Reviewer's report

Title: Developmental Fluoride Neurotoxicity: An updated review

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Reviewer: Christine Till

Reviewer's report:

This is a very timely review given the number of studies that have been published in recent years. The review is well-written and organized. It integrates relevant information, such as the importance of examining critical windows of exposure and the evidence that fluoride (at levels that are realistic for human exposure) crosses the BBB in the developing fetus and adult. I also appreciated the nuanced discussion of some of the variability in results and the direct comparison of serum concentrations associated with neurotoxicity for lead versus fluoride. Finally, the calculation of the benchmark dose provides a new way of presenting the data. I have some minor comments and suggestions:

1. Line 59: change to "Potential sources of fluoride exposure"

2. Line 66: It would be more accurate to state: "For adults in the U.S., fluoride in water and beverages contributes an average of about 80% of the daily total fluoride intake (estimated to average 2.91 mg) in fluoridated communities." (fluoride intake only from water is estimated at 60%).

3. Line 91. The pineal gland is a structure that is not protected by the blood-brain barrier (https://www.ncbi.nlm.nih.gov/pubmed/28177105 ). Thus, calcification of this structure should not be interpreted as evidence of fluoride crossing the BBB.

4. Line 163: change to "...NTP focused on fluoride neurotoxicity in regard to learning and memory."


6. Line 434: Minor typo: (CI, 4:12; -0:59) should use decimals (not ":").

7. Benchmark calculations:

   a. Table 3. The title for this table is "adjusted differences in IQ per mg fluoride per liter maternal urine during pregnancy". However, the estimate that is provided in the table for the ELEMENT study is per 0.5 mg/L. In contrast, the estimate that is provided for the MIREC study is per 1.0 mg/L. Units should be consistent.
b. The estimates in Table 3 are shown for the ELEMENT cohort using the WASI outcome (FSIQ) with the sample of 211 mother-child pairs. Why show this outcome as opposed to the McCarthy scale outcome (GCI)? The outcome on the McCarthy scale has a larger N and is more similar in age at testing (4 year olds) with the MIREC cohort.

8. Line 480 and in Acknowledgements: typo: ELEMENTS (should read ELEMENT).

9. Line 567: delete "the" in "as the thyroid hormone is crucial..."

10. Conclusion. I am not clear why the evidence today "may well underestimate the true extent of the fluoride toxicity". With non-differential measurement error of the exposure, there can also be an overestimate of the true effect.

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