Developmental Fluoride Neurotoxicity: Clinical Importance versus Statistical Significance

We were interested to read the article by Choi et al. (2012), who investigated the effects of increased fluoride exposure and delayed neurobehavioral development by reviewing published studies and performing a meta-analysis. Of the 39 studies identified, the authors considered 27 to be eligible. Choi et al. reported a mean difference in IQ (intelligence quotient) score between exposed and reference populations of −0.4 (95% confidence interval: −0.5, −0.3) using a random-effects model. Thus, children in high-fluoride areas had significantly lower IQ scores than those who lived in low-fluoride areas.

Even if we ignore the weaknesses of the study (Choi et al. 2012), including a lack of individual-level information and the high probability of confounding because the authors did not adjust for covariates, a difference of 0.4 in mean IQ is clinically negligible (Jeckel et al. 2007; Rothman et al. 2008; Szkl and Nieto 2007) even though it was statistically significant. In general, clinical importance takes priority over statistical significance. The p-value can easily change from significant to nonsignificant because of sample size or the mean difference and standard deviation of the variable in the study population (Jeckel et al. 2007; Rothman et al. 2008; Szkl and Nieto 2007). As Choi et al. (2012) pointed out in their conclusion, there is “a possibility of an adverse effect of high fluoride exposure on children’s neurodevelopment.” Such a conclusion can be considered an ecological fallacy, which can easily lead to misinterpretation of the results. It is important to know that statistics cannot provide a simple substitute for clinical judgment (Jeckel et al. 2007; Rothman et al. 2008; Szkl and Nieto 2007).

The authors declare they have no actual or potential competing financial interests.

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Developmental Fluoride Neurotoxicity: Choi et al. Respond

We appreciate this opportunity to clarify the factual information about the reported IQ measure.

The standardized weighted mean difference (SMD) in IQ score between exposed and reference populations was −0.45 (95% confidence interval: −0.56, −0.35) using a random-effects model (Choi et al. 2012). We used the SMD because the studies we included used different scales to measure the general intelligence. The SMD is a weighted mean difference standardized across studies, giving the average difference in standard deviations for the measure of that outcome. For commonly used IQ scores with a mean of 100 and an SD of 15, 0.45 SDs is equivalent to 6.75 points (rounded to 7 points). As research on other neurotoxins has shown, a shift to the left of IQ distributions in a population will have substantial impacts, especially among those in the high and low ranges of the IQ distribution (Bellinger 2007).

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Bellinger DC. 2007. Interpretation of small effect sizes in scientific plausibility, with urine arsenic concentrations in the United States, > 4 million would become diabetic, attributable to low arsenic exposure. However, the OR estimate lacks scientific plausibility, with urine arsenic concentrations in the United States about 10 times lower than those related to diabetes in Taiwan, Bangladesh, and elsewhere, and with U.S. water arsenic concentrations about 50 times lower.

In their Table 2, Maull et al. (2012) also cited another paper by the same authors that claims there are increased risks of diabetes related to arsenic in the United States (Navas-Acien et al. 2009). Again, the OR suddenly jumped up after inappropriately adding variables into the multivariate analysis (Steinmaus et al. 2009b). Yet this review from Maull et al. (2012) presented Navas-Acien et al.’s results as if they were from valid methods of analyzing the data. These analyses should not have been cited or their mistakes should have been acknowledged.