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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; Szklo 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; Szklo 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; Szklo and Nieto 2007).

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Developmental Fluoride Neurotoxicity: Choi et al. Respond

Sabour and Ghorbani's comments about the reported mean difference in IQ (intelligence quotient) scores reported in our article (Choi et al. 2012) suggest a misunderstanding of the scale unit we used and the public health significance of even a small decrease in the average IQ associated with exposure. 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 neurotoxicants 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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Arsenic and Diabetes

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.

With regard to the point that studies should assess arsenic concentrations 150–500 μg/L in drinking water, there is good evidence that arsenic in water may increase the incidence of diabetes. However, every study that has produced strong evidence has included water arsenic concentrations > 500 μg/L at, or before, the time of the study. Indeed, Maull et al. (2012) cited one large, well-designed study in Bangladesh (Chen et al. 2010) with water arsenic concentrations up to 500 μg/L that found no evidence of increased diabetes, even among the > 2,000 participants with urinary arsenic concentrations > 200 μg/L.

In courts of law, experts may be entitled to their opinions, but in science we are not. We must focus only on the evidence and its logical interpretation. The logical interpretation of the evidence here should lead us to pursue studies in populations exposed to arsenic in drinking water in the range of 150–500 μg/L and to dismiss the notion that millions of people in the United States with very low exposure to arsenic in drinking water have major increased risks of diabetes.

In the past, I was attacked for exaggerating the effects of arsenic in drinking water, including in this journal (Carlson-Lynch et al. 1994). Now I find myself on the other side. In 1995, it was said that epidemiology was facing its limits (Taubes 1995); at that time I thought these criticisms were unfair (Smith 1995). But now epidemiology is going beyond its limits. Limited research resources should focus on biologically plausible, detectable risks, recognizing that protecting the general population which has very low exposure involves extrapolating risks downward from higher exposure studies, and accepting that we may never prove whether risk estimates at very low exposures are real or not.

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Arsenic and Diabetes: Navas-Acien et al. Respond

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The goal of the National Toxicology Program (NTP) workshop review was to comprehensively evaluate the association between arsenic and diabetes, including epidemiologic and experimental evidence (Maull et al. 2012). Members of the arsenic breakout group carefully evaluated differences in methodologic approaches used to analyze general population studies, including NHANES (National Health Nutrition and Examination Survey) studies, trying to understand the biology and technical limitations of biomarkers of inorganic arsenic exposure measured in urine, as well as their implications for study findings.

In his letter, Smith presents his arguments in a selective manner, overlooking important evidence and facts. First, multiple studies included in the NTP workshop review [see our Table 2 (Maull et al. 2012)] support the relationship of low-to-moderate arsenic exposure levels (< 150 μg/L in drinking water) with diabetes and diabetes-related end points. Second, when indicating that subtracting arsenobetaine from total arsenic is the recommended method to evaluate inorganic arsenic exposure, Smith ignored research conducted in the last decade showing that other seafood arsenicals (arsenosugars, arsenolipids) also contribute to total urinary arsenic (European Food Safety Authority 2009; Francesconi et al. 2002; Maull et al. 2012). Subtracting arsenobetaine from total arsenic is insufficient to eliminate the contribution of seafood arsenicals in populations where seafood is common (see Figure 1 of Maull et al. 2012). Third, Smith criticized the adjustment of the association between total urinary arsenic and diabetes for arsenobetaine without mentioning that total urinary arsenic was associated with diabetes without adjusting for arsenobetaine in NHANES participants with very low or undetectable arseno-betaine (Navas-Acien et al. 2008, 2009),

populations where total urinary arsenic likely reflects inorganic arsenic exposure. These results at low arsenobetaine concentrations exclude collinearity as an explanation for the findings. The consistency between analyses that are restricted to very low arsenobetaine concentrations and analyses that statistically adjust for arsenobetaine is not a surprise because both epidemiologic strategies are able to minimize the contribution of other seafood arsenicals to total urine arsenic concentrations. In a transparent manner, the NTP workshop review acknowledged the differing interpretations of the NHANES studies, concluding that the

lack of consistency… warrants caution in interpreting results and highlights the importance of having good analytical methods to distinguish inorganic arsenic.

As summarized in our NTP workshop review (Maull et al. 2012), the evidence is currently insufficient to conclude that arsenic is associated with diabetes at low-to-moderate exposure levels. Limitations of many of the available studies included the lack of prospective evidence, limitations in exposure and outcome assessment, and lack of adjustment for appropriate confounders. Since the publication of the NTP workshop review, additional cross-sectional (Gribble et al. 2012) and prospective (James et al. 2012; Kim et al., in press) studies conducted in the United States and supporting the association between arsenic and diabetes have been published.

Millions of Americans are exposed to arsenic through drinking water and food. Smith recommended that arsenic research focus on levels in drinking water that are 15 times higher than the current safety standards of the World Health Organization, U.S. Environmental Protection Agency, and European Union. In our opinion, research and public health efforts should focus on preventing arsenic exposure. At low-to-moderate levels, state-of-the-art epidemiologic tools—including cost-effective designs, high quality exposure and outcome assessment, careful evaluation of dose–response relationships, and integrated methods to evaluate gene–environment interactions and mechanistic pathways—can provide insight into the health effects of arsenic exposure through drinking water and food.

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