Toxicological Effects of Methylmercury

Committee on the Toxicological Effects of Methylmercury

Board on Environmental Studies and Toxicology

Commission on Life Sciences

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differences in the findings. The New Zealand study used a research design and entailed a pattern of exposure similar to the Seychelles study, but it reported associations with Hg that were similar to those found in the Faroe Islands.

The committee concludes that there do not appear to be any serious flaws in the design and conduct of the Seychelles, Faroe Islands, and New Zealand studies that would preclude their use in a risk assessment. However, because there is a large body of scientific evidence showing adverse neurodevelopmental effects, including well-designed epidemiological studies, the committee concludes that an RfD should not be derived from a study, such as the Seychelles study, that did not observe any associations with MeHg.

In comparing the studies that observed effects, the strengths of the New Zealand study include an ethnically mixed population and the use of end points that are more valid for predicting school performance. The advantages of the Faroe Islands study over the New Zealand study include a larger study population, the use of two measures of exposure (i.e., hair and umbilical-cord blood), extensive peer review in the epidemiological literature, and re-analysis in response to questions raised by panelists at a 1998 NIEHS workshop and by this committee in the course of its deliberations.

The Faroe Islands population was also exposed to relatively high levels of polychlorinated biphenyls (PCBs). However, on the basis of an analysis of the data, the committee concluded that the adverse effects found in the Faroe Islands study, including those seen in the Boston Naming Test,[5] were not attributable to PCB exposure and that PCB exposure did not invalidate the use of the Faroe Islands study as the basis of risk assessment for MeHg.

The committee concludes that, given the strengths of the Faroe Islands study, it is the most appropriate study for deriving an RfD.

Estimation of Dose and Biological Variability

In epidemiological studies, uncertainties and limitations in estimating

[5]The Boston Naming Test is a neuropsychological test that assesses an individual's ability to retrieve a word that appropriately expresses a particular concept.

committee's calculations involved a series of steps, each involving one or more assumptions and related uncertainties. Alternative assumptions could have an impact on the estimated BMDL value. In selecting a single point of departure, the committee followed established public-health practice of using the lowest value for the most sensitive, relevant end point.

In addition to deriving a BMDL based on the Faroe Islands study, the committee performed an integrative analysis of the data from all three studies to evaluate the full range of effects of MeHg exposure. The values obtained by the committee using that approach are consistent with the results of the benchmark analysis of the Boston Naming Test from the Faroe Islands study. Because an integrative analysis is not a standard approach at present, the committee does not recommend that it be used as the basis for an RfD.

Public-Health Implications

The committee's margin-of-exposure analysis based on estimates of MeHg exposures in U.S. populations indicates that the risk of adverse effects from current MeHg exposures in the majority of the population is low. However, individuals with high MeHg exposures from frequent fish consumption might have little or no margin of safety (i.e., exposures of high-end consumers are close to those with observable adverse effects). The population at highest risk is the children of women who consumed large amounts of fish and seafood during pregnancy. The committee concludes that the risk to that population is likely to be sufficient to result in an increase in the number of children who have to struggle to keep up in school and who might require remedial classes or special education. Because of the beneficial effects of fish consumption, the long-term goal needs to be a reduction in the concentrations of MeHg in fish rather than a replacement of fish in the diet by other foods. In the interim, the best method of maintaining fish consumption and minimizing Hg exposure is the consumption of fish known to have lower MeHg concentrations.

In the derivation of an RfD, the benchmark dose is divided by uncertainty factors. The committee identified two major categories of uncertainty, based on the body of scientific literature, that should be consid-

specific meals to improve estimates of dietary intakes and temporal variability in MeHg intake.

- The assessment of factors that can influence individual responses to MeHg exposures in humans and animals. Such factors include age, sex, genetics, health status, nutritional supplement use, and diet. Food components considered to be protective against MeHg toxicity in humans also deserve closer study (e.g., wheat bran and vitamin E).

To determine the most appropriate methods for handling model uncertainty in benchmark analysis, the committee recommends that further statistical research be conducted.

To better characterize the risk to the U.S. population from current MeHg exposures, the committee recommends obtaining data on the following:

- Regional differences in MeHg exposure, populations with high consumptions of fish, and trends in MeHg exposure. Characterization should include improved nutritional and dietary exposure assessments and improved biomonitoring of subpopulations.
- Exposure to all chemical forms of Hg, including exposure to elemental Hg from dental amalgams.

RECOMMENDATIONS

On the basis of its evaluation, the committee's consensus is that the value of EPA's current RfD for MeHg, 0.1 μg/kg per day, is a scientifically justifiable level for the protection of public health. However, the committee recommends that the Iraqi study no longer be used as the scientific basis of the RfD. The RfD should still be based on the developmental neurotoxic effects of MeHg, but the Faroe Islands study should be used as the critical study for the derivation of the RfD. Based on cord-blood analyses from the Faroe Islands study, the lowest BMD for a neurobehavioral end point the committee considered to be sufficiently reliable is for the Boston Naming Test. For that end point, dose-response data based on Hg concentrations in cord blood should be modeled using

most highly exposed is consistently below 10. That indicates that the exposure levels of high-end consumers are close to those at which there are observable adverse neurodevelopmental impacts.

To further characterize the risks of MeHg, the committee developed an estimate of the number of children born annually to women most likely to be highly exposed through high fish consumption (highest 5% estimated to consume 100 g per day). Available consumption data and current population and fertility rates indicate that over 60,000 newborns annually might be at risk for adverse neurodevelopmental effects from in utero exposure to MeHg.

The MeHg-associated performance decrements on the neuropsychological tests administered in the Faroe Islands and New Zealand studies suggest that prenatal MeHg exposure is likely to be associated with poorer school performance. In the Faroe Islands sample, MeHg-related deficits were seen across a broad range of specific domains, including vocabulary, verbal learning, visuospacial attention, and neuromotor function. Deficits of the magnitude reported in these studies are likely to be associated with increases in the number of children who have to struggle to keep up in a normal classroom or who might require remedial classes or special education.

Revision of the RfD for MeHg can have far-reaching implications for public health and environmental protection. Currently, 40 states have issued advisories concerning consumption of certain freshwater fish. Any revision of the RfD will have implications for the market for fish and seafood and the dietary choices of Americans. Regulatory impacts might also be substantial, because federal and state agencies use the RfD to develop water-quality criteria and set limits on Hg releases in air and water. Additionally, there are implications for industrial use of Hg and Hg-containing materials, as well as decisions about disposal methods and recycling options.

Ideally, the application of the RfD in risk management should provide a margin of safety for all of the population. The application of the RfD to guide regulatory and risk-management policies must also consider risk tradeoffs, economic and technological limitations, as well as cultural and political influences. It must be recognized that the refinement of the RfD might not eliminate agency differences in risk management. However, improving the scientific basis for decision-making represents an important step forward in developing a cohesive strategy to prevent adverse effects from MeHg.