The Panel on Health Risks and Toxicological Effects of Methylmercury:
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Methylmercury Exposure and Health Effects in Humans: A Worldwide Concern

The paper builds on existing literature, highlighting current understanding and identifying unresolved issues about MeHg exposure, health effects, and risk assessment, and concludes with a consensus statement. Methylmercury is a potent toxin, bioaccumulated and concentrated through the aquatic food chain, placing at risk people, throughout the globe and across the socioeconomic spectrum, who consume predatory fish or for whom fish is a dietary mainstay. Methylmercury developmental neurotoxicity has constituted the basis for risk assessments and public health policies. Despite gaps in our knowledge on new bioindicators of exposure, factors that influence MeHg uptake and toxicity, toxicokinetics, neurologic and cardiovascular effects in adult populations, and the nutritional benefits and risks from the large number of marine and freshwater fish and fish-eating species, the panel concluded that to preserve human health, all efforts need to be made to reduce and eliminate sources of exposure.

INTRODUCTION

The Panel on Health Risks and Toxicological Effects of Methylmercury received the mandate to describe and synthesize current scientific knowledge on methylmercury (MeHg) exposure and its effects in humans and to identify research gaps. The present paper is not intended to be a comprehensive review and presentation of all the literature on MeHg exposure and effects in humans but builds on earlier literature, other reviews, and more recent literature in highlighting the current understanding in the field and what we consider to be remaining unresolved issues. Humans are exposed to different forms of mercury (Hg), and potential health risks from forms other than MeHg can occur, including mercury vapor from dental amalgams, as well as from occupational exposures (e.g., dental offices, chloralkali plants, fluorescent lamp factories, mercury mining) and from artesanal and small-scale gold and silver mining operations (1–5), the present document does not cover these exposures, because the pathways of exposure and effects differ from those for MeHg. Here, we examine issues of MeHg exposure, studies on its health effects and major risk assessments, and conclude with our consensus statement.

MeHg Exposure

Sources of exposure. Methylmercury contamination poses a particular challenge to public health because this toxicant is mainly contained in fish, a highly nutritious food, with known benefits for human health. Moreover, fish are culturally vital for many communities and constitute an important global commodity. Although we often refer to "fish" in a generic way, all fish do not have similar amounts of mercury. As a result of bioaccumulation of MeHg through multiple levels of the aquatic food web, higher tropic-level pelagic fish can be contaminated with MeHg at concentrations in excess of 1 part per million (ppm). The concentrations of total Hg vary widely across fish and shellfish species, with the mean values differing by as much as 100-fold (6). Methylmercury is bound to proteins, as well as to free amino acids, that are components of muscle tissues, and are not removed by any cooking or cleaning processes that do not destroy muscle tissues.

Although in general, MeHg accumulates in fish through the food chain, consumption of farmed fish can also lead to MeHg exposures, in part, because of the presence of MeHg in feed (7). Some studies have shown no significant difference in MeHg levels in farmed *vs*. wild salmon, although concentrations in both cases are relatively low (8, 9). Although fish and shellfish are the predominant sources of MeHg in the diets of humans and wildlife, a few reports of other sources exist. Rice cultivated in areas contaminated with mercury can contain relatively high levels of MeHg (10). Methylmercury has also been reported in organ meats of terrestrial animals (11), as well as in chicken and pork, probably as a result of the use of fish meal as livestock feed (12). Some communities also have higher MeHg exposure because of the consumption of fish-eating marine mammals (13, 14).

Profiles of exposure. Although most reports on MeHg exposure focused on specific populations generally assumed to have high levels of fish consumption, estimates of general populations exposure exist for the United States (15, 16), Germany (17), and Japan (18) [summarized in Pirrone and Mahaffey (19)]. For populations that are not selected on the basis of high fish consumption, mean hair Hg levels generally range from >0.1 $\mu g\ g^{-1}$ to <1.0 $\mu g\ g^{-1}$ (20–25). The mean blood Hg for such populations is generally in the range of <1.0 $\mu g\ L^{-1}$ to <5.0 $\mu g\ L^{-1}$, although, worldwide there are fewer data on MeHg exposure based on blood than on hair. In the United States nationally, about 5–10% of the population of women of childbearing age have hair levels exceeding 1.0 $\mu g\ g^{-1}$ (16) and blood levels exceeding 5 $\mu g\ L^{-1}$ (26). In Japan, where more fish is consumed, 73.7% of women of this age have hair levels above 1.0 $\mu g\ g^{-1}$ and 1.7% above 5 $\mu g\ g^{-1}$ (18). In Germany, the 1998 geometric mean blood level was 0.58 $\mu g\ L^{-1}$ (17).

High levels of Hg exposure were identified in numerous fish-eating populations throughout the world [for reviews see: Pirrone and Mahaffey (19)]. Many of these live near oceans, major lakes and rivers, or hydroelectric dams, and are often dependent on local catch, with fish an integral part of their cultural traditions. In the sea islands of the Faroes and Seychelles, median mothers' hair Hg concentrations were 4.5 $\mu g\ g^{-1}$ [with 27% above 10 $\mu g\ g^{-1}$ (27)] and 5.8 $\mu g\ g^{-1}$ (28), respectively. In the river basins of the Amazon, where a large number of studies was carried out on populations for whom freshwater fish is a dietary mainstay, median hair Hg levels typically range between 5 $\mu g\ g^{-1}$ and 15 $\mu g\ g^{-1}$ (29–34).

Despite the importance of local catch, fish is also a global commodity and market fish, such as shark, tuna, and swordfish, or canned white tuna (35), consumed by persons living far away from the source can likewise have high levels of MeHg. In the United States, individuals with high blood Hg concentrations were reported among affluent urbanites who ate large quantities

of marine fish, high in the food web (36, 37). Thus, elevated MeHg exposure is present around the globe, with no geographic, social, economic, or cultural boundaries.

Biomarkers of MeHg exposure. Hair and blood Hg concentrations are both accepted as valid biomarkers of MeHg exposure, although each provides a somewhat different reflection of exposure (38). Blood gives an estimate of exposure over the most recent one to two half-lives, with the half-life of MeHg in blood being 50–70 days, whereas hair reflects the average exposure over the growth period of the segment (28). Hair Hg is predominantly MeHg, with MeHg constituting from 80% to 98% of hair total Hg (33, 39). For populations with regular and frequent fish consumption, hair total Hg and blood MeHg are consistently correlated (40). Generally, hair is 250 to 300 times more concentrated in mercury than is blood (39). However, in populations and individuals with infrequent fish consumption or where bolus doses of MeHg occur, there can be considerable inter- and intraindividual variability in the relation between hair and blood Hg levels resulting from temporal differences in the retention of Hg by each biomarker (33, 40, 41). Segmental analyses of hair Hg can provide a chronology of exposure over time (24, 28, 29, 33). However, information on short-term peaks in exposure is not well represented by such analyses (38). Another consideration is that the growth rate of hair, generally estimated at 1 cm mo^{-1}, can have both inter-and intraindividual variability (38). Recent advances in a single hair-strand analysis (42), including measurement of Hg at micron resolution by using laser ablation (43) should yield more information on the relation between Hg uptake and Hg deposition in hair.

The Hg levels in toenails and fingernails also were used as biomarkers of Hg exposure, mostly in major studies of the cardiovascular effect of MeHg (see below) (44, 45), but to what extent these reflect organic or inorganic Hg exposures remains to be clarified (46). A recent study of women, with no history of occupational exposure to Hg, showed similar correlations between Hg intake through fish consumption and both toenail and hair Hg concentrations; however, only total Hg was assessed (47). In this study, hair, toenail, and urinary total Hg were highly correlated. Urinary Hg levels largely reflect exposure to inorganic Hg (40) and are not considered useful bioindicators of MeHg exposure. There are, however, several recent reports of positive correlations between fish consumption and urinary Hg (48–50), and investigators of these studies propose that demethylation may account, at least partially, for this observation. The relation of fish consumption and inorganic Hg in different biological tissues, and its consequence for human health still need to be elucidated.

Health effects from low to moderate levels of MeHg exposure were reported in a variety of systems and domains. Each of these effects may depend on different aspects of exposure [e.g., fish-eating patterns, time of exposure (first, second, or third trimester, childhood, adulthood)]. Therefore, the different reflections of exposure provided by hair and blood Hg concentrations may provide different information about dose-response for different exposure populations and different exposure scenarios. Few studies investigated side-by-side dose-response relations for both biomarkers. In the study in the Faroe Islands, maternal hair and fetal-cord blood predicted similar but not identical patterns of effect across various measures of neurologic performance (38).

Fish Consumption as a Predictor of MeHg Exposure

Exposure dose. Although most studies identified a clear association between the quantity and the frequency of fish consumption and Hg exposure, there is considerable interindividual and intergroup variability in the relation between the amount or the frequency of fish consumption and the levels of biomarker of MeHg exposure. Several factors mediate this relation. The MeHg concentration within and across species of dietary fish is an obvious source of variability. For example, those who eat mainly carnivorous fish and/or fish-eating mammals have relatively higher levels of Hg compared with those who eat mainly noncarnivorous fish (14, 29, 33, 51–54). Independent of the MeHg concentration, the frequency of fish consumption is also an important factor in this variability. Because biomarkers reflect the weighted average of exposure over time, short-term reporting of fish consumption may not correspond with a longer-term average of MeHg exposure. Under some circumstances, episodic exposures can result in large bolus doses of MeHg. Bolus doses can arise, for example, from the infrequent consumption of fish or fish-eating mammals with high concentrations of MeHg. Given practical limitations in sampling frequency, as well as the nature of some of the biomarkers themselves, bolus doses during putative discrete windows of sensitivity in fetal development may not be fully revealed by biomarkers of exposure.

Toxicokinetics. Although most experimental studies on the gastrointestinal absorption of MeHg indicated that nearly 100% of MeHg in fish is absorbed, recently reported animal and human data suggest that there may be substantial variability (55, 56). In animal studies, variation in absorption kinetics was related to factors such as sex and age (57). A further gap exists because human absorption studies were primarily conducted in adult male subjects.

Toxicokinetic (pharmacokinetic) models and physiologically based pharmacokinetic (PBPK) models are applied to estimate internal dose, given a known intake dose, as well as the intake dose, given a measured internal dose (38). The basic one-compartment model (39, 58, 59) is a steady-state model that is intended to predict concentration in a single compartment only (generally, blood). As such, it is less flexible than the PBPK models in predicting nonsteady state conditions and concentrations in other compartments. However, its relative simplicity has allowed it to be used with probabilistic input parameters to obtain estimates of population variability in predictions of blood concentration and intake dose (60). Estimates of concentrations in other compartments (e.g., cord blood) can be made based on empirical ratios relating mercury concentration in blood to mercury concentrations in those compartments (61).

The PBPK models have the potential to predict changes in MeHg concentration in various tissues in response to changes in MeHg intake and in response to physiological changes (e.g., pregnancy, growth). They can be used to predict short-term changes in MeHg concentrations in different compartments during intake and distribution among compartments, if the parameters are correct (62–65).

The validity of these models overall is not thoroughly established under a range of exposures to MeHg by comparison with actual human data. Although they have the theoretical advantage of making predictions under dynamic conditions, the PBPK models are computationally complex and require data on many parameters whose MeHg-specific values have not been defined. This lack of MeHg specific values is a major limitation, particularly for predicting population variability. The extent to which these models rely on coefficients derived from metabolic studies and/or physiological parameters obtained in different populations and subpopulations and studies with other metals/elements, limits their utility. Nonetheless, both simple toxicokinetic models and PBPK models have been used with reasonable consistency for setting public health guidance.

In humans, there is increasing evidence from environmental epidemiology studies of ethnic differences in the relation

between Hg intake from fish consumption and bioindicators of exposure (56), suggesting that diet and/or metabolic differences may be influencing mercury uptake and/or excretion. As yet, such differences have not been investigated in metabolic studies. Several studies suggest that selenium (Se) may play a role in MeHg absorption or excretion (66–68), but these data are not consistent. In the Brazilian Amazon, fruit consumption was associated with lower hair Hg concentrations (69). A positive relation was reported between iron and Hg in blood samples collected from Sweden (70). Overall, little is known about the factors that may modulate Hg absorption in humans, and research is needed to better understand this complex issue.

Fetal and infant exposure. One area in which the toxicokinetic data is consistent is the finding that MeHg is actively transferred to the fetus across the placenta via neutral amino acid carriers during gestation (71, 72). Although maternal and cord blood Hg concentration is highly correlated, cord blood MeHg is consistently higher than the corresponding maternal concentration, with an average ratio of about 1.7 (24, 61, 73, 74). Consequently, biomonitoring adult women's blood MeHg as a surrogate for potential fetalexposure, the corresponding fetal level will be, on average, 70% higher than maternal blood and up to three times higher at the 95th percentile. The maternal body burden of MeHg tends to decrease during gestation consistent with hemodilution and a transfer of a portion of the maternal body burden to the fetus (24).

Neonatal and infant exposure to MeHg occurs through intake of mother's milk, which is derived from maternal plasma, has a lower level of MeHg, and is enriched in inorganic Hg relative to the whole blood (75). Thus, lactational exposure to MeHg is reduced compared with what would be expected on the basis of maternal blood MeHg. Human and animal studies showed that, after birth, there is a decline in MeHg levels, reaching 40–50% at 2–3 months of age (76–78). During this period, infant body weight increases about 1.5–2 times. Consequently, the rapid increase in body volume and the limited MeHg transfer appear to explain the dilution of MeHg in infants during breast feeding.

HEALTH EFFECTS

Neurological Endpoints

Clinical manifestations. In 1958, McAlpine and Araki (79) linked the unusual neurological disease that was associated with fish consumption from Minamata Bay to MeHg exposure. This historic recognition of the brain and nervous system as the primary target organ for MeHg poisoning, resulting in marked distal sensory disturbances, constriction of visual fields, ataxia, dysarthria, auditory disturbances, and tremor, remains unchanged (80, 81). Based on analysis of the studies of human poisoning, the World Health Organization (WHO) (39) estimated that 5% of MeHg-exposed adults would experience neurologic effects with a blood Hg level of 200 $\mu g\ L^{-1}$ (corresponding to a hair level of approximately 50 $\mu g\ g^{-1}$). This estimate, however, was called into question by a re-analysis of these studies by Kosatsky and Foran (82), who suggested that the lowest observed effect level for clinical effects is likely to be considerably lower. Indeed, anecdotal and case reports of diffuse and subjective neurologic symptoms in adults and older children with moderately elevated MeHg exposures continue to appear (36, 83). In many cases, cessation or significant curtailing of fish consumption results in improvement of symptoms in conjunction with reduction in biomarker concentrations. These suggest the possibility of clinical effects, perhaps in a sensitive subset of the general population, at levels of exposure considerably below those previously associated with clinical effects in poisoning episodes. Currently, there is no formal case description or diagnostic criteria for such effects.

Although exposures throughout the world are lower than those producing the historical epidemics of MeHg poisoning, there is growing evidence that for many populations, exposures are sufficient to alter normal functioning of several systems, constitutes an important public health problem.

Effects in neonates, infants, and children. The poisoning in Minamata brought attention to the risk from fetal exposure. Exposed to MeHg through the placenta of the exposed mother, infants showed severe cerebral palsy–like symptoms, even when their mothers had mild or no manifestation of the poisoning (84). Mental retardation, cerebellar ataxia, primitive reflexes, dysarthria, and hyperkinesias were observed. These symptoms, described over 25 years ago (80, 85), continue as the clinical hallmark of congenital MeHg poisoning. Reconstruction of maternal or fetal doses resulting in these symptoms is difficult because of a lack of concurrent sampling. An estimate of the mean maternal hair concentration, resulting in such symptoms of $41 \mu g\ g^{-1}$ ppm was proposed (86); however, a large uncertainty surrounds this estimate. Health effects observed with frank poisonings should not be confused with the more subtle, populational effects observed at lower levels of exposure.

At the subclinical and the population level, several studies in different parts of the world report poorer neurologic status and slower development in newborns, infants, and/or children exposed to MeHg *in utero* and/or during early childhood (87–98), although some studies did not observe effects (99–101). In children, MeHg exposure *in utero* is associated with lower performance on tests of language, attention, memory, and/or visuospatial and/or motor functions. Although most child studies focused on fish-eating populations with relatively high levels of MeHg exposure, in a recent study, Oken et al (90) observed an inverse relation between mercury concentration in maternal hair and infants' performance on a visual recognition memory task at levels of mercury exposure consistent with background exposure in the US population (maternal hair levels varied between 0.02–2.38 $\mu g\ g^{-1}$). Interestingly, in this study, fish consumption *per se* was associated with better performance, suggesting that some positive aspects of fish consumption, perhaps n-3 (omega-3) fatty acids, are reduced or antagonized by the MeHg contained in the same fish. A similar picture is emerging among adults for the some of the cardiovascular effects of MeHg (see below).

The two major ongoing longitudinal cohort studies on children from the Faroe Islands and the Seychelles are worthy of particular mention because they have both been following children through teenage years, assessing neuropsychological performance as a function of current, childhood, and *in utero* exposure. The Faroes study consistently observed neurobehavioral deficits associated with *in utero* exposure, even when children whose mother's hair Hg levels above 10 $\mu g\ g^{-1}$ were excluded (91). In the initial studies of the Seychelles cohort, no effects were observed (100–103). However, recent reports of the Seychelles 9-year-old cohort shows decreases in fine motor function associated with higher fetal exposure levels ($\geq 10 \mu g\ g^{-1}$ maternal hair); the investigators suggest that adverse effects may become apparent on higher-order cognitive functions that develop with maturity (104, 105). There has been much discussion about the differences between these two well-performed studies. Factors such as type of exposure (one of the main exposure pathways in the Faroes study is through pilot whale, while in the Seychelles, it is entirely marine fish), biomarkers of exposure (cord blood *vs*. maternal hair), differences in test batteries and age of testing; cohort size and power were considered as possible explanations for the

differences in observed outcomes. However, none of these explanations proved entirely satisfactory or clearly decisive (38, 106). Other hypotheses, such as dietary intake of nutrients that may modify Hg metabolism or toxicity, were also proposed (69). Despite whatever significant differences do, in fact, exist between the Seychelles and Faroes studies that may explain differences in results that were observed to this time, the most recent results from the Seychelles appear to indicate a convergence in findings. More work needs to be done on factors that may affect the patterns of manifestation of Hg toxicity.

Neurophysiologic studies offer strong support for nervous-system alterations associated with MeHg exposure. These studies showed mercury-related delayed latencies for auditory and visual evoked potentials (107–110). In the Faroes longitudinal study, latency delays were observed at 7 and 14 years (107, 109). No significant dose-effect relations for evoked potentials were observed in a study of Japanese children with low mercury exposure (maternal and children hair mercury levels of 1.6 $\mu g\ g^{-1}$) (111).

Nervous system endpoints in adults. Fewer studies addressed the neurotoxic effects of Hg exposure in adults. Mercury-related deficits in motor, psychomotor, visual and/or cognitive functions have been reported for different populations within the Brazilian Amazon (112–115) and for tuna consumers from the Mediterranean (116). A recent study, in the United States, of older adults (50–70 years old) with considerably lower blood Hg levels (mean, 2.1 $\mu g\ L^{-1}$) showed inconsistent evidence of effect across neurobehavioral tests (117). Studies of associations between neurobehavioral outcomes and MeHg exposure in adult populations in which frequent and lifetime fish consumption is a cultural norm, generally cannot distinguish between effects because of adult exposure and permanent developmental effects because of gestational and early childhood exposures.

Cardiovascular Endpoints

A body of evidence was developed that addresses potential associations between MeHg and a range of cardiovascular effects. These include cardiovascular disease [coronary heart disease, acute myocardial infarction (AMI), ischemic heart disease], blood pressure and hypertension effects, and alterations in heart rate variability [see Chan and Egeland (118) and Stern (119) for recent reviews]. The strongest evidence for causal associations is for cardiovascular disease, particularly AMI in adult men (44, 120–122). In general, the relative risk and the odds ratios for AMI from these studies showed a doubling in the upper range of the observed Hg exposures. Comparison of exposures in these studies to exposures in Western populations suggests that the upper percentiles of current levels of exposure in these populations may result in a significantly elevated risk of AMI. Another well-conducted study of US health professionals, however, did not find an association between Hg exposure and coronary heart disease (123). This may be because dentists with possible exposure to elemental mercury accounted for 63% of controls and had a Hg exposure more than twice that of the other groups in the cohort. It is not known whether elemental or inorganic Hg acts similarly to MeHg with respect to cardiovascular effects. In addition, two of these studies used toenail Hg as the biomarker of exposure. Because this biomarker has not been adequately compared with the more common exposure biomarkers of hair or blood Hg, it is difficult to assess the dose-response implications of these studies in relation to current exposures.

The evidence for an association between MeHg and other cardiovascular endpoints is weaker. An association was found between increased systolic and diastolic blood pressure in Faroese children at 7 years old and gestational exposure to MeHg (124). However, the association did not persist when the cohort was re-examined at 14 years old (125). Decreased heart rate variability was also associated with MeHg exposure, and this effect persisted through 14 years of age, but the implications of this effect in children for clinically significant outcomes is not clear. There are few studies that relate adult blood pressure to MeHg exposure. A recent study in the Brazilian Amazon reported that persons with 10 $\mu g\ g^{-1}$ hair Hg were three times more likely to have elevated systolic blood pressure ($\geq$130 mm Hg) (126), whereas in a study of women from the United States, no clear association was observed (127).

Reproductive Outcomes

The effect of MeHg on the sex ratio of offspring at birth and stillbirth in Minamata City, Japan, in the 1950s and 1960s, including the period when MeHg pollution was most severe, showed decreases in male birth in offspring in the overall city population, among fishing families (72, 128). An increase in the proportion of male stillborn fetuses raises the possibility that increased susceptibility of male fetuses to death *in utero* could explain the altered sex ratio.

Immune System Effects

Inorganic mercury was shown to suppress immune functions and to induce autoimmunity in multiple species (129). Both MeHg and inorganic Hg were shown to produce an autoimmune response, as well as an immunosuppressive effect in several strains of genetically susceptible mice (130, 131). However, data on the immune effects of MeHg in general are sparse, and research is required in this area.

Co-contaminants

Fish tend to accumulate halogenated organics, including polychlorinated biphenyls (PCB), dioxins, and related compounds. The neurodevelopmental effects of PCBs and, to a lesser extent, dioxins, share some similarities to those observed for MeHg (132). This can potentially present difficulties in determining causality and in constructing MeHg-specific dose-response relations. Because MeHg tends to associate more with proteins than with fats, fish species with elevated levels of MeHg are not necessarily those with elevated levels of the lipophilic halogenated organics. Thus, for fish consumption where both exposures occur, the influence of the individual contaminants can potentially be separated by statistical techniques if a variety of fish species is consumed and sufficiently precise exposure metrics are collected. In the Faroe Islands studies, both MeHg and PCBs appear to jointly affect some developmental endpoints. However, although MeHg appeared to enhance the PCB-attributable effects, the PCBs appeared to make a relatively minor contribution to the MeHg-specific effects (132, 133). Contradictory findings were observed in a study of cognitive development associated with exposures to MeHg and PCBs in the Lake Oswego area of New York State (134). In that study, elevated PCB exposure appeared to potentiate MeHg effects. However, both MeHg and PCB levels were considerably lower than in the Faroes study, and no PCB-MeHg association was observed on follow-up testing of the cohort. More work remains to be done on the joint influence of MeHg and halogenated organics, as well as other metal contaminants that may also be present in fish (135).

Elemental Hg continues to be used in dental amalgam for the treatment of dental carries. In populations with significant amalgam use, elemental Hg may account for a proportion of total Hg exposure comparable with or greater than MeHg (38).

Table 1. Differences in decision choices between the NAS/NRC (2000) and the JECFA (2003) risk assessments for mercury intake.

Variable	NAS/NRC (2000)	JECFA (2003)
Studies	Considered Faroes, New Zealand, Seychelles. Final value based on Faroes	Faroes and Seychelles
Biomarker used as index	Cord blood, $\mu g\ L^{-1}$	Maternal hair [Hg], $\mu g\ g^{-1}$ or ppm.
BMDL selected	58 $\mu g\ L^{-1}$ cord blood	14 $\mu g\ g^{-1}$ maternal hair
Uncertainty factor	Uncertainty factor = 10. 3.2 for toxicokinetics. 3.2 for toxicodynamics	3.2 (100.5) (individual variation) × 2 for overall average interindividual variation = 6.4 No toxicodynamic factor.
Exposure limit	Reference dose of 0.1 $\mu g\ kgbw^{-1}\ d^{-1}$ (equal to 0.7 $\mu g\ kgbw^{-1}\ wk^{-1}$)	1.6 $\mu g\ kgbw^{-1}\ wk^{-1}$ (equal to 0.23 $\mu g\ kgbw^{-1}\ d^{-1}$)

It is known that elemental Hg vapor can cross the placenta and accumulate in fetal tissue (136–138), and animal data suggest that elemental Hg has the potential to cause adverse neurologic developmental effects (139). Both elemental Hg and MeHg are metabolized in the brain to the inorganic mercuric form (38). It is not known whether the ultimate neurodevelopmental toxicant of MeHg is MeHg itself, the inorganic mercuric ion, free radicals generated in the conversion to the inorganic species, or some combination of these. If the inorganic form is the ultimate toxicant of MeHg in the developing brain or if MeHg and inorganic Hg share common neurodevelopmental toxic mechanisms, then current estimates of risk based on MeHg exposure alone could underestimate the population risk. Additional research is clearly needed to address these questions.

Potential Benefits of Fish Consumption

Several investigators have addressed the issues surrounding the risks and benefits associated with fish consumption, in general and for remote communities that depend on fish traditionally and/or as their dietary mainstay (69, 140–142). Indeed, for many populations, fish is the primary source of protein and other nutrients. Moreover, some fish can be an important source of the omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, that appear to have positive effects on at least some of the same systems adversely affected by MeHg. However, similar to MeHg, there is considerable variability in the occurrence of omega-3 fatty acids across species (143). Fatty fish have higher levels of omega-3s compared with lean fish, and freshwater fish largely have lower levels of omega-3 fatty acids compared with ocean fish (15). There is no association between MeHg concentration of the fish or shellfish species and the omega-3 fatty acid level of the species (15). Several fish and shellfish species that are low in MeHg are high in omega-3 fatty acids (e.g., anchovies, herring, salmon), whereas others that are high in MeHg can be comparatively low in omega-3 fatty acids (e.g., shark, swordfish, pike) (15).

Omega-3 fatty acids are associated with beneficial effects on neurologic development in some studies (15), as has fish consumption in general, possibly as a correlate of omega-3 intake (90). However, not all studies found such a benefit (15, 144). Omega-3 fatty acids also were linked to a reduction in the risk of cardiovascular disease (44), although such an association recently were called into question in a comprehensive review (145). For both endpoints, there is some evidence suggesting that, in addition to its intrinsic toxicity, MeHg also antagonizes the beneficial effects of the omega-3 fatty acids (44, 119, 146). Because intake of both substances arises from the same food source, this suggests that the risk-benefit analysis for either the omega-3s or MeHg will depend on an understanding of this complex interaction.

Some animal studies suggest that micronutrients that are normally found in high levels in seafood, such as Se and vitamin E, may protect against Hg toxicity without specifically modulating MeHg absorption or excretion (55). For Se, differences across studies in the forms of Se and Hg, and the route and duration of exposure make interpretation difficult. Although there is some evidence showing protection against inorganic Hg toxicity by selenite, there is almost no evidence showing protection against MeHg toxicity by the organic Se compounds, such as selenomethione or selenocysteine, that are the forms of Se commonly found in the human diet. There is no human data that support a protective role for Se with respect to Hg neurotoxicity. For vitamin E, there is a suggestion that its antioxidant properties may protect against some of the adverse effects of MeHg (147, 148). However, there are few *in vivo* studies, and no epidemiological studies have addressed vitamin E intake.

RISK ASSESSMENT FOR MeHg

The risk assessment process for chemicals in foods is based on hazard identification, exposure assessment, dose-response evaluation, and risk characterization. The most commonly used paradigms for risk assessment are those reflecting the processes developed by the National Academy of Sciences/National Research Council (NAS/NRC) in the United States (149) and a similar process used internationally by the Joint Expert Committee on Food Additives and Contaminants (JECFA) under the Food and Agriculture Organization and the WHO (150). The NAS/NRC provided recommendations on MeHg in 2000, and JECFA continues to evaluate MeHg after their evaluation published in WHO Food Additives Series Number 52 (151).

In the risk assessment for MeHg, both NAS\NRC and JECFA used a benchmark dose approach based on a predetermined change in response rate of an adverse effect. Both used the benchmark dose lower limit (BMDL), which is the statistical lower confidence limit on the dose. Because these two major risk assessments recommend different intake levels [0.1 μg kg-body-weight $(bw)^{-1}\ d^{-1}$ and 0.23 $\mu g\ kgbw^{-1}\ d^{-1}$, respectively], here we examine the choices throughout the process that lead to these differences (Table 1):

i. Choice of study. Currently both rely on neurodevelopment effects of MeHg as the adverse health effect used in their respective risk assessments. The NAS/NRC based their analyses on the Faroes Islands study as the primary source of epidemiological data and relied on the studies from New Zealand (87) and the Seychelles as secondary sources and derived a BMDL, based on cord blood of 58 $\mu g\ L^{-1}$. The JECFA excluded the New Zealand study and, basing their BMDL calculation only on the Faroe Islands and the Seychelles studies, derived a BMDL of 12 $\mu g\ g^{-1}$ in maternal hair.
ii. Biomarker of exposure. The NAS/NRC based their analyses on cord blood, and the JECFA used maternal hair. Because some of the critical studies for these risk assessments measured only one of these biomarkers converting between cord blood and maternal hair concentration (or vice versa)

involves uncertainty. Furthermore, as the most critical period(s) of gestation for the neurodevelopmental toxicity of MeHg are not yet known, it is not clear which lengths of maternal hair are most appropriate to measure

iii. Uncertainty factor. This factor accounts for adequacy of the pivotal study, interspecies extrapolation, interindividual variability in humans, adequacy of the overall data base, and the nature of the toxicity. These are not "safety factors" in that they are intended to factor in quantitatively to address areas of uncertainty in the risk assessment rather than provide "safety" *per se*. The magnitude of the uncertainty factors is intended as an estimate of the influence of these uncertainties, rather than the application of an arbitrary layer of safety. In the assessment conducted by the NAS/NRC committee, a composite uncertainty factor of 10 was used to account for variability and uncertainty in toxicokinetics and toxicodynamic, as well as database insufficiency for endpoints possibly more sensitive than neurodevelopmental (e.g., cardiovascular endpoints). The JECFA used an overall uncertainty factor of 6.4 to address variability in both toxicokinetics and toxicodynamics. The toxicokinetic portion accounts for a factor of 3.2 based on a generalized estimate of intraspecies toxicokinetic variability (152). The toxicodynamic portion likewise accounts for a factor of 2.0 based on a generalized estimate of interindividual variability in response.

The starting points for derivation of their respective recommended intakes differ both with respect to the actual values and the approaches taken. The JECFA Committee estimated that a steady-state intake of 1.5 μg kgbw^{-1} d^{-1} would be an exposure that would have no appreciable adverse effects on children, in contrast to the NAS/NRC determination of a BMDL of 1.0 μg kgbw^{-1} d^{-1}, which is an effect level. However, neither of these assessments reflected bioconcentration of MeHg across the placental circulation from the mother to the fetus (61). This bioconcentration and its population variability suggests that the full toxicokinetic variability is significantly larger (60, 153) than previously estimated (38, 151, 154).

The NAS/NRC used cord blood mercury for their BMDL of 58 μg L^{-1}, as did the US Environmental Protection Agency in 2001. However, the subsequent increased recognition that cord blood mercury is, on average, 60% to 70% higher in Hg than maternal blood, coupled to the coefficient of variation around the mid-point of 1.7 described by Stern and Smith (61) as 0.56 with a 95th percentile of 3.4, supports the use of a blood mercury concentration in the mid-30 μg L^{-1} range to recognize this fetal-maternal blood mercury difference (152, 155). By contrast, assessments based on association of maternal hair Hg with adverse neurobehavioral outcomes in the child after *in utero* exposures to MeHg need no such adjustment for MeHg concentration.

PANEL CONSENSUS CONCLUSIONS

Methylmercury is a potent toxicant, bioaccumulated and concentrated through the aquatic food chain, placing at risk humans who consume high-end aquatic predators or for whom fish is a dietary mainstay. Elevated levels of MeHg exposure occur worldwide and are not restricted to isolated populations. Rather, exposure to MeHg at levels above those that can be considered clearly safe and without risk of adverse effect occur throughout the globe and across the socioeconomic spectrum.

Hair and blood Hg concentrations (including cord blood Hg concentrations) are valid biomarkers of MeHg exposure. Each conveys somewhat different information on exposure. The most useful picture of exposure is likely to be obtained by data from both biomarkers, along with specific dietary information on fish consumption and other dietary data. Urinary Hg concentration is a biomarker of inorganic Hg. More research characterizing the relations between toenail Hg, hair Hg, blood Hg, and urinary Hg, and the relations between MeHg and inorganic Hg should be considered a priority. Single-strand and, particularly, continuous single-strand hair analysis of Hg concentration should be pursued as the best method for elucidating dynamic changes in MeHg exposure. This is particularly relevant for studies of the effect of *in utero* exposure to MeHg to assess the significance of bolus doses.

Total fish consumption without differentiating fish species is not necessarily a dependable metric for estimating MeHg exposure. To be useful for such purposes, valid data on the MeHg concentration of each species, as well as the frequency and the amount of consumption for each species must be included.

There is sufficient evidence to state that MeHg is a developmental neurotoxin, and developmental or fetal neurotoxicity has constituted the basis for risk assessments and public health policies. Although uncertainties in the risk assessment for the neurodevelopmental effects of MeHg remain, there is sufficient evidence to warrant a public health response based on prudent selection of fish species in the diet. Development of a formal case description and diagnostic criteria for the clinical effects of MeHg observed in some adults and older children with moderately elevated MeHg exposure should be a priority for clinicians involved with MeHg research.

Current studies suggest that present levels of exposure to MeHg have the potential to result in an elevated risk of cardiovascular disease to a significant fraction of the population. However, additional studies in other populations would clarify this picture. Quantitative dose-response assessment of existing studies should be undertaken. The potential effect of MeHg on the immune system should be investigated with respect to adverse effects on immune response, as well as with respect to individual sensitivities to MeHg, potentially including autoimmune responses.

To date, it has been possible to statistically separate the neurodevelopmental effects of MeHg and PCBs in key studies where both exposures occur in the fish-consuming population. However, knowledge of the mechanisms and interactions of PCBs and other halogenated organics with MeHg is an important missing piece in understanding the overall risk for fish consumption. Research into the potential interactions of inorganic Hg and MeHg should be considered a priority. Although the possible interactions between Se and MeHg are a fruitful area for further research, there is currently no clear evidence that dietary Se can modulate the toxicity of MeHg.

Because the intake of both omega-3 fatty acids and MeHg occurs from fish consumption and because MeHg appears to antagonize the beneficial effects of the omega-3s as well as exerting its own intrinsic toxicity, a proper assessment of risks and benefits for the combination of the two must address their complex interaction. Currently, there are insufficient data on this interaction to describe a coherent picture. Despite the lack of a clear picture of the interaction of the omega-3 fatty acids and MeHg, there are fish with high levels of omega-3s and relatively low levels of MeHg. Consumption of fish with low levels of MeHg and organic contaminants constitute a "win-win" situation and should be encouraged regardless of the underlying nature of the omega-3-MeHg interaction.

To preserve human health, all efforts need to be made to reduce and eliminate sources of exposure, through regulation and dissemination of information. In addition to documenting the multiple health hazards associated with exposure to MeHg throughout the lifespan, research needs to focus on identifying factors that influence the uptake and the toxicity of MeHg and

on examining the potential benefits of different fish species. These studies will provide information on maximizing nutritional intake from consumption and minimizing risk from exposure to MeHg.

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