Reviewer's report

Title: Developmental Fluoride Neurotoxicity: An updated review

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Reviewer: John Hirzy

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Peer Review Comments by J. William Hirzy, Ph.D. on Developmental Fluoride Neurotoxicity: An updated review

This is a very important paper that clearly summarizes the latest evidence on this subject. It also states the implications of that evidence for public health in a matter of fact way. In that connection, the author also does an excellent job of noting the latest publications by those who oppose action to lower exposures to fluoride.

He brings to the reader's attention evidence of fluoride's toxic effects on thyroid function, pointing out how these effects may be contributing to neurotoxicity that is manifested in ways other than diminished intelligence.

I was impressed by the author's finding publications involving use of radio-fluoride in cancer treatment that showed fluoride appeared to accumulate in brain areas responsible for memory and learning.

The text on the relationship between maternal serum fluoride levels and umbilical cord serum levels was fascinating, illustrating how measurement of maternal serum levels could be used as indicative of fetal exposure. (In the paper of which I was co-author and is cited in this paper, we postulated that in utero exposures could be a significant issue.) Relative to the parenthesized comment, the paragraph from lines 437 -442, particularly the last sentence indicating the lack of evidence for a post-natal fluoride exposure-related adverse effect (albeit in a very small sample) on IQ was very interesting. But….

The paragraph starting at Line 569 points out the importance of more work to tease out other possible time windows of vulnerability, pointing out how formula-fed neonates may be particularly vulnerable.

Further on this point, the author does a great service in pointing out the +6.2 IQ point advantage to breast fed vs. formula fed infants in the Broadbent et al. study.

I found it a bit hard to grasp exactly what was being conveyed in this excerpt from lines 102- 104 In adults, the fasting plasma-fluoride concentration, when expressed in micromoles per liter [µmol/L], is approximately equal to the concentration in the drinking water or in the urine expressed in mg/L. Does this mean, e.g., if the plasma fluoride level is x µmol/L, then the approximate concentration in drinking water or urine is x mg/L?
Toward the end of Line 455 the word "material" appears, and doesn't seem to fit.

All in all this is a very impressive and important piece of scientific analysis.

Additional Comment.

I would like to publish as a Comment (I would hope in the same Volume/Number) to the above paper when it is published:

One can take the excellent work reflected in Developmental Fluoride Neurotoxicity: An updated review (1) one further step into the realm of risk analysis. This would be to use the BMDLs (the lower one-sided 95% confidence limit of the Benchmark Doses in the linear mode) reported in that study to estimate a Reference Dose (RfD) for fluoride.

As defined by the U.S. Environmental Protection Agency, the RfD for a chemical is the daily dose, within one order of magnitude, that could be experienced for a lifetime without expectation of an adverse effect. Reference Doses are customarily used in standard setting efforts pursuant to various statutes by regulatory agencies.

If one assumes protection should focus on pregnant women (citation of the above publication) and a daily consumption of 2 liters/day of drinking water (2, Table 7.1), using a BMDL of 0.20 mg/L leads to 0.40 mg/day as a Lowest Observed Adverse Effect Level (LOAEL). Using a single Uncertainty Factor of 10 to convert the LOAEL to a No Observed Adverse Effect Level leads to an RfD of 0.04 mg/day.

If one uses the most conservative of the BMDLs reported in (1) viz. 0.13 mg/L, then an RfD of 0.03 mg/day obtains.

References


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