EDITORIAL

Is Fluoride Potentially Neurotoxic?

David C. Bellinger, PhD, MSc

Environmental epidemiology is a field replete with controversies, but the intensity of the debate inspired by the fluoridation of municipal water supplies to reduce dental caries is perhaps unrivaled. Governments, as well as individuals, differ in their assessments of water fluoridation as public policy. The US Centers for Disease Control and Prevention consider water fluoridation to be one of the top 10 public health achievements in the 20th century,[1] reducing both overall caries prevalence and socioeconomic disparities.[2] Regions in which water fluoridation is rare, such as Europe, rely on more targeted strategies to deliver fluoride (eg, supplements, dental treatments and products, fortification of milk and salt). Notably, in most Western European countries, the prevalence of decayed, missing, or filled teeth is similar to or lower than the prevalence in the United States.[3]

Editor's Note

Related article

Initially, opposition to water fluoridation centered on the ethical objection that it is, in effect, a compulsory medication administered indiscriminately to water consumers without their consent. Over time, adverse health effects of excessive fluoride intake, such as tooth enamel fluorosis and skeletal fluorosis, were identified. The emerging hypothesis that fluoride is also a neurodevelopmental toxicant[4] has provided opponents of fluoridation with another, potentially even more powerful, argument.

Many studies have reported inverse associations of children's fluoride exposure with their cognition, but the inferences that can be drawn from these studies are limited by their generally poor quality. A 2012 systematic review of 27 studies,[5] most from China and most ecologic in design, concluded that children in communities with water fluoride concentrations that are naturally high have lower intelligence scores than children in communities with lower natural fluoride concentrations. The fluoride concentrations were as high as 11.5 mg/L, however, well above the target of 0.7 mg/L recommended by the US Public Health Service for water fluoridation programs.[6] Moreover, in the ecologic studies, water fluoride concentration was likely not the only relevant variable that distinguished exposed and control communities, creating fertile ground for residual confounding. An ecologic study involving more than 900 members of a complete birth cohort in New Zealand (Dunedin)[7] evaluated concentrations more typical of fluoridated communities and reported no differences between the IQ scores, either in childhood or adulthood, of individuals who lived in areas in which water was fluoridated and those who did not. Although many potential confounders were considered, biomarkers of fluoride exposure were not measured. Because individuals were classified into exposure groups based solely on community of residence, some misclassification was inevitable. If the errors were random, the most likely result is that effect estimates were biased towards the null. In 2017, a prospective cohort study in Mexico City[8] moved the field forward by measuring a biomarker, reporting that the concentration of fluoride in maternal urine during pregnancy (mean [SD] concentration, 0.9 [0.4] mg/L) was inversely associated with children's cognitive scores at both age 4 years and 6 to 12 years.

In this issue of *JAMA Pediatrics*, Green et al[9] report an important contribution to the debate about the potential developmental neurotoxicity associated with fluoride. The authors studied 512 mother-child pairs from 6 major Canadian cities, approximately 40% of whom lived in fluoridated communities. Children's prenatal exposure to fluoride was estimated in 2 ways: (1) mean fluoride concentration in maternal urine samples collected in each trimester of pregnancy (reflecting fluoride intake from all sources) and (2) daily maternal fluoride intake during pregnancy based on self-reported first and third trimester water and water-based beverage consumption in a subset of 400 maternal-child dyads with complete data. The median (range) maternal urinary fluoride concentration was 0.41 (0.06-2.44) mg/L. Mean (SD) urinary fluoride concentration was significantly greater among women from fluoridated communities (0.7 [0.4] mg/L) than nonfluoridated communities (0.4 [0.3] mg/L). The most important finding was a significant inverse association of maternal urinary fluoride concentration with children's Full Scale IQ scores at age 3 to 4 years in boys, such that a 1-mg/L increase in concentration was associated with a deficit of 4.5 (95% CI, −8.4 to −0.6) points. Boys with a mother in the 90th percentile of urinary fluoride concentration scored approximately 3 points lower than boys with a mother in the 10th percentile. However, the association was not significant in girls. A sex difference was not found when the exposure index was daily maternal fluoride intake, but the main effect was significant. A 1-mg increase in estimated daily maternal fluoride intake was associated with a deficit of 3.7 (95% CI, −7.2 to −0.1) points in Full Scale IQ.

No doubt aware of the close scrutiny their study will receive, Green et al[9] considered numerous potential threats to the validity of the findings. Analyses were adjusted for important covariates (eg, maternal education, race, quality of the home environment), including other chemicals (lead, mercury, manganese, perfluorooctanoic acid, or arsenic). Fluoride concentrations in the spot maternal urine samples were adjusted for dilution using both specific gravity (primary analy-

ses) and creatinine levels, with similar results. Regression models were evaluated for collinearity, influential observations, and outliers. The distributions of residuals and plots of residuals vs fitted values were examined to confirm that model assumptions were met. Spline regression was used to assess whether the association between the dose and effect was nonlinear. The results appear to be robust. The effect size seen in boys (4.5 IQ points per 1-mg/L increase in maternal urinary fluoride concentration) is generally consistent with the effect sizes reported in the Mexico City study (2.5 points per 0.5-mg/L increase in maternal urinary fluoride concentration)[8] and in a 2018 Chinese study (5.3 points per 1-mg/L increase in children's urinary fluoride concentration).[10]

All studies have limitations, and Green et al[9] acknowledge several. Most notably, they identify ways in which future studies might improve on the methods they used to measure biomarkers of fetal fluoride exposure and to estimate fluoride intake.

No single observational study provides a definitive test of a hypothesis, and early studies of an association that is subsequently confirmed tend to report larger effect sizes than do later studies.[11] These considerations notwithstanding, the hypothesis that fluoride is a neurodevelopmental toxicant must now be given serious consideration. It is likely to take some time before the implications of the study by Green et al[9] can be fully appreciated. It is instructive to recall that the hypothesis that subclinical lead exposures pose a neurodevelopmental hazard was bitterly contested in the 1980s and 1990s, and it was only the weight of evidence that eventually accumulated that led to the now widely held consensus that no level of lead exposure is safe. Research on fluoride as a potential neurodevelopmental toxicant is still at an early stage, and compelling weight of evidence from high-quality epidemiological studies has not yet developed. If the hypothesis is true, the implications are worrisome. Exposure to fluoride has increased substantially in recent decades. Between the 1986-1987 and 2011-2012 National Health and Nutrition Examination Surveys, the prevalence of moderate/severe dental fluorosis among US adolescents had increased from 1% to 30%.[12] If the effect sizes reported by Green et al[9] and others are valid, the total cognitive loss at the population level that might be associated with children's prenatal exposure to fluoride could be substantial.[13] At present, there is no reference value for urinary fluoride concentration in pregnancy, and guidance on fluoride use to prevent caries does not include separate recommendations for pregnant women.[14]

Many questions remain. How replicable and generalizable are the associations reported by Green et al?[9] Is there a maternal urinary fluoride concentration below which the risk of neurotoxicity is negligible? Although the association with IQ did not depart from linearity, suggesting that there might not be such a level, the Mexico City study found 0.8 mg/L to be a possible threshold.[8] Are boys more vulnerable than girls? Unlike the study by Green et al,[9] no sex difference was found in the Mexico City study.[8] Is IQ just the tip of the iceberg, with some developmental domains more sensitive than others? Green et al[9] suggested that nonverbal skills might be more affected than verbal skills, and greater fluoride exposure has also been associated with attention-deficit/hyperactivity disorder–related behaviors.[15,16] Is the prenatal period the most critical window of exposure? Does postnatal exposure also confer risk? Green et al[9] did not measure children's postnatal exposure to fluoride. Although the Mexico City study measured urinary fluoride concentration in a subset of the cohort at age 6 to 12 years,[8] it was only considered a covariate in a sensitivity analysis. Therefore, these studies do not provide any guidance regarding the management of children's postnatal exposures to fluoride, such as the age at which fluoride toothpaste should be introduced and the quantity that should be applied to a child's brush at different ages.

Hume advised, "The wise man proportions his belief to the evidence."[17] The findings of Green et al[9] and others indicate that a dispassionate and tempered discussion of fluoride's potential neurotoxicity is warranted, including consideration of what additional research is needed to reach more definitive conclusions about the implications, if any, for public health.

ARTICLE INFORMATION

Author Affiliations: Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; Harvard T. H. Chan School of Public Health, Boston, Massachusetts.

Corresponding Author: David C. Bellinger, PhD, MSc, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115 (david.bellinger@childrens.harvard.edu).

Published Online: August 19, 2019. doi:10.1001/jamapediatrics.2019.1728

Conflict of Interest Disclosures: None reported.

REFERENCES

1. US Centers for Disease Control and Prevention. Ten great public health achievements: United States, 1900-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48(12):241-243.

2. Sanders AE, Grider WB, Maas WR, Curiel JA, Slade GD. Association between water fluoridation and income-related dental caries of US children and adolescents. *JAMA Pediatr*. 2019;173(3):288-290. doi:10.1001/jamapediatrics.2018.5086

3. Malmö University. Country oral health profiles. https://www.mah.se/CAPP/Country-Oral-Health-Profiles/. Accessed May 29, 2019.

4. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. *Lancet Neurol*. 2014;13(3):330-338. doi:10.1016/S1474-4422(13)70278-3

5. Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. *Environ Health Perspect*. 2012;120(10):1362-1368. doi:10.1289/ehp.1104912

6. US Department of Health and Human Services Federal Panel on Community Water Fluoridation. US Public Health Service recommendation for fluoride concentration in drinking water for the prevention of dental caries. *Public Health Rep*. 2015;130(4):318-331. doi:10.1177/003335491513000408

7. Broadbent JM, Thomson WM, Ramrakha S, et al. Community water fluoridation and intelligence: prospective study in New Zealand. *Am J Public Health*. 2015;105(1):72-76. doi:10.2105/AJPH.2013.301857

8. Bashash M, Thomas D, Hu H, et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in Mexico. *Environ Health Perspect*. 2017;125(9):097017. doi:10.1289/EHP655

9. Green R, Lanphear B, Hornung R, et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada [published online August 19, 2019]. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2019.1729

10. Yu X, Chen J, Li Y, et al. Threshold effects of moderately excessive fluoride exposure on children's health: a potential association between dental fluorosis and loss of excellent intelligence. *Environ Int*. 2018;118:116-124. doi:10.1016/j.envint.2018.05.042

11. Ioannidis JP. Why most discovered true associations are inflated. *Epidemiology*. 2008;19 (5):640-648. doi:10.1097/EDE.0b013e31818131e7

12. Neurath C, Limeback H, Osmunson B, Connett M, Kanter V, Wells CR. Dental fluorosis trends in US oral health surveys: 1986 to 2012 [published online March 6, 2019]. *JDR Clin Trans Res*. doi:10.1177/2380084419830957

13. Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect*. 2012;120(4):501-507. doi:10.1289/ehp.1104170

14. US Centers for Disease Control and Prevention. Recommendations for using fluoride to prevent and control dental caries in the United States. *MMWR Recomm Rep*. 2001;50(RR-14):1-42.

15. Bashash M, Marchand M, Hu H, et al. Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6-12 years of age in Mexico City. *Environ Int*. 2018;121(pt 1):658-666. doi:10.1016/j.envint.2018.09.017

16. Malin AJ, Till C. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. *Environ Health*. 2015;14:17. doi:10.1186/s12940-015-0003-1

17. Hume D. *An Inquiry Concerning Human Understanding*. Hendel CW, ed. New York, NY: Bobbs-Merrill Educational Pub; 1955.