99 Editorial
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FURTHER RECOGNITION OF FLUORIDE-INDUCED NEUROTOXICITY

ABSTRACT: The recognition by Bellinger in 2018 that fluoride may induce neurotoxicity in children follows the description by Grandjean and Landrigan in 2006 of fluoride as an emerging neurotoxic substance and in 2014 as a developmental neurotoxicant. By putting their names to the association between fluoride and neurotoxicity, the authors may attract some criticism from the advocates of water fluoridation but by reviewing the literature on fluoride and neurotoxicity, the authors are performing a valuable service which adds to the public good and eventually, given the strength of the evidence, the deliberate addition of fluoride to community water supplies will be universally prohibited.

Keywords: Community water fluoridation; Fluoride; Neurotoxicity.

David Bellinger, who did pioneering work with Herbert Needleman, Alan Leviton, and others on lead-associated intellectual deficit,[1] has commented in a recent review on "Environmental chemical exposures and neurodevelopmental impairments in children" that children are widely regarded as the population subgroup that is most vulnerable to the toxicities that result from exposure to environmental chemicals due to a variety of behavioural and physiologic factors.[2] He notes that for many chemicals, the central nervous system is the most sensitive target organ and the paper considers the impacts on children's intellectual development. The review focuses on metals or metalloids including mercury, lead, arsenic, and fluoride, as well as on pesticides, air pollution, synthetic organic chemicals, and endocrine disruptors. He has also highlighted that environmental chemicals cause many adversities other than a reduction of intelligence and that a full accounting of the burden of disease imposed by chemicals must include the late downstream impacts, e.g., mental health and economic success, that can reduce the quality of life. Bellinger observes that we have a responsibility to future generations to reduce or, when possible, to eliminate the threats that these chemicals pose to their future well-being.[2]

Photo courtesy of David Bellinger

Dr Alan Leviton (left), Dr Herbert Needleman (13 December 1927–18 July 2017), and Dr David Bellinger at the Charles A. Dana Foundation Award ceremony in 1989. Needleman won an award for his research on lead poisoning.

The current approach in the USA for the regulation of chemicals is to restrict their use only after it has been shown unequivocally that exposure impairs human health.[2] However, even rudimentary toxicological data are available for only a small fraction of the approximately 80,000 chemicals in use, and most of these data pertain to relatively gross health endpoints, such as death, cancer, and birth defects, rather than subtle alterations in brain development and function.[2]

Bellinger states that fluoride differs from most other environmental chemicals in that children are intentionally exposed to it because of its role in the prevention of caries. To support the case that fluoride may induce neurotoxicity, Bellinger refers to the concern raised by a large number of basic neuroscience studies about the potential effects of excessive fluoride exposure in developing animals. It is mentioned that in some areas of the world high fluoride levels in groundwater may cause dental and skeletal fluorosis. In the USA, in 1999–2004, according to the Centers for Disease Control, nearly 40% of US children, aged 12–15 yr, showed signs of at least mild dental fluorosis, an increase of nearly 100% over the rate observed in 1986–1987.[3]

The author also refers to the 2012 systematic review and meta-analysis by Choi, Sun, Zhang, and Grandjean of 27 studies from China (n=25) and Iran (n=2).[4] These were mostly ecologic in design and compared children from a low-exposure village to a high-exposure village. The conclusion of the meta-analysis was that exposure to water with greater fluoride concentrations was associated with lower intelligence quotient (IQ) scores. However, the studies were seen to provide only weak evidence as the data lacked internal exposure (i.e., the blood concentrations of fluoride or the severity of dental fluorosis in individual participants). Also, some of the villages compared were likely to have differed in factors other than the water fluoride concentrations such as socioeconomic status, access to medical care, quality of schools, etc.

Bellinger records that these deficiencies have been addressed in three recent studies:

(i) In 2015, Choi, Zhang, Sun, Bellinger, Wang, Yang, Li, Zheng, Fu, and Grandjean reported on a relatively small pilot study on 51 first-grade children in China which found negative associations between the severity of dental fluorosis, which reflected the lifetime fluoride exposure, and the children's scores on some neuropsychological tests.[5] The WISC-IV digit span subtest appeared to be the most sensitive outcome measure and moderate and severe dental fluorosis was associated with a digit span total score difference of –4.28 (95% CI –8.22, –0.33) and a backward score difference of –2.13 (95% CI –4.24, –0.02).[5]

(ii) In 2015, Kahn, Singh, Navit, Chadha, Johri, Navit, Sharma, and Bahuguna compared the IQ levels of 429 school children, aged 6–12 yr, in two different locations, in and around the Lucknow district, India, with different fluoride levels in the water (Tiwarigan 0.19 ppm and Unnao 2.41 ppm).[6] The majority of the dental fluorosis free-children (76.3%) had an IQ of grade 2 (definitely above average) while the majority of the children suffering from very mild and mild dental fluorosis were found to have IQ of grade 3 (intellectually average). Children with a moderate degree of dental fluorosis were found to have IQ of grade 4 (definitely below average). Only 5 children with severe fluorosis were included in the study and they were all found to have an IQ of grade 5 (intellectually impaired). Hence, a trend for an increase in the IQ grade (a decrease in intellectual capacity) with increased levels of dental fluorosis was observed indicating that there was a strong correlation between the fluorosis grade and the IQ grade (Spearman's p=0.766). The overall IQ of the children exposed to high fluoride levels in the drinking water, and hence suffering from dental fluorosis, was significantly lower than those of the low fluoride area.[6]

(iii) In 2017, Bashash, Thomas, Hu, Martinez-Mier, Sanchez, Basu, Peterson, Ettinger, Wright, Zhang, Liu, Schnaas, Mercado-Garcia, Téllez-Rojo, and Hernández-Avila reported on a study in Mexico where children's prenatal fluoride (F) exposure (concentration in maternal urine during pregnancy) was found to be inversely associated with the IQ scores at ages 4 and 6–12 yr.[7] Urine samples were taken from the mothers during pregnancy and from their children, when aged 6–12 years old, and adjusted for urinary creatinine and specific gravity, respectively. Child intelligence was measured by the Spanish versions of the General Cognitive Index (GCI) of the McCarthy Scales of Children's Abilities at age 4 yr and the full scale 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.[7]

Bellinger also mentioned further two studies linking fluoride to attention-deficit/hyperactivity disorder (ADHD): firstly, an ecological study by Malin and Till on fluoride and ADHD prevalence in the USA[8] and, secondly, a cohort study by Bashash et al. on fluoride and ADHD symptoms in Mexican children.[9]

(i) In 2015, Malin and Till analysed data on the ADHD prevalence among 4–17-year-olds collected in 2003, 2007, and 2011 as part of the National Survey of Children's Health, and data on the state water fluoridation prevalence from the Centers for Disease Control and Prevention (CDC) collected between 1992 and

2008.[8] They found the state prevalence of artificial water fluoridation in 1992 significantly positively predicted the state prevalence of ADHD in 2003, 2007, and 2011, even after controlling for socioeconomic status. A multivariate regression analysis showed that after socioeconomic status was controlled for, each 1% increase in artificial fluoridation prevalence in 1992 was associated with approximately 67,000 to 131,000 additional ADHD diagnoses from 2003 to 2011. Overall state water fluoridation prevalence (not distinguishing between fluoridation types) was also significantly positively correlated with the state prevalence of ADHD for all but one of the years examined. They concluded that parents reported higher rates of medically-diagnosed ADHD in their children in states in which a greater proportion of people receive fluoridated water from public water supplies and that the relationship between fluoride exposure and ADHD warranted future study.[8]

(ii) In 2018, Bashash et al., examined the association between prenatal fluoride exposure and symptoms associated with ADHD.[9] They studied 213 Mexican mother-children pairs of the Early Life Exposures to Environmental Toxicants (ELEMENT) birth cohort study for whom there was available maternal urinary samples during pregnancy and child assessments of ADHD-like behaviors at age 6–12 yr. They measured urinary fluoride levels adjusted for creatinine (MUF_{cr}) in spot urine samples collected during pregnancy. The Conners' Rating Scales-Revised (CRS-R) was completed by the mothers, and the Conners' Continuous Performance Test (CPT-II) was administered to the children. They found that the mean MUF_{cr} was 0.85mg/L (SD=0.33) and the Interquartile Range (IQR) was 0.46 mg/L. In multivariable adjusted models using gamma regression, a 0.5 mg/L higher MUF_{cr} (approximately one IQR higher) corresponded with significantly higher scores on the CRS-R for DSM-IV Inattention (2.84 points, 95% CI: 0.84, 4.84) and DSM-IV ADHD Total Index (2.38 points, 95% CI: 0.42, 4.34), as well as the following symptom scales: Cognitive Problems and Inattention (2.54 points, 95% CI: 0.44, 4.63) and ADHD Index (2.47 points; 95% CI: 0.43, 4.50). The shape of the associations suggested a possible ceiling effect of the exposure. No significant associations were found with outcomes on the CPT-II or on symptom scales assessing hyperactivity. Their conclusion was that higher levels of fluoride exposure during pregnancy were associated with global measures of ADHD and more symptoms of inattention as measured by the CRS-R in the offspring.[9]

The recognition by Bellinger that fluoride may induce neurotoxicity in children follows the description by Grandjean and Landrigan in 2006[10] of fluoride as an emerging neurotoxic substance and in 2014[11] as a developmental neurotoxicant.

Bellinger noted that fluoride differs from most other environmental chemicals in that children are intentionally exposed to it because of its role in the prevention of dental caries. The recognition by Bellinger, Grandjean, and Landrigan of the neurotoxic potential of fluoride is based on careful analyses of the scientific evidence. Using standard techniques, the levels of fluoride to which pregnant women are exposed to with community water fluoridation have been shown to be unsafe for the developing foetus.[12]

There is, at present, a divergence between current scientific theory, which indicates that community water fluoridation is unsafe, and public health practice which considers that community water fluoridation is valuable for reducing dental caries. A scientific revolution on the place of fluoride in community water supplies is currently underway in the USA and some of the countries that have been have been influenced by its community water fluoridation policy. As described by Thomas Kuhn in 1962 in *The Structure of Scientific Revolutions*, it is not easy for scientists to make a paradigm shift and many are not able to make the change.[13] He found that Nicolaus Copernicus and Isaac Newton were slow to make converts, Joseph Priestley never accepted the oxygen theory, and Lord Kelvin rejected the electromagnetic theory and at first pronounced X-rays to be an elaborate hoax. Kuhn concluded that techniques of persuasion were more important in changing paradigms than the documentation of proof and the demonstration of error. If a paradigm is ever to triumph it must gain some first supporters—people who will develop it to the point where hardheaded arguments can be produced and multiplied. Then as more scientists are converted, the exploration of the new paradigm may continue until, at last, only a few elderly hold-outs remain, and a new scientific community reforms as a single group. However, embracing a new paradigm at an early stage must often be done in faith that the new paradigm will succeed with the many large problems that confront it, knowing only that the older paradigm has failed with a few. He viewed the transfer of allegiance from a widely-held paradigm to one that contradicts it as a conversion experience that cannot be forced. Thus a conversion experience, rather than a logical analysis of information, may be involved in accepting a new paradigm on fluoridation.[14]

Bellinger, Grandjean, Landrigan, and many others have done important pioneering work on fluoride-induced neurotoxicity. By putting their names to the association between fluoride and neurotoxicity, these authors may attract some criticism from the advocates of water fluoridation[15] but, by reviewing the literature on fluoride and neurotoxicity, the authors are performing a valuable service which adds to the public good and eventually, given the strength of the evidence, the deliberate addition of fluoride to community water supplies will be universally prohibited.

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