the heterogeneity found in the SMD meta-analysis.

Honghu,

Please meet Mark Moss, DDS, PhD. Mark and I have coauthored many papers on fluoridation and its health effects. In addition, we have worked together on the draft manuscript. Before moving to California, we had developed the Fluoride Science website to educate and inform dental and medical professionals.

Looking forward to the presentation.

Thanks.

Jay

Jayanth Kumar, DDS, MPH
State Dental Director
Office of Oral Health, Center for Healthy Communities
California Department of Public Health

Unauthorized redisclosure or failure to maintain confidentiality may subject you to federal and state penalties. If you are not the intended recipient, please immediately notify us by return email, and delete this message from your computer.

Appendix 3

From: Kumar, Jayanth@CDPH
To: Tim_Wright@unc.edu
Subject: FW: Decision on submission to The Journal of the American Dental Association
Date: Saturday, November 13, 2021 6:41:00 AM
Attachments: Ibarluzea.Spain F and IQ.pdf
Figures 2-3-4.docx

Tim,

I have revised the manuscript titled Meta-Analyses of Fluoride and Neurodevelopmental Hazards and am ready to submit it as soon as I get departmental approval. Reviewers 1 and 2 criticized my manuscript as it did not include a maternal urinary F (MUF) and IQ meta-analysis. I was waiting for the new study from Spain to be published (attached). This study found that exposure to fluoride during pregnancy increased IQ among boys.

With the availability of the data from this study, I was able to conduct a MUF-IQ meta-analysis (attached). This finding strengthens my conclusions.

I hope my manuscript resubmission deadline will be extended.

Jay

Jayanth Kumar, DDS, MPH
State Dental Director
Office of Oral Health, Center for Healthy Communities
California Department of Public Health

-----Original Message-----
From: em.jada.0.762815.80afe753@editorialmanager.com <em.jada.0.762815.80afe753@editorialmanager.com> On Behalf Of The Journal of the American Dental Association
Sent: Tuesday, September 21, 2021 4:59 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Subject: Decision on submission to The Journal of the American Dental Association

EXTERNAL EMAIL. Links/attachments may not be safe. To report suspicious emails, click “Report Phish” button.

Manuscript Number: JADA-D-21-00365
Meta-Analyses of Fluoride and Neurodevelopmental Hazards: No Adverse Effect on Children’s Intelligence at Lower Fluoride Exposure Levels

Dear Dr. Kumar,

Thank you for submitting your manuscript to The Journal of the American Dental Association.

I have completed my evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following major revision. I invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by Oct 21, 2021.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. In your cover letter please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. In addition, make sure your revised manuscript shows the changes by highlighting them or using track changes. Please note that your revised submission may need to be re-reviewed. To submit your revised manuscript, please log in as an author at https://urldefense.com/v3/__https://www.editorialmanager.com/jada/__;!!AvL6XA!iaAU6NWj-fQXLW8bSTASX342THBfdssFy17woaUSZC7oV0dE_pmW9qUVQYCanuezUXy34ek3$, and navigate to the "Submissions Needing Revision" folder.

The Journal of the American Dental Association values your contribution and I look forward to receiving your revised manuscript.

Kind regards,

Tim Wright, DDS
Editor-in-Chief
The Journal of the American Dental Association

Editor and Reviewer comments:

Reviewer 1: Given the serious weaknesses of this submission, I shall limit my comments to major issues only.
Meta-analyses: The manuscript is said to provide two meta-analyses of fluoride and neurodevelopmental hazards (with the conclusion of no adverse effect already given in the title). Each meta-analysis is said to be based on an extensive search using multiple data bases, but a surprisingly small number of studies was selected. The literature search is very far from a systematic review and lacks detail on the methodology. Substantial heterogeneity is said to be present and to demonstrate variability of results. However, it would be surprising if two epidemiological studies showed similar results, and indeed, most of such variability is likely due to differences in designs and methods - a highly relevant issue not considered.
Selection of evidence: The manuscript claims that the results of previous meta-analyses have no relevance to U.S. policy-making, as water-fluoride levels were above 1.5 mg/L. A similar argument would remove much of the evidence on hazards, such as asbestos or lead. The manuscript further disregards studies that involved "endemic" areas (not defined). An advantage of countryside studies in countries like China is that the study populations were fairly stable, i.e., that the current water-mediated exposures had remained fairly constant (i.e., since conception), an issue not considered in the manuscript. Nonetheless, the restriction removed most previous studies, even when water-fluoride were at or only slightly above 1.5. A further restriction was to focus on childhood urine-fluoride (age not defined), despite the fact that several sources document that the most vulnerable time regarding developmental neurotoxicity is prenatal and early postnatal. Apart from the erroneous claim that contemporaneous urinary-fluoride also reflects prenatal exposure, the manuscript offers no justification for focusing on postnatal exposure, nor can I think of one. The term "children's urinary exposure" in fact is not specified in regard to sampling method or adjustment.
Misinformation: A recent MIREC study (#2) is misquoted to focus only on a finding that was not statistically significant (those that were significant were ignored). The most recent report (#21) from this prospective study elaborated on an apparent sex-dependent difference, where boys are more sensitive to fluoride exposure prenatally, girls during early infancy. Obviously, these results are counter to the methodology chosen for the present study and are ignored. The first major meta-analysis (#18) comprised 27 studies and included several sensitivity analyses, funnel plot, etc. (not mentioned); the estimated average fluoride-associated IQ loss was given as -0.45, which is said to be the standardized mean difference. But the original paper explains that this number is the relative s.d., which corresponds to an average loss of 6.75 IQ points. The subsequent meta-analysis (6 years later, #19) showed similar results, and 18 of the 27 studies referred to water-fluoride concentrations below 4 mg/L, with fluoride-associated IQ reductions observed at only slightly elevated concentrations of 1 to 2 mg/L. This information is not provided or commented upon.
A paper listed as #42 is referred to as evidence that many stressors can affect children's general cognitive ability, but this study found that fluoride in fact had the greatest impact on cognitive ability, often reported to affect memory and cognitive deficits - a conclusion that was not mentioned. Several epidemiological papers are cited to stress that associations may not be valid or causal. However, while prospective studies are likely more informative than cross-sectional evidence, the manuscript relies on cross-sectional evidence in children and ignores most prospective data (except for the misleading coverage of reference #2). Also, nothing is said about the likely bias toward the null associated with imprecise exposure assessment (e.g., fluoride in a single spot urine from childhood). Overall, the Discussion is unbalanced and misleading.
References: Most of the first several references (#4-9) are agency documents, some not yet complete, and one being a court testimony that is not accessible and authored by a person who appears not to have important credentials in fluoride research or epidemiology. Several of the subsequent references (#10-15) look like agency reports, perhaps in defense of fluoridation. Only one of the three Canadian reports cited has a link, and it does not work. Studies that are reported only as abstracts are said to be ignored, yet ref #33 is an abstract only but is still referred to as evidence of absent neurotoxicity.
Conclusion: The manuscript passionately concludes: "This study provides consistent evidence from two meta-analyses showing that exposure at the level of fluoride used in community water fluoridation is not associated with lower IQ scores." This unashamed exaggeration amply characterizes this poorly researched study and its inherent biases. The manuscript refers to "a contentious debate largely fueled by exploratory studies" and proposes more research before conclusions can be drawn. I'm afraid that the misinformation in this manuscript will fuel more controversy rather than stimulate prudent science-based decisions.

Reviewer 2: This is an intriguing meta-analysis. I was curious and confused about the limited scope of the meta-analysis on IQ in children. My interpretation of the high-quality studies is that no association was observed in most studies of contemporaneous childhood fluoride exposure and IQ decrements. The critical question is not whether contemporaneous childhood exposure is associated with IQ decrements, but whether prenatal exposure - exposure during fetal development - is associated with IQ decrements. Yet the evidence linking prenatal fluoride exposure to cognitive deficits wasn't mentioned; indeed, the author ignored it.

Several toxic chemicals - including mercury and PCBs - exhibit their greatest or negative impact on intellectual abilities only if exposure occurs during fetal brain development. By contrast, lead appears to be particularly toxic during early childhood (Lanphear, 2015).

The author dismissed observational studies as "unreliable" twice in the manuscript. Observational studies are the optimal study design to address some of the most important questions in public health. For example, observational studies were the key studies used to infer a causal association between tobacco smoke and lung cancer, asbestos and mesothelioma, and lead and IQ deficits. The reduction of tooth

decay from fluoride exposure was predominantly based on observational studies. Observational studies have limitations, but so do randomized controlled trials. RCTs, for example, are rarely based on random or even representative samples of the population.

Page 6: The author used the NTP's selection of CUF (child urinary fluoride) as the rationale for dismissing MUF (maternal urinary fluoride). This approach ignores evidence from studies that link prenatal fluoride exposure and IQ deficits. Was the author intentionally trying to mislead the reader from asking the more pertinent question about prenatal exposure?

Page 7: The author wrote: In studies conducted in fluoridated and nonfluoridated communities, the contemporaneous children's urinary fluoride exposure likely reflects prenatal and postnatal exposure rather than the MUF. I agree this especially true for comparisons of villages or communities with high endemic fluoride with those having low endemic fluoride. This is one explanation why the studies of endemic fluoride exposure found IQ decrements; it wasn't simply because the levels of fluoride exposure were higher as the author argued, but because the fluoride exposure also capture prenatal exposure. It is likely to be less true for community-wide studies with varying levels of fluoride exposure from community water fluoridation, black tea and oral hygiene products.

Page 9: The author concluded, "These meta-analyses show consistent evidence of no adverse effect of fluoride on IQ from two measures of fluoride exposure at levels below approximately 1.5 mg/L." The author should specify that this is true for contemporaneous children; the author did not examine prenatal exposure.

Farmus and others showed that prenatal and infant exposure was associated with diminished IQ scores, but not for older children. (Farmus, Env Res 2021).

Page 10: The author described possible explanations for the effects observed in studies conducted in endemic fluorosis areas of China, Iran, and India. They did not, however, include that possibility that the endemic areas are not only a good measure of childhood fluoride exposure, but also prenatal exposure.

Page 11: The author wrote, "Thus far no cogent explanation has emerged for the mechanism of action of fluoride on neurodevelopmental effect." Thyroid disruption is one possible explanation for fluoride's toxicity on fetal brain development. The evidence indicating that thyroid disruption is an underlying mechanism - or the key mechanism - for fluoride neurotoxicity is not definitive, but it is a cogent hypothesis supported by considerable evidence.

Limitations:

I was confused why the author concluded that, "investigators have not adequately accounted for urinary dilution and postnatal exposure". Two high-quality studies cited by the author that examined fluoride exposure at levels < 1.5 mg/L accounted for urine dilution (Bashash, 2017; Farmus, 2021).

Page 14: The author suggests that more pertinent questions are about IQ deficits at higher levels. I disagree; the key questions raised by three existing prospective birth cohort studies - all of which found intellectual deficits with prenatal exposure - is whether fluoride is neurotoxic at optimal levels observed in fluoridated or even non-fluoridated communities.

In the conclusion, the author wrote: "This study provides consistent evidence from two meta-analyses showing that exposure at the level of fluoride used in community water fluoridation is not associated with lower IQ scores", without citing or acknowledging three prospective cohort studies that consistently linked maternal urinary fluoride exposure with IQ deficits in their offspring. The author could, of course, specify that their conclusions are based on contemporaneous childhood exposure.

Reviewer 3: The manuscript, "Meta-analyses of fluoride and neurodevelopmental hazards: No adverse effect of children intelligence at lower fluoride exposure levels" is a manuscript that reports on two meta-analyses comparing children's IQ scores to non-endemic elevated fluoride levels. With proper exclusion of studies the findings of the current manuscript show no effect of increased urinary fluoride/exposure to higher fluoride in non-endemic area to IQ. This is important and timely information. This paper also is noteworthy because of its expert analysis of problems identified from other similar report, such as studies in very high fluoride level areas, use of convenience samples, not blind assessments, sampling clustering errors, mechanistically implausible explanations, publication bias, limitations of urinary and maternal urinary testing, etc. This current version of the manuscript, however, is very difficult to read by the intended audience.

Specific comments:

1. The title is poorly constructed and needs to be revised and shortened.
2. As mentioned above, the entire manuscript is difficult to read and should be revised for the readership. For example sentences such as: "The resulting exposure misclassification may lead to exaggeration of the risk, its attenuation, or no change in the association when the error structure involve multiple confounders and covariates, also measure with errors, correlate measurement errors , interaction terms, presence of threshold effect, and ecological exposure measures." need to be shortened and simplified.
3. The Conclusions of the paper and the Practical Implications do not follow the results. There was no investigation or results regarding preventing skeletal fluorosis, and investigating endemic fluorosis in China and India.

Reviewer 4: Overall, this is a very nicely written manuscript. However, I have a few questions/suggestions.

The authors note that, "Two meta-analyses of standardized mean difference (SMD) in children's intelligence quotient (IQ) scores have shown an effect at high fluoride levels in endemic fluorosis areas" (abstract). These studies were based on observational studies, so it is appropriate to say that the authors found a "relationship," but, short of a RCT, I don't think this can be called an "effect."

Along the same lines, the authors note, "fluoride exposure studies showed an increase in IQ score of 0.22 (95% confidence interval: -0.46, 0.90; I2=18%; P=0.30) for every 0.5 mg/L F increase in urinary fluoride. . . " (abstract, and elsewhere). The authors do note that this difference was not statistically significant. Not to quibble, but, if it was not statistically significant, then it is not an "increase," statistically speaking.

The phrase "approximately <1.5 mg/L F" is used repeatedly. It may have appeared in one of the manuscripts analyzed, but I'm not sure what it means.

Page 8 Problem: "Furthermore, when the group effects are not separated in from individual effects in regression analysis. . . ."

The authors interpret I-squared as "no heterogeneity." It might be more accurate to say "no observed heterogeneity."

Page 10 Problem: "Third, Ioannidis demonstrated that newly discovered associations often have inflated effects than true effect sizes."

I wonder about the advisability of combining the results of studies that used differing sets of covariates (Table 2). The effect sizes will differ, based on the covariates chosen. Can the authors provide an explanation as to how and why this is valid?

In Figure 2, it appears that the authors copied the results from a fixed effect forest plot, but the caption indicates that it is based on a random effects analysis.

Reviewer 5: This paper presents a meta-analysis that adds to the literature on fluoride and neurodevelopment in that it focuses on examining associations in the range that is pertinent to water fluoridation, namely <1.5 mg/l. The previous meta-analyses are noted to have included a sizable number of studies (the vast majority) conducted in settings in which endemic levels of water fluoride were substantially higher, exclusively in Asia. The studies appear to have been carefully identified, the analysis was done using standard tools of meta-analysis, and the results are clearly presented.

There are a number of concerns, largely with the clarity of the methods and composition of the manuscript:
1) The Introduction is quite long and mixes a summary of previous work by NTP and a critique of that work with some general statements about health risks and benefits of fluoride. While a synopsis of the evolution of this issue is appropriate, the main purpose of the study could be much more clearly and directly stated as assessing potential effects in the range of concern for Western countries that bear on water fluoridation. In the Introduction and elsewhere in the manuscript, there is a somewhat a defensive tone in trying to counter the proponents of the claim that fluoride is a neurotoxicant, drifting into aspects of the debate that are tangential to the content of the paper. It is important to let the data speak for itself and avoid the impression that it's been assembled to promote a point of view.
2) In the Methods, it would be helpful to simply state the exact criteria for inclusion on the two meta-analyses that were conducted and not going back and forth between the approach used here and the one used by NTP. It seems to be included in the text but is not easy to extract. While it is appropriate to contrast between these findings with those of the NTP meta-analysis and others, that should be in the Discussion, noting the different mix of studies that were available for addressing the hypothesis of possible adverse effects at lower levels.
3) Again, the Discussion should focus on the contribution of this analysis and put it in the context of previous meta-analyses of this issue. Noting the limited research quality and volume on which this conclusion is based is appropriate, but the Discussion drifts into some more general comments about observational studies in general and an argument to not focus so much on neurodevelopment. Again, there is value in summarizing the risks and benefits of fluoride, independent of this issue. In the absence of clearer evidence supporting adverse effects of fluoride on neurodevelopment at lower levels, this report makes a clear case against modifying the current efforts to achieve fluoride's benefits while avoiding skeletal fluorosis.

Minor points:
P. 2 - In citing the Green et al. article, the contradiction between their results and their recommendations seems odd, perhaps suggesting that some secondary analyses provided hints of an adverse effect. Another sentence or two to reconcile this would be helpful. P. 4, top

P. 5, top - Clarify exposure ranges included and nature of contrasts for ecological comparisons, just "higher" vs. "lower"? Are all studies "non-endemic" or just those for the SMD analysis with the others restricted by maximum exposure levels? Carefully distinguishing selection of studies based on the source of fluoride (endemic vs. non-endemic) and maximum levels of exposure would be helpful.

It seems questionable to include thesis and conference abstract from recent papers which were likely not included in earlier reports and especially for abstracts, lack the detail needed for inclusion in a meta-analysis

I would recommend describing results with point estimates and CIs in text, not just noting statistical significance

P. 10 - Not accounting for design effect only understates variance but does not change point estimates

More information and support

FAQ: How do I revise my submission in Editorial Manager?
https://urldefense.com/v3/__https://service.elsevier.com/app/answers/detail/a_id/28463/supporthub/publishing/__;!!AvL6XA!iaAU6NWj-fQXLW8bSTASX342THBfdssFy17woaUSZC7oV0dE_pmW9qUVQYCanuezUST3ZHI0$

You will find information relevant for you as an author on Elsevier's Author Hub:
https://urldefense.com/v3/__https://www.elsevier.com/authors__;!!AvL6XA!iaAU6NWj-fQXLW8bSTASX342THBfdssFy17woaUSZC7oV0dE_pmW9qUVQYCanuezUYSWtFnc$

FAQ: How can I reset a forgotten password?
https://urldefense.com/v3/__https://service.elsevier.com/app/answers/detail/a_id/28452/supporthub/publishing/__;!!AvL6XA!iaAU6NWj-fQXLW8bSTASX342THBfdssFy17woaUSZC7oV0dE_pmW9qUVQYCanuezUbnIYnFA$
For further assistance, please visit our customer service site:
https://urldefense.com/v3/__https://service.elsevier.com/app/home/supporthub/publishing/__;!!AvL6XA!iaAU6NWj-fQXLW8bSTASX342THBfdssFy17woaUSZC7oV0dE_pmW9qUVQYCanuezUewdwygS$
Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about Editorial Manager via interactive tutorials. You can also talk 24/7 to our customer support team by phone and 24/7 by live chat and email

---

Appendix 4

On 1/4/22, 8:26 PM, "Kumar, Jayanth@CDPH" <Jayanth.Kumar@cdph.ca.gov> wrote:

This email originated from outside ECU.

My manuscript is rejected! I am not surprised because I am the sole author. I knew this could be a problem. The word limit for a systematic review and meta-analyses is 3700.

Surprisingly, Reviewer #2 never commented.

Any thoughts? I started this manuscript as a commentary because I was concerned that this meta-analysis would not be considered without a systematic review.

-----Original Message-----
From: em.jada.0.78769e.c0ddf84b@editorialmanager.com <em.jada.0.78769e.c0ddf84b@editorialmanager.com> On Behalf Of The Journal of the American Dental Association
Sent: Tuesday, January 4, 2022 4:36 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Subject: Decision on submission to The Journal of the American Dental Association

EXTERNAL EMAIL. Links/attachments may not be safe. To report suspicious emails, click “Report Phish” button.

Manuscript Number: JADA-D-21-00365R1
Meta-Analyses of Fluoride at Lower Exposure Levels and Children’s Intelligence

Dear Dr. Kumar,

Thank you for submitting your manuscript to The Journal of the American Dental Association.

I regret to inform you that the reviewers recommend against publishing your manuscript, and I must therefore reject it. My comments, and any reviewer comments, are below. I hope these comments are helpful to you and your work on this and future manuscripts.

For alternative journals that may be more suitable for your manuscript, please refer to our Journal Finder (https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Furldefense.com%2Fv3%2F__https%3A%2F%2Fnam02.safelinks.protection.outlook.com%2F%3Furl%3Dhttps*3A*2F*2Furldefense.com*2Fv3*2F__http*3A*2F*2Fjournalfinder.elsevier.com__*3B!!AvL6XA!nRkruK_JyWfXw_859jGBpWWL_om7Ud0Gj0zmMBjhNi7WIUb4YRT0rsrbIMok2AW77yxLb7XA*24%26amp%3Bdata%3D04*7C01*7CMOSSM17*40ECU.EDU*7C7e0b95f27de34b221b1108d9cfea597d*7C17143cbb385c4c45a36ac65b72e3eae8*7C0*7C0*7C637769427716956828*7CUnknown*7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0*3D*7C3000%26amp%3Bsdata%3Dk3G8P4*2FfDsbNncHDqD0xS1z7R6GWxsD0H16hNQ0

kIsc*3D%26amp%3Breserved%3D0__%3BJSUlJSUlJSUlJSUlJSUlJSUlJSUlJSUl!!AvL6XA!gi-yAjomI6gu9MfGnBLCkN6HcIjAlRlzlNCxSTMCtHGQ27EAfZjOl0UY06gEafXp0VzynWWi%24&data=04%7C01%7CMOSSM17%40ECU.EDU%7C94906f1fdc0d4a04312108d9d06bcd99%7C17143cbb385c4c45a36ac65b72e3eae8%7C0%7C0%7C637769983713897252%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=MAHtJy2Bm5ZYeYEfU%2BLg9RWaWVY8xhiezogcocS2JWQ%3D&reserved=0).

We appreciate you submitting your manuscript to The Journal of the American Dental Association and thank you for giving us the opportunity to consider your work. Please consider JADA for publication of your future works.

Kind regards,

Tim Wright, DDS
Editor-in-Chief
The Journal of the American Dental Association

Editor and Reviewer comments:

Reviewer 1: The author should be greatly appreciative that the JADA editor generously offered the option of revising the unsuitable manuscript first submitted. But the written response unfortunately reveals that the author in general refused to consider the advice of the reviewers. The revision is therefore no better than the first draft.

My main comments emphasized the following major deficiencies:

The meta-analyses were based on very small selections of studies where water-fluoride, childhood or maternal pregnancy urine-fluoride were used as exposure indicator, as if all three are equally valid, and the author even raised serious doubt about the one that is most relevant.

Selection of studies from "non-endemic" areas using inappropriate reasons to exclude studies that happened to support a connection between fluoride and neurotoxicity.

Serious misinformation is conveyed in the Discussion and the Conclusions.

The responses from the author are overall non-satisfactory and have resulted in minor, if any, improvements of the manuscript. I shall first briefly comment on the responses to the critique that I raised.

Despite my comment on referring to grey literature references and a court statement (#4, which seems not to be publicly available), to introduce the subject of the study, the author has made no change in the selection of references. I'm aware of several reviews in scholarly journals that could have been referred to, but the author is silent on the approach to selection of references.

Surprisingly, the introduction does not refer to the previous NAS review (later mentioned as #29 in another connection) or to the WHO monograph (not mentioned at all), where the author could have found useful information on fluoride metabolism and on the interpretation of urine-fluoride measurements - issues that remain misinterpreted in the revised manuscript.

I pointed out in my review that the former reference #42 from the U.S.EPA actually highlighted fluoride as an important developmental neurotoxicity risk. Surprisingly, the author decided to

remove the reference, apparently because the findings were unwelcome. No justification is given. This decision supports a suspicion that the author selected references based on a preferred conclusion.

The author still does not explain why studies from endemic areas are excluded, although he/she claims that the criteria are "clearly defined". But a proper definition is still missing. My comment why studies from China might be relevant is countered by this brief response: "This assertion is based on speculation." Nonetheless, the author lists numerous shortcomings (that I would call speculative) of observational studies in the Discussion, while failing to recognize that similar concerns could be raised against some of the studies that the author selected for inclusion in the present study.

The author finds that "The serious weaknesses are in the base studies and not with the meta-analyses." Similarly, he/she dismisses most of my other comments, without justification. I find it amusing that the author continues to use the term "children's urinary fluoride exposure".

The author provides no discussion why fluoride in spot urine samples from children at different ages should be treated as valid proxy exposure variables at par with or better than maternal pregnancy urines. Here, the WHO monograph and the NAS review might have been helpful to the author. In attempting to discredit the studies that referred to individual exposure measures from maternal urines, the author notes that urine-fluoride changes during pregnancy but fails to mention that some of the studies took this into account by analyzing urine from different trimesters and adjusting for the differences. The literature on prenatal vulnerability to neurotoxicant exposure is likewise ignored.

The author claims that the "concept that the likely bias is always toward the null is outdated" and then provides a long quote from a source that is not provided (footnote missing?). I doubt that any established epidemiologist would agree to that, although we all know that other potential biases exist. The awkward dismissal of exposure imprecision as an important issue adds to the serious bias of the manuscript.

In commenting on lead as another developmental neurotoxicant, the author is apparently unaware that the CDC in 2012 lowered the reference level of blood-lead to 5 ug/dl and in 2021 to 3.5. That would not be in agreement with the arguments that the author refers to the Australian NHRMC (in 2015, I assume, there is no reference), but the author seems unaware of this. The author also overlooks the fact that the mechanism of lead neurotoxicity is still unclear (although there are multiple candidates, as with fluoride).

Given the serious weaknesses of the author's responses to my review, I shall only briefly mention some of the continued major problems in the revised text, which remains unclear, poorly argued and difficult to read.

The title has been revised, but "lower exposure level" is not widely understood and is not defined in the abstract.

Despite the author's concerns about causation in regard to associations, the abstract claims that "These meta-analyses show that…".

A level of 1.5 mg/L (water or urine?) is introduced (line 60) without any reference or justification. In the subsequent paragraph, WHO's guideline value of 1.5 mg/L is mentioned, which may originate from the 1980s, but again no reference is given. The author later (line 261) refers to EPA's limit of 4 mg/L drinking water. Given that water-fluoride concentrations up to this level are permitted in the U.S. and do occur, why not focus on exposures up to this level? The manuscript is silent on this.

In selecting references, the author "excluded studies where the description of subject recruitment, exposure assessment, and the outcome was not provided." This cursory information

(lines 90ff) is provided in passing in connection with IQ measurement, and the manuscript fails to justify properly why some studies are included and others are excluded. The NTP described their process in great detail, but the present manuscript fails on this account and even includes additional studies without comment.

The section on urine-fluoride (lines 94ff) fails to distinguish between water-fluoride exposure and urinary fluoride excretion, and the paragraph confuses matters further by suddenly referring to IQ measures at different ages without commenting on comparability of IQ scales or age adjustment.

The simplistic selection of "higher and lower exposure groups" results in a serious reduction of information from many studies, in particular those that include a wide range of individual exposure measures, where a more advanced form of regression analysis would have been more appropriate and would have preserved statistical power.

In regard to criteria for Quality assessment (lines 122ff), the author refers to eight publications, only two of which are from a peer-reviewed journal, both of which have the same authorship and were published in the same toxicology journal, for which the senior author is the editor. In referring to the NASEM review, the author misses an important chance to discuss the possible biases toward the null, in particular due to exposure imprecision. As with the first version, I find the methodology description to be seriously lacking and misleading.

In the Results, the author highlights "a longitudinal investigation of the health and behavior of a complete birth cohort from New Zealand" (line142), but reference #26 reveals that this ecological study was established after childbirth and did not take into full account the (outdated) usage of fluoride supplements during pregnancy. The author then claims that "the primary source of fluoride was drinking water" and fails to recognize the importance of tea as a major source of fluoride exposure (New Zealand has one of the largest per capita tea consumptions).

The single sentence in the section on sensitivity analysis (lines 167-169) is insufficient and does not pay justice to previous meta-analyses that included or excluded various groups of studies in their sensitivity analyses.

In the Discussion, the author claims to "provide consistent evidence of lack of an adverse effect on IQ" (line 172), despite the fact that the confidence intervals are wide. The next sentence then suddenly introduces a Swedish ecological study (of military conscripts) that has serious weaknesses that are not mentioned. Then the reader is informed that the intake of fluoride in water is 2-2.5 times higher in China than in the U.S., perhaps because of differences in climate? It is unclear why this concept is introduced here. There is simply no justification for the strong conclusion.

In the next paragraph, the author claims that children's urinary fluoride concentrations represent "a direct measure of fluoride exposure to the developing brain", with no justification or reference provided. Then the author informs the reader that mean urine-fluoride levels were similar in mothers and their children in a Canadian study, but correlation coefficients are not provided.

I'm not familiar with the new Spanish study that is cited in the revision, but I understand that the study population was originally selected due to elevated exposures to neurotoxic metals. The possible suitability of this study for inclusion needs to be more carefully considered. The author believes that salt is "the source of fluoride" (line 200) in Mexico and then speculates that high fluoride exposure therefore indicates unhealthy dietary habits. The reference (#31) given by the author does mention in the Discussion this theoretical possibility as a potential weakness, but no evidence is provided for this assertion. Again, while salt is thought to be the only source of fluoride, tea is not mentioned by the author.

In discussing the validity of maternal urine-fluoride, reference is made to a study from Mexico

and some studies from the 1960s, and again the more recent monographs are ignored. The following paragraph states that "it is unclear whether the misclassification or mismeasurement is differential or non-differential in these studies," but the reference given (#35) has nothing to do with fluoride. Also, possible reasons that imprecision might be differential (which would be against expectation) are not given. The fact that covariables may also be imprecise may well worsen the situation, as they may steal variance from the independent exposure variable that the equation assumes is measured without error. Overall, the discussion of this problem is superficial and misleading.

The following paragraph (lines 226ff) contains a long list of speculative reasons why previous studies may have shown erroneous associations between elevated fluoride exposure and developmental neurotoxicity. I don't think these far-fetched allegations are proper for an article in a scientific journal. The author then refers to Ioannidis' famous article (#37) that initial findings often appear inflated when further evidence has become available. However, reference to this study is inappropriate, as the author should have recognized that a hypothesis of fluoride neurotoxicity is not new. In fact, numerous experimental studies have appeared from about 1995 and onwards, and likewise epidemiological studies began to appear in the 1990s. The author then claims that the earlier study findings are "likely spurious in the absence of an explanation of the mechanism of action" and then refers to a study from 1998 that has nothing to do with fluoride. In the next paragraph, the author cites the McPherson et al study (#39) that was conducted in a rodent strain that is apparently resistant to fluoride toxicity (many studies in other strains have shown fluoride neurotoxicity). The McPherson et al study is later on singled out as a "high-quality study conducted by NTP researchers" (line 312). Although most would agree that the exact mechanism of fluoride neurotoxicity is unknown, this problem is not unique for fluoride, and exact modes of action are not known for many recognized neurotoxicants.

At the end of this paragraph, the author discusses publication bias. As proof of this problem, the author refers to a PhD thesis - which however is indicated as being publicly available (#42). A second reference is said to show that "China has incentives to publish only "positive" statistically significant results," but the reference provided (#43) refers to genetic epidemiology, and its relevance is unclear.

Under strengths and weaknesses, the author repeats some erroneous statements on the lack of validity of observational studies (which would include the ones selected for meta-analyses), and that fluoride "has a short half-life".

Not surprisingly, the Conclusions again exaggerate the biased results obtained in this study and claims that "(u)ncritical acceptance of fluoride-IQ studies (…) has stunted methodological progress". In my mind, the present manuscript is seriously deficient and prejudiced, and if published, it will more likely increase an already existing and unfortunate controversy that may well hamper or confound more proper scientific progress that could benefit dental health.

Reviewer 3: This is a re-review manuscript, now called, "Meta-Analyses of Fluoride at Lower Exposure Levels and Children's Intelligence". With proper exclusion of studies their findings show no effect of increased urinary fluoride or exposure to higher fluoride in non-endemic area to IQ. This is important and timely information.

The authors did a remarkable job at addressing the comments of the reviewers and this revised version is much improved. This revised manuscript should make an important contribution to the issue of fluoride and neurodevelopment hazards.

Reviewer 4: The authors have addressed all of my concerns.

Reviewer 5: This is written in a very technical way, unnecessarily complex for users to understand The paper is framed as "meta analyses" instead of a systematic review. An analogy would be to see a paper that says at the beginning of the methods "the author performed a chi square test". Meta-analysis is just a statistical technique, should not be the focus of a clinically relevant paper if it's not in the context of a properly conducted SR.

Concerns:

1. there's only one author. Minimizing error in SRs requires at least 2 people doing many of the steps of a review. There is no acceptable reason for there to be only 1 author and compromise the methodological quality 2. there are no explicit eligibility criteria for the studies to include Some results seem to be presented in the methods 3. the results focus on statistical significance 4. there is no assessment of the certainty of the evidence.

Nothing regarding limitations such as risk of bias, inconsistency, imprecision, indirectness, and publication bias is considered in interpreting results and making conclusions. The authors themselves acknowledge that there are limitations in the included studies but fail to properly account for this when making conclusions. They mention a "quality assessment" in the methods (at the study level, not at the outcome level), implying they don't need to do it because it was done elsewhere

More information and support:

You will find information relevant for you as an author on Elsevier's Author Hub:
https://nam02.safelinks.protection.outlook.com/?url=https%3A%2F%2Furldefense.com%2Fv3%2F__https%3A%2F%2Fnam02.safelinks.protection.outlook.com%2F%3Furl%3Dhttps*3A*2F*2Furldefense.com*2Fv3*2F__https*3A*2F*2Fwww.elsevier.com*2Fauthors__*3B!!AvL6XA!nRkruK_JyWfXw_859jGBpWWL_om7Ud0Gj0zmMBjhNi7WIUb4YRT0rsrbIMok2AW772GgLOm7*24%26amp%3Bdata%3D04*7C01*7CMOSSM17*40ECU.EDU*7C7e0b95f27de34b221b1108d9cfea597d*7C17143cbb385c4c45a36ac65b72e3eae8*7C0*7C0*7C637769427716956828*7CUnknown*7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0*3D*7C3000%26amp%3Bsdata%3D1juz1HpfSmFMMqysDzmzqGNUPbJ7*2FpGgiRmBSWgr5aI*3D%26amp%3Breserved%3D0__%3BJSUlJSUlJSUlJSUlJSUlJSUlJSUlJQ!!AvL6XA!gi-yAjomI6gu9MfGnBLCkN6HcIjAlRlzlNCxSTMCtHGQ27EAfZjOl0UY06gEafXp0VrpKLsS%24&data=04%7C01%7CMOSSM17%40ECU.EDU%7C94906f1fdc0d4a04312108d9d06bcd99%7C17143cbb385c4c45a36ac65b72e3eae8%7C0%7C0%7C637769983713897252%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000&sdata=jpZ3b7eX9MiWk6%2BPbLaFS7%2BBVn%2BgvC39Ew16fUJHU8A%3D&reserved=0

FAQ: How can I reset a forgotten password?

Appendix 5

From: pediatricseditorial@aap.org <pediatricseditorial@aap.org>
Sent: Wednesday, June 22, 2022 8:38 AM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Cc: mossm17@ecu.edu; hhliu@dentistry.ucla.edu; susan.fisher-owens@ucsf.edu
Subject: PEDIATRICS/2022/058047 - Manuscript Decision

MS ID#: PEDIATRICS/2022/058047
MS TITLE: Association Between Community Water Fluoridation and Children's Intelligence: A Meta-analysis

Dear Dr. Kumar,

Thank you for submitting your manuscript to *Pediatrics.* The executive editorial board has decided not to accept it for publication. Unfortunately, due to a high volume of submissions, we must reject many worthy manuscripts. Rejection reflects the priorities of the journal; it does not necessarily indicate that your manuscript is unsuitable for publication elsewhere.

The reviews are accessible via your Author Area at https://submit-pediatrics.aappublications.org and as an unformatted summary below my signature. Reviewer input is only one of several factors involved in making decisions on papers. Even papers receiving positive reviewer comments may be rejected.

We hope you will continue to submit articles to *Pediatrics*.

Please take a moment to complete a brief survey about your manuscript submission experience: https://www.research.net/r/YFPKB8Q

Sincerely,
Lewis First, MD
Editor-in-Chief, *Pediatrics*
University of Vermont Larner College of Medicine
89 Beaumont Ave, Given S250
Burlington VT 05405-0068
lewis.first@uvm.edu
[redacted]
pediatricseditorial@aap.org

Reviewer 1 Comments for the Author:
p.3 cite three meta-analyses that have been conducted, but present results of only one of them.

The title suggests that the focus is primarily on water fluoridation as the exposure, but the meta-analyses consider studies in which urinary F was the exposure metric. This obscures the fact that exposure to F occurs by other routes of exposure than water fluoridation (e.g. in studies that involve individuals from non-fluoridated areas, urinary F is not zero and, as noted on p.5, in Canada the mean among individuals in non-fluoridated areas was nearly 60% of the mean in fluoridated areas). Failure to consider the multiple other sources of an individual's F exposure thus would introduce an unknown degree of exposure misclassification, jeopardizing the interpretation of comparisons of outcomes in fluoridated versus non-fluoridated areas, most likely biasing towards the null the results of studies that rely solely on water F as the exposure metric.

Given the title of the paper and the fact that water is not fluoridated in Mexico, the Bashash et al. and Thomas et al. studies are not informative about the potential impacts of water fluoridation, yet they are included in the analyses and figure extensively in the discussion.

p. 5 Argument for excluding studies that used dental fluorosis as the exposure metric on grounds that moderate or severe fluorosis is uncommon in fluoridated areas needs expansion. Many studies indicating substantial (and increasing) prevalence of mild dental fluorosis in US children, presumably many of whom reside in fluoridated areas. Excluding studies in which moderate or severe fluorosis was common in the study cohort is reasonable, but excluding studies that relied on dental fluorosis as the exposure metric and in which the distribution of Dean's Index scores among children was skewed toward fluorosis of lesser severity eliminates potentially informative studies from consideration.

p.5 I would suggest using a different word than "significant" to describe study sample size. "Largest" would be more accurate.

p.11 The authors note different effect estimates from studies conducted in endemic fluorosis areas of China, India, and Iran and from studies conducted in lower F areas. They offer several hypotheses, involving such mechanisms as differential migration, parental avoidance of F exposure, and government relocation policies. The authors conclude that comparing IQ scores in endemic and low F areas "would seem inherently fallacious," yet no data are presented to support any of these hypotheses. It is the authors' conclusion, being based completely on speculation, that seems fallacious.

p.12 The claim is made that the results of studies conducted in endemic areas prior to 2014 can be discounted because of the absence of a known mechanism of action. Since the second sentence following this one says that there is still no cogent explanation for a mechanism of action, it is unclear why this limitation on interpretation doesn't apply to studies conducted post-2014 as well. Is that a sufficient reason to discount the findings of any study suggesting an association?

p.12 The definitive statement is made that "China has incentives to publish "positive" statistically significant results." The Pan et al. reference cited to support this statement focused solely on gene-disease association studies, however, which seem of limited relevance to F studies. If anything, one might imagine that publication of studies identifying a significant potential health threat from F would be discouraged rather than encouraged in China insofar as it would demand a governmental response (and the authors' statement intimates, without support, governmental interference in the publication process). This facile style of citation increases concern about the balance of this work.

Acknowledge that populations living in unfluoridated areas might use other strategies to increase their F intake, thus biasing towards the null the results of studies that rely solely on water F as exposure metric.

The authors conclude that the challenges involved in establishing cause-effect relationship in observational studies conducted in nonendemic areas may be "insurmountable," identifying many limitations of the available database and the many challenges involved in conducting such studies. One would think that these considerations would require that extreme caution be exercised in drawing conclusions. The authors should provide the reader with some guidance on the how the limitations in the available data are likely to bias the effect estimates, i.e., towards or away from the null. After all, the problems in interpreting F studies are not unique, and many topics, especially in environmental epidemiology, are not amenable to RCTs, so the task is to draw inferences about the likely impact of the database limitations on study inferences.

The Conclusion section (p.17) seems internally inconsistent. In spite of the authors' list of the weaknesses in the quality of the data, a very strong, unqualified conclusion is drawn, i.e., "These meta-analyses show that fluoride

concentration used in community water fluoridation is not associated with lower IQ scores."

*****

Reviewer 2 Comments for the Author:
The authors performed a meta-analysis of a possible association between community water fluoridation and the intelligence of children. They included studies from nonendemic fluorosis regions and report lack of evidence of an adverse effect fluoride on IQ.
The study seems to be well-performed, is clearly described and critically discussed. I recommend publication after minor revision.

In the discussion the authors address, why studies in some endemic areas may have found a significant association between high fluoride exposure and low IQ of the children:
"The higher IQ of parents and families might have avoided high fluoride water or migrated out of the endemic 216 fluorosis areas to escape the debilitating effects of skeletal fluorosis."
This is a good argument but could be explained a bit better. I think they mean that better educated individuals in endemic areas (who on average have a higher IQ) are more likely aware of possible adverse effects of high fluoride exposure such as fluorosis. Therefore, they reduce fluoride uptake; thus, high intelligence may have influenced exposure to fluoride and not vice versa that high fluoride exposure reduced intelligence.? This is indeed a critical aspect that should be controlled in epidemiological studies.

The inclusion criteria appear useful to this reviewer:
The exposure variable included water or urinary F; (2) outcomes included information to calculate the standardized mean difference and/or regression coefficient for the change in cognition and IQ scores; (3) the study design was an observational study; (4) the article was available in English; (5) the population was children ages 1 to 18 years old.
A short paragraph in the discussion to explain/justify these criteria may be helpful.

Appendix 6

From: pediatricseditorial@aap.org
To: Kumar, Jayanth@CDPH
Cc: mossm17@ecu.edu; hhliu@dentistry.ucla.edu; susan.fisher-owens@ucsf.edu
Subject: PEDIATRICS/2022/058047 - Manuscript Decision
Date: Monday, July 18, 2022 8:23:51 AM

MS ID#: PEDIATRICS/2022/058047
MS TITLE: Association Between Community Water Fluoridation and Children's Intelligence: A Meta-analysis

Dear Dr. Kumar,

The executive editorial board received the additional review of your manuscript (see new reviewer comments below) and engaged in further discussion. After examining the new and old reviews and the priorities of the journal, we have concluded that the rejection stands. We receive many manuscripts worthy of publication and simply cannot accept them all. Rejection reflects the priorities of the journal and does not necessarily indicate that the manuscript is unsuitable for publication elsewhere.

Sincerely,
Lewis First, MD
Editor-in-Chief, *Pediatrics*
University of Vermont Larner College of Medicine
89 Beaumont Ave, Given S250
Burlington VT 05405-0068
lewis.first@uvm.edu
[redacted]
pediatricseditorial@aap.org

*****
Reviewer 3 Comments for the Authors:

Fluoridation of municipal water systems has long been advocated by such prestigious organizations as the ADA and the AAP as a successful public health program for the prevention of childhood caries. However recent research suggesting a causative relationship between prenatal maternal fluoride exposure and subsequent adverse effects on the IQ of offspring has raised questions about the wisdom of this practice. The ensuing controversy over possible negative neurocognitive effects of fluoride has left many health policy makers, let along pediatric clinicians and parents, confused. And so, any analyses that might shed some clarity on this compelling public health dilemma are welcome. This paper describes the results of a meta-analysis of research investigating causal links between fluoride exposure and children's intelligence.

Authors are mindful of the limitations of the 29 published studies they examined that were yielded from a careful Internet search using pertinent keywords and exploiting the prior work of such reputable scientific organizations as the NTP and NASEM. The authors have performed a variety of sophisticated statistically-based analyses of the secondary data, acknowledging the universal truth that results from a meta-analysis is no more accurate than are data from the individual studies it relies upon. To their credit, authors assessed 'Risk of Bias' in the studies, performed tests of sensitivity and heterogeneity, and have submitted their review for consideration by the PROSPERO international register, completing their 2020 PRISMA checklist.

The meta-analysis includes studies in which the biomarker is urinary fluoride. But clearly the sources and doses of fluoride are not all attributable to that contained in water. Authors must defend how they accounted for or adjusted for inclusion of data from studies confounded by non-water sources of environmental fluoride.

Frankly the authors' discourse on the shortcomings of studies from endemic areas, such as China, seem a bit cavalier and may or may not be true without more references to prove their credibility. Lines 211-237 should be rewritten with these points in mind. There are known non-water sources of fluoride in China that might account for high rates of severe skeletal fluorosis. For example, it is well-known in parts of China that use of fluoride-containing coal for home heating can be a major source of excessive fluoride intake resulting in severe fluorosis.

On page 4 LN 62-63, authors state the goal of the investigation is to answer the question: "does fluoride exposure recommended for caries prevention decrease children's cognition and IQ scores? However, authors clearly have 2 additional objectives for this paper: 1. to describe shortcomings and weaknesses of the extant observational studies of fluoride and 2. to suggest future directions of needed research. While the Discussion section attempts to address these 3 goals, it is disorganized and does not flow well and should be re-written to enhance clarity and direction. For example, on page 14 LN 275-278 an animal study by the NTP is injected awkwardly into a section outlining the problems with using MUF as a biomarker of exposure in human studies. Perhaps that paragraph could be better placed in the Introduction of the paper? Authors might want to move some of the DISCUSSION text to a "Data Synthesis" section under RESULTS or some other such maneuver to separate their analytic strategy from their critique of variables used in other studies.

Authors are not always clear throughout the manuscript as to when they are referring to water as the source of fluoride dosing versus non-water sources. They are also unclear in some parts of the paper as to which studies they are referencing in their analyses. This is evident on pages 9 and 10. Are lines 162-166 referencing 8 studies? Are lines 168-174 referencing 6 studies? Lines 174 to 176 referencing Figure 4 do not indicate how many studies are included in this analysis. And Figure 4 has 36 separate points plotted but there were 29 studies included. What is the explanation for the difference? Lines 178-180 apparently reference 4 studies and lines 181-185 apparently reference 5 other studies? Again, in the Abstract under RESULTS, authors identify 8 studies as showing no significant difference. However, they go on to reference "Meta-analyses" of CUF and MUF but do not indicate how many studies they are talking about.

In their Discussion section, authors never really address specifically (beyond casting aspirations on studies from China, India and Iran) why their conclusions about fluoride and IQ

differ from other, similar meta-analyses, some of which are including data from some of the same studies as this one. For example, Choi concludes that their results "support the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment" and Duan concludes "summary results indicated that high water fluoride exposure was associated with lower intelligence levels." Are there design choices, methodological strategies, and/or differences in analytic techniques might explain these disparate conclusions? Authors might consider a boxed list of bullet points to help clarify.

On page 17 ln 336-337, authors opine that "fluoride exposure at the concentrations used in community water fluoridation is not associated with lower IQ scores." However, their own Discussion section describing the limitations of the studies upon which they relied and the further prospective studies needed. Such a definitive sentence seems a stretch. Authors should consider tempering their conclusions to simply state, for example, that their meta-analysis "could not confirm a definitive association or causal relationship between water fluoridation and children's IQ scores".

Table 1 simply lists points of the study already covered in text and seems unnecessary.

Appendix 7

DEBRA J. CARFORA
JOHN THOMAS H. DO
BRANDON N. ADKINS
U.S. Department of Justice
Environmental Defense Section
P.O. Box 7611
Washington, D.C. 20044
Tel: (202) 514-2640
Fax: (202) 514-8865
Email: debra.carfora@usdoj.gov

Attorneys for Defendants

Additional Attorneys Noted Below

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

FOOD & WATER WATCH, INC, et al., Plaintiffs, v. U.S. Environmental Protection Agency, et al., Defendants.	Case No.: 17-cv-02162-EMC **JOINT PRETRIAL CONFERENCE STATEMENT** Date: January 7, 2020 Time: 2:30 p.m. Place: Courtroom 5, 17th floor

In accordance with the Court's June 13, 2019 Amended Case Management and Pretrial Order for Trial (ECF No. 107), the undersigned counsel of record respectfully submit the following Joint Pretrial Conference Statement:

1. The Action.

a. Substance of the Action: Plaintiffs have brought this case under Section 21 of the Toxic Substances Control Act (15 U.S.C. § 2620), on the grounds that the addition of fluoridation chemicals to drinking water presents an unreasonable risk of neurologic harm. Plaintiffs contend that the recent NIH-funded prospective cohort studies, taken

together with the many other studies of fluoride neurotoxicity in animals and humans, demonstrate that fluoridation chemicals pose an unreasonable risk when assessed according to well-established risk assessment methods. EPA contends that Plaintiffs cannot set forth a scientifically defensible basis to conclude that any persons suffer an unreasonable risk of neurotoxic harm as a result of exposure to fluoride in the U.S. through the addition of fluoridation chemicals to drinking water.

b. Relief Prayed: Pursuant to 15 U.S.C. § 2620(b)(4)(B), Plaintiffs seek injunctive relief in the form of an Order requiring EPA to initiate the rulemaking proceeding requested by Plaintiffs in their Petition to EPA. The remedy provided for in Section 21(b)(4)(B)(ii) is an order that EPA "initiate a proceeding for the issuance of a rule," 15 U.S.C. § 2620(a), which order may not proscribe the content of a rule or the outcome of such a proceeding. Further, pursuant to 15 U.S.C. § 2620(b)(4)(C), Plaintiffs seek recovery of their costs of suit and reasonable fees for attorneys and expert witnesses. Finally, Plaintiffs seek such further relief as the Court may deem just and proper. Defendants deny that Plaintiffs are entitled to relief.

2. Factual Basis of the Action.

a. **Undisputed Facts**:

1. According to the United States Centers for Disease Control and Prevention (CDC), as of 2014, approximately 200,000,000 people in the United States live in communities that add fluoridation chemicals to the drinking water.

2. Plaintiffs' Citizen Petition sought to prohibit the addition of fluoridation chemicals to water on the grounds that this condition of use presents an unreasonable risk of neurologic harm.

3. Fluoridation chemicals are added to drinking water to prevent tooth decay (i.e., dental caries). In addition to being added to water, fluoride is added to dental products and certain pesticides.

4. In epidemiology, a cross-sectional study is a comparison of the prevalence of a specific health outcome across levels of a specific exposure in study

subjects (or vice versa), with the exposure and outcome both measured at a given time, providing a "snapshot" of the association between the exposure and the health outcome at one time.

5. In epidemiology, a cohort study is a comparison of incidence rates of a specific health outcome between study subjects with various levels of a specific exposure who are observed over time.

6. A person's individual response to fluoride exposure depends on factors such as age, kidney function, body weight, activity level, nutrition, and other factors.

7. Human urine fluoride concentrations (biomonitoring) measures an internal dose.

8. Various factors can affect the concentration of fluoride in a urine sample, such as an individual's metabolism, when a urine sample is collected, and the time since the last void of the individual who provided the sample.

9. Historically, most studies to investigate the impact of fluoride on IQ in humans have used cross-sectional study designs. Most of these cross-sectional studies have been conducted in China, and other countries with elevated levels (>1.5 mg/L) of naturally occurring fluoride in water. By contrast, fluoride is added to water in the United States to reach a concentration of 0.7 mg/L.

10. Prospective cohort studies have been conducted in Mexico City (ELEMENT cohort), where fluoride is added to salt, and Canada (MIREC cohort), where fluoride is added to water. These studies are the most methodologically reliable human studies to date on the impact of fluoride on neurodevelopment.

11. Risk assessment is the process by which scientific judgments are made concerning the potential for toxicity in humans.

12. The National Research Council (NRC, 1983) has defined risk assessment as including the following components: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

13. The term "risk evaluation" is a specialized term under TSCA.

14. Together, the components of EPA's risk assessment process, coupled with the ultimate risk determination, constitute a "risk evaluation" under TSCA.

15. The final step of a risk evaluation is to weigh a variety of factors to determine whether the chemical substance, under the conditions of use, presents an unreasonable risk of injury to health or the environment, referred to as the "risk determination" step in the TSCA risk-evaluation process.

16. EPA does not require that human exposure levels exceed a known adverse effect level to make an unreasonable risk determination under TSCA. For example, if human exposure levels exceed a known no-adverse effect level divided by combined uncertainty factors, EPA may make an unreasonable risk determination under TSCA.

17. In the ideal world, all risk assessments would be based on a very strong knowledge base (i.e., reliable and complete data on the nature and extent of contamination, fate and transport processes, the magnitude and frequency of human and ecological exposure, and the inherent toxicity of all of the chemicals). However, in real life, information is usually limited on one or more of these key data needed for risk assessment calculations. This means that risk assessors often have to make estimates and use judgment when performing risk calculations, and consequently all risk estimates are uncertain to some degree. For this reason, a key part of all good risk assessments is a fair and open presentation of the uncertainties in the calculations and a characterization of how reliable (or how unreliable) the resulting risk estimates really are.

18. EPA's *Guidelines for Neurotoxicity Risk Assessment* were designed in 1998 to guide EPA's evaluation of substances that are suspected to cause neurotoxicity, in line with substantive standards established in the statutes administered by the Agency.

19. EPA's *Guidelines for Neurotoxicity Risk Assessment* preceded the 2016 TSCA amendments.

20. The current non-enforceable health goal for fluoride under the Safe Drinking Water Act ("SDWA"), or Maximum Contaminant Level Goal (MCLG), of 4.0 mg/L was promulgated in 1985 to protect against a condition known as crippling skeletal fluorosis (i.e., "stage III skeletal fluorosis"). Crippling fluorosis is the final, and most severe, stage of skeletal fluorosis.

21. Based on its 2006 review, the National Research Council (NRC) of the National Academies of Science (NAS) recommended that the MCLG of 4 mg/L be lowered to prevent children from developing severe dental fluorosis and reduce the lifetime accumulation of fluoride into bone that the majority of the committee concluded is likely to put individuals at increased risk of bone fracture and possibly skeletal fluorosis.

22. Based on the NRC's recommendation, in 2010, EPA's Office of Water completed a dose-response analysis using available data between 2000 and 2010 to calculate a reference dose ("RfD")—an estimate of the fluoride dose protective against severe dental fluorosis, stage II skeletal fluorosis, and increased risk of bone fractures—of 0.08 milligrams per kilograms per day (mg/kg/day), a measure of daily intake by body weight.

23. In addition to the tooth and bone effects, the NRC also evaluated neurotoxicity as an effect of fluoride exposure, among other health effects. The NRC concluded that the available data were inadequate to demonstrate a risk for neurotoxicity at 4.0 mg/L and made recommendations for additional research. Since that time, additional research has been conducted and the scientific database for studies that have examined neurotoxicity as an effect of fluoride exposure has grown.

24. In determining whether adding fluoridation chemicals to drinking water presents an unreasonable risk of neurotoxic effects under TSCA, EPA's Office of Pollution Prevention and Toxics would not rely on the 2010 RfD, but would instead apply a weight of the scientific evidence approach for identifying and characterizing the best available science from the most up-to-date scientific database of studies that have

examined neurotoxicity as an effect of fluoride exposure.

25. In conducting TSCA risk evaluations, EPA generally uses the Margin-of Exposure (MOE) approach to characterize the risk as a step in the risk assessment process. Using this approach, an MOE is calculated by comparing (dividing) the point-of departure directly to the expected exposure level. The MOE is then compared to a benchmark MOE, which is the product of all relevant uncertainty factors.

26. EPA considers the MOE, relative to the benchmark MOE, in addition to other factors, in determining whether risks are unreasonable under TSCA.

27. The National Research Council has stated that "the inference that results from animal experiments are applicable to humans is fundamental to toxicologic research."

28. EPA agrees that effects observed in animals are relevant to humans unless human data counterindicate.

29. The developing brain is distinguished by the absence of a blood-brain barrier. The development of this barrier is a gradual process, beginning in utero and complete at approximately 6 months of age.

30. Fluoride passes through the placenta and gets into the fetal brain.

31. Whether harm would actually occur depends on the dose and nature of exposure.

b. **Disputed Factual Issues**:

1. Plaintiffs contend that fluoridation chemicals pose an unreasonable risk of neurotoxicity when added to drinking water because

(A) neurotoxicity is a *hazard o*f fluoride exposure when the scientific literature is assessed according to EPA's Guidelines on Neurotoxicity Risk Assessment;

(B) neurotoxicity is a *risk* at the exposure levels produced by fluoridation chemicals when assessed according to EPA's long-standing risk assessment methodologies, including Benchmark Dose and Margin of Exposure analysis, and

(C) the risk of neurotoxicity posed by fluoridation chemicals is

unreasonable when assessed according to the risk-related factors that EPA has identified as relevant to risk determinations under TSCA.

2. EPA contends that the following disputed facts are material to Plaintiffs claim:

i. Plaintiffs did not conduct an exposure assessment.

ii. Plaintiffs did not conduct a systematic review.

iii. The existing body of evidence for fluoride neurotoxicity does not support the identification of a hazard of neurotoxicity at the levels of exposure to fluoridation chemicals under the condition of use being assessed.

iv. The existing body of evidence for fluoride neurotoxicity does not support the identification of a dose response that is probative of water fluoride concentrations in the United States at or below 0.7 mg/L.

v. Fluoridation of public drinking water systems has been demonstrated as an effective public health intervention in reducing dental caries.

vi. Plaintiffs have not set forth a scientifically defensible basis to conclude that any persons suffer an unreasonable risk of neurotoxic harm as a result of exposure to fluoride in the U.S. through the addition of fluoridation chemicals to drinking water.

3. Disputed Legal Issues:

1. For the reasons set forth in Plaintiffs' Motion *in Limine* No. 1, Plaintiffs contend that the benefits (or lack thereof) of fluoridation chemicals are "nonrisk factors" that cannot be considered in the unreasonable risk determination.

2. For the reasons set forth in Plaintiffs' Motion *in Limine* No. 2, Plaintiffs contend that any evidence to support a deferral in the rulemaking under Section 21(b)(4)(B)(ii) should be excluded because EPA cannot demonstrate one of the requisite factors, and thus introduction of evidence would be futile and waste judicial resources.

3. EPA contends that the Court must apply the substantive requirements of TSCA's statutory scheme for determining whether the use of fluoridation chemicals to

understand the full extent of the risk posed by adding fluoridation chemicals to drinking water, if at all, as determined by the Court and the full extent of the risks to which it must take action pursuant to the ongoing risk evaluations under TSCA section 6. If the issue of deferral under section 21(b) were not bifurcated from the issue of unreasonable risk, EPA would be prejudiced by requiring it to demonstrate the full extent of the risks to which it is taking action before the time allowed by statute to complete the first ten risk evaluations under the amended TSCA and before the Court has make any unreasonable risk determination on fluoride.

Plaintiffs oppose EPA's bifurcation request for the reasons set forth in Plaintiffs' Motion *in Limine* No. 2.

6. Witnesses.

a. See attached Appendix A.

7. Exhibits:

a. See attached Appendix B.

8. Use of Discovery Responses.

a. See attached Appendix C.

Dated: December 19, 2019

Respectfully submitted,

/s/ *Debra J. Carfora*
DEBRA J. CARFORA
JOHN THOMAS DO
BRANDON N. ADKINS
Environmental Defense Section
4 Constitution Square,
150 M Street NE, Room 4.1114
Washington, DC 20001
Tel: (202) 514-2640
Email: debra.carfora@usdoj.gov

Attorneys for Defendants

/s/ *Michael Connett* (by permission)
MICHAEL CONNETT
C. ANDREW WATERS
Waters Kraus & Paul
222 N. Pacific Coast Hwy

El Segundo, CA 90245
Tel: (310) 414-8146

Attorneys for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by Notice of Electronic Filing this 19th day of December, 2019, upon all ECF registered counsel of record using the Court's CM/ECF system.

/s/ *Debra J. Carfora*

Debra J. Carfora, Trial Attorney

Appendix 8

Volume 5

Pages 709 - 906

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

BEFORE THE HONORABLE EDWARD M. CHEN

FOOD & WATER WATCH, INC., et al, Plaintiffs, vs. U.S. ENVIRONMENTAL PROTECTION AGENCY, et al, Defendants.	)	No. C 17-2162 EMC San Francisco, California Monday June 15, 2020 8:30 a.m.

TRANSCRIPT OF REMOTE ZOOM BENCH TRIAL PROCEEDINGS

APPEARANCES:

For Plaintiffs:

WATERS KRAUS & PAUL
222 North Pacific Coast Highway
Suite 1900
El Segundo, California 90245
BY: MICHAEL P. CONNETT, ESQ.
CHARLES ANDREW WATERS, ESQ.

WATERS & KRAUS LLP
3141 Hood Street
Suite 700
Dallas, Texas 75219
By: KAY GUNDERSON REEVES, ESQ.

(APPEARANCES CONTINUED ON FOLLOWING PAGE)

Reported By: ***Debra L. Pas, CSR 11916, RPR, RMR, CRR***
Official Reporter - US District Court
Computerized Transcription By Eclipse

ELLEN CHANG,

called as a witness for the Defendant, having been duly sworn, testified as follows:

THE WITNESS: Yes, I do.

THE CLERK: Thank you.

THE COURT: You may proceed.

MS. BHAT: Thank you, Your Honor.

DIRECT EXAMINATION

BY MS. BHAT

Q. Dr. Chang, you are an epidemiologist; correct?

A. Yes.

Q. Briefly, can you explain what epidemiology means?

A. Yes. Sure. It's the scientific study of the causes and patterns of diseases in populations, especially human populations.

Q. What are your qualifications to speak to the Court about epidemiology?

A. I have a doctorate degree in epidemiology with a minor in biostatistics from the Harvard School of Public Health.

I also completed a post doctoral fellowship in medical epidemiology and biostatistics at the Karolinska Institute in Stockholm Sweden.

I previously held jobs as a research scientist at the Cancer Prevention Institute of California, which is a non-profit cancer research center. That was affiliated with

The 2019 actually refers to an abstract. So, like, a conference abstract on the same cohort, MIREC.

So I don't know how to make this clearer. You could add "plus abstract" after "Green 2019 in press." Because there was the full-length in press manuscript, plus an abstract.

Q. Okay. Thank you for that.

Now, you recognized, Dr. Chang, that there is a difference between relevance and reliability; correct?

A. Yes.

Q. And you agree, Dr. Chang, that the Canadian MIREC studies and the Mexico City ELEMENT studies are the most reliable studies to date on fluoride and neurodevelopment; correct?

A. I think because they look at prenatal fluoride exposure, they are more -- see, I -- I wouldn't say that the other ones are unreliable. It's that the MIREC and ELEMENT cohort studies are better conducted. They -- they assess a wider range of exposure windows or potential exposure windows. And that makes them more informative.

But as far as reliability goes, for me that pertains to validity in terms of whether the data, the underlying data are valid.

So for looking at associations with childhood exposure, for example, I don't think that the other ones are less reliable. But the other ones don't look specifically at prenatal exposure, and that is a limitation relative to MIREC

and ELEMENT.

MR. CONNETT: Your Honor, at this time I would like to read impeachment testimony into the record.

THE COURT: Okay. Identify the pages.

MR. CONNETT: It's 208, Line 16 to 210, Line 2.

THE COURT: I'll give counsel a chance to look.

MS. BHAT: 208/16 to 209/2?

MR. CONNETT: 210/2.

MS. BHAT: 210/2.

(Brief pause.)

MS. BHAT: No objection, Your Honor.

THE COURT: Okay. Go ahead and read it.

MR. CONNETT: Paul?

(Document displayed.)

BY MR. CONNETT

Q. (As read)

"QUESTION: Okay. So of these ten most relevant studies, which do you find to be the most reliable studies from a methodological standpoint?

"ANSWER: I think they are all more reliable, for example, than the ecological cross-sectional studies from non-western populations. Just methodologically even, they are better.

"QUESTION: Uh-huh.

"ANSWER: Among these ten, I would say that the

prospective cohort studies are, in general, more rigorous in design than those that are not. And then among the prospective cohort studies, I would say that those that adjusted for multiple confounders and had individual level measures of exposure are relatively better than those that lack those elements.

"QUESTION: Okay. So of the ten studies, which study do you -- which single -- do you have -- which single study do you find to be the most rigorous from a methodological standpoint?

"ANSWER: Of these ten, I think that the methods are quite comparable among the Bashash studies --

"QUESTION: Uh-huh.

"ANSWER: -- the Green and Till studies. So Thomas is, I believe, an abstract, but it's -- it's related to the Bashash studies. Those are the ones. So Bashash -- the last five that are listed, those are the Bashash, et al 2017 and '18. The Thomas, et al study under the reasonable assumption that the methods described in that abstract are the same as used in the full-length papers. And then the Green, et al, and the Till, et al studies, I think, are relatively more rigorous than the other five."

MR. CONNETT: Thank you, Paul.

(Document removed from display)

BY MR. CONNETT

Q. So, Dr. Chang, you agree that the ELEMENT -- the three ELEMENT studies -- I'll bring back the table here. I'll start again.

(Document displayed.)

Q. Dr. Chang, based on your testimony there, you agree that the three ELEMENT studies that you identified as being most relevant, as well as the MIREC studies that you identified as being most relevant, that these are the five most rigorous studies that you evaluated in your causal assessment; correct?

A. Yeah. I think they are the most -- they are more rigorous. They are the most rigorous two study populations, five analyses, yes.

Actually, the MIREC one we can count as two maybe, the Green 2019 full-length paper and then the abstract. But, yeah. Those -- those two cohort studies are more rigorously conducted.

Q. And you agree that the Broadbent study is a weaker study than the ELEMENT and MIREC studies; right?

A. For looking for neurodevelopmental effects or potential neurodevelopmental effects of fluoride exposure, I would say yes. They don't have maternal prenatal exposure.

Q. And you agree that the Shannon study is a weaker study than the ELEMENT and MIREC studies; correct?

A. For the same reason; correct.

Appendix 9

U.S. FEDERAL COURT

ACTION NO. 17-CV-02162

FOOD AND WATER WATCH, *et al.* v. U.S. EPA

EXPERT DECLARATION OF PHILIPPE GRANDJEAN, MD, DMSc

PREPARED ON BEHALF OF PLAINTIFFS

20 May 2020

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

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

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

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

VII. SYSTEMATIC REVIEW

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

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

Appendix 10

YORK
UNIVERSITÉ
UNIVERSITY

December 6, 2019

RE: Re-analysis of Green et al, 2019

Dear Dr. Fraser, Dr. Arbuckle, and members of the MBMC,

We are writing on behalf of the authors in regard to Dr. Tomar's request to access and re-analyze the raw data that we used in our study published in JAMA Pediatrics, entitled "*Association between Maternal Fluoride Exposure during Pregnancy and IQ Scores in Offspring in Canada*".

We fully support an independent re-analysis of the dataset used in the Green et al study. We have some recommendations, however, about how the quality and validity of our conclusions should be evaluated in a re-analysis study.

We appreciate and concur with the Biobank's decision to incorporate the 'core principles of study re-analysis' as outlined by Christakis and Zimmerman (2013)[1] in the Biobank application. These principles are critical for maintaining rigour and transparency in scientific investigations.

As Christakis and Zimmerman note, "The value of reanalysis accordingly hinges critically on reducing the presumed threats to equipoise that come from a financial, ideological, or political interest in the results. A reanalysis is most likely to be useful when such interests are substantially lower among the reanalysis team than in the original team. Conversely, if the presumption of bias is higher in the reanalysis team, data sharing will more likely impede, not improve, scientific understanding."

Given the importance of an unbiased re-analysis team, we wish to share a few of our concerns about some of the behaviours demonstrated by Dr. Tomar and the signatories of the October 23, 2019 NIEHS letter that indicate strong bias against the Green et al study and group of authors. Biases are revealed in the following actions:

1. Dr. Tomar's quotes from the Medscape article dated August 19, 2019 reveal confirmation bias. https://www.medscape.com/viewarticle/916977#vp_2 (see Appendix for direct quotes).

2. We have verified with two signatories of the NIEHS letter that Dr. Tomar has not shared the email sent by Dr. Fraser on October 29, 2019 outlining the procedures for accessing MIREC Biobank data. To this day, a false narrative has been perpetuated that the Green et al authors are refusing to release the data. In reality, we have never "declined to respond affirmatively to requests from other researchers for access to the data" as purported. Dr. Tomar notes the importance of being transparent to provide clarity amid concerns our article has raised. We concur and feel that Dr. Tomar should be held to the same level of accountability.

[1] Christakis DA, Zimmerman FJ. Rethinking reanalysis. *JAMA*. 2013:310(23): 2499-2500.

On November 1, the following blog was posted by Dr. Grant Ritchey (one of the signatories of the NIEHS letter) on Science-Based Medicine and retweeted by other signatories of the letter, including Dr. Tim Caulfield: https://sciencebasedmedicine.org/maternal-fluoride-and-iq-the-scientific-community-pushes-back/

This blog article is riddled with biases and factual misinformation related to the request for the MIREC data. Dr. Ritchey reports some "updates", including: 1. The anonymized CADTH report on the Green et al study which is completely inconsistent with the conclusions made by the NTP 2019 report on developmental neurotoxicity of fluoride released in the same week; 2. the email reply from NIEHS to their letter requesting the data, but not the reply by Dr. Fraser (written October 29); and 3. a selective quote from Dr. Schwarcz from McGill in a National Post article saying: "What are you hiding? Whoever owns the data should be willing to release it", despite this same National Post article including a clear explanation of the procedures for accessing the MIREC Biobank data. Dr. Tomar then tweeted the link to this blog post on November 1st despite Dr. Fraser clarifying the procedures on October 29th. This raises concerns about integrity and bias against our group demonstrated by these signatories.

3. The signatories of the NIEHS letter show questionable ethical behaviour that continually denigrate our research team through a series of posts on Twitter (see examples in Appendix from posts made in November 2019). Not only is this bullying behavior unprofessional, it raises concerns about the extent to which potential interactions between our research groups will be fruitful and motivated by scientific truth-seeking.

4. Many of the criticisms noted in the NIEHS letter were claims originally made by the American Council on Science and Health (ACSH) and the UK-based Science Media Centre, which are both heavily funded by the pharmaceutical and food and beverage industries. Some of these criticisms are false, such as "the results are driven by outliers", and presenting claims with little scientific basis, such as "sex differences are frowned upon". These are attempts to undermine the substantive conclusions of our study.

Several sites have investigated the UK-based Science Media Centre and the ACSH for an industry bias and financial conflicts. You can find the original critiques here: https://www.sciencemediacentre.org/expert-reaction-to-study-looking-at-maternal-exposure-to-fluoride-and-iq-in-children/

5. Several of the signatories of the NIEHS letter – including Drs. Jennifer Myers, Mark Moss and John Morris – serve as scientific advisors of the American Fluoridation Society. We don't know their source of funding for the American Fluoridation Society, but it is an outspoken advocacy organization for community water fluoridation. The advisors may have good intentions, but their tweets indicate a strong bias, as does their affiliation with the American Fluoridation Society.

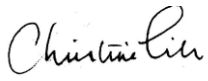
A core principle of a re-analysis is that it consists of a detailed and pre-specified analytic plan. As Christakis and Zimmerman noted, "A reanalysis should not be a statistical fishing expedition. The new methodological approach must be explicitly stated and justified in advance." A template designed for researchers preregistering a secondary data analysis is included in our Appendix.

Given the concerns noted above, **it is critical that the re-analysis is conducted by an independent and objective group of scientists who have no financial conflict or ideological biases**. This group would be analogous to the Health Effects Institute that independently re-analyzed studies of air pollution and health outcomes. We further recommend that Dr. Tomar's group provide funding for this independent re-analysis.

Finally, Christakis and Zimmerman write, "The authors of the original report being subjected to re-analysis should be provided with the opportunity to review and comment on the reanalysis before its acceptance for publication." We agree and request that this be built into a re-analysis plan. We would also like clarity on how any serious disagreements would be resolved.

We appreciate your effort and attention in helping to ensure that re-analysis of the Green et al paper is done carefully and in an ethically acceptable manner. While we appreciate that these recommendations won't be easy, we believe that they are critical to protect the scientific process and, ultimately, the integrity of MIREC.

Sincerely,



Christine Till, PhD

Bruce Lanphear, MD, MPH

CC: Rick Woychik, PhD, Acting Director, NIEHS

Gwen Collman, PhD, Acting Deputy Director, NIEHS

Dimitri Christakis, MD, MPH, Editor in Chief, *JAMA Pediatrics*

APPENDIX
(note: additional content added to Appendix after Dec 6, 2019 to reflect ongoing activity)

1. **Quotes by Dr. Tomar from August 19, 2019 Medscape article: Prenatal Fluoride Exposure and IQ in Kids: Is There a Link?**

   Written by Tara Haelle on August 19, 2019

…

"But Scott Tomar, DMD, MPH, DrPH, a professor of dental public health at the University of Florida College of Medicine in Gainesville, was more skeptical of the findings. Tomar, a consultant to the US Food and Drug Administration (FDA) and American Dental Association, questioned why the only association seen in the urinary concentration analysis is in boys and how much the data supported the conclusions given that most participants consumed less than 1 mg/L of fluoride daily.

"I really don't think this should have an effect on the policy of recommending water fluoridation in the United States or Canada," Tomar told *Medscape Medical News*. "There's nothing remotely resembling a linear relationship in the range at which the overwhelming majority of these subjects fell."

>>If he read the article, it was reported that we examined separate models with 2 linear splines set at 3 knots and found that the slope estimate at lower values of MUF (i.e., < X (give MUF value)) was approximately the same as the slope estimate at higher levels of MUF. So if the two models don't significantly differ (as we found), then that indicates that the two spline slopes do not significantly differ. His claim is unfounded."

The authors made no recommendations related to water fluoridation policies but did suggest that women should reduce their fluoride intake during pregnancy. Still, Tomar said he does not see a real association "between exposure to fluoride in the concentrations typically found in water fluoridation and IQ" in the study.

>>The design of our study was not intended to compare IQ scores in children living in fluoridated versus non-fluoridated communities. We interpreted the IQ loss to fluoride from all sources of fluoride. A pregnant woman can have a MUF value of 1 mg/L regardless of fluoridation status, though it is much more probable if the woman lives in a fluoridated region.

"If this effect were real," he continued, "we would have seen widespread declines in IQ from the 1940s through the early 21st century in the United States, as exposure to fluoridated water increased from about 10% of the population to around 80%. We saw just the opposite."

>>This is an example of a vacuous statement.

Tomar also pointed out that other differences in the cities may account for the IQ differences — though the authors included city as a covariate — and suggested the regression analysis relied too much on outliers with higher fluoride exposure levels. Till, however, said they found no effect difference in the model when they excluded outliers from the analysis."

>>Another example of a vacuous statement as we presented models with and without outliers.

2. Email sent to Drs. Tomar, Woychik and Collman on October 29, 2019.

Scott Tomar, DMD, MPH, DrPH
stomar@dental.ufl.edu
Professor & Director of Institutional Analysis and Evaluation
University of Florida College of Dentistry

Rick Woychik, PhD
rick.woychik@nih.gov
Acting Director,
National Institute of Environmental Health Sciences

Gwen W. Collman, Ph.D.
collman@niehs.nih.gov
Acting Deputy Director,
National Institute of Environmental Health Sciences

October 29, 2019

Dear Drs. Tomar, Woychik and Collman,

We appreciate your concerns regarding the availability of the raw data for validation from the Green et al. study on maternal fluoride exposure and child IQ that was recently published by JAMA Pediatrics. This study was a MIREC (Maternal-Infant Research on Environmental Chemicals) Biobank project. The data and biospecimens in the MIREC Biobank were collected with the informed consent of the MIREC Study participants.

In all Biobank activities we work to honor the consent provided by the participants, which includes ensuring that individual level data are released only for approved Biobank projects. That said, we are in an era of data sharing. We understand that we need to make the data from the Green et al. publication accessible for other researchers to perform validation of the initial findings. The data would be available only for this purpose to the team seeking to perform the validation. It should be noted, however, that our privacy policy does not allow individual-level data to leave Canada.

If you can identify a team of independent researchers interested in taking this on, we would be happy to work with them to ensure they have the raw data they need, providing that they adhere to the MIREC Biobank policies. See http://www.mirec-canada.ca/en/research/ for further information on the Biobank policy and process.

Please contact the MIREC Biobank Manager, Nicole Lupien(nicole.lupien@recherche-ste-justine.qc.ca), to arrange access to the data needed to validate the Green et al. study.

Sincerely,

William D. Fraser, M.D., M.Sc., FRCSC
Chair, MIREC Biobank Management Committee

c.c. Tye Arbuckle, PhD, MIREC Co-PI, Health Canada
Nicole Lupien, Manager, MIREC Biobank, Ste. Justine's Research Center
Christine Till, PhD, York University (ctill@yorku.ca)

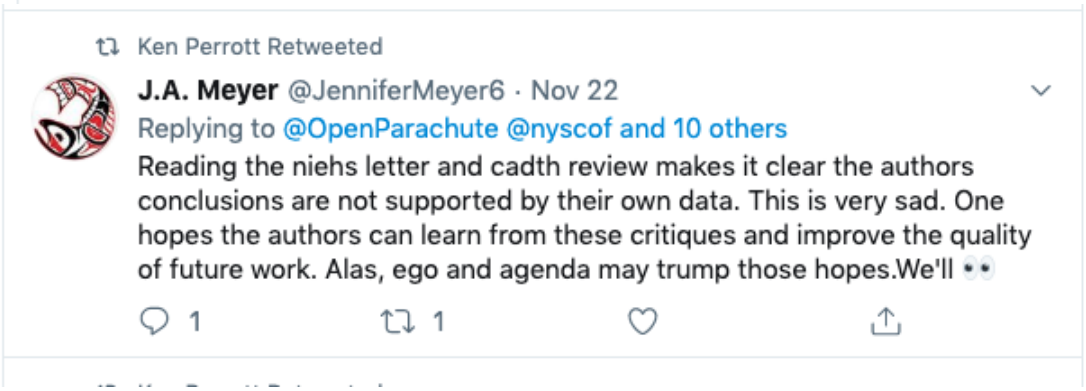
---

3. Some recent tweets sent or re-tweeted by signatories of the NIEHS letter:

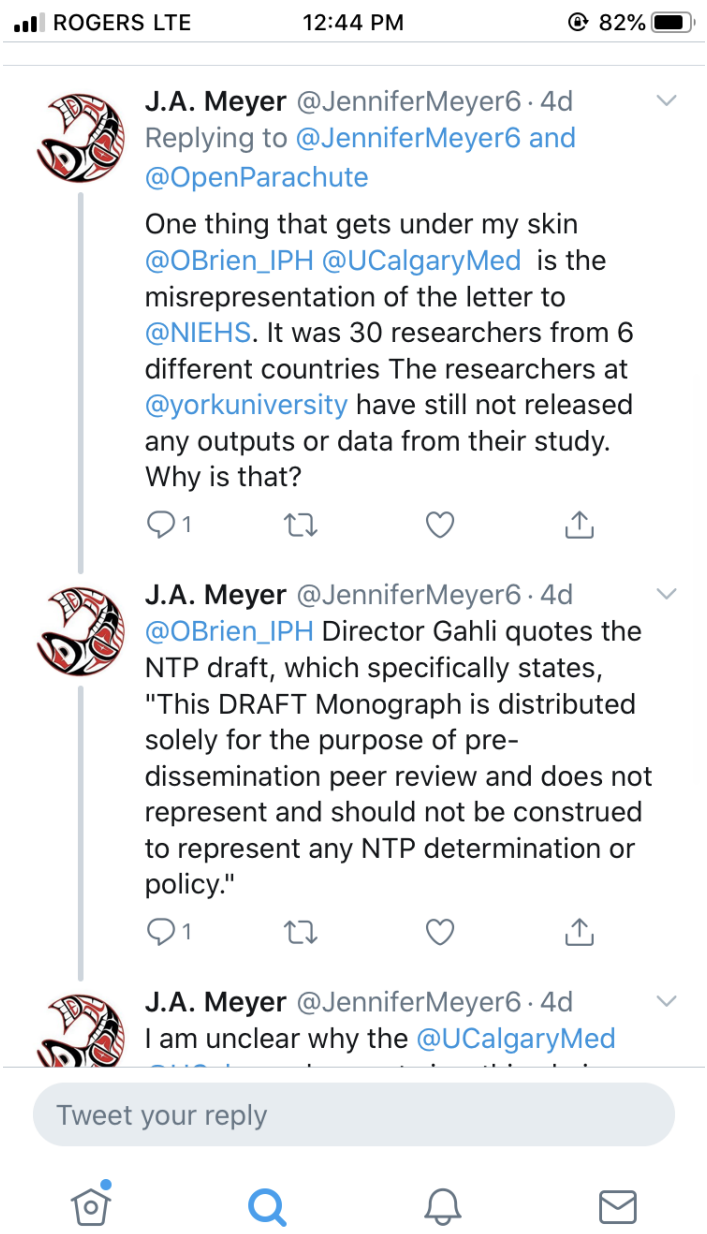
We note here that signatories of the letter are disseminating the above-mentioned blog post on November 27th – one month after the response from Dr. Fraser.

We note here the fluoridation society endorsing industry-funded organizations.

We note here bullying behaviour by signatories of the letter:

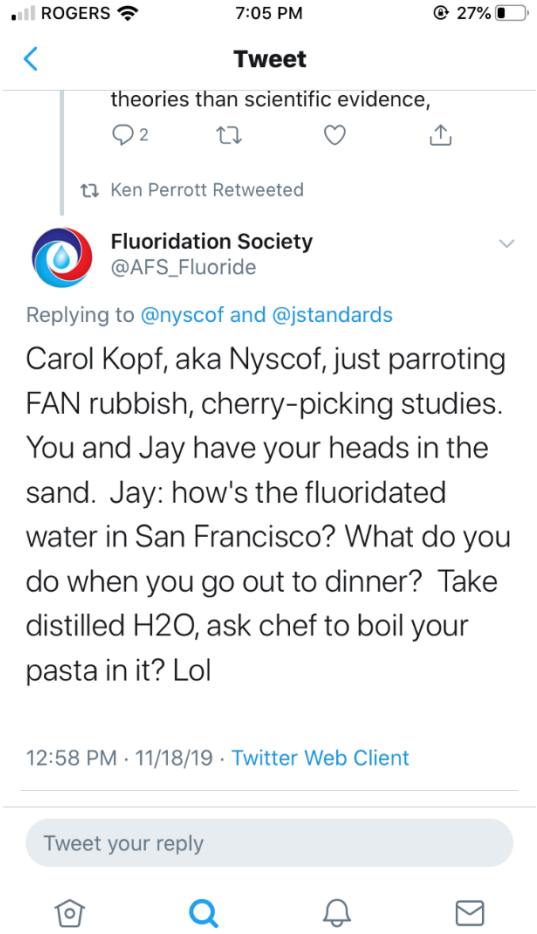


Tweets sent December 9, 2019 by Dr. Meyer (one of the signatories of the letter)



4. Other tweets by members of the AFS demonstrating unprofessional and questionable ethical behaviour:


ROGERS
7:19 PM
46%
Tweet
Johnny Johnson
@drjohnnyjohnson
A fantastic display of international unity in the scientific community!! A #fluoridation study by Green et al claimed an association of fluoridated H2O w/ lowered IQ in boys was challenged as the authors refuse to share data. So a joint letter was sent bit.ly/NIEHS-Ltr
6:40 PM · 10/25/19 · Twitter for iPhone
5 Retweets 10 Likes
Tweet your reply


ROGERS
7:05 PM
27%
Tweet
theories than scientific evidence,
2
Ken Perrott Retweeted
Fluoridation Society
@AFS_Fluoride
Replying to @nyscof and @jstandards
Carol Kopf, aka Nyscof, just parroting FAN rubbish, cherry-picking studies. You and Jay have your heads in the sand. Jay: how's the fluoridated water in San Francisco? What do you do when you go out to dinner? Take distilled H2O, ask chef to boil your pasta in it? Lol
12:58 PM · 11/18/19 · Twitter Web Client
Tweet your reply

5. Required information for pre-registering a re-analysis (adapted from OSF; see: https://help.osf.io/hc/en-us/articles/360019738834-Create-a-Preregistration)

Preregistration is designed to make clear the distinction between confirmatory tests, specified prior to seeing the data, and exploratory analyses conducted after observing the data. Therefore, creating a research plan in which existing data will be used presents unique challenges.

For each of the research questions listed, provide one or multiple specific and testable hypotheses, or one or more specific estimates related to those research questions. If doing hypothesis testing, please state if the hypotheses are directional or non-directional. If directional, state the direction. A predicted effect is also appropriate here.

For example:

A. Research Question (RQ) 1

A1: Hypothesis 1 (related to RQ1)

A1.1: Statistical test of hypothesis 1

A1.2: Statistical test of hypothesis 1

A2: Hypothesis 2 (related to RQ1)

A2.1: Statistical test of hypothesis 2

B. Research Question 2

B1: Hypothesis 3 (Related to RQ2)

B1.1: Statistical test of hypothesis 3

Etc

Appendix 11

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Pour l'amour des enfants
Université de Montréal

MIREC
Maternal-Infant Research on Environmental Chemicals

Montreal, September 18, 2020

RE: Response to request to access MIREC Biobank data for reanalysis of Green et al. paper (preBBK39)
Project title: Re-Analysis of the Association between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada

Mark E Moss, DDS, PhD
Associate Professor
ECU School of Dental Medicine
1851 MacGregor Downs Road – MS 701
East Carolina University
Greenville, NC 27834-4354

Dear Dr. Moss:

The members of the MIREC Biobank Committee have attentively reviewed your responses to their latest comments. The Committee members recognize the importance of the debate around fluoride and IQ, and support the reanalysis of MIREC data on child IQ and prenatal exposure to fluoride. The Committee also recognizes the importance of the principles for reanalysis proposed by Christakis & Zimmerman in 2013. However, the current application does not demonstrate sufficient expertise or methodological improvement to meet the requirements for a robust reanalysis; and unfortunately, they did not approve your application, for the following reasons:

1. Based on the CVs of the applicants and team members, and the methodology proposed, the Committee members feel that your team does not have the level of knowledge and expertise in the required specific areas to address this research question.

2. The responses to the additional information and clarification requested through the 3 rounds of review by the Committee did not fully address the Committee's questions.

3. As a core principle for reanalysis, the "methodological improvement should be recognizable and significant. While there are legitimate methodological differences, the posited improvement from the reanalysis should be well grounded and substantiated by a significant portion of the methodological literature." (Christakis & Zimmerman in 2013). The Committee members do not find that this application makes recognizable and significant methodological improvements to the analysis that Green et al. conducted.

4. The Committee members do not find that this application identifies any clear limitation of the Green et al. study. The proposal speaks of eliminating outliers, but the Green paper did take into consideration extreme values of MUF. The approach that the team proposes for establishing an effect threshold is not clear.

5. Regarding a possible city effect, there is a lack of clarity as to how this effect would be dealt with (collider versus confounder). This is an example, found throughout the proposal, where the methods are not clearly defined. The Committee had asked for more details, but insufficient detail was provided.

6. The application indicates a plan to "add variables to the model", but there should be a good justification of including adjustment variables in a model to explore an association. The applicants have not explained how they would determine which variables would be included to the model, and how they would be selected.

Best regards,

Nicole Lupien
MIREC Biobank Manager
CHU Sainte-Justine Research Centre
3175, Côte-Sainte-Catherine
Montreal (Qc) Canada H3T 1C5
nicole.lupien@recherche-ste-justine.qc.ca

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Pour l'amour des enfants
Université de Montréal

MIREC
Maternal-Infant Research on Environmental Chemicals

Montreal, March 15, 2021

RE: **Response to request to access MIREC Biobank data for reanalysis of Green et al. paper (preBBK46)**
Project title: **Re-Analysis of the Association between Maternal Fluoride Exposure During Pregnancy and IQ Scores in Offspring in Canada**
Co-Applicants: **Mark E Moss**, DDS, PhD
Associate Professor, ECU School of Dental Medicine, East Carolina University
Sonica Singhal, MPH, PhD
Assistant Professor, University of Toronto

Dear Co-Applicants:

The review committee has come to the decision to not approve the above cited application for data access. The following is a summary of the key points that led to this decision.

First, one of the core principles of reanalysis is that the posited improvement from the reanalysis should be well grounded and substantiated by advanced methodological literature. The panel did not consider that the above criterion is fulfilled in the application.

Second, there are concerns about whether the team was free of bias/conflict of interest. Several MBMC members noted that Dr. Moss is on the scientific advisory committee for the American Fluoridation Society, which advocates for fluoridation. He also specifies in his CV having served as editor of a website committed to improving health literacy for professionals and community stakeholders by summarizing and critiquing published studies that raise concerns about fluoride. Given the contentious nature of this topic, a truly arms-length team is needed to conduct the "definitive" reanalysis.

Third, while the team has some experience in perinatal biomonitoring and child neurodevelopment, the team has not demonstrated sufficient expertise in the application to conduct an epidemiological analysis. Here are some examples: the applicants state they will use DAGs but the DAG presented in the application is not developed according to the rules of causal inference; the applicants advocate for using multiple approaches to identifying confounders rather than one clearly defined approach, which could be viewed as data dredging; the applicants seem to treat interaction variables as potential confounders rather than an indication of heterogeneity.

Given that members of the same team of applicants have previously been unsuccessful in their requests for data access, and that many of the issues that were raised by the committee in previous reviews were not addressed in the current application, the committee is not disposed to review further requests from this same group of investigators.

Yours sincerely,

William Fraser

William Fraser, MD
Chair, MIREC Biobank Management Committee

Appendix 12

From:	Chris Wood
To:	Barefoot, Adam; Bev Isman; Chris Farrell; Dean Perkins; Jason Roush; Jayanth Kumar ; John Welby; Julia Wacloff; Mona Van Kanegan; Russ Dunkel; Zwetchkenbaum, Samuel (RIDOH)
Subject:	[EXTERNAL] : FW: Complaint letter to US DHSS Office of Research Integrity - need BOD approval to sign on by 2 pm ET tomorrow
Date:	Thursday, July 15, 2021 5:45:34 PM
Attachments:	image001.png Complaint to Various Institutions July 14 2021.pdf
Importance:	High

I apologize for the short tun around but please let me know if you want me to sign on, on behalf of ASTDD by no later than 2 pm ET tomorrow

From: Judith Feinstein jafme52@gmail.com
Sent: Thursday, July 15, 2021 2:31 PM
To: Chris Wood cwood@astdd.org; 'Bruce Austin' baustinLMT@gmail.com
Cc: 'Kumar, Jayanth@CDPH' Jayanth.Kumar@cdph.ca.gov; 'Howard Pollick' Howard.Pollick@ucsf.edu
Subject: Letter of complaint - ASTDD sign on?
Importance: High

Chris,
I've read enough to be as convinced as a non-researcher can be that the concerns expressed in the complaint are valid. I highlighted chunks as I went through (skipped some of the middle) – my highlighting is a lighter yellow. I'm appalled at the responses to Mark Moss's attempts to obtain the data (at the end), along with all the rest, and we know what Jay has been telling us all along.

Please note in the email from Professor Meyer that she describes the letter as defamatory (that is, could be taken as libelous or slanderous). Do you want to run this by the BOD or the Management Team? – but note that the requested deadline for signing on is Saturday – see the second attached email – and I need to know how ASTDD should be listed – whose name, etc.

FYI, what I find, from our annual report to NFAC last year, is this:

> ASTDD submitted a letter to the National Academy of Sciences expressing concerns about the draft National Toxicology Program (NTP) monograph on fluoridation, as did Fluorides Committee member Jay Kumar. Howard Pollick and others submitted a response to an article in JAMA Peds; it was published online 12/30/19, and in print in February 2020.

So, let me know what we'll do next. I can reply to Jennifer Meyer tomorrow or Saturday, not a problem.

Judy

From: Judith Feinstein <jafme52@gmail.com>
Sent: Thursday, July 15, 2021 4:44 PM
To: 'Kumar, Jayanth@CDPH' <Jayanth.Kumar@cdph.ca.gov>; 'Howard Pollick' <Howard.Pollick@ucsf.edu>
Cc: 'Chris Wood' <cwood@astdd.org>; Bruce Austin <baustinLMT@gmail.com>
Subject: RE: [FLUORIDERESPONDERS] Letter of complaint - ASTDD sign on?

Thanks Jay. I am just skimming through the complaint, and the writers of the complaint are absolutely tearing the methodology and lack of fidelity with research standards apart. They're picking up things that would have earned most of us grades of F- on papers in graduate school. I'm seeing no reason not to sign on, but will read just a little more.

I think Howard might be away this week.

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Thursday, July 15, 2021 4:24 PM
To: Judith Feinstein <jafme52@gmail.com>; Howard Pollick <Howard.Pollick@ucsf.edu>
Subject: RE: [FLUORIDERESPONDERS] Letter of complaint - ASTDD sign on?

I encourage ASTDD to sign on. I don't see any downside. The authors have published three papers, and they cannot replicate the findings. The authors are not releasing the data. NIEHS is not interested in obtaining clarification. We don't have any other options.

From: Judith Feinstein <jafme52@gmail.com>
Sent: Thursday, July 15, 2021 12:51 PM
To: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; Howard Pollick <Howard.Pollick@ucsf.edu>
Subject: FW: [FLUORIDERESPONDERS] Letter of complaint - ASTDD sign on?

Hi – meant to send this first thing today. I'm in the process of reading through the complaint, attached in one of the emails attached here. Both Chris Wood and Bruce Austin think we (ASTDD) should consider it. I'm wondering about the two of you?

Thanks –
Judy

From: Judith Feinstein <jafme52@gmail.com>
Sent: Wednesday, July 14, 2021 9:04 PM
To: Bruce Austin <baustinLMT@gmail.com>; 'Chris Wood' <cwood@astdd.org>; Chris Farrell <farrellc@michigan.gov>
Subject: FW: [FLUORIDERESPONDERS] Letter of complaint

Not much time here, but I will email Jennifer Meyer to review the complaint, and let you know

if I think that ASTDD might sign on to the letter – if such an action is appropriate?

Thanks –
Judy

From: T and J S-M <ProfessorMeyer@outlook.com>
Sent: Wednesday, July 14, 2021 6:40 PM
To: Judith Feinstein <jafme52@gmail.com>
Subject: Re: Complaint

Thank you. And of course, you are also welcome to sign as individuals.

This particular group of researchers shows no signs of slowing down, even with the NASEM rejection of the NTP conclusion that fluoride was a developmental neurotoxin, twice. Just today someone sent me this https://www.sciencedirect.com/science/article/pii/S0013935121006095 [sciencedirect.com] It's the same group of researchers with the same false claims and poor methods. The damage from these poor quality studies will move more preventable suffering as communities cease CWF or fail to reinstate/start CWF programs because of the fear these studies generate.

I am reminded of Paul Offit's quote. "Pseudoscience is not a victimless crime."

With gratitude,
Jennifer

From: Judith Feinstein <jafme52@gmail.com>
Sent: Wednesday, July 14, 2021 5:33 PM
To: 'T and J S-M' <ProfessorMeyer@outlook.com>
Subject: RE: Complaint

Thank you – I'll look at the document, go back through my files, and then run it by ASTDD leadership.. I'll share your email as well; the caveat about this being defamatory is important. I think we can manage to reply by Saturday, one way or the other.
Judy

From: T and J S-M <ProfessorMeyer@outlook.com>
Sent: Wednesday, July 14, 2021 9:29 PM
To: Judith Feinstein <jafme52@gmail.com>

Subject: Complaint

Thank you Judy for your email.
That would be wonderful if ASTDD wanted to sign on. The document is written in a legal format. The purpose of the complaint is to initiate an investigation regarding the study published in JAMA Pediatrics in 2019 that alleged that exposure to fluoride during pregnancy is associated with diminished IQ. In the development of the complaint, we have consulted with several experts and legal advisors. I kindly ask you to cautiously share the document, as it is defamatory. Our purpose with the complaint is to initiate an official investigation into the inconsistencies, mishandling of statistical procedures, and false claims they continue to publish in various forms.

If you are willing to sign this complaint, then please know that it will go to seven institutions - to each of the five institutions with which the authors are associated (with relevant references to the institutions specific rules), to the US DHHS Office of Research Integrity which oversees NIH funded research, and to JAMA Pediatrics to request a retraction. The substance of the complaint will not change in these letters.

The seven institutions are:

1. US Office of Research Integrity
2. JAMA Pediatrics
3. York University
4. Simon Fraser University
5. Laval University
6. University of Cincinnati
7. University of Indiana

In choosing to sign, please reply to me directly with:

1. your full name;
2. how you would like your professional title to be listed; and
3. your electronic signature.

The first signer is listed as an example.
We aim to submit on Monday, July 19th by the close of business. Please reply by Saturday so we can prepare the documents.

Thank you in advance for your time and attention. I very much hope you can join us in helping investigations to begin.

Yours sincerely,
Jennifer Meyer

From: Judith Feinstein <jafme52@gmail.com>
Sent: Wednesday, July 14, 2021 5:11 PM
To: ProfessorMeyer@outlook.com <ProfessorMeyer@outlook.com>
Subject: FW: [FLUORIDERESPONDERS] Letter of complaint

Dear Professor Meyer:

The Association of State and Territorial Dental Directors may well be interested in signing on to the complaint. I believe we expressed concern directly to JAMA Pediatrics after they published that study but need to check my files. In any case, please do share the complaint with me, and I'll follow up with ASTDD leadership.

Thank you very much for taking this on.

Judy
Judith A. Feinstein, MSPH
Coordinator, ASTDD Dental Public Health Policy Committee
Coordinator, ASTDD Fluorides Committee
jafme52@gmail.com

astdd
Where oral health lives

From: Fluoride Responders <FLUORIDERESPONDERS@LISTSERV.AAP.ORG> **On Behalf Of** T and J S-M
Sent: Wednesday, July 14, 2021 2:52 PM
To: FLUORIDERESPONDERS@LISTSERV.AAP.ORG
Subject: Re: [FLUORIDERESPONDERS] Letter of complaint

Thank you so much, Matt.

The purpose of the complaint to the US DHSS Office of Research Integrity https://ori.hhs.gov/ [na01.safelinks.protection.outlook.com] is to request they initiate an investigation of research misconduct regarding the study published in JAMA Pediatrics in 2019 which alleged that exposure to fluoride during pregnancy is associated with diminished IQ in children. In the development of the complaint, we have consulted with several experts and advisors.

If you would like to review the complaint and consider signature please email me directly at ProfessorMeyer@outlook.com and I would be happy to share it with you. We aim to submit on Monday 7. 19 by close of business.

Sincerely,
Jennifer Meyer

From: Fluoride Responders <FLUORIDERESPONDERS@LISTSERV.AAP.ORG> on behalf of Matt Jacob <mattlivesindc@GMAIL.COM>
Sent: Wednesday, July 14, 2021 8:40 AM
To: FLUORIDERESPONDERS@LISTSERV.AAP.ORG <FLUORIDERESPONDERS@LISTSERV.AAP.ORG>
Subject: [FLUORIDERESPONDERS] Letter of complaint

Friends and colleagues - A number of public health researchers and faculty have been troubled by the lack of transparency and other ethical issues related to the research paper about fluoride [na01.safelinks.protection.outlook.com] that was published in 2019 by JAMA Pediatrics. Several people have worked for the past few months to draft the language for a letter of complaint to the U.S. Office of Research Integrity.

Jennifer Meyer, an assistant professor at the University of Alaska, has been involved in this effort. She participates in this listserv, so I invite Jennifer to share additional information, including how people who wish to consider adding their names to the letter can do so.

Jennifer - please share additional info . . .

MATT JACOB

Jacob Strategies LLC

2311 Connecticut Ave. NW #205

Washington, DC 20008

202-770-6265

My LinkedIn profile [na01.safelinks.protection.outlook.com]

Pronouns: he / him / his

By using or accessing this e-mail list you signify your acknowledgment and assent to the AAP E-mail List Terms of Use and Disclaimer (https://www.aap.org/en-us/Pages/Listserv-Terms-of-Use.aspx [na01.safelinks.protection.outlook.com]). You further acknowledge that you remain solely responsible for the content of the messages you post. You may not use this e-mail list to engage in communications leading or related to an agreement in restraint of trade, to exchange specific information relating to prices, profits, or costs, to engage in any fraudulent conduct, or to further any other unlawful purpose. TO UNSUBSCRIBE, click the following link: http://listserv.aap.org/scripts/wa.exe?SUBED1=FLUORIDERESPONDERS&A=1 [na01.safelinks.protection.outlook.com]

By using or accessing this e-mail list you signify your acknowledgment and assent to the AAP E-mail List Terms of Use and Disclaimer (https://www.aap.org/en-us/Pages/Listserv-Terms-of-Use.aspx [na01.safelinks.protection.outlook.com]). You further acknowledge that you remain solely responsible for the content of the messages you post. You may not use this e-mail list to engage in communications leading or related to an agreement in restraint of trade, to exchange specific information relating to prices, profits, or costs, to engage in any fraudulent conduct, or to further any other unlawful purpose. TO UNSUBSCRIBE, click the following link: http://listserv.aap.org/scripts/wa.exe?SUBED1=FLUORIDERESPONDERS&A=1 [na01.safelinks.protection.outlook.com]

Appendix 13

From: Kumar, Jayanth@CDPH
To: [redacted] Dunkel, Russell D - DHS; Johnny Johnson; matt jacob
Subject: RE: MWU Water Quality Technical Advisory Committee - April 12, 2021
Date: Monday, March 1, 2021 11:42:01 PM
Attachments: image001.png

I agree - I would interpret that further as "as best we can tell, there is no effect".

NTP made the following statement about 0.7 mg/L without limiting the analysis to this level. They looked at 1.5 mg/L F as the highest level. NASEM stated that you cannot make a statement about a hazard at levels used in water fluoridation based on this analysis. All NTP has shown is an effect above 1.5 mg/L. FAN is not interested in a finding above 1.5 mg/L. So, NTP slanted the report to give the impression that it is a hazard even below 1.5 mg/L.

> **"When focusing on findings from studies with exposures in ranges typically found in drinking water in the United States (0.7 mg/L for optimally fluoridated community water systems)2 that can be evaluated for dose response, effects on cognitive neurodevelopment are inconsistent, and therefore unclear. However, when considering all the evidence, including studies with exposures to fluoride levels higher than 1.5 mg/L in water, NTP concludes that fluoride is presumed to be a cognitive neurodevelopmental hazard to humans."**

I think the reason for the NTP statement that the effect below 1.5 mg/L is inconsistent and unclear is because the direction of the effect is positive with respect to water fluoride and negative with respect to urine but both are not statistically significant.

NTP should have concluded there was no effect. An effect size of SMD 0.32 or -0.13 is considered small. It was not statistically significant.

NTP report Page 253-
Water Fluoride

> "Based on the linear model, the decrease in mean SMD between exposed and reference groups was −0.14 (95% CI: −0.19, −0.08) (Table A5-3). When the analysis was restricted to studies with the "high" group exposed to < 1.5 mg/L fluoride in drinking water (n = 9; 2 lower risk-of-bias studies and 7 higher risk-of-bias studies), the mean SMD became positive and nonsignificant (0.32; 95% CI: −0.57, 1.20). However, when including groups exposed to < 2 mg/L fluoride in drinking water, the mean SMD in children's IQ scores was both negative and statistically significant (SMD = −0.27; 95% CI: −0.36, −0.17) (n = 9; 2 lower risk-of-bias studies and 7 higher risk-of-bias studies)."

F in Water - The mean IQ score analysis when limited to studies below 1.5 mg/L F showed that IQ increased with increasing fluoride level in water. (Not statistically significant)

Urinary Fluoride

> "When the analyses were restricted to studies with the "high" group with < 1.5 mg/L fluoride in urine (n = 4; 2 lower risk-of-bias studies and 2 higher risk-of-bias studies), the direction of the effect did not change, but it was no longer statistically significant (SMD = −0.13; 95% CI: −0.29, 0.03)."

F in urine - The mean IQ score analysis when limited to studies below 1.5 mg/L F showed that IQ decreased with increasing fluoride level in urine. (Not statistically significant)

NTP did not show the data they used for this analysis. To me this whole analysis of mean IQ scores is deeply flawed because it is based on unweighted mean, incorrect standard error and unadjusted for covariates.

From: [redacted]
Sent: Monday, March 1, 2021 3:52 PM
To: 'Dunkel, Russell D - DHS' <Russell.Dunkel@dhs.wisconsin.gov>; 'Johnny Johnson' <drjohnnyjohnson@gmail.com>; Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>; 'Matt Jacob' [redacted]
Subject: RE: MWU Water Quality Technical Advisory Committee - April 12, 2021

Joe seems to have excerpted important clauses from the NASEM review. I hope he and his committee realize that the statement: "there is little or no conclusive information about the effects of fluoride below 1.5 mg/L" is a bit misleading. Almost all the studies included in the NTP review had subjects with those below 1.5 mg/L exposure. Yet taken all together there is no clear effect of fluoride at these levels. My interpretation is "they were looking for effects at these low levels, but no consistent pattern that would indicate that there is an effect emerged". And I would interpret that further as "as best we can tell, there is no effect". That is a lot different than an interpretation that we simply don't know if there is an effect at the level used to fluoridate drinking water. They looked. They didn't find one.

Bill

From: Dunkel, Russell D - DHS <Russell.Dunkel@dhs.wisconsin.gov>
Sent: Monday, March 1, 2021 3:20 PM

To: Johnny Johnson (drjohnnyjohnson@gmail.com) <drjohnnyjohnson@gmail.com>; 'Kumar, Jayanth@CDPH' <Jayanth.Kumar@cdph.ca.gov>; [redacted] 'Matt Jacob' [redacted]

Subject: FW: MWU Water Quality Technical Advisory Committee - April 12, 2021

FYI.
Just received this from Joe Grande from the Madison Technical Advisory Committee.

Russ

Dr. Russell Dunkel, DDS, FPFA, FICD, FACD
Wisconsin State Dental Director
Wisconsin Department of Health Services
1 W. Wilson St., Rm. 253
P.O. Box 2659
Madison, WI 53701-2659
Russell.Dunkel@dhs.wisconsin.gov
608-266-3702
[redacted]

From: Grande, Joseph <JGrande@madisonwater.org>
Sent: Monday, March 1, 2021 1:42 PM
To: 'Gary Krinke' <gary.krinke@slh.wisc.edu>; 'Greg Harrington' <gwharrin@wisc.edu>; 'Henry Anderson MD' [redacted]; 'Janet Battista' <janet@grammata.com>; 'Jocelyn Hemming' <jocelyn.hemming@slh.wisc.edu>; 'Sharon Long' [redacted]
Cc: Demorett, Joseph <jdemorett@madisonwater.org>; Deming, Amy <ADeming@madisonwater.org>; Rodefeld, Daniel <DRodefeld@madisonwater.org>; Miess, Kelly <KMiess@madisonwater.org>; Water Utility Board <WaterUtilityBoard@cityofmadison.com>; Dunkel, Russell D - DHS <Russell.Dunkel@dhs.wisconsin.gov>; Kuester, Robbyn L - DHS <Robbyn.Kuester@dhs.wisconsin.gov>; Lafferty, Jeffery <jlafferty@publichealthmdc.com>; [redacted]
Subject: MWU Water Quality Technical Advisory Committee - April 12, 2021

Good afternoon WQTAC members –

Hope you are all well and enjoying the seasonal changes upon us: more sunshine and warmer weather. Possibly a sign of better things to come.

There is a free webinar offered by the University of Toronto School of the Environment entitled, *The Evolving Science of Fluoride Neurotoxicity*. The virtual lecture is scheduled for this **Wednesday,**

March 3 from 4 to 6 p.m. Maybe you are available to attend?

This message is a reminder of our next committee meeting which is scheduled for **Monday, April 12, 2021 at 5 p.m.**

Our committee is reviewing the fluoridation policies and practices at Madison Water Utility. The National Academies of Sciences Engineering Medicine recently completed their peer-review of the *Revised NTP [National Toxicology Program] Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*. The NASEM response can be found here. In short, it concludes that NTP has identified the underlying epidemiological information it needs to evaluate possible neurodevelopmental effects of fluoride and that, "the revised monograph seems to include a wealth of evidence and a number of evaluations that support its main conclusion …" However, there is little or no conclusive information about effects of fluoride at levels below 1.5 mg/L. [The target fluoride level at MWU is 0.7 mg/L.] Finally, NASEM cautions that, "NTP therefore should make it clear that the monograph cannot be used to draw any conclusions regarding low fluoride exposure concentrations, including those typically associated with drinking-water fluoridation." Conclusions about these low level exposures would require a dose-response assessment; precisely what our committee concluded at its January 11th meeting. **Please review the NASEM response document (26 pages) before our next meeting**.

Also, please recall that additional fluoride resources can be found on the SharePoint site:

- SharePoint: non-utility access – **share.cityofmadison.com/sites/WaterUtility/WQTAC**
- Water Utility employees – **share/sites/WaterUtility/WQTAC/Forms/AllItems.aspx**

Sincerely,
Joe

Joe Grande
Interim General Manager
Madison Water Utility
119 E Olin Avenue
Madison, WI 53713
Office 608 261 9101 ● ***Cell*** [redacted]
jgrande@cityofmadison.com

Follow us on Facebook and Twitter. You never know what you may learn!

Appendix 14

From: Weintraub, Jane A
To: Kumar, Jayanth@CDPH
Subject: RE: Manuscript under review
Date: Thursday, May 12, 2022 6:08:34 PM

Thanks very much Jay. I’m so glad you are on top of this issue.
Jane

From: Kumar, Jayanth@CDPH <Jayanth.Kumar@cdph.ca.gov>
Sent: Monday, May 2, 2022 5:39 PM
To: Weintraub, Jane A <Jane_Weintraub@unc.edu>; cfox@iadr.org; Makyba Charles-Ayinde <mcayinde@iadr.org>
Subject: RE: Manuscript under review

Jane,

I am sharing a manuscript Association Between Community Water Fluoridation and Children’s Intelligence: A Meta-analysis. This manuscript is currently under review. We conducted multiple meta-analyses, and there is no effect of fluoride on IQ at levels below 1.5 mg/L F. NTP authors also noticed this but didn’t want to state it.

The studies conducted at higher fluoride levels are from endemic areas of China, India, and Iran. Although they report consistent evidence of an association, we believe the association reported is spurious for many reasons. We explain it in the manuscript.

Jay

Appendix 15

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

ADA American Dental Association®

1111 14th Street, N.W.
Suite 1200
Washington, DC 20005

T 202.898.2400
F 202.898.2437
www.ada.org

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).