

**Oral presentation to NAS committee peer-reviewing
NTP monograph on fluoride neurotoxicity
(plus additional comments)**

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The Fluoride Action Network nominated fluoride for review by the NTP more than 4 years ago, and although it has taken a long time, we feel the NTP has carefully weighed the evidence to reach their conclusion that fluoride is **a presumed neurotoxin in humans.**

The systematic literature search, extraction of data, and risk of bias scoring are excellent. NTP found 149 human studies and 339 animal studies, many of which they scored as relatively low risk of bias. There are few neurotoxins with so much supporting evidence. However, we found the NTP monograph consistently downgraded the evidence of neurotoxicity at each step of their assessment:

- First, the scope of the review focused largely on learning and memory outcomes and gave little weight to other measures of neurotoxicity.
- The scope of the review also downgraded studies in humans and animals that were at exposure levels higher than 1.5 mg/L in drinking water or its equivalent, by considering them not relevant to human exposures below 1.5 mg/L. This goes against basic principles in toxicology. Animal and human studies are often at exposures higher than in the general population, yet can be validly extrapolated to lower levels.
- The NTP equivocates on whether fluoride is a “presumed” neurotoxin at exposures below 1.5 mg/L.
- If NTP had followed their own pre-specified methodology, they should have concluded that fluoride is not just “presumed” but a “known” neurotoxin at exposures below 1.5 mg/L.

- That is because **the human studies with exposures below 1.5 mg/L are actually the strongest studies.**
- Indeed, NTP has identified 20 high quality, low risk of bias, human studies as shown in their Figure A1-01. Of these 20 studies, only 1 did not find a statistically significant adverse effect. Nine are at exposures below 1.5 and six are at exposures below 0.7 mg/L. There is remarkable consistency amongst these studies, and the effect magnitudes are large, with many finding average IQ losses of 4 or more points. NTP’s claim that the evidence from these low exposure studies is “inconsistent” is plainly wrong.

As if these 20 studies were not enough, there are now two new high quality studies. These new studies are so strong, and relevant, that we believe it is essential to consider them in your peer-review.

Two new papers

The first of the papers was published just 2 weeks ago and comes from the same Canadian group that produced the Green [2019] paper published in *JAMA Pediatrics* [Riddell 2019]. It found a strong association between fluoride exposure and diagnoses of ADHD in a Canadian sample that is representative of the entire country. The sample is from a survey that is Canada’s equivalent to NHANES in the US. Adolescents living in fluoridated places had **a 3-fold greater odds of being diagnosed with ADHD** as those in non-fluoridated areas. This finding suggests that fluoridated water may cause the majority of all ADHD cases in Canada and the US.

The second “bombshell” study, which has been accepted for publication and was presented at a recent conference, is from the same Canadian group [Till 2019]. It used their mother-child cohort to examine the effect on IQ of early infant exposure to fluoride, which is dominated by infant formula made up with fluoridated tap water. They found that **for every 1 mg/L increase in tap water fluoride there was a 9 IQ point decrease in the formula-fed infants** but almost no decrease in exclusively breastfed infants. Breast milk is highly protective against fluoride exposure to the baby because concentrations of fluoride in breast milk are at least 100 times lower than in formula made from fluoridated water.

The magnitudes of the effects in these two studies are enormous.

Analogy to lead (Pb) debate of 1990s

The NTP's downgrading of the evidence of fluoride neurotoxicity, and vocal criticisms of each new study, are reminiscent of the debate about whether "low-level" lead was neurotoxic in the 1990s, when Herbert Needleman was criticized and personally attacked because his work challenged the safety of lead industry products [Needleman 1979, 1982]. It took more than two decades, until 2012, for the NTP to issue a monograph concluding that "low-level" lead was indeed neurotoxic [NTP 2012]. Millions of children suffered loss of IQ and behavioral problems during those two decades of official indecision.

The science right now for fluoride neurotoxicity at exposure levels experienced by hundreds of millions of Americans is as strong as it was for lead back in 1990.

Needleman did his own systematic review and meta-analysis in 1990 and found only 12 qualified human studies [Needleman 1990]. Yet, he concluded that these 12 studies provided strong evidence that lead was neurotoxic at "low-levels" and he has been proven correct.

The Fluoride Action Network does not pretend to reach the stature of Herbert Needleman in the field of environmental public health, but we urge each of you on this committee to aspire to that stature and integrity when assessing the evidence for fluoride neurotoxicity.

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FIGURES

[see attached]

Additional comments

NTP monograph consistently downgrades strength of evidence

The NTP monograph consistently downgrades the evidence at several steps in their hazard assessment, especially for exposure levels below 1.5 mg/L water F and its equivalent (see also figures in attached file).

The downgrading occurs in the subjective steps of the assessment, while we find the objective steps to be well done and thorough. The objective steps include:

1. the systematic literature search
2. decisions on inclusion and exclusion of papers
3. extraction of data from the papers
4. Risk of Bias (RoB) scoring of each paper

The subjective steps are:

1. the scope of the review
2. decisions on subdividing study designs and outcomes into multiple categories which effectively weakens the evidence for each category
3. the decisions on the initial confidence rating for each category of human and animal studies
4. application of “modifying factors” to each initial confidence rating to reach final confidence ratings
5. integration of the human, animal, and mechanistic evidence
6. decisions regarding the generalizability of the evidence to exposures in the USA
7. decision to not conduct dose-response analysis and instead conduct the more subjective assessment of generalizability
8. decision to not conduct Level of Concern (LoC) assessment as specified in the OHAT handbook; LoC integrates population exposure information with dose-response information to produce a more objective way of assessing generalizability; LoC is also the proper way to address what should have been the ultimate question (see below).

At each subjective step, we believe NTP's choices effectively downgraded the certainty that the body of evidence supports a conclusion that fluoride causes developmental neurotoxicity, and that it causes it at exposures commonly experienced in the USA. Furthermore, each of these subjective decisions lacked adequate transparency and justification.

The stated objective of the NTP review was to be a hazard assessment, with no pre-specified goal of conducting any dose-response analysis, exposure assessment, or Level of Concern assessment. There is no mention of any of these, nor any mention of generalizability to the population of the USA in the NTP's protocol for the review [NTP 2019a Protocol]. However, such an analysis was essentially tacked on in the section on generalizability to the USA. From the outset—rather than as an afterthought—the goal should have been to address this ultimate question:

**Does fluoride at exposures experienced in the USA
cause neurotoxic harm?**

Instead of designing the review to address this question, the NTP essentially adopted an ad hoc methodology in their “generalizability” section. We believe the “generalizability” section does not accurately reflect the available body of evidence.

One way to assess the NTP monograph to see whether it followed OHAT and other accepted methodology is to compare it to NTP monographs of other substances. The OHAT handbook and the March 2019 clarification document [NTP OHAT 2019b, NTP OHAT 2019c] acknowledge that the OHAT methodology is “evolving”. There have been very few hazard assessments conducted using the OHAT methodology that can be used as points of comparison to the NTP fluoride monograph. However, in 2017, the NAS produced their own report on the OHAT method that included full hazard assessments of two substances using OHAT methodology. One of the assessments was of PBDE and its neurotoxic effects [NAS 2017]. The NAS applied OHAT methodology to the human and animal evidence and then integrated the results from those, so is a good model for the NTP fluoride monograph. The specific congener BDE-47 had the strongest

evidence. Several of the current NAS panel members were involved with the NAS 2017 review.

A comparison of the NAS 2017 review of BDE-47 neurotoxicity to the present NTP review of fluoride neurotoxicity suggests a double standard has been applied. The BDE-47 body of evidence is substantially weaker than the fluoride evidence, yet the conclusion of hazard by NAS was as strong or stronger. Furthermore, the BDE-47 animal studies were at exposure levels orders of magnitude higher than occur in humans, they used the same tests (Morris water maze), and they were scored as probably at high risk of bias, yet the final rating for the animal evidence was “moderate” confidence. The animal evidence assessed in NTP’s fluoride monograph was at internal doses close to those in humans, was stronger, more consistent, more relevant, and more numerous, yet the monograph’s conclusion was that it was “inadequate” (see figure on attachment Page A-4). Furthermore, this represents a downgrading of NTP’s own 2016 animal review of fluoride neurotoxicity that concluded the evidence rating was “low to moderate”.

A broader comparison can also be made between the NTP monograph for fluoride and the 27 other NTP monographs on developmental toxins NTP has produced since 2003 [NTP 2019 website, <https://ntp.niehs.nih.gov/publications/monographs/index.html>]. Several reached a level of “presumed”, yet had much weaker human and animal evidence than F. This again suggests a double standard, with fluoride downgraded in comparison to other assessed chemicals.

We are still assessing the NTP monograph and will be providing the NAS panel with more detailed and specific comments on the four objective steps and eight subjective steps of the NTP assessment identified above, as well as comparisons to the NAS assessment of BDE-47 and to comparable NTP monographs of other chemicals.

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