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Fluoride and thyroid function: What is a safe level of fluoride in drinking water to protect the most vulnerable?

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ABSTRACT

A recent systematic review and dose response meta-analysis, by Iamandii et al., considered the question "Does fluoride exposure affect thyroid function?" The authors concluded that, overall, exposure to high-fluoride drinking water appears to non-linearly affect thyroid function and increase TSH release in children, starting above a threshold of exposure, and to increase the risk of some thyroid diseases. The threshold of exposure for the TSH increase was 2 mg/L, or 2.5 mg/L when the studies with the best quality were considered. Although the lowest-observed-adverse-effect level (LOAEL) observed for TSH was a water fluoride level of approximately 2.5 mg/L, the changes in Total T3 and Total T4, a negative association, were present from very low levels, e.g. a water fluoride level of 0.2 mg/L and did not show a threshold effect. Fluoride in drinking water has been associated, by Hall et al., with an increased risk of hypothyroidism in pregnant women. A 0.5 mg/L increase in drinking water fluoride concentration was associated with a 1.65 (95% confidence interval [CI]: 1.04, 2.60) increased odds of primary hypothyroidism. Children born to women with primary hypothyroidism had lower FSIQ scores compared to children of euthyroid women, especially among boys (B coefficient : –8.42; 95%CI: –15.33, –1.50).

The threshold, or point of departure, for fluoride in drinking water varies for different adverse effects such as the development of crippling skeletal fluorosis, dental fluorosis, an elevated TSH, a decreased Total T3 and Total T4, and impaired IQ in children. A recent paper by Grandjean et al. provides evidence that foetal toxicity can occur with a reduction in IQ when the maternal urinary fluoride is above 0.3 mg/L. A BMCL fluoride concentration in maternal urine during pregnancy of about 0.3 mg/L can be estimated to occur with a drinking water fluoride level of 0.24 mg/L, or approximately 0.3 mg/L. These findings suggest that, in order to protect the most vulnerable, a foetus *in utero*, public health attention should be given to elevated fluoride intakes during pregnancy, whether from drinking water, black tea, or other sources.

Key-words: Developmental neurotoxicity; Fluoride level in water; IQ; Thyroid hormone metabolism; Total T3; Total T4; TSH.

A recent systematic review and dose response meta-analysis, by Iamandii et al., considered the question "Does fluoride exposure affect thyroid function?" The authors noted that fluoride exposure may have various adverse health effects, including affecting thyroid function and disease risk, but the pattern of such relation is still uncertain.[1] They systematically searched human studies assessing the relation between fluoride exposure and thyroid function and disease and compared the highest versus the lowest fluoride category across these studies. The authors then performed a one-stage dose-response meta-analysis for aggregated data to explore the shape of the association.

The results were that most retrieved studies (27 of which with a cross-sectional design) were conducted

in Asia and in children, and assessed fluoride exposure through its concentrations in drinking water, urine, serum, or dietary intake.[1] Twenty-four studies reported data on thyroid function by measuring thyroid-related hormones in blood, mainly thyroid stimulating-hormone (TSH). Nine studies reported data on thyroid disease, and 4 reported on thyroid volume. By comparing the highest versus the lowest fluoride categories, they found that the overall mean TSH difference was 1.05 µIU/mL. The dose-response curve showed no change in TSH concentrations in the lowest water fluoride exposure range, while the hormone levels started to linearly increase around 2.5 mg/L, also depending on the risk of bias of the included studies. The association between biomarkers of fluoride exposure and TSH was also positive, with little evidence of a threshold. Evidence for an association between fluoride exposure and blood concentrations of thyroid hormones was less evident, though there was an indication of an inverse association with triiodothyronine. The dose-reponse curves for total T3 (6 studies) and total T4 (6 studies) showed fluoride exposure was negatively associated with T3 and T4 at very low levels and up to 2.0 mg/L when the T3 curve started to flatten while for T4 there was an upward pattern resulting in a U-shaped curve. For thyroid disease, the few available studies suggested a positive association of fluoride exposure with goitre and with hypothyroidism in both children and adults.

The authors concluded that, overall, exposure to high-fluoride drinking water appears to non-linearly affect thyroid function and increase TSH release in children, starting above a threshold of exposure, and to increase the risk of some thyroid diseases.[1] The threshold of exposure for the TSH increase was 2 mg/L or 2.5 mg/L when the studies with the best quality were considered. They commented that in the pooled analysis on thyroid function the removal of the studies with the lowest methodological quality had a limited impact on the results, suggesting that the effect of biases on the thyriod effect estimates was not relevant. The positive but non-linear relation between exposure to fluoride through drinking water and circulating TSH concentrations was remarkably consistent across the many studies carried out about this association and included in the dose-response analysis.

The ranges of the ages of the children studied were given in years in the paper as: >12, 7–18, 7–12, 7–12, 8–14, 7–18, 6–15, 7–16, 8–15, 8–15, 10–15, 9–13, 8–15, 7–13, 7–12, 7–12, 8–14, 10–12, 7–18, and 7–18.[1]

Although the lowest-observed-adverse-effect level (LOAEL) observed for TSH was a water fluoride level of approximately 2.5 mg/L, the changes in Total T3 and Total T4, a negative association, were present from very low levels, e.g., a water fluoride level of 0.2 mg/L and did not show a threshold effect.[1]

The threshold or point of departure varies for different adverse effects such as the development of crippling skeletal fluorosis, dental fluorosis, an elevated TSH, a decreased Total T3 and Total T4, and impaired IQ in children.

The sensitivity to a various adverse effects of fluoride varies at different ages. Dental fluorosis can only occur while the teeth are still forming, up until the age of approximately 8 years. The fluoride-induced developmental disorders include short stature, bone deformities, cognitive impairment, delayed dental eruption, and dental fluorosis.[2] They may be seen to be the result of disturbed thyroid hormone metabolism and sonic hedgehog signalling.[2] The disturbances include the functioning of the deiodinases[3,4] and cell metabolism,[5] such as choline and arachnidonic acid metabolism.

Fluoride in drinking water has been associated, by Hall et al., with an increased risk of hypothyroidism in pregnant women.[6] A 0.5 mg/L increase in drinking water fluoride concentration was associated with a 1.65 (95% confidence interval [CI]: 1.04, 2.60) increased odds of primary hypothyroidism.[6] Children born to women with primary hypothyroidism had lower FSIQ scores compared to children of euthyroid women, especially among boys (B coefficient : –8.42; 95%CI: –15.33,–1.50).

A recent paper by Grandjean et al. provides evidence that foetal toxicity can occur with a reduction in IQ when the maternal urinary fluoride is above 0.3 mg/L.[7] Grandjean et al. merged new data from a prospective Odense Child Cohort (OCC) in Denmark with results from two previous birth cohort studies from Mexico[8] and Canada[9] to characterize the dose–effect relationship in greater detail. The OCC contributed 837 mother-child pairs to the total of >1500. The joint analysis of all three cohorts showed a statistically significant association between urinary fluoride and IQ, with a BMC of 0.45 mg/L (BMCL, 0.28 mg/L), slightly higher than the BMC previously reported for the two North American cohorts alone. Grandjean et al. concluded that the BMCL reflects an approximate threshold for developmental neurotoxicity and that the results suggest that pregnant women and children may need protection against fluoride toxicity.

A BMCL fluoride concentration in maternal urine during pregnancy of about 0.3 mg/L can be estimated to occur with a drinking water fluoride level of 0.24 mg/L or approximately 0.3 mg/L.[10,11]

These findings suggest that, in order to protect the most vulnerable, a foetus *in utero*, public health

attention should be given to elevated fluoride intakes during pregnancy, whether from drinking water, black tea, or other sources.[7]

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