

## **Developmental arsenic neurotoxicity in retrospect**

Philippe Grandjean\* and Katsuyuki Murata†

From \*Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark, and Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts; and †Department of Environmental Health Sciences, Akita University School of Medicine, Akita, Japan

Correspondence: Philippe Grandjean, Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115. E-mail: pgrand@hsph.harvard.edu

Developmental neurotoxicity is of crucial public-health importance. The vulnerability of the brain originates from the combination of immaturity and ongoing development; the damages incurred are likely to be permanent. However, epidemiological studies in this field must confront some serious challenges. First of all, the functional deficits are likely to depend on the developmental stage at which the exposure or the peak exposure happened. Further, neurobehavioral outcomes will be affected by the age at examination and many other covariates. For example, nutritional deficiencies may cause serious delays in mental development (1). The neurotoxicity literature on lead (2) and methylmercury (3) contains ample demonstration that neurobehavioral responses vary between populations and may be blurred by the effects of the covariates.

Causative exposures may have happened during gestation or early postnatally, and valid assessment of cognitive functions may require testing at school age several years later. Thus, the key study parameters will be separated by a substantial time interval. Still, for feasibility reasons, most epidemiological studies are cross-sectional with some form of retrospective exposure assessment. Estimates of past exposures from questionnaires and residence data are bound to be imprecise and

would generally tend to bias the findings toward null. Although unknown, the imprecision will likely exceed the substantial variability documented for exposure biomarkers, i.e., contaminant concentrations in body fluids and tissues (4).

The paper by von Ehrenstein et al. in this issue (5) presents a valiant attempt to utilize measurements of arsenic in water in combination with residence information to obtain a record of past arsenic exposures in Bengali children. Although this effort failed to demonstrate any significant impact on measures of school-age cognitive function, the data are of interest as a demonstration that past exposure information may be obtained and applied in epidemiological studies.

The authors chose to split the exposures into wide groupings according to regulatory limits. Perhaps some different classification could have provided better separation of exposures. In contrast, current exposure was based on both water intake and urine-arsenic concentrations, therefore likely to be more precise. Thus, the counter-intuitive finding that current exposure at ages 5-15 years is associated with a cognitive deficit, while exposure during gestation is not, could conceivably be due to a different degrees of imprecision of the exposure variables. This caveat is recognized by the authors and needs emphasis, since the impact of confounders measured with better precision (such as age), may increase the bias toward the null (6).

In addition to the level of arsenic exposure, in this case the concentration in drinking water, the timing of exposure deserves careful consideration. Arsenic passes the placental barrier, but transfer via human milk seems to be limited (7). The infant may therefore be relatively protected against environmental arsenic exposure during the breast-feeding period. Thus, future studies should preferably take into account the time when postnatal water exposure began after the cessation of breast-feeding or the time of introduction of supplementary foods.

As von Ehrenstein et al. (5) note, several recent cross-sectional studies have reported links between arsenic exposures and neurobehavioral deficits in school children. This evidence supports the notion that arsenic is a developmental neurotoxicant. More substantial support derives from evidence of severe clinical effects caused by arsenic contamination of milk powder used for preparation of milk substitute for infants. The reports on this tragedy appeared in Japanese language

journals and have only been recently reviewed in English (8). The records show that clinical poisoning occurred following total doses of about 60 mg within about one month, and that the prepared milk contained arsenic concentrations of 2 mg/L or more. Limited follow-up of the children exposed to contaminated milk powder revealed neurological diseases, neurobehavioral dysfunction and decreased cognitive skills (8).

This information would suggest that, at least among the Bengali children with the highest exposure levels, some neurotoxicity would likely be present at the time of examination. Further, if the evidence on lead and methylmercury is of any guidance in regard to arsenic neurotoxicity, subclinical effects might even occur at exposure levels that are 1/100 of the doses that cause clinical poisoning. Accordingly, developmental arsenic exposure within the ranges studied by von Ehrenstein et al. could be associated with adverse neurobehavioral effects, although not detected in this study. Given the current information on arsenic neurotoxicity, the absence of significant associations should therefore not be taken as evidence of safety of the arsenic exposure levels studied.

The issue of developmental neurotoxicity has been ignored in previous risk assessments of environmental arsenic exposure. Thus, cancer risk was chosen as the basis for current exposure limits (9,10), while developmental neurotoxicity was not considered at all. It would seem unwise to continue overlook arsenic as a likely developmental neurotoxicant, and further studies on this issue ought to be an important priority in environmental epidemiology research.

#### ABOUT THE AUTHORS

PHILIPPE GRANDJEAN is Professor and Chair of Environmental Medicine at the University of Southern Denmark and Adjunct Professor of Environmental Health at Harvard School of Public Health. His main field of epidemiology research is developmental neurotoxicity. KATSUYUKI MURATA is Professor and Chair of Environmental Health Sciences, Akita University School of Medicine in Japan. His main field of research is neurophysiological assessment of neurotoxicity in exposed populations. The authors have collaborated since 1993 on prospective studies of children

exposed to methylmercury.

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