THE SAFE EXPOSURE LEVEL TO FLUORIDE IN PREGNANCY

ABSTRACT: Three studies have now examined the safe exposure level to fluoride in pregnancy using benchmark dose analysis. In 2016, Hirzy et al. found that, for a benchmark response (BMR) of 1 IQ point, the lower confidence limit of the benchmark dose (BMDL) was a daily intake of approximately 0.27 mg/day, corresponding to a drinking water fluoride concentration of 0.22 mg/L. In 2019, Grandjean found the BMDL for the maternal urinary fluoride concentration to be about 0.2 mg/L or below, a level that was similar to the result calculated by Hirzy et al., and considered that a protective limit for fluoride in drinking water would likely require that the current maximum contaminant level goal (MCLG) of the Environmental Protection Agency (EPA) in the United States of America of 4.0 mg/L MCGL should be reduced by a more than a 10-fold factor, i.e., to less than 0.4 mg/L, below the level currently achieved by fluoridation of approximately 0.7 mg/L. On November 4, 2020, a preprint of a benchmark dose analysis for maternal pregnancy urine fluoride and IQ in children by Grandjean et al.[3] was posted online. The authors included authors from the Mexican (Early Life Exposure in Mexico to Environmental Toxicants, ELEMENT) and Canadian (Maternal-Infant Research on Environmental Chemicals, MIREC) studies by Bashash et al. and Green et al., respectively, as well as two biostatisticians. The joint data from the ELEMENT and MIREC studies showed that the two prospective studies, which had maternal urine-fluoride exposure at levels commonly occurring in the general population, showed benchmark concentration level (BMCL) results, for a BMR of 1 IQ point, for the maternal urinary fluoride level of about 0.2 mg/L. With the proviso that the preprint had not yet been certified by peer review and that it should not be used to guide clinical practice until this had been done, the authors concluded that the results can be used to guide decisions on preventing excess fluoride exposure in vulnerable populations. They also observed that the two prospective studies offered strong evidence of prenatal neurotoxicity and should inspire a revision of water fluoride regulations based on the benchmark results, especially for pregnant women and young children. They considered that although systemic fluoride exposure may be associated with some benefits in dental health, these benefits appeared to be small and non-essential prior to tooth eruption and other means of caries prevention, such as fluoridated toothpaste and other topical treatment, might be considered.

Keywords: Benchmark dose analysis; Drinking water fluoride; Fluoride in pregnancy; Maternal urinary fluoride; Safe exposure level.

Further to the earlier studies examining the threshold for fluoride-induced developmental neurotoxicity using benchmark dose analysis by Hirzy et al.[1] and Grandjean,[2] a preprint on a benchmark dose analysis for maternal pregnancy urine fluoride and IQ in children by Grandjean et al.[3] was posted online on Nov 4, 2020.

In 2016 Hirzy et al.[1] generated benchmark dose results for fluoride-induced developmental neurotoxicity from a study by Xiang et al.[4] of more than 500 children in China. The authors used a high benchmark response (BMR) of 5 IQ points, but the results were also given for a BMR of 1 IQ point for which the benchmark dose lower confidence limit (BMDL) was calculated to be a daily intake level of 0.27 mg/day. Using an average water intake of 1.24 L/day in non-pregnant women, this BMDL corresponds to a water fluoride concentration of 0.22 mg/L. The daily safe dose known as the reference dose (RfD), the dose, within one order of magnitude that can be experienced throughout life without adverse effect, with an uncertainty factor (UF) for inter-individual variability of 10 and for *in utero* toxicity of 3 was calculated to be 0.0090 mg F/day. The report did not provide data for urinary fluoride concentrations.

In his 2019 paper, Grandjean[2] used the regression coefficients and their standard deviations, as provided in the published reports of the Mexican (Early Life Exposure in Mexico to Environmental Toxicants, ELEMENT) and Canadian (Maternal-Infant Research on Environmental Chemicals, MIREC) studies by Bashash et al.[5] and Green et al.,[6] respectively, to estimate tentative bench mark dose (BMD) values for fluoride-induced developmental neurotoxicity. Assuming linearity and Gaussian distributions, he calculated the results for these two prospective studies with the maternal urinary fluoride concentration as the exposure parameter in regard to the cognitive function measures (both boys and girls). Overall, the BMDL results appeared to be in agreement. The Canadian children had lower prenatal exposures than the Mexican study subjects, and along with the apparent lack of fluoride effects in girls, the BMD results are higher than in the Mexican study, although the greater uncertainty resulted in a fairly low BMDL. The results suggested a BMDL for the maternal urinary fluoride concentration of about 0.2 mg/L or below, a level that was similar to the result calculated by Hirzy et al.[1] of a BMDL corresponding to a water fluoride concentration of 0.22 mg/L and clearly below commonly occurring exposure levels, including in communities with drinking water fluoridation.

In the 2020 preprint by Grandjean et al.,[3] Grandjean is joined by authors from the Mexican ELEMENT study (Bashash and Tellez-Roujo) and the Canadian MIREC study (Till, Green, Flora, and Lanphear) as well as two biostatisticians from Michigan, USA (Song) and Copenhagen, Denmark (Budyz-Jørgensen). The authors noted that, as a safe exposure level for fluoride in pregnancy had not been established, they used data from mother-child pairs in two prospective studies, ELEMENT and MIREC for benchmark dose modeling. The children were assessed for IQ at age 4 years (n=211) and between 6 and 12 years (n=287) in the ELEMENT cohort and between ages 3 and 4 years (n=512) in the MIREC cohort. They calculated covariate-adjusted regression coefficients and their standard errors to explore the concentration-effect function for maternal urinary fluoride with children's IQ, including possible sex-dependence. Assuming a benchmark response of 1 IQ point, they derived benchmark concentrations (BMCs) of maternal urinary fluoride and benchmark concentration levels (BMCLs). No deviation from linearity was detected from the results of the two studies. Using a linear slope, the BMC for maternal urinary fluoride associated with a 1-point decrease in IQ scores of preschool-aged boys and girls was 0.29 mg/L (BMCL, 0.18 mg/L). The BMC was 0.30 mg/L (BMCL, 0.19 mg/L) when pooling the IQ scores from the older ELEMENT children and the MIREC cohort. Boys showed slightly lower BMC values compared with girls. Relying on the two prospective studies which had maternal urine-fluoride exposure at levels commonly occurring in the general population, the joint data showed BMCL results of about 0.2 mg/L. They concluded that the results can be used to guide decisions on preventing excess fluoride exposure in vulnerable populations.

In their discussion, the authors observed that the two prospective studies offered strong evidence of prenatal neurotoxicity and should inspire a revision of water fluoride regulations based on the benchmark results, especially for pregnant women and young children. They considered that although systemic fluoride exposure may be associated with some benefits in dental health, these benefits appeared to be small

and non-essential prior to tooth eruption[7] and other means of caries prevention, such as fluoridated toothpaste and other topical treatment, might be considered.[8]

Grandjean[2] noted that although the current maximum contaminant level goal (MCLG) of the Environmental Protection Agency (EPA) in the USA was 4.0 mg/L and might be protective against crippling skeletal fluorosis, it was clearly not protective against fluoride-induced developmental neurotoxicity. He considered that, depending on the use of uncertainty factors, a protective limit for fluoride in drinking water would likely require that the MCGL be reduced by more than a 10-fold factor, i.e., to less than 0.4 mg/L, below the levels currently achieved by fluoridation of approximately 0.7 mg/L. Although the preprint by Grandjean et al. has not yet been certified by peer review and should not be used to guide clinical practice until this has been done, the consistency of the findings in it with those of the earlier studies gives further guidance to the safe exposure level to fluoride in pregnancy.

Fluoride (F) is not an essential trace element in humans or necessary for the development of healthy teeth and bones.[9,10] It is likely that there is no threshold for fluoride-induced developmental neurotoxicity in drinking water, and the only assuredly safe level of fluoride in drinking water is zero.[10,11,12] The currently recommended level of 0.7 mg F/L for community water systems[10,11] and the provision of fluoridated salt are no longer appropriate for preventing dental caries because they will result in pregnant women and children having a fluoride intake above the estimated safe daily intakes of approximately 0.04 mg F/day (0.0007 mg F/kg bw/day for a 56 kg woman) and 0.15 mg F/day (0.003 mg F/kg bw/day for a 45 kg child, the 90th percentile children's body mass at 8–13 yr), respectively.[10,11] The oral reference value for longer-term (up to 10% of an average life span) exposure (RfV_{LO}) can be calculated to be approximately 0.0007 mg/kg bw/day (0.04÷56=0.00071). Preventing fluoride-induced developmental neurotoxicity in children by lowering the dietary fluoride intake to the estimated safe level for pregnant women and children may not be easily achievable but a start could be made by relatively simple measures such as avoiding fluoridated water, fluoride-rich foods, and fluoridated dental products.

A pea-sized amount of fluoridated toothpaste (250 mg), with 1000 ppm of F (1 mg of F/1000 mg of toothpaste), contains 0.25 mg of F, a smear or rice grain-sized amount of fluoridated toothpaste (100 mg) contains 0.1 mg of F, and a large strip of fluoridated toothpaste (1000 mg) contains 1 mg of F.[10,13,14] If a child younger than 3 years brushed their teeth twice daily, morning and night, with a rice grain-sized amount of fluoridated toothpaste with 1000 ppm of F they would be placing 0.1×2=0.2 mg of F in their oral cavity and would exceed the estimated safe daily dose of 0.15 mg F if more than 75% of the toothpaste was swallowed. Similarly, a 3–6-year-old child brushing with a pea-sized amount twice daily (2×0.25=0.5 mg) would have to not swallow not more than 30% of the toothpaste to avoid exceeding the safe daily dose. A pregnant woman using a large strip of toothpaste twice daily (1×2=2 mg) would need to avoid swallowing more than 2% of the toothpaste to stay within estimated safe daily F intake. Thus, the use of fluoridated toothpaste by children up to the age of 6 years and pregnant women is problematic and would best be avoided if IQ loss in children is to be prevented.

Prevention will also be assisted by having an adequate dietary intake of vitamins, antioxidants, and selenium: e.g., vitamin C, vitamin E, and other antioxidants, from fruits and vegetables, which are seen to be able to protect against F-poisoning and fluorosis.[10,15,16] Selenium can improve mitochondrial membrane stability and protect against fluoride toxicity in skeletal muscles[10,17] although at higher levels selenium is synergistic with fluoride and arsenic in causing toxicity.[10,18]

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