Developmental Fluoride Neurotoxicity: Choi et al. Respond

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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; Szklö 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; Szklö 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; Szklö and Nieto 2007).

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

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Arsenic and Diabetes
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Maull et al. (2012) reviewed evidence linking arsenic with diabetes in an evaluation that I believe could divert research resources from where they should properly be allocated. I wish to make two points:

- The review gives credibility to flawed studies that conclude that the prevalence of diabetes is increased in people having urine arsenic concentrations in the upper 20% of the general U.S. population.
- The authors implied that we need studies assessing arsenic concentrations < 150 µg/L in drinking water, whereas research should actually focus on 150–500 µg/L.

Regarding the first point, Table 2 of the review by Maull et al. (2012) reported an adjusted odds ratio (OR) of 3.58 for diabetes in the upper quintile of U.S. urinary arsenic concentrations (Navas-Acien et al. 2008). When adjusted for sex, age, race, and creatinine (Navas-Acien et al. 2008), the OR was 0.82, and adjustment for four more factors resulted in an OR of 1.05. Navas-Acien et al. inserted two more variables into the regression model, including arsenobetaine (a nontoxic form of arsenic originating from fish), and the OR jumped up to 3.58. Never in the history of epidemiology have valid findings emerged from results like these. For > 20 years, arsenic researchers have been subtracting arsenobetaine from total arsenic in urine when assessing exposure to inorganic arsenic. When this is done, the OR estimate is 1.15 (Steinmaus et al. 2009a).

If the OR of 3.58 were valid, then very low concentrations of arsenic in water would be a major risk factor for diabetes. Among the 40 million or so adults within the highest quintile of urinary 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.