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# Toxicological Effects of Methylmercury

National Research Council

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Committee on the Toxicological Effects of Methylmercury

Board on Environmental Studies and Toxicology

Commission on Life Sciences

National Research Council

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# EXECUTIVE SUMMARY

Mercury (Hg) is widespread and persistent in the environment. Its use in many products and its emission from combustion processes have resulted in well-documented instances of population poisonings, high-level exposures of occupational groups, and worldwide chronic, low-level environmental exposures. In the environment, Hg is found in its elemental form and in various organic compounds and complexes. Methylmercury (MeHg), one organic form of Hg, can accumulate up the food chain in aquatic systems and lead to high concentrations of MeHg in predatory fish,[1] which, when consumed by humans, can result in an increased risk of adverse effects in highly exposed or sensitive populations. Consumption of contaminated fish is the major source of human exposure to MeHg in the United States.

In recent years, the U.S. Environmental Protection Agency (EPA) has issued two major reports on Hg to the U.S. Congress on Hg—the *Mercury Study Report to Congress* (issued in December 1997) and the *Utility Hazardous Air Pollutant Report to Congress* (issued in March 1998). In those reports, fossil-fuel power plants, especially coal-fired utility boilers, were identified as the source category that generates the greatest Hg emissions, releasing approximately 40 tons annually in the United States. EPA is currently considering rulemaking for supplemental controls on Hg emissions from utilities. However, because of gaps in the scientific data regarding Hg toxicity, Congress directed EPA, in the appropriations report for EPA's fiscal 1999 funding, to request the National Academy of Sciences to perform an independent study on the toxicological effects of MeHg and to prepare recommendations on the establishment of a scientifically appropriate MeHg exposure reference dose (RfD).[2]

## THE CHARGE TO THE COMMITTEE

[1] In this report, the term fish includes shellfish and marine mammals, such as pilot whales, that are consumed by certain populations.

[2] A reference dose is defined as an estimate of a daily exposure to the human population (including sensitive subpopulations) that is likely to be without a risk of adverse effects when experienced over a lifetime.

In response to the request, the National Research Council (NRC) of the National Academies of Sciences and Engineering convened the Committee on Toxicological Effects of Methylmercury, whose members have expertise in the fields of toxicology, pharmacology, medicine, epidemiology, neurophysiology, developmental psychology, public health, nutrition, statistics, exposure assessment, and risk assessment. Specifically, the committee was assigned the following tasks:

1. Evaluate the body of evidence that led to EPA's current RfD for MeHg. On the basis of available human epidemiological and animal toxicity data, determine whether the critical study, end point of toxicity, and uncertainty factors used by EPA in the derivation of the RfD for MeHg are scientifically appropriate. Sensitive subpopulations should be considered.
2. Evaluate any new data not considered in the 1997 *Mercury Study Report to Congress* that could affect the adequacy of EPA's MeHg RfD for protecting human health.
3. Consider exposures in the environment relevant to evaluation of likely human exposures (especially to sensitive subpopulations and especially from consumption of fish that contain MeHg). The evaluation should focus on those elements of exposure relevant to the establishment of an appropriate RfD.
4. Identify data gaps and make recommendations for future research.

## THE COMMITTEE'S APPROACH TO ITS CHARGE

To gather background information relevant to MeHg toxicity, the committee heard presentations from various government agencies, trade organizations, public interest groups, and concerned citizens. Representatives from the offices of Congressman Alan Mollohan (West Virginia) and Senator Patrick Leahy (Vermont) also addressed the committee.

The committee evaluated the body of evidence that provided the scientific basis for the risk assessments conducted by EPA and other regulatory and health agencies. The committee also evaluated new findings that have emerged since the development of EPA's current RfD and met with the investigators of major ongoing epidemiological studies to examine and compare the methods and results.

The committee was not charged to calculate an RfD for MeHg. Instead, in its report, the committee provides scientific guidance to EPA on the development of an RfD. To develop such guidance, the committee reviewed the health effects of MeHg to determine the target organ, critical study,

end point of toxicity, and dose on which to base the RfD. Because various biomarkers of exposure (i.e., concentrations of Hg in hair and umbilical-cord blood) have been used to estimate the dose of MeHg ingested by individuals, the committee evaluated the appropriateness of those biomarkers for estimating dose and the extent to which individual differences can influence the estimates. Other sources of uncertainty in the MeHg data base that should be considered when deriving an RfD were also evaluated. To estimate the appropriate point of departure[3] to use in calculating an RfD, the committee statistically analyzed

[3] The point of departure represents an estimate or observed level of exposure or dose which is associated with an increase in adverse effect(s) in the study population. Examples of points of departure include NOAELs, LOAELs, BMDs, and BMDLs.

available dose-response data. A margin-of-exposure[4] analysis was also performed to assess the public-health implications of MeHg.

## THE COMMITTEE'S EVALUATION

### Health Effects of Methylmercury

MeHg is rapidly absorbed from the gastrointestinal tract and readily enters the adult and fetal brain, where it accumulates and is slowly converted to inorganic Hg. The exact mechanism by which Hg causes neurotoxic effects is not known, and data are not available on how exposure to other forms of Hg affects MeHg toxicity.

MeHg is highly toxic. Exposure to MeHg can result in adverse effects in several organ systems throughout the life span of humans and animals. There are extensive data on the effects of MeHg on the development of the brain (neurodevelopmental effects) in humans and animals. The most severe effects reported in humans were seen following high-dose poisoning episodes in Japan and Iraq. Effects included mental retardation, cerebral palsy, deafness, blindness, and dysarthria in individuals who were exposed in utero and sensory and motor impairment in exposed adults. Chronic, low-dose prenatal MeHg exposure from maternal consumption of fish has been associated with more subtle end points of neurotoxicity in children. Those end points include poor performance on neurobehavioral tests, particularly on tests of attention, fine-motor function, language, visual-spatial abilities (e.g., drawing), and verbal memory. Of three large epidemiological studies, two studies—one conducted in the Faroe Islands study and one in New Zealand—found such associations, but those effects were not seen in a major study conducted in the Seychelles Islands.

Overall, data from animal studies, including studies on nonhuman primates, indicate that the developing nervous system is a sensitive target organ for low-dose MeHg exposure. Results from animal studies have reported effects on cognitive, motor, and sensory functions.

There is also evidence in humans and animals that exposure to MeHg can have adverse effects on the developing and adult cardiovascular system (blood-pressure regulation,

[4] A margin-of-exposure analysis compares the levels of MeHg to which the U.S. population is exposed with the point of departure to characterize the risk to the U.S. population. The larger the ratio, the greater degree of assumed safety for the population.

heart-rate variability, and heart disease). Some research demonstrated adverse cardiovascular effects at or below MeHg exposure levels associated with neurodevelopmental effects. Some studies demonstrated an association between MeHg and cancer, but, overall, the evidence for MeHg being carcinogenic is inconclusive. There is also evidence in animals that the immune and reproductive systems are sensitive targets for MeHg.

On the basis of the body of evidence from human and animal studies, the committee concludes that neurodevelopmental deficits are the most sensitive, well-documented effects and currently the most appropriate for the derivation of the RfD.

## Determination of the Critical Study for the RfD

The standard approach for developing an RfD involves selecting a critical study that is well conducted and identifies the most sensitive end point of toxicity. The current EPA RfD is based on data from a poisoning episode in Iraq. However, MeHg exposures in that study population were not comparable to low-level, chronic exposures seen in the North American population, and there are a number of uncertainties associated with the Iraqi data. In light of those considerations and more recent epidemiological studies, the committee concludes that the Iraqi study should no longer be considered the critical study for the derivation of the RfD.

Results from the three large epidemiological studies—the Seychelles Islands, Faroe Islands, and New Zealand studies—have added substantially to the body of knowledge on brain development following long-term exposure to small amounts of MeHg. Each of the studies was well designed and carefully conducted, and each examined prenatal MeHg exposures within the range of the general U.S. population exposures. In the Faroe Islands and New Zealand studies, MeHg exposure was associated with poor neurodevelopmental outcomes, but no relation with outcome was seen in the Seychelles Islands study.

Differences in the study designs and in the characteristics of the study populations might explain the differences in findings between the Faroe and the Seychelles studies. Differences include the ways MeHg exposure was measured (i.e., in umbilical-cord blood versus maternal hair), the types of neurological and psychological tests administered, the age of testing (7 years versus 5.5 years of age), and the patterns of MeHg exposure. When taking the New

Zealand study into account, however, those differences in study characteristics do not appear to explain the 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 Islands, 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 Island 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 exposures can make it difficult to quantify dose-response associations and can thereby lead to

[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.

inaccuracies when deriving an RfD. An individual's exposure to MeHg can be estimated from dietary records or by measuring a biomarker of exposure (i.e., concentration of Hg in the blood or hair).

Dietary records, umbilical-cord-blood Hg concentrations, and maternal-hair Hg concentrations all provide different kinds of exposure information. Dietary records can provide information on Hg intake but depend on accurate knowledge of Hg concentrations in fish. The records also might be subject to problems with estimating portion size and capturing intermittent eating patterns. Umbilical-cord-blood Hg concentrations would be expected to correlate most closely with fetal-brain Hg concentrations during late gestation and correlate less well with Hg intake than do the other measures (e.g., dietary records and maternal-hair Hg concentration). Maternal-hair Hg concentrations can provide data on Hg exposure over time, but they might not provide as close a correlation with fetal-brain Hg concentrations as umbilical-cord-blood Hg concentrations, at least during the latter period of gestation. Use of data from two or more of these measurement methods increases the likelihood of uncovering true dose-response relationships. The use of either umbilical-cord-blood or maternal-hair Hg concentrations as biomarkers of exposure is adequate for estimating a dose received by an individual.

Individual responses to MeHg exposure are variable and a key source of uncertainty. Factors that might influence the responses include genetics, age, sex, health status, nutritional supplements, nutritional influences, including dietary interactions, and linking the time and intensity of MeHg exposure to the critical periods of brain development. In addition, people exposed to the same amount of MeHg can have different concentrations of Hg at the target organ because of individual variability in the way the body handles MeHg. Individual differences that affect the estimation of dose can be addressed in the derivation of the RfD by applying an uncertainty factor to the estimated dose. If an RfD is based on a Hg concentration in maternal-hair or umbilical-cord blood, adjusting by an uncertainty factor of 2-3 would account for individual differences in the estimation of dose in 95% to 99% of the general population.

## Modeling the Dose-Response Relationships

An important step in deriving an RfD is choosing an appropriate dose to be used as the "point of departure" (i.e., the dose to which uncertainty factors will be applied to

estimate the RfD). The best available data for assessing the risk of adverse effects for MeHg are from the Faroe Islands study. Because those data are epidemiological, and exposure is measured on a continuous scale, there is no generally accepted procedure for determining a dose at which no adverse effects occur. The committee concludes, therefore, that a statistical approach (i.e., calculation of a benchmark dose level, BMDL[6]) should be used to determine the point of departure for MeHg instead of identifying the dose at which no adverse effects occur or the lowest dose at which adverse effects occur. The committee cautions, however, that the type of statistical analysis conducted (i.e., the model choice—K power, logarithmic, or square root) can have a substantial effect on the estimated BMDL. The committee recommends the use of the K-power model with the constraint of K _ 1, because it is the most plausible model from a biological perspective and also because it tends to yield the most consistent results for the Faroe Islands data. It should be noted that, for the data from the Faroe Islands study, the results of the K-power model with the constraint of K _ 1 are equivalent to the results of the linear model.

The adverse effects observed in the Faroe Islands study were most sensitively detected when using cord blood as the biomarker. 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. The most sensitive, reliable BMDL based on cord-blood analyses from the Faroe Islands study is for the Boston Naming Test. Thus, on the basis of that study and that test, the committee's preferred estimate of the BMDL is 58 parts per billion (ppb)[7] of Hg in cord blood. To

[6]A benchmark dose level is the lowest dose, estimated from the modeled data, that is expected to be associated with a small increase in the incidence of adverse outcome (typically in the range of 1% to 10%).

[7] The BMDL of 58 ppb is calculated statistically and represents the lower 95% confidence limit on the dose (or biomarker concentration) that is estimated to result in an increased probability that 5% of the population will have an abnormal score on the Boston Naming Test.

estimate this BMDL, the committee's calculations involved a series of steps, each involving one or more assumptions and related uncertainties. Alternative assumptions would 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 Island 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 considered when revising the RfD: (1) biological variability when estimating dose and (2) data-base insufficiencies. On the basis of the available scientific data, the committee concludes that a safety factor of 2-3 will account for biological variability in dose

estimation. The choice of an uncertainty factor for data-base insufficiencies is, in part, a policy decision. However, given the data indicating possible long-term neurological effects not evident at childhood, immunotoxicity, and cardiovascular effects, the committee supports an overall composite uncertainty factor of no less than 10.

## RESEARCH NEEDS

To better characterize the health effects of MeHg, the committee recommends further investigation of the following:

- The impacts of MeHg on the prevalence of hypertension and cardiovascular disease in the United States. Such data should be considered in a re-evaluation of the RfD as they become available.
- The relationships between low-dose exposure to MeHg throughout the life span of humans and animals and carcinogenic, reproductive, neurological, and immunological effects.
- The potential for delayed neurological effects resulting from Hg remaining in the brain years after exposure.
- The emergence of neurological effects later in life following low-dose prenatal MeHg exposure.
- The mechanisms underlying MeHg toxicity.

To improve estimates of dose and to clarify the impact of biological variability and other factors on MeHg dose-response relationships, the committee recommends the following:

- The analysis of hair samples to evaluate the variability in short-term exposures, including peak exposures. Hair that has been stored from the Seychelles and Faroe Islands studies should be analyzed to determine variability in exposures over time.
- The collection of information on what species of fish are eaten at 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 ìg/kg per day, is a scientifically appropriate 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 the K-power model ($K \geq 1$). That approach estimates a BMDL of 58 ppb of Hg in cord blood (corresponding to a BMDL of 12 ppm of Hg in hair) as a reasonable point of departure for deriving the RfD. To calculate the RfD, the BMDL should be divided by uncertainty factors that take into consideration biological variability when estimating dose and MeHg data-base insufficiencies. As stated earlier, given those considerations, an uncertainty factor of at least 10 is supported by the committee.

The committee further concludes that the case of MeHg presents a strong illustration of the need for harmonization of efforts to establish a common scientific basis for exposure guidance and to reduce current differences among agencies, recognizing that risk-management efforts reflect the differing mandates and responsibilities of the agencies.