PREVENTION OF FLUORIDE ION-INDUCED IQ LOSS IN CHILDREN

ABSTRACT: New research suggests that the intrauterine period is the time when the developing brain is most at risk for fluoride ion (F)-induced neurotoxicity. The prevention of F-induced neurotoxicity and IQ loss in children must therefore start in pregnancy and continue during childhood, especially early childhood up to the age of 7 yr. A safe daily intake of F for pregnant women and children of all ages to give protection from F-induced neurotoxicity can been estimated to be approximately 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 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. The quantities of water, fluoridated with 0.7 mg F/L (0.7 ppm) which contain 0.04 and 0.15 mg of F are 72 and 214 mL, respectively, approximately a third of a cupful and a cupful (1 cup = 8 oz = 237 mL). With this being less than 30% of the mean daily water intake for persons aged <0.5–6, 7–19, and ≥20 yr, in order to prevent F-induced IQ loss in children, pregnant women and children, up to the age of 7 yr, should avoid the use of fluoridated community water supplies and other dietary sources high in F including tea and fluoridated dental products that may be swallowed such as fluoridated toothpaste and professionally applied fluoride gels and varnishes. Using the safe dose of F for preventing *in utero* foetal neurotoxicity, derived with the LOAEL/NOAEL method, of 0.04 mg F/day, and taking the body weight of a pregnant adult woman as 70 kg, the oral reference value for longer-term (up to 10% of an average life span) exposure (RfV_{LO}) can be calculated to be approximately 0.0006 mg/kg bw/day (0.04÷70=0.00057). This level is 100 times less than the current reference dose (RfD) of 0.06 mg/kg bw/day for preventing objectionable dental fluorosis of moderate or severe severity.

Keywords: F-induced neurotoxicity; Prevention of F-induced IQ loss; Safe daily dose of F.

The science on specific topics, such the safety of taking, systemically, supplemental fluoride ions (F) in tablet form or in community water supplies, milk, or salt for the purpose of preventing dental caries, is never settled. The emergence of new research may necessitate a revision of the views which are generally held at a particular time. Recent developments suggest it is now appropriate to review our understanding of F-induced IQ loss in children.

The studies by Xiang et al. on 512 children aged 8–13 yr found a dose-response relationship was present between drinking water F levels and IQ after consideration of the possible confounding factors of family income, parental education, urinary iodine, drinking water arsenic, and blood lead.[1-7] A 1.5 mg increase in the daily oral dose of F, going from 0.5 to 2.0 mg F/day, was associated with a loss of IQ of 5 IQ points.[8] The safe daily dose of F for children of all ages to protect against a 5 point IQ loss was estimated by the Lowest Observed Adverse Effect Level/No Observed Adverse Effect Level (LOAEL/NOAEL) and the Benchmark Dose (BMD) methods to be 0.047 and 0.045 mg F/day, respectively.[8] In the discussion of the limitations of this study on estimating a safe daily dose for children it was noted that the timing effect of F exposure on neurodevelopment was not precisely known and that the F exposure of the pregnant mother may, at least partially, influence the outcome for the child.[8] Because of the stability of the site of residence and the water supply being used, the subjects were exposed the same relatively high or low level of F from the time of conception until the time of being studied, at ages 8–13 yr. Exposure to a high or low level of F at age 8–13 yr may have simply been a marker for high or low exposure of the mother during pregnancy and the level of exposure during childhood

may not have been relevant. Whether the neurotoxic damage occurred during the intrauterine period, the neonatal period, or later in childhood was not able to be determined in the study design. In estimating the safe daily dose of F for children, an uncertainty factor (UF) of 3 was used to allow for *in utero* toxicity in addition to an UF of 10 to allow for inter-individual variability, and, with the LOAEL/NOAEL method, an UF of 3 was used to estimate the NOAEL from the LOAEL.[8]

Studies by Bashash et al.[9] and Thomas et al.[10] have shed light on the timing of the F-exposure which leads to F-induced IQ loss. In 2017, Bashash et al. studied prenatal fluoride exposure and cognitive outcomes in Mexican children at 4 and 6–12 yr of age in a longitudinal study.[9] Urine samples were taken from the mothers during pregnancy and from their children, when aged 6–12 yr old, and adjusted for urinary creatinine and specific gravity, respectively. Child intelligence was measured by Spanish versions of the General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities at age 4 yr and the full scale intelligence quotient (IQ) from the Wechsler Abbreviated Scale of Intelligence (WASI) at age 6–12 yr. By virtue of living in Mexico, the subjects were exposed to fluoridated salt at 250 ppm and varying degrees of naturally occurring F in the drinking water, the range from the literature being 0.15–1.38 mg/L. The authors obtained complete data on 299 mother-child pairs of whom 287 and 211 had data for the GCI and IQ analyses, respectively. Maternal bone lead and blood mercury levels were measured but there was a lack of information about environmental neurotoxicants, such as arsenic, or about iodine in salt which could modify the associations between F and cognition. However, there was no evidence to suggest the subjects were exposed to significant levels of arsenic or other known neurotoxicants. The mean urinary F value for all of the mothers with complete data (n=299) was 0.90±0.35 mg/L (mean±SD) and for the children with available urine samples (n=211) it was 0.82±0.38 mg/L. For all 512 of the mothers studied, including those with incomplete data, the urinary F was 0.88±0.34 mg/L, range 0.02–2.36 mg/L, and 0.64, 0.82, and 1.02 mg/L for the 25th, 50th, and 75th percentiles, respectively. Using multivariate models, the authors found that an increase in the maternal urine F of 0.5 mg/L (approximately the interquartile range [IQR]) predicted 3.15 (95% CI= –5.42, –0.87) and 2.50 (95% CI –4.12, –0.59) lower offspring GCI and IQ scores, respectively. They concluded that higher prenatal F exposure, in the general range of exposures reported for other general population samples of pregnant women and nonpregnant adults, was associated with lower scores on tests of cognitive function in the offspring at age 4 yr and 6–12 yr. No clear, statistically significant association was present between the contemporaneous children's urinary fluoride at age 6–12 yr and IQ.[9]

In 2018, Thomas et al,[10] a team of authors similar to Bashash et al.,[9] reported that higher *in utero* exposure to F also had an adverse impact on offspring cognitive development in the first three years of life. This study again utilised the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) birth cohort and archived pregnancy samples to study prenatal F exposure and its association with subsequent child neurobehavioral outcomes at ages 1, 2, and 3 yr. A Generalised Mixed Model (GMM) was used to model the association between mean creatinine-

adjusted urinary F (MUFcr), averaged over three trimesters, and the Mental Development Index (MDI), a subscale of the Bayley Scales of Infant Development-II (BSID-II) test, among 401 mother-infant pairs. The analysis controlled for maternal age, education, marital status, ELEMENT cohort, child's sex, and child's age. The authors found the median MUFcr was 0.835 mg/L (range 0.195–3.673 mg/L). The MUFcr was significantly inversely associated with the offspring MDI scores, with an increase in MUFcr of 0.5 mg/L (roughly the interquartile range value) corresponding to a decrease in the MDI of 1.20 points (95% CI: –2.19, –0.20).[10]

Bashash et al.[9] and Thomas et al.[10] found an increase in the maternal urine F of 0.5 mg/L during pregnancy was associated with impaired cognitive development at ages 1–3 yr (a 1.2 point decrease in the MDI),[10] at age 4 yr (a 3.15 point decrease in the GCI),[9] and at ages 6–12 yr (a 2.5 IQ point decrease in the IQ measured with the WASI).[9] Because of the lack of a significant correlation between urinary F and IQ at age 6–12 yr and the presence of a significant negative relationship between the maternal urine F during pregnancy and the cognitive functioning tests at 1–3, 4, and 6–12 yr, it appears that the intrauterine period is the time when the developing brain is most at risk for F neurotoxicity.[9,10]

The mean maternal urinary F level, adjusted for urinary creatinine, in the Bashash et al. study for all of the mothers with complete data (n=299) was 0.90±0.35 mg/L (mean±SD) and for all 512 of the mothers studied, including those with incomplete data, the urinary F was 0.88±0.34 mg/L, range 0.02–2.36 mg/L, and 0.64, 0.82, and 1.02 mg/L for the 25th, 50th, and 75th percentiles, respectively.[9] In the Thomas et al. study, the median maternal urinary F adjusted for urinary creatinine was 0.835 mg/L (range 0.195–3.673 mg/L).[10] These levels of 0.90 (mean), 0.88 (mean), and 0.835 (median) mg/L are comparable to the median urinary F concentration of 0.82 (0.62, 1.03) mg/L (μg/mL) found by Brough et al. in 59 pregnant women in Palmerston North, New Zealand, in 2009–2011, where the community water supply was fluoridated, in accordance with the New Zealand Ministry of Health recommendation, to give a concentration of 0.7–1.0 mg/L.[11] The levels of exposure to F experienced by the mothers in the studies by Bashash et al. and Thomas et al. were thus comparable to those in a community with water fluoridation at the level of 0.7–1.0 mg/L.

That intrauterine exposure to F can cause IQ loss is also supported by the study by Valdez Jiménez et al.[12] They evaluated the association between *in utero* exposure to F and Mental and Psychomotor Development (MDI and PDI) evaluated through the Bayley Scale of Infant Development II (BSDI-II) in infants. The sample included 65 mother-infant pairs. Environmental exposure to F was quantified in tap and bottled water samples and F in maternal urine was the biological exposure indicator. The samples were collected during the 1st, 2nd, and 3rd trimesters of pregnancy. The mean values of F in tap water for the 1st, 2nd, and 3rd trimester were 2.6±1.1, 3.1±1.1, and 3.7±1.0 mg/L, respectively, with 80% of the samples exceeding the reference value of 1.5 mg/L (NOM-127-SSA1-1994). The mean values for the maternal urinary F were 1.9±1.0, 2.0±1.1, and 2.7±1.1 mg/L for the 1st, 2nd and 3rd trimesters, respectively. The percentages of infants with MDI and PDI scores of less

than 85 points were 38.5% and 20.9%, respectively. After adjusting for potential confounding factors (gestational age, age of child, marginalization index, and type of water consumed), the MDI showed an inverse association with the maternal urinary F levels for the first (β= –19.05, p=0.04) and second (β= –19.34, p=0.01) trimesters. The data suggested that cognitive alterations in children born to mothers exposed to F could start in the early prenatal stages of life.[12] Fluoride toxicity can result in pre-term delivery(<34 weeks gestational age)[13] which is a risk factor for impaired IQ[14] but, as gestational age was allowed for as a confounding factor by Valdez Jiménez et al., their study supports the first and second trimesters of pregnancy as an *in utero* period when the embryo or foetus is at risk of F-induced neurotoxicity.

In addition, studies of the brains of aborted foetuses of mothers with dental fluorosis or both dental and skeletal fluorosis show that *in utero* F exposure can produce neurologic damage.[15-17]

Grandjean and Landrigan note that exposures in early life to neurotoxic chemicals can cause a wide range of adverse effects on brain development and maturation that can manifest as functional impairments or disease at any point in the human life span, from early infancy to very old age.[18] The developing human brain is inherently much more susceptible to injury caused by toxic agents than is the brain of an adult.[19] During the 9 months of prenatal life, the human brain must develop from a strip of cells along the dorsal ectoderm of the foetus into a complex organ consisting of billions of precisely located, highly interconnected, and specialized cells.[19] If a developmental process in the brain is halted or inhibited, there is little potential for later repair, and the consequences can therefore be permanent.[19] The human brain continues to develop postnatally, and the period of heightened vulnerability therefore extends over many months, through infancy and into early childhood.[19] Although most neurones have been formed by the time of birth, growth of glial cells and myelination of axons continues for several years.[19] Wang et al. note that a child's intellectual development corresponds to the development of the brain which develops most rapidly before the age of 3 yr, is 80% complete by the age of 5 yr, and is essentially similar to those of adults by the age of 7 yr.[7] However, the brain remains susceptible to F-induced neurotoxicity throughout life with, for example, cognitive impairment occurring with occupational exposure to airborne hydrogen fluoride in aluminium potroom[20,21] and petroleum industry[22] workers.

Ideally, the prevention of F-induced neurotoxicity and IQ loss in children should start before a pregnancy commences, as the F previously stored in the bones will be slowly released into the blood when the F intake is lowered, and continue during childhood, especially early childhood up to the age of 7 yr. A safe daily intake for pregnant women to give protection from F-induced foetal neurotoxicity has been calculated to be 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 kg woman).[23] A safe daily intake for children of all ages to give protection from F-induced neurotoxicity has been calculated to be 0.045–0.047 mg F/day, ≈ 0.05 mg F/day (0.0010 mg F/kg bw/day for a 45 kg child, the 90th percentile children's body mass at 8–13 yr).[8] In calculating this safe daily dose for children of ≈ 0.05 mg F/day, an uncertainty factor (UF) of 3 was used to allow for the possibility the toxicity occurred

in utero, with the foetus being more sensitive to toxins that older children or adults. With the evidence now available showing that toxicity does indeed occur *in utero*, it would be appropriate to use the safe daily intake calculated for pregnant women of 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 kg woman) to protect the foetus and to remove the *in utero* UF from the calculation of the safe dose for children. Removing this UF gives a safe dose for children of ≈ 0.05×3 = 0.15 mg F/day (0.003 mg F/kg bw/day using the 90th percentile children's body mass at 8–13 yr of 45 kg).

An oral reference value for longer-term exposure (RfV_{LO}) for F can also be calculated. The final report in 2002 of a Reference Dose/Reference Concentration Technical Panel noted that there were issues with the current definition of the chronic oral reference dose (RfD), the United States Environmental Protection Agency's estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.[24] They proposed the use of a reference value, an estimate of an exposure designated by duration and route, to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. It is derived from a BMDL (benchmark dose lower bound), a NOAEL, a LOAEL, or another suitable point of departure, with uncertainty/variability factors applied to reflect limitations of the data used. The generalized durations were acute (<24 hr), short-term (up to 30 days), longer-term (up to 10% of an average life span), and chronic (up to a lifetime), all considered to be continuous exposure throughout the duration specified. Susceptible subgroups could refer to life stages, e.g., children, the elderly, or other segments of the population. They recommended that endpoint- or life stage-specific reference values such as the RfD_{DT} (reference dose for developmental toxicity) should not be derived. Rather, a sample reference value should be calculated for each relevant and appropriate endpoint and these should then be considered in the derivation of various duration reference values. Reference values should be derived to be protective of all types of effects for a given duration of exposure and are intended to protect the population as a whole, including potentially susceptible subgroups. Thus, the RfD_{DT} concept of a critical window of exposure for some health effects is addressed in the adoption of less-than-chronic reference values. Therefore, using the safe dose of F for preventing *in utero* foetal neurotoxicity, derived with the LOAEL/NOAEL method, of 0.04 mg F/day, and taking the body weight of a pregnant adult woman as 70 kg, the RfV_{LO} can be calculated to be approximately 0.0006 mg/kg bw/day (0.04÷70=0.00057). This level is 100 times less than the current RfD of 0.06 mg/kg bw/day for preventing of objectionable dental fluorosis of moderate or severe severity, which has been considered to be a cosmetic effect and not a toxic and/or adverse health effect.[25]

The quantities of water, fluoridated with 0.7 mg F/L (0.7 ppm) which contain 0.04 and 0.15 mg of F are 72 and 214 mL, respectively, approximately a third of a cupful and a cupful (1 cup = 8 oz = 237 mL). The mean consumption of municipal water for adults aged ≥20 yr, both direct and indirect involving beverages and foods that include water as an ingredient, has been estimated to be, in the USA, 1.1 L/day.[8] The

ranges, at the 90th percentile level, of the mean daily ingestion of water by children in the United States of America who consume water from community sources at ages <0.5–6 and 7–19 yr are 719–950 and 955–1669 mL/day, respectively.[8] With 72 and 214 mL being less than 30% of the mean daily water intake for persons aged <0.5–6, 7–19, and ≥20 yr, in order to prevent F-induced IQ loss in children, pregnant women and children up to the age of 7 yr should avoid the use of fluoridated community water supplies.

Similarly, these groups should avoid fluoride-rich foods, other dietary sources of F, and other environmental sources of F such as (i) tea; (ii) beverages prepared with fluoridated water; (iii) ocean fish including the bones and skin of salmon and sardines; (iv) shrimps; (v) canned fish and fruit juices where F has been used as a preservative; (vi) gelatin; (vii) skin of chicken; (viii) grapes, raisins, and grape-juice where the grapes have been treated with F-containing pesticides such as cryolite (Na_3AlF_6); (ix) food fumigated with sulfuryl fluoride (SO_2F_2); (x) F-containing spices and foods containing these, e.g. black rock salt (*kala namak,* fluorite rock powder, fluorite (also called fluorspar) is the mineral form of calcium fluoride (CaF_2); red rock salt; "Himalayan salt" from the Punjab region of Pakistan which has been found to contain 231 mg F/kg (ppm); daalmoth and other salty snacks; *chat masala*, pickles, and *garam masala* prepared using black rock salt; churans containing black rock salt, (*hajmola*, *hingoli, satmola*); *chat-papri* containing black rock salt; and packaged food products containing black rock salt; (xi) dental products which may be swallowed such as fluoridated toothpaste, mouth rinse, and professionally applied fluoride gels and varnishes; and (xii) other sources of environmental fluoride including cigarette smoke and environmental pollution.[26-31]

F is not an essential trace element in humans or necessary for the development of healthy teeth and bones.[32] It is likely that there is no threshold for F neurotoxicity in drinking water, and the only assuredly safe level is zero.[23,33] The currently recommended level of 0.7 mg F/L for community water systems[23] 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 F intake above the estimated safe daily intakes of approximately 0.04 mg F/day (0.0006 mg F/kg bw/day for a 70 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.[23] The oral reference value for longer-term (up to 10% of an average life span) exposure (RfV_{LO}) can be calculated to be approximately 0.0006 mg/kg bw/day (0.04÷70=0.00057). Preventing F-induced IQ loss in children by lowering the dietary F 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, F-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.[34,35] If a child younger than 3 yr 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-yr-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 yr 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.[27,36] Selenium can improve mitochondrial membrane stability and protect against F toxicity in skeletal muscles[37] although at higher levels selenium is synergistic with fluoride and arsenic in causing toxicity.[38]

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