VIEWPOINT

ON MERCURY RISKS

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Mercury Risks: Controversy or Just Uncertainty?

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TWO RECENT PAPERS IN *PUBLIC HEALTH REPORTS*[1,2] HAVE EMPHASIZED the need to limit the risks of excess exposure to methylmercury from eating contaminated fish. However, different interpretations of the epidemiologic evidence are reflected in a four-fold difference between the exposure limits used by the Food and Drug Administration and the Environmental Protection Agency. Because the agencies have access to the same scientific publications on human health risks due to mercury exposure, the question may be asked: must interpretation of epidemiologic evidence always lead to controversy?

The answer must first consider the nature of epidemiologic studies. Like other scientific inquiries, they will always render tentative knowledge. While no scientific process can provide absolute proof, observational studies in particular will lead to conclusions that are likely to be refined as the depth of understanding improves. Given evidence that can never be final, a truly scientific method of decision-making does not exist.

Preventive action must therefore be based on all relevant documentation, but as in the case of medical diagnosis, decisions must recognize the uncertainty of the data as well as the potential costs and consequences of the interventions being considered. For example, control of mercury-related air pollution may be very costly, and must be balanced in the long term against the benefits associated with decreased contamination of fish. In addition, fish species that accumulate mercury contain essential nutrients; the benefits of avoiding eating contaminated fish as a short-term solution must therefore be balanced against possible nutritional disadvantages. Further, government agencies may be bound by specific mandates and past decisions, some of which may be difficult to change. Yet while these issues are important considerations in the decision-making process, they should not be confused with a critical assessment of the scientific evidence.

IS THE MERCURY EVIDENCE CONTRADICTORY?

Two prospective cohort studies on the health effects of prenatal methylmercury exposure have been published, each conducted in a population with a high intake of seafood. One study was conducted in the Seychelles Islands in the Indian Ocean,[3] and the other in the Faroe Islands in the North Atlantic.[4] As principal investigator of the Faroes study, I noted many differences between the populations when I recently visited the Seychelles. Residents of the Seychelles live in a tropical climate and have easy access to fruits and vegetables. The Faroese live in the northern temperate zone, their lifestyle is entirely Western, and most food items other than seafood and lamb are imported. Many Faroese are exposed to PCBs from eating whale blubber—which is also thought to cause developmental neurotoxicity.[5] At the same time, alcohol use is lower than in the Seychelles.

While no association between deficits and maternal hair-mercury concentrations was evident in developmental tests in children up to 5.5 years of age in the Seychelles,[3] clear associations with cord-blood mercury levels were seen on neuropsychological tests administered to 7-year-old Faroese children.[4] These findings hold in the full Faroes dataset in analyses controlled for age and confounders, and they persist after exclusion of high-exposure subjects.

However, despite the apparent differences between the two studies of mercury-exposed populations, they may not necessarily be in disagreement. The two studies used different methods for assessment of exposures and outcomes, and the children were examined at different ages. The epidemiological literature on lead toxicity includes clear examples in which the strongest associations with intellectual deficits appeared only after long-term follow-up.[6] To resolve the confusion that has resulted from one mercury study being perceived as "positive" while the other is seen as "negative," several federal agencies held a workshop in late 1998, at which about 30 invited experts spent three days listening to presentations and discussing the evidence.[7]

Almost by default, the primary effort focused on questioning the reported associations between mercury exposure and adverse effects in the Faroes. Within the time frame of the meeting, less effort was spent on exploring the reasons why some epidemiologic efforts had failed, at least up to that point, to document adverse effects associated with mercury in seafood, despite the clinical evidence from poisoning incidents in Japan and Iraq[1] and the results of studies on laboratory animals (including nonhuman primates).

CONCERNS ABOUT CONFOUNDING

In general, three major reasons were noted at the workshop as to why a mercury effect might have been overestimated in the Faroese study: (*a*) association of mercury intake with exposure to other neurotoxic pollutant(s); (*b*) other types of residual confounding; and (*c*) inadequate adjustment for multiple comparisons. A main concern was whether concomitant exposure to organochlorine compounds, especially polychlorinated biphenyls (PCBs), might explain the reported associations. Detailed information on this issue has now been published.[8] Although residual confounding of some unknown type can never be completely ruled out, at least PCB exposure does not seem to explain the mercury-associated dysfunctions.

A standard statistical approach to controlling for confounding bias is to adjust for relevant covariates in the analysis. However, this strategy may be counterproductive if carried to its extreme, as its success depends on the precision with which these parameters reflect the "true" confounders. Inclusion of an increasing number of covariates with little explanatory power will inevitably

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attenuate the precision of the estimated mercury effect. Although the *P*-value may increase above a limit of 0.05, this approach will not lead to any deeper understanding of the underlying structure of the data.

In discussing the generalizability of the mercury studies, the intriguing suggestion was made[3] that methylmercury-associated effects, as demonstrated in the Faroes, are relevant only to whale-eating populations. In other words, the concern was raised as to whether the Faroes findings can be generalized to North American populations exposed through consumption of fish. However, using this same point of view concerning generalizability, one might question whether mercury neurotoxicity is negligible only in a population like the Seychellois, especially because some of them exhibit hair-mercury concentrations similar to those that have been associated with toxicity in the poisoning incidents in Iraq.[1]

PUBLIC HEALTH RELEVANCE

Once the quality of a set of scientific data has been considered, the health relevance of the findings needs to be determined. Accordingly, to the extent possible, scientific findings should be expressed in terms that would facilitate an evaluation of their public health significance. Important societal issues may be raised—for example, are small deficits of any concern if they fall within the normal variation of performance seen in subjects thought not to be exposed to neurotoxicants? The authors of a *Science* commentary proposed that subtle decrements in neuropsychological test performance of children exposed to mercury through fish consumption would be of questionable relevance in the light of the benefits of eating fish.[9]

Epidemiologists have recently debated their relationship to the development of public health policies, in particular the thorny issue of balancing between being an advocate for particular policies and being an ivory tower scientist.[10] Although this debate is likely to continue, societal concerns can never overrule the need to consider the epidemiologic evidence on its merits alone. In this regard, last year's mercury workshop was an important step forward.

The Faroes study showed that each doubling in prenatal mercury exposure corresponded to a delay of one or two months in mental development at age 7 years.[4] Because rapid development occurs at that age, such delays may be important. Also, even small shifts in a measure of central tendency may be associated with large changes in the tails of the distribution. However, the crucial and yet unanswered point is whether such delays are permanent and what the long-term implications may be. The experience with lead neurotoxicity suggests that such effects are likely to remain and may even become more apparent with time.

In addition, the mercury effects may well have been *underestimated* even in the Faroes study. A bias toward the null hypothesis is likely to occur as a result of the random misclassification that results from imprecise exposure assessments and outcome measurements. For example, although the cord-blood mercury concentration may be the best available estimate of the amount of the neurotoxicant that has reached the fetal brain,[4] it does not reflect peak exposures. Likewise, neurobehavioral tests differ in their psychometric properties, and many factors other than mercury may influence test performance. For example, methylmercury exposure originated from seafood, and essential nutrients in fish could have potentially counteracted some of the adverse effects.

Similar issues have been considered in other situations in which developmental toxicity is the issue of concern, again perhaps most notably in connection with childhood lead exposure.[6] The potential for overestimation of a toxic effect was raised without paying equal attention to the risk of underestimation. Needleman has listed seven methodological solecisms that have clouded judgment on lead toxicity at low doses.[6] For example, if a *P*-value was above 0.05, that was taken as indication of no lead effect. However, considerations of statistical power and meta-analyses would have been more informative. Also, while the existence of residual confounding can never be fully excluded, there is little reason to invoke "phantom" covariates to explain away an association that is biologically plausible. The lead experience

deserves to be taken into account when interpreting the evidence concerning methylmercury neurotoxicity.

FROM EVIDENCE TO ACTION

Some scientific uncertainties are bound to remain, and new prospective cohort studies on methylmercury neurotoxicity are unlikely to emerge within the near future. The documentation is therefore not going to expand substantially or otherwise provide much clearer guidance for regulatory agencies. Most important perhaps, the question as to whether to base decisions either on proof of harm or on precaution cannot be settled from epidemiological evidence.

The experience with lead research has amply illustrated that apparent disagreement is likely to occur between studies carried out by different methods in different settings.[6] We therefore should not anticipate full coherence among all available evidence. Accordingly, decisions on preventive efforts should be justified by the scientific database at large, taking into account its various uncertainties and inconsistencies.

The potential costs and other societal consequences of policy decisions also deserve fair consideration. However, these issues should be addressed in parallel to and separate from the discussion of toxicological concerns. Otherwise, the erroneous impression will be generated that disagreements on preventive measures are solely due to uncertainties in epidemiologic evidence.

THE WIDER PERSPECTIVE

The current regulatory impasse on mercury must also be seen in a wider perspective. Methylmercury is not the only developmental neurotoxicant. Much more evidence exists about lead in this regard, and it is likely that PCB or PCB-related compounds may have similar effects. And these compounds represent only a very small selection of the chemical universe. A large number of chemicals are known to cause neurotoxicity in experimental animals, but only about 150 chemicals neurotoxic to humans have been identified from case reports and epidemiological studies.[11] More important, although the fetus is thought to be much more sensitive than the adult to neurotoxic effects, solid information has been published only on a mere handful of environmental chemicals that have been shown to cause developmental neurotoxicity in humans following *in utero* exposure.

Thus, while methylmercury is just one of many chemicals that may be toxic to the developing brain, current information in this field is extremely limited, and we have probably discovered only a small proportion of environmental chemicals that share this toxic potential. The evidence on exposure to lead, methylmercury, and PCBs indicates that clear-cut conclusions should not be expected. Still, epidemiologic evidence, however uncertain, deserves to be taken seriously so that links between neurotoxicant exposures and developmental deficits are not missed.

The current disagreement between regulatory agencies concerning mercury should not be blamed on discrepancies in the epidemiologic evidence. A wealth of highly relevant information already exists on this pollutant. Given the existence of many other neurotoxicants about which we know much less, a regulatory stalemate on mercury is bad news for the protection of the brains of future generations.

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