

October 16, 2020

National Academies of Sciences, Engineering, and Medicine
Board on Environmental Studies and Toxicology
500 Fifth Street NW
Keck WS625
Washington, DC 20001

Re: Revised NTP Monograph on Fluoride Exposure and Neurodevelopmental and Cognitive Health

To Whom It May Concern:

On behalf of our 163,000 dentist members, we are pleased to comment on the Revised National Toxicology Program Monograph on Fluoride Exposure and Neurodevelopmental and Cognitive Health. We would like to reiterate the concerns expressed in our letter of November 19, 2019, for consideration at your peer review meeting of October 19, 2020.

First, NTP should either discard its monograph and start over, or change its classification of fluoride from a “presumed” neurotoxin to an “unknown” neurotoxin. There is not a wide body of literature examining fluoride as a potential neurotoxin. The literature that *is* available, and which NTP used, is either lacking, unreliable, inconclusive, conflicting, or subject to widespread interpretation. Even NTP acknowledged that its claim of “presumed” neurotoxin are based on a “low-to-moderate level of evidence.”

Second, if NTP *does* decide to move forward with its claim that fluoride is a “presumed” neurotoxin, it is critical to clearly and consistently qualify—throughout the document—that its claim applies only to abnormally high levels of fluoride exposure (≥ 1.5 mg/L). Failing to do so will endanger the public’s health and leave the agency vulnerable to charges of risk bias. We suggest some version of the following:

The findings and conclusions in this monograph are based on fluoride concentrations that are higher (≥ 1.5 mg/L) than those typically found in fluoridated drinking water in the United States (0.7 mg/L). The preponderance of scientific literature has not demonstrated a relationship between exposure to fluoride at levels recommended by the Centers for Disease Control and Prevention and the U.S. Public Health Service (0.7 mg/L) and neurocognitive development.

There are perhaps two or three places in the background, findings, and conclusions where NTP acknowledges that studies of fluoride exposure at levels recommended for community water fluoridation (0.7 mg/L) have not consistently or reliably demonstrated effect on cognitive neurodevelopment. It is a key finding that is overshadowed by the frequently repeated blanket statement that fluoride is presumed to be a neurotoxin—without any context or qualification.

We recognize that the oral health benefits of fluoride are not addressed in this monograph. However, failing to clearly and prominently acknowledge that NTP's findings apply only to abnormally high concentrations of fluoride (≥ 1.5 mg/L) will generate confusion about the safety of community water fluoridation at levels recommended by the Centers for Disease Control and Prevention and the U.S. Public Health Service (0.7 mg/L). This lack of clarity will add to the many myths and misperceptions about community water fluoridation, and likely undermine state and local efforts to expand the practice.

For your consideration, we are enclosing our comments of November 19, 2019, a critique of the literature used for the monograph, and a copy of the ADA's premier resource on community water fluoridation—*Fluoridation Facts*.

The 2018 edition of *Fluoridation Facts* contains evidence-based answers to the question of whether there is a relationship between consumption of optimally fluoridated water and lowered intelligence quotients or behavioral disorders in children. The evidence from individual studies and systematic reviews does not support claims of a causal relationship.

The CDC hailed community water fluoridation as one of ten great public health achievements of the 20th century.¹⁻² It is an inexpensive way to reduce tooth decay by at least 25 percent in the population.³ It would be a shame to distract from 75 years of public health success over a simple matter of communicating the science, which is often more nuanced than a sound bite can convey.

Whatever final form the monograph takes, we appreciate the opportunity to comment. If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/

Chad P. Gehani, D.D.S.
President

/s/

Kathleen T. O'Loughlin, D.M.D., M.P.H.
Executive Director

CPG:KTO:rjb
Enclosures (3)

¹ Centers for Disease Control and Prevention. Ten Great Public Health Achievements -- United States, 1900-1999. *MMWR* 1999; 48 (12): 241-243.

² Vivek H. Murthy, Surgeon General's Perspectives: Community Water Fluoridation—One of CDC's 10 Great Public Health Achievements of the 20th Century, *Public Health Rep* 2015; 130(4): 296-298.

³ American Dental Association, *Fluoridation Facts*, 2018.

National Fluoridation Advisory Committee Analysis and Comments

REVISED DRAFT NTP MONOGRAPH ON FLUORIDE EXPOSURE AND NEURODEVELOPMENTAL AND COGNITIVE HEALTH EFFECTS

October 16, 2020

The American Dental Association's National Fluoridation Advisory Committee is pleased to offer the following scientific/technical comments on the National Toxicology Program's Draft Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects.

The hazard rating of fluoride as "*presumed to be a cognitive neurodevelopmental hazard to humans*" is not supported by the systematic review of fluoride exposure.

Our team has two asks for the National Toxicology Program:

- 1. A clear statement of no effect below 1.5 mg/L F in water is needed.**

The revised *Draft NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects*ⁱ acknowledges that it lacks the dose-response assessment data to conclude a neurotoxic effect from the fluoride exposure that is present in fluoridated tap water in the US. The report correctly states that "the highest quality experimental animal study [NTP study] reviewed for this monograph (McPherson et al. 2018)ⁱⁱ did not find effects of fluoride on learning, memory or motor activity in the critical <20 ppm in drinking water concentration range (page 58)". It is also worth noting that the magnitude of effect changed from a "relatively large magnitude of effect" observed in the NTP 2019 Draft Monograph to one "where the overall pooled effect estimate from the meta-analysis of studies with individual-level measures does not demonstrate a large magnitude of effect" (Page 65). For epidemiological studies the "dose response assessment" Table A5-3 does not present the relationship between degree of exposure and magnitude of neurodevelopmental health effects at or below 0.7 mg/L (i.e., 0-0.7 mg/L, 0.8-1.5 mg/L, >1.6 mg/L etc.) (page 254). **The analysis below 1.5 mg/L F in water shows the absence of an effect [SMD 0.32 (-0.57, 1.20)].** Therefore, the statement that "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) that can be evaluated for dose response effects on cognitive neurodevelopment are inconsistent and, therefore, unclear" is not supported by the analysis. **A clear statement of no effect below 1.5 mg/L F in water is needed.** This is consistent with the recent review from the Leibniz Research Centre, Germanyⁱⁱⁱ that reported that "based on the totality of evidence the present review does not support the presumption that fluoride should be considered as a human developmental neurotoxicant at current exposure levels in European countries."

2. Include how Standardized Mean Difference calculations were completed

The meta-analysis was difficult to understand because the details are not described in the protocol. For example, it is not clear how the authors calculated standardized mean difference (SMD) when the means are not presented in the publications or how they handled multiple regression coefficients in generating pooled estimates. Another example is that Table A5-2 and Figure A5-16 list 6 studies that contributed to the analysis of Full-scale IQ, Verbal IQ, and Performance IQ. But the Verbal and Performance IQ data analysis are found only in the Green 2019 paper. How did NTP get the Verbal and Performance IQ data for the other 5 studies?

ⁱ NTP. Draft NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects. Revised September 16, 2020.

ⁱⁱ McPherson CA, Zhang G, Gilliam R, Brar SS, Wilson R, Brix A, Picut C, Harry GJ. 2018. An evaluation of neurotoxicity following fluoride exposure from gestational through adult ages in Long-Evans hooded rats. *Neurotoxicol Res*: 1-18.

ⁱⁱⁱ Guth S, Hüser S, Roth A. et al. Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses. *Archives of Toxicology*. Published online 08 May 2020. <https://doi.org/10.1007/s00204-020-02725-2>

November 19, 2019

National Toxicology Program
c/o National Academy of Sciences
500 Fifth Street NW
Keck WS625
Washington, DC 20001

Re: Draft Monograph on the Systematic Review of Fluoride Exposure and
Neurodevelopmental and Cognitive Health Effects

To Whom It May Concern:

On behalf of our 163,000 dentist members, we are pleased to comment on the National Toxicology Program's Draft Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects.

At appropriate concentrations, doses and frequency of use in drinking water and dental products, fluoride has proven to reduce the prevalence and severity of tooth decay, a disease with potentially serious consequences. Tooth decay is the most common chronic disease of childhood which also affects the majority of adults. The Centers for Disease Control and Prevention (CDC) hailed community water fluoridation as one of ten great public health achievements of the 20th century.¹⁻²

For the last 75 years, people have raised well-meaning questions about the safety and effectiveness of fluoride exposure, including whether fluoride is somehow associated with neurological development. So, in 1977, the ADA established its National Fluoridation Advisory Committee (NFAC), a standing panel of experts who are able to provide ongoing advice about the safety and effectiveness of fluoride.

Enclosed you will find NFAC's observations and comments about the draft monograph and a roster of current members. Our panel of experts concluded that the available literature is insufficient to establish causation between fluoride exposure as experienced in the United States and neurocognitive development. It found that the literature generally is either lacking, unreliable, inconclusive, conflicting or subject to widespread interpretation.

We are also enclosing copy of *Fluoridation Facts*—the ADA's premier informational resource on community water fluoridation. *Fluoridation Facts* provides answers to frequently asked questions about fluoride and community water fluoridation. Our goal is to provide clear answers—supported by numerous of credible scientific articles—to help policy makers and the public navigate through the many myths and misperceptions about fluoride.

The 2018 edition of *Fluoridation Facts* contains evidence-based answers to the question of whether there is a relationship between consumption of optimally fluoridated water and lowered intelligence quotients or behavioral disorders in children. The evidence from systematic reviews and individual studies does not support claims of a causal relationship.

Given the state of the literature, we ask that you revisit the monograph's draft hazard rating that fluoride is "presumed to be a cognitive neurodevelopmental hazard to humans." It is also critical to the public's health that you include some type of modifier to distinguish the health benefits of optimally fluoridated drinking water, currently recommended at 0.7 parts per million (ppm), from the higher level exposures the monograph addresses (above 1.5 ppm).

Whatever final form the monograph takes, we appreciate the opportunity to comment. If you have any questions, please contact Mr. Robert J. Burns at 202-789-5176 or burnsr@ada.org.

Sincerely,

/s/

Chad P. Gehani, D.D.S.
President

/s/

Kathleen T. O'Loughlin, D.M.D., M.P.H.
Executive Director

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National Fluoridation Advisory Committee Scientific/Technical Comments

on the

National Toxicology Program Draft Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

November 19, 2019

The American Dental Association's National Fluoridation Advisory Committee is pleased to offer the following scientific/technical comments on the National Toxicology Program's Draft Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects.

On November 6, 2019, the Overview of the Systematic Review shared that the NTP found a "moderate level of evidence that high fluoride exposure is associated with decreased IQ and other cognitive effects in children".

However, we believe that the hazard rating of fluoride as "*presumed to be a cognitive neurodevelopmental hazard to humans*" is not supported by the systematic review of fluoride exposure.

We offer these comments and summarize our concerns in the following paragraphs:

1. The literature review did not take into account the lack of support for a neurobehavioral effect of fluoride from animal studies conducted in the U.S.

The NTP animal study concluded that "At these exposure levels, we observed no exposure-related differences in motor, sensory, or learning and memory performance on running wheel, open-field activity, light/ dark place preference, elevated plus maze, pre-pulse startle inhibition, passive avoidance, hot-plate latency, Morris water maze acquisition, probe test, reversal learning, and Y-maze... No evidence of neuronal death or glial activation was observed in the hippocampus at 20 ppm F⁻ ." (McPherson et al., 2018, p. 781)¹." Whitford et al. also concluded that "Chronic ingestion of fluoride at levels up to 230 times more than that experienced by humans whose main source of fluoride is fluoridated water had no significant effect on appetitive-based learning (Whitford, et al, 2009)."² It is worth noting these two US studies are not in agreement

¹ McPherson CA, Zhang G, Gilliam R, et al. An Evaluation of Neurotoxicity Following Fluoride Exposure from Gestational Through Adult Ages in Long-Evans Hooded Rats. *Neurotox Res.* 2018;34(4):781–798. doi:10.1007/s12640-018-9870-x

² Whitford, G, Whitford, J, Hobbs, S. Appetitive-based learning in rats: Lack of effect of chronic exposure to fluoride. *Neurotoxicology and Teratology.* 2009; 31(4):210-215. <https://doi.org/10.1016/j.ntt.2009.02.003>

with many of the animal studies conducted in China and India, thus raising questions about the validity of those other studies.

- 2. No meta-analysis was conducted to determine a summary effect size. It appears that the determination that the IQ effect size was large is based on subjective assessment and does not take into account measurement error.**

Figure D 7 in the review shows 53 beta estimates. Of these 23 are listed as significant (red) and the remaining 30 are not. None of these estimates accounted for the cluster sample design used (the samples were drawn from cities, schools or prenatal clinics). Accounting for cluster design effect may result in larger standard errors, thus reducing the p-value (statistical significance) associated with the results.

- 3. The characterization that effect sizes observed were of relatively large magnitude is not consistent with the data that show small effect sizes.**

IQ assessment in young children is subjective and influenced by multiple factors. Thus, small IQ score differences such as 1.5 points or even 4.5 points are not likely to be readily detectable due to measurement challenges between noise and signal nor have implications for normal children's activities. The review states that the IQ effect is relatively large and thus classifies fluoride as a "presumed" neurotoxin. There are differing views whether the IQ differences are large, and the Canadian Agency for Drugs and Technologies in Health (CADTH) have called the reported IQ effects as small³. Therefore, the panel should re-assess the clinical significance of the IQ studies.

- 4. The NTP report's assertion that "There is a low expectation that new studies would change the hazard conclusion" is not adequately justified considering that there are no prospective epidemiological studies that were designed to assess the neurobehavioral effects of fluoride.**

A reanalysis of the Canadian and Mexican studies that takes into account the cluster sampling design may not show an effect. Furthermore, a recent study conducted by Santa-Marina, et al., 2019, in Spain showed, "At the age of 4-5 years, an increase of 1 mg/l in the level of fluoride in urine during pregnancy (mean level of 1st and 3rd trimesters) was related to a higher score on the perceptual-manipulative scale of 4.44

³ Canadian Agency for Drugs and Technology in Health. Community Water Fluoridation: A Review of Neurological and Cognitive Effects. Ottawa: CADTH; 2019 Oct. (CADTH rapid response report: summary with critical appraisal). ISSN: 1922-8147 (online)
Available at
<https://cadth.ca/sites/default/files/pdf/htis/2019/RC1198%20Community%20Water%20Fluoridation%20Exposure%20Final.pdf>

(0.13, 0.75) points.⁴ If additional consideration and peer review of this study's results are forthcoming, this certainly would contradict this assertion from the NTP draft report.

With the concerns about the validity, reliability, and generalizability of the research used, we ask the team to reconsider how they classify Fluoride's Hazard Conclusion. With the research community of experts raising questions about the evidence used, the correlation between fluoride exposure in drinking water as publicly available in the United States and neurocognitive development is still unknown.

Also, very importantly, even if the NTP report's classification does not change, an extremely important element that is missing from the conclusion is a modifier to distinguish the difference between a high level of fluoride exposure and any exposure. Without replicated study findings showing strong correlations between fluoride exposures near 0.7 ppm (which is much less than 1.5 ppm, and a relatively rare level in the US) and neurodevelopment, the results are misleading to the public.

The ADA is truly gratified when, in the interest of the public's health and welfare, communities provide optimally fluoridated water to their residents. The current classification is misleading to the public, could scare them unnecessarily, and could ultimately decrease the oral health status of individuals and communities.

⁴ Santa-Marina, L, Jimenez-Zabala, A, Molinuevo, A, et al. Fluorinated water consumption in pregnancy and neuropsychological development of children at 14 months and 4 years of age. *Environmental Epidemiology*. October 2019 Volume 3 Supplement 1 p 386-387
doi: 10.1097/01.EE9.0000610304.33479.18

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