OUTLINE of Submission to NAS on the revised draft NTP Monograph on the Systematic Review of Fluoride Exposure and Neurodevelopmental and Cognitive Health Effects

1. Introduction

The revised NTP monograph strengthens support for presumed neurotoxic hazard conclusion. It includes new studies and has improved rating criteria and clarity. However, section generalizing to the US is improperly done risk assessment and underestimates confidence that neurotoxicity is likely in the US population.

Figure 1.

STRENGTHS

2. How has the revised NTP monograph addressed our comments and the recommendations of the NAS?

Addressed many recommendations to strengthen review and conclusions. Updated literature search found additional higher quality studies. Increase from 18 to 29 higher quality studies, with 27 finding statistically significant adverse effects.
3. Improvements to RoB scoring validity in revised NTP monograph
   Arsenic and lead potential confounding criteria are more valid.

4. Comparisons to NTP systematic reviews of other chemicals
   Comparing fluoride evidence to that of other chemicals evaluated by NTP and rated “presumed hazard”, fluoride has greater quantity, quality, and consistency of finding adverse effects. Therefore, the conclusion for fluoride of presumed hazard is fully justified.

5. Meta-analyses support conclusion of presumed hazard
   Meta-analyses clarify consistency and large magnitude of effect.

WEAKNESSES

6. OHAT guidance on “unexplained inconsistency” ignored
   Monograph concludes evidence at exposures below 1.5 mg/L is inconsistent and downgrades conclusions, but OHAT guidance says only unexplained inconsistency is grounds for downgrading. Inconsistencies are only in magnitude of effect, not direction of effect, and can be explained by differences in study design, population, exposures, and outcomes, all of which are acceptable explanations under OHAT.

7. NTP used inappropriate methods for “Generalizability to the U.S.”
   Ad hoc un-planned risk assessment used inappropriate exposure assessment and dose-response assessment methods. The improper methods produced underestimate of likelihood of harm from lower-dose exposures.

8. Exposure assessment is simplistic and inadequate
   Exposure assessment consisted of one footnote with link to non-publicly available data. Exposure assessment ignored wide range of internal doses in different people all drinking water with the same concentration, leading to underestimation of risk at lower exposure levels.

9. Proper exposure assessment demonstrates that the NTP’s presumed hazard conclusion applies directly to doses from artificial fluoridation
Proper exposure assessment classifies 18 of 29 higher quality studies as applicable to exposures below 1.5 mg/l. Very high consistency of those 18 lower dose studies because 17 find adverse effects.

10. Leading experts historical perspective; analogy with childhood Pb poisoning

Leading experts in fluoride and developmental neurotoxicity have recently equated neurotoxic harm from fluoridated water to that from childhood Pb poisoning. Many have also advised that pregnant women and infants should avoid fluoridated water. When similar warnings were made about low-level Pb exposure in children there was disbelief and questioning of the evidence that caused years of delay in taking action to reduce the problem.

11. Specific examples of downgraded evidence in revised NTP monograph

• Excluding largest effect in the strongest study.

In Bashash 2017, NTP focused on a minor secondary analysis that found no affect and excluded the primary analysis finding the largest effect from some meta-analyses and discussions.

• Excluding strongest low-dose studies from dose-response meta-analysis.

Despite protocol intention to do dose-response meta-analysis with the high quality studies having individual-level exposure data, NTP decided not to do analyses without justification. This excluded 10 mostly higher quality studies, many of which found adverse effects at low doses.

• Unnecessary division of studies lowers power in dose-response meta-analyses.

In dose-response meta-analysis of group-level studies the water F studies were separated from the urine F studies, resulting in lower power to find statistically significant pooled effects, especially at lower doses.

• Simplistic exposure assessment underestimates hazard at doses relevant to US.

Conflated water concentration with internal dose. 95th percentile water consumers drink twice as much water as average consumers so they get twice the internal dose at the same concentration of water. High water consumers of water with 0.7 mg/L will receive the same dose as average water consumers with 1.5 mg/L water. Therefore, NTP’s presumed hazard conclusion for studies with water concentrations above 1.5 mg/L will also apply to the millions of high water consumers with water concentration of 0.7 mg/L.

Figure 6. Distribution of fluoride intake from fluoridated water, USA

• NTP’s simplistic dose-response meta-analysis methods underestimated effects at low doses because they used the mean exposure while most studies had individual-level exposures that ranged well below the mean.
Figures 7 and 8 show how individual-level data that covers a wide range of doses has been reduced to a single mean dose by NTP and then dichotomized. This loss of information causes NTP to overstate the doses found to cause adverse effects in its dose-response meta-analyses. A more valid dose-response assessment using Benchmark Dose method (Figure 9) shows the dose that is likely to cause harm is much lower than the mean dose for the study population.

12. Additional weaknesses of the revised NTP monograph
- Improperly downgraded the animal evidence to “inadequate” despite the NTP 2016 review of the animal evidence concluding it was “low to moderate”.

No justification for downgrading animal evidence from “low to moderate” to “inadequate”. Figure 11 shows additional newer animal studies identified after the NTP 2016 review, which are shown in Figure 12. Several of the new studies and several of the old studies are higher quality. There is great consistency in finding statistically significant adverse effects, and doses were comparable to doses in the general human population after differences in metabolism between animals and humans are accounted for. The total animal evidence for a different chemical with an NTP review is shown in Figure 10 (BDE-47). BDE-47 had only 6 animal studies and all of them were lower quality, yet the BDE-47 animal evidence received a confidence rating of “moderate”. Fluoride has 31 animal studies with 13 being higher quality, yet NTP concluded it rated “inadequate”. Downgrading the fluoride animal evidence to “inadequate” represents a severe double-standard.

- The NTP monograph deviated from the OHAT guidelines in its section “Generalizability to the U.S. Population”.

OHAT guidance requires valid exposure and dose-response assessment when extending Hazard Assessment to risk assessment. NTP monograph did not do valid exposure or dose-response assessments.
• Meta-analyses have inadequate documentation.
  The dose-response meta-analyses have no visualizations or information on which studies were included in which analyses or the doses assigned to the studies. NTP should include forest plots and bubble plots for the dose-response meta-analyses. The HAWC data repository has no data on any meta-analyses.

13. NTP should consider publication bias due to institutional conflicts of interest
  The NAS was concerned that FAN’s translations of Chinese-language studies may have produced publication bias. NTP investigated this and found no evidence of publication bias or of inaccurate translations. Given the assumption that a non-profit environmental health group has a conflict of interest that may bias the scientific literature, the NTP should also consider the potential conflict of interest of institutions that promote artificial fluoridation. As with non-profit environmental health groups, the conflict is not financial. Institutions with the greatest potential for conflict of interest are government agencies that promote fluoridation and dental institutions including dental schools and dental researchers. Examination of the authorship of studies finds that there is a much greater chance of a study finding “no effect” if the authors are predominantly affiliated with dental schools, and even more so if the authors are in a country with artificial fluoridation.

14. “Presumed hazard” is de facto highest confidence rating possible under OHAT method
  Comparison of NTP monographs for other chemicals found only the chemical warfare agent sarin to receive the confidence rating “known hazard” and that was because there were controlled human experiments. NTP should acknowledge that the rating “presumed hazard” is the highest confidence rating normally achievable by environmental chemicals.

15. Literature search update missed important recent study on adolescents
  Malin et al 2019 found sleep disruption in adolescents in NHANES data for the US. This is first study of F and sleep disruption, and the first study of any neurotoxic effect using NHANES data. It also points to possible neurotoxicity at older ages than most of the existing literature.

16. Availability of NHANES data for fluoride studies in US: urine samples unanalyzed and dental fluorosis data withheld
  Future studies may be able to take advantage of NHANES water F and plasma F data, but NHANES samples for urine F analyses have apparently never been analyzed. Similarly, special dental fluorosis imaging systems collected objective fluorosis data in NHANES but have also never been released. NTP should call for these relevant data sets to be released publicly.

17. Conclusion
  The revised NTP monograph strengthens the already strong evidence foundation for a conclusion that fluoride is a presumed developmental neurotoxin in children. Furthermore, the body of evidence is also sufficient, when using proper methods, to make a Level of Concern conclusion (a risk assessment conclusion) that water fluoride concentrations below 1.5 mg/L and below 0.7 mg/L are likely to be a developmental neurotoxin in at least a portion of the population.
**APPENDIX #1**

ISEE 2020 Conference poster and abstract [Neurath et al 2020].

**APPENDIX #2**

Rigorous risk assessment including exposure assessment and dose-response assessment applicable to doses due to artificial water fluoridation in the US. The risk assessment will include proper dose-response meta-analysis of both group-level exposure and individual-level exposure studies.

**APPENDIX #3**

FAN comments to first NAS committee meeting October 2019

1. Summary followed by additional details
2. Figures to accompany FAN comments