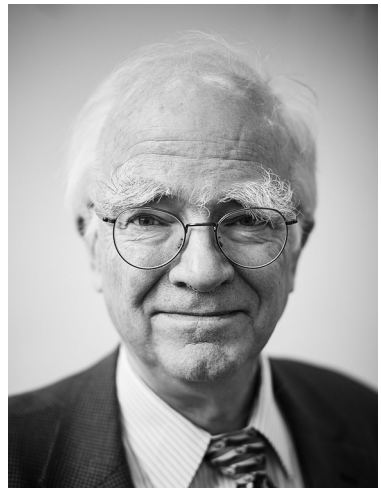
UPDATED REVIEW BY GRANDJEAN OF DEVELOPMENTAL FLUORIDE NEUROTOXICITY

ABSTRACT: An updated review by Philippe Grandjean, published in *Environmental Health* on December 19, 2019, of developmental fluoride neurotoxicity concluded that recent epidemiological results support the notion that elevated fluoride intake during early development can result in IQ deficits that may be considerable. He noted that the recognition of neurotoxic risks is necessary when determining the safety of fluoride-contaminated drinking water and fluoride uses for preventive dentistry purposes.

Keywords: Developmental fluoride neurotoxicity; Grandjean; Review.

An updated review by Philippe Grandjean, published in *Environmental Health* on December 19, 2019, of developmental fluoride neurotoxicity concluded that recent epidemiological results support the notion that elevated fluoride intake during early development can result in IQ deficits that may be considerable.[1] He noted that the recognition of neurotoxic risks is necessary when determining the safety of fluoride-contaminated drinking water and fluoride uses for preventive dentistry purposes.



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Grandjean, from the Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA, and the Department of Public Health, University of Southern Denmark, Odense, Denmark, has co-authored three previous reviews that have referred to fluoride neurotoxicity. In addition, in 2013 he authored a book *Only one chance: how environmental pollution impairs brain development—and how to protect the brains of the next generation*, in which he highlighted the silent pandemic that is occurring as industrial chemicals disrupt brain development.[2,3] He noted that we get only one chance to develop a brain and that damage to the developing brain of a fetus or child is likely to have lifelong effects. His list of 213 industrial chemicals, that are known to be able to reach the brain and cause brain toxicity, included fluoride.

In 2006, in a review of industrial chemicals with Landrigan, he described fluoride as an emerging neurotoxic substance.[4] In 2012, in a review and meta-analysis of developmental fluoride neurotoxicity with Choi, Sun, and Zhang, he concluded that the results supported the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment.[5] In 2014, in a further review with Landrigan on the neurobehavioural effects of developmental toxicity, he characterized fluoride as an emerging neurotoxic substance.[6]

In his 2019 integrated literature review on fluoride exposure and intellectual disability, he focussed on studies on children published subsequent to his 2012 meta-analysis.[1] He found that 14 recent cross-sectional studies from endemic areas with naturally high fluoride concentrations in the groundwater supported the previous findings of cognitive deficits in children with elevated fluoride exposures. In addition, three recent prospective studies from Mexico[7,8] and Canada[9] with

individual exposure data showed that early-life exposures to fluoride were negatively associated with children's performance on cognitive tests. Neurotoxicity appeared to be dose-dependent, and tentative benchmark dose calculations suggested that the safe exposures were likely to be below the currently accepted or recommended fluoride concentrations in drinking water.

Grandjean commented that more weight must be placed on prospective studies that include assessment of individual levels of fluoride exposures in early life. Two prospective studies from New Zealand[10,11] explored the possible neurobehavioral consequences of community water fluoridation. The first study, from 1986,[10] reported no association between behavioral problems and residence in a fluoridated community during the first 7 years of life. However, like the subsequent New Zealand study, from 2015,[11] the authors had no access to individual measurements of fluoride exposure, and the exposure status relied solely on residence in a fluoridated community and its duration, where age at the time of residence was apparently not considered. In the more comprehensive 2015 study,[11] based on a birth cohort established in Dunedin, New Zealand, from births in 1972–1973, 1037 children were recruited at age 3 years, and IQ tests were administered at ages 7, 9, 11, and 13 years, and again at age 38. The average IQ result for 992 subjects was used for comparison between residents in areas with and without water fluoridation. No significant differences in IQ in regard to fluoridation status were noted, and this finding was independent of potential confounding variables that included sex, socioeconomic status, breastfeeding, and birth weight. Prenatal fluoride exposure was not considered. The average difference in childhood exposure between the fluoridated vs. nonfluoridated areas was estimated to be 0.3 mg/day. However, the 93 cohort subjects who did not live in a fluoridated area may well have received fluoride supplements, as was the case for a total of 139 children in the study, thereby impacting on the exposures. A further concern was that formula may have contributed substantial fluoride exposure, and it is therefore interesting that breastfeeding—and thus avoidance of formula—in the fluoridated areas contributed an advantage that averaged 6.2 IQ points at age 7–13 years, while the advantage was less (4.3) in the non-fluoridated areas. Subsequently, the authors estimated the average total fluoride intake up to age 5 years, including tablets, toothpastes, and dietary sources, without finding any IQ difference. However, information on maternal tea consumption during pregnancy was not obtained, although tea has long been recognized as an important source of fluoride in New Zealand. Lead exposure in this cohort was later reported to cause IQ deficits, but control for the blood-lead concentration at age 9 years showed no change in the results for fluoride. Grandjean observed that despite the shortcomings, this study has been hailed as evidence that fluoridated water is "not neurotoxic for either children or adults, and does not have a negative effect on IQ". Grandjean commented that this conclusion seemed rather optimistic, given the fact that the exposure assessment was imprecise (especially for prenatal exposure) and that the statistical power was probably insufficient to allow identification of any important IQ deficit.

In contrast to the two New Zealand studies, two more recent studies from Mexico (2017)[7,8] and one from Canada (2018)[9] were seen to provide more robust evidence. In the first prospective study from an area in Mexico[7] with elevated levels of fluoride

in drinking water, maternal urinary fluoride during the pregnancy (corrected for specific gravity) was examined for its association with scores on the Bayley Scales among 65 children evaluated at age 3–15 months. The mothers in the study had average urinary fluoride concentrations at each of the three trimesters of pregnancy of 1.9, 2.0, and 2.7 mg/L (higher than in the following study from Mexico). The fluoride exposure indicators during first and second trimesters were associated with significantly lower scores on the Bayley Mental Development Index score after adjustment for covariates.

For the second prospective study from Mexico,[8] the existence of the ELEMENT (Early Life Exposure in Mexico to Environmental Toxicants) birth cohort allowed longitudinal measurements of urinary fluoride in pregnant mothers and their offspring and their associations with measures of cognitive performance of the children at ages 4 and 6–12 years. The cohort had been followed to assess developmental lead neurotoxicity, and biobanked urine samples were available for fluoride analysis and adjustment for creatinine and density.

Most of the mothers provided only one or two urine samples, thereby introducing some imprecision in the exposure estimate. Child cognitive function was determined by the General Cognitive Index (GCI) of the McCarthy Scale at age 4 years in 287 children, and IQ by the Wechsler Abbreviated Scale of Intelligence (WASI) at age 6–12 years in 211 children. Urinary fluoride (mg/L) in the mothers averaged 0.90 (SD 0.35) and, in the children, 0.82 (SD 0.38). Covariates included gestational age, birth weight, sex, parity, age at examination, and maternal characteristics, such as smoking history, marital status, age at delivery, maternal IQ, and education. After covariate adjustment, an increase in maternal urinary fluoride by 1 mg/L during pregnancy was associated with a statistically significant loss of 6.3 (95% CI, –10.8; – 1.7) and 5.0 (95% CI, – 8.2; – 1.2) points on the GCI and IQ scores, respectively. These associations remained significant, and the effect sizes appeared to increase, in sensitivity analyses that controlled for lead, mercury, and socioeconomic status.

Although adjustment could not be made for iodine deficiency or arsenic exposure, any residual confounding was judged to be small in this population. Important strengths were that the cohort was followed from birth with meticulous documentation for lead exposure and other neurobehavioral risks. This study also ascertained the childhood fluoride exposure at the time of IQ testing (6–12 yr) and found no indication of an adverse impact on the IQ in the cross-sectional analysis.

In the Canadian prospective study,[9] between 2008 and 2011, 2001 pregnant women were recruited into the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort in Canada. A subset of 601 of their children were examined at age 3–4 years, slightly less than half of them residing in fluoridated communities. Maternal spot urine samples were obtained from each of the three semesters of pregnancy, and the results were analyzed for those 512 mother-child pairs where urine was available from all three semesters, so that the overall average urinary fluoride could be used as an exposure biomarker, with adjustment for specific gravity and creatinine. Information was obtained on food and beverage intakes, including tea (assuming a fluoride content of 0.52 mg in each cup of black tea). Intellectual abilities were assessed using the age-appropriate Wechsler scale that provided a full-scale IQ. Covariate adjustment included exposures to other neurotoxicants and other

relevant covariates, such as sex, age at examination, and maternal exposure to indirect smoking, race, and education. As had been shown by the same research group in a previous study of a larger population, women residing in fluoridated communities had higher urinary fluoride concentrations (0.69 vs 0.40 mg/L) and also higher calculated daily fluoride intakes from water and other beverages (0.93 vs. 0.30 mg/day). Regression analyses showed that an increase in urinary fluoride of 1 mg/L was associated with a statistically significant loss in IQ of 4.49 points in boys, though not in girls. An increase of 1 mg/L of fluoride in water and an increase of 1 mg/day of fluoride intake was associated with an IQ loss of 5.3 points and 3.66 points, respectively, for both boys and girls. Thus, this study at somewhat lower exposures is in good agreement with the data from the two studies carried out in Mexico. In an extension of the MIREC study of prenatal fluoride exposures, the authors subsequently assessed the possible impact of fluoride exposure from reconstituted formula in fluoridated and non-fluoridated communities. After adjustment for prenatal fluoride exposure and other covariates, each increase by 1 mg/L in the water fluoride concentration was found to be associated with a statistically significant decrease of 8.8 IQ points in the children who had been formula-fed in the first 6 months of life, while no such difference was seen among the exclusively breastfed children. Although the results were somewhat unstable and included only 68 formula fed children from fluoridated communities, these results support the notion that early postnatal brain development is also likely to be vulnerable to neurotoxicant exposures, as is well documented, e.g., from arsenic exposure in infancy.

The substantial IQ losses associated with elevated water-fluoride concentrations are in accordance with the difference of almost 7 IQ points between exposed groups and controls in the meta-analysis from 2012.[5] Also, the largest cross-sectional study from 2018 showed a statistically significant loss of 8.6 IQ points for each increase by 1 mg/L in the fluoride concentration in water, although somewhat less in another recent study.

The studies reviewed showed dose-dependent fluoride neurotoxicity that appeared to be statistically significant at water concentrations of or below 1 mg/L, but the studies themselves did not identify a likely threshold. Regulatory agencies often use benchmark dose calculations to develop non-cancer health-based limits for dietary intakes, such as drinking water. Grandjean noted one recent report by Hirzy et al.[12] used this approach to generate benchmark results from a study by Xiang et al. of more than 500 children in China.[13] The authors used a high benchmark response (BMR) of 5 IQ points, but results were also given for a more appropriate BMR of 1 IQ point. For the latter, the benchmark dose (lower confidence limit) (BMDL) was calculated to be a daily intake level of 0.27 mg/day.[12] Using the average water intake of 1.24 L/day in non-pregnant women, the BMDL corresponds to a water concentration of 0.22 mg/L. The report did not provide data for urinary fluoride concentrations.

Grandjean used the regression coefficients and their standard deviations, as provided in the published reports of the Mexican and Canadian studies by Bashash et al.[8] and Green et al.,[9] respectively, to estimate the tentative bench mark dose (BMD) values. 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 ELEMENT study, although the greater uncertainty results in a fairly low BMDL. The results suggest a BMDL of about 0.2 mg/L or below, a level that is similar to the result calculated from the Xiang et al. study in China[12,13] and clearly below commonly occurring exposure levels, even in communities with drinking water fluoridation.

Grandjean's review updated the conclusions from his 2012 meta-analysis of cross-sectional studies of intellectual deficits associated with elevated fluoride exposure.[5] He noted subsequent epidemiological studies have strengthened the links to deficits in cognitive functions with several of them providing individual exposure levels, though most of the new studies were cross-sectional and focused on populations with fluoride exposures higher than those typically provided by fluoridated water supplies. However, prospective studies from the most recent years document that adverse effects on brain development happen at elevated exposure levels that occur widely in North America and elsewhere in the world, in particular in communities supplied with fluoridated drinking water. His assessment was that these new prospective studies are of very high quality and, given the wealth of supporting human studies and biological plausibility, leave little doubt that developmental neurotoxicity is a serious risk associated with elevated fluoride exposure, especially when this occurs during early brain development. While evidence on the neurotoxic impact of early postnatal exposure remains limited, other neurotoxicity evidence suggests that adverse effects are highly plausible. Research on laboratory animals confirms that elevated fluoride exposure is toxic to the brain and nerve cells, as already indicated by the 2006 National Research Council of the National Academies (NRC) review *Fluoride in drinking water: a scientific review of EPA's standards*. The evidence today is substantially more robust. The 2016 National Toxicology Program (NTP) review placed more confidence in fluoride impairing learning in adult animals due to fewer experimental studies being available on developmental exposure. Still, not all studies are in agreement, perhaps due to species or strain differences in vulnerability. However, fluoride is known to pass the placental barrier and to reach the brain, and the animal studies bear out the importance of the prenatal period for fluoride neurotoxicity. Toxicant exposures in early life can have much more serious consequences than exposures occurring later in life, and the developing brain is known to be particularly vulnerable. Thus, the vulnerability of early brain development supports the notion that fluoride neurotoxicity during early life is a hazard of public health concern.

Dental fluorosis has been dismissed as a "cosmetic" effect only, but the association of dental changes with intellectual deficits in children suggests that dental fluorosis should no longer be ignored as non-adverse. Dental fluorosis may perhaps serve as a sensitive indicator of prenatal fluoride exposure, and information is needed to determine to which extent the time windows for dental fluorosis development in different tooth types overlap with vulnerable periods for brain development.

Although the adverse outcome pathway is unclear, several epidemiological studies suggest that thyroid dysfunction is a relevant risk at elevated fluoride exposures. Thus, studies in children have reported deficient thyroid functions, including elevated TSH (thyroid stimulating hormone) with elevated fluoride exposure, and one study linked elevated fluoride exposure to both thyroid dysfunction and IQ deficits.[14] In Canada, elevated urinary fluoride was associated with increased TSH among iodine-deficient adults, though not in the general population, after exclusion of those with known thyroid disease. In England, the diagnosis of hypothyroidism was nearly twice as frequent in medical practices located in a fully fluoridated area, as compared to non-fluoridated areas. These findings are highly relevant to the neurotoxicity concerns, as thyroid hormones are crucial for optimal brain development.

Given that fluoride is excreted only in minute amounts in human milk, the focus on prenatal exposure appears justified, but formula-mediated neonatal exposures represent an additional concern, as indicated by dental fluorosis studies and the most recent study by Till et al. from Canada.[15] The human brain continues to develop postnatally, and the period of heightened vulnerability therefore extends over many months through infancy and into early childhood. Fluoride exposures during infancy are of special concern in regard to formula produced with fluoride-containing water.

One prospective study suggested that boys may be more vulnerable to fluoride neurotoxicity than girls.[9] Given that endocrine disrupting mechanisms often show sex-dependent vulnerability, further research is needed to understand the extent that males may require additional protection against fluoride exposure.

Recent studies have also identified possible genetic predisposition to fluoride neurotoxicity. This means that some subgroups of the general population will be more vulnerable to fluoride exposure so that exposure limits aimed at protecting the average population may not protect those with susceptible genotypes, as has been shown, e.g., for methylmercury neurotoxicity. The impact of iodine deficiency on fluoride vulnerability also needs to be considered.

Past studies of fluoride-exposed workers suggest possible neurotoxicity, but recent evidence rather points to possible accelerated aging in fluoride-exposed adults. As has been proposed for other developmental neurotoxicity, early-life exposure to fluoride deserves to be examined in regard to its possible impact on the risk of adult neurodegenerative disease.

Despite the growing evidence, health risks from elevated exposures to fluoride have received little attention from regulatory agencies. The appearance of prospective studies that offer strong evidence of prenatal neurotoxicity should inspire a revision of water-fluoride regulations. The benchmark results calculated from these new studies, although only tentative at this point, support the notion that the current maximum contaminant level goal (MCLG) of 4 mg/L is much too high. 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 0.4 mg/L which is below the levels currently achieved by fluoridation of approximately 0.7 mg/L.

The notion that fluoride is primarily a developmental neurotoxicant means that fluoride—an element like lead, mercury, and arsenic—can adversely affect brain

development at exposures much below those that cause toxicity in adults. For lead and methylmercury, adverse effects in children are associated with blood concentrations as low as about 10 nmol/L. Blood-fluoride concentrations associated with elevated intakes from drinking-water may exceed 20 µg/L, or about 1 µmol/L, i.e., about 100-fold greater than the serum concentrations of the other trace elements that cause neurodevelopmental damage. Thus, although fluoride is neurotoxic, it appears to be much less potent than some other elements, such as lead and mercury, that occur at much lower concentrations in the Earth's crust. Although substances that occur naturally in the biosphere may be thought to be innocuous, or even beneficial as in the case of fluoride, the anthropogenic elevations in human exposures may well exceed the levels that human metabolism can successfully accommodate.

Grandjean speculated that perhaps dentistry interests in promoting water fluoridation had affected the risk assessment and reduced the regulatory attention to fluoride toxicity. He noted that while water fluoridation continues to be recommended, the benefits appear to be minimal in recent studies of caries incidence. He commented that perhaps due to the modern use of topical fluoride products, especially fluoridated toothpaste, countries that do not fluoridate the water have seen drops in dental cavity rates similar to those observed in fluoridated countries. This finding is in agreement with the observation that fluoride's predominant benefit to dental health comes from topical contact with the surface of the enamel, not from ingestion, as was once believed.[16,17] Already in 2001, the U.S. Centers for Disease Control (CDC) concluded that fluoride supplementation during pregnancy did not benefit the child's dental health. Consensus has since then been building on the lack of efficacy of water fluoridation in preventing caries. It therefore appears that population-based increase of systemic fluoride exposure may be unnecessary and, according to the evidence considered in Grandjean's review, counterproductive. He recommended that the focus should therefore shift from the population-wide provision of elevated oral fluoride intake to the consideration of the risks and consequences of developmental neurotoxicity associated with elevated fluoride exposure in early life. The prospective studies suggest that prevention efforts to control human fluoride exposures should focus on pregnant women and small children. In addition to drinking water, attention must also be paid to other major sources of fluoride, such as black tea. Thus, excessive tea-drinking is known to potentially cause skeletal fluorosis, and the possible impact of tea drinking deserves to be considered along with other possible sources that may affect pregnant women and small children.

In conclusion he found that there is little doubt that developmental neurotoxicity is a serious risk associated with elevated fluoride exposure, whether due to community water fluoridation, natural fluoride release from soil minerals, or tea consumption, especially when the exposure occurs during early development. In Grandjean's view, given that developmental neurotoxicity is considered to cause permanent adverse effects, the next generation's brain health presents a crucial issue in the risk-benefit assessment for fluoride exposure.

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