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Mercury

Assessing the environmental burden of disease at national and local levels

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A Microsoft Excel spreadsheet for calculating the estimates described in this document can be obtained from WHO/PHE. E-mail contact: EBDassessment@who.int

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Table of Contents

List of Tables

List of Figures

Preface

The disease burden of a population and how that burden is distributed across different subpopulations (e.g. infants, women), are important pieces of information for defining strategies to improve population health. For policy-makers, disease burden estimates provide an indication of the health gains that could be achieved by targeted action against specific risk factors. The measures also allow policy-makers to prioritize actions and direct them to the population groups at highest risk. To help provide a reliable source of information for policy-makers, WHO analysed 26 risk factors worldwide in the *World Health Report* (WHO, 2002).

The Environmental Burden of Disease (EBD) series continues this effort to generate reliable information, by presenting methods for assessing the environmental burden of mercury at national and local levels. The methods in the series use the general framework for global assessments described in the *World Health Report* (WHO, 2002). The introductory volume in the series outlines the general method (Prüss-Üstün et al., 2003), while subsequent guides address specific environmental risk factors. The guides on specific risk factors are organized similarly, first outlining the evidence linking the risk factor to health, and then describing a method for estimating the health impact of that risk factor on the population. All the guides take a practical, step-by-step approach and use numerical examples. The methods described in the guides can be adapted both to local and national levels, and can be tailored to suit data availability.

This document was reviewed in Geneva at the Informal preparatory meeting for the Chemical Task Force of the Foodborne Disease Epidemiology Reference Group (FERG), held by the World Health Organization Department of Food Safety, Zoonoses, and Foodborne Diseases on 29 June 2007. For a list of invited experts and other attendees, see Appendix 1.

Affiliations and acknowledgements

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Glossary and abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
CI	Confidence interval
DALYs	Disability-Adjusted Life Years
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
IPCS	International Programme on Chemical Safety
IOM	Institute of Medicine
IQ	Intelligence Quotient
µg	Micrograms
MMR	Mild mental retardation
NRC	National Research Council
OR	Odds ratio
PTWI	Provisional tolerable weekly intake
RfD	Reference dose
RR	Relative risk
US EPA	Environmental Protection Agency of the USA
WHO	World Health Organization
WISC	Wechsler Intelligence Scales for Children

Summary

This document provides a review of the health effects of elemental, inorganic, and methylmercury and methods for estimating the burden of disease for methylmercury. Elemental mercury can cause a variety of health effects. Methylmercury has been associated with adult neurological problems, and there is some evidence that methylmercury exposure affects the adult cardiovascular system. However, the data for these effects are insufficient for a quantitative analysis. As a result, the quantitative aspect of this report focuses on the neurodevelopmental toxicity of methylmercury.

Cognitive deficits in infants are represented as IQ point deficits caused by prenatal exposure to methylmercury. The disease burden is assessed using the distribution of hair mercury concentrations among pregnant women or women of childbearing age as a measure of infant exposure. Although small IQ deficits may not be visible on an individual basis, they can be significant in a population with high exposure or among those affected by endemic diseases that impair neurological function. IQ deficits have the greatest population impact among children with IQ scores just above 69 points, for whom lowered IQ score would result in mild mental retardation (defined as an IQ between 50 and 69 points). The rate of mild mental retardation caused by methylmercury-related IQ loss and the resulting number of disability-adjusted life years (DALYs) lost are calculated from the exposure distribution. DALYs measure the health impact in a population as the number of healthy years of life lost based on the severity and length of the illness.

This report estimates the disease burden for several populations, including subsistence fishers, sport fishers, and indigenous communities near industrial and mining activities. The incidence rate for mild mental retardation is estimated to be as high as 17.37 per 1000 infants born among a subsistence fishing population in the Amazon, resulting in a loss of 202.8 disability-adjusted life years per 1000 infants. Due to the lack of exposure data from representative populations in the various regions throughout the world, the global burden of disease could not be estimated. Quantification of the disease burden in subpopulations for which exposure is known, however, provides an important basis for targeting populations at risk for significant health deficits.

Because elemental mercury can be transported long distances in air, regions with little or no mercury emissions may have high environmental mercury levels. Minimizing the amount of mercury emitted into the environment to reduce methylmercury concentrations in fish and seafood requires global cooperation. Furthermore, some elemental mercury is emitted as a result of natural processes (e.g. volcanoes, forest fires). Thus, reducing the consumption of seafood with high methylmercury concentrations is the most direct way to reduce the risk of methylmercury-related cognitive deficits in a highly exposed population. However, consumption recommendations must also consider the nutritional value of fish and shellfish, particularly in populations without access to alternative sources of protein. Additionally, there is evidence that omega-3 fatty acids in fish and shellfish have a beneficial effect on neurodevelopment. The risks and benefits of fish consumption depend on the amount and species of fish consumed and must be weighed carefully for each subgroup in the population.

1. Introduction

The toxic effects of mercury have been observed for centuries. The phrase "mad as a hatter" was coined due to neurological problems suffered by hat makers who inhaled mercuric nitrate vapour. Mercurous chloride in teething powders and ointments caused cases of acrodynia (pink disease) among young children in the 1900s. In the 1950s, mercury was released from a chemical plant into the Minimata Bay of Japan, contaminating fish that were consumed by fishermen and their families. Another poisoning episode occurred in the 1970s when seed grain coated with a methylmercury fungicide was mistakenly used as flour in Iraq. These incidents dramatically demonstrated mercury's neurotoxic effects, which were particularly severe among infants exposed during the prenatal period. In recent years, concern has centred on exposure to methylmercury in fish and elemental mercury from industrial and mining activities.

This document estimates the burden of disease from prenatal methylmercury exposure in several high-risk groups and provides methods for determining the burden of disease in populations with elevated methylmercury exposure. Mercury exposure sources, health effects, and exposure-response relationships are described and used in a quantitative methodology for measuring the disease burden of methylmercury-induced neurodevelopmental deficits. Although exposure to elemental mercury and inorganic mercury compounds is known to cause a variety of adverse health outcomes, the data are insufficient to conduct a burden of disease estimate for these effects. This does not diminish the significance of elemental mercury toxicity in highly-exposed populations (e.g. artisanal and small scale gold miners), and lack of this information is a critical research need for estimating the disease burden from mercury.

The burden of disease in each population is determined by estimating the impact of methylmercury-induced IQ deficits in infants. The following are the basic steps of the assessment:

1. Determine the distribution of hair mercury concentrations in women of child-bearing age consuming methylmercury-contaminated fish.
2. Calculate IQ deficits in infants based on the distribution of hair mercury concentrations in women of child-bearing age.
3. Estimate the incidence rate of methylmercury-induced mild mental retardation and the resulting disease burden in DALYs.

2. Sources of mercury and exposure pathways

Mercury is a metallic element that exists naturally in the earth's crust and can be transported throughout the environment in air and water. Mercury is released into the air as vapour during natural processes such as volcanic activity, forest fires, water body movement, weathering of rock, and biologic processes. Elemental mercury can combine with other elements to form inorganic mercury compounds (e.g. mercuric acetate, mercuric chloride, mercurous chloride, mercuric nitrate, mercuric oxide, mercuric sulfide). As mercury cycles through the environment, it deposits in water bodies where it undergoes biotransformation by aquatic microorganisms, forming methylmercury. Other organic forms of mercury include ethyl mercury and phenyl mercury.

Anthropogenic sources of mercury contribute significantly to levels in the environment and include mining operations, industrial processes, combustion of fossil fuels, cement production, and incineration of medical, chemical, and municipal wastes. Current mercury levels in the atmosphere are between 3 and 6 times higher than levels estimated to have existed before industrialization (WHO, 2003). Due to global mercury cycling through air and water, even regions without mercury emissions can have substantial environmental mercury levels.

2.1 Elemental and inorganic mercury

General population exposure to inorganic forms of mercury can occur from a wide variety of sources. While not an exhaustive list, some of the major sources include:

- contact with mercury-containing products (e.g. thermometers, barometers, thermostats, blood pressure monitors, electrical switches, batteries, paint, etc.);
- exposure from dental amalgams fillings:
- playing in contaminated soil or with mercury from thermometers (children);
- inhalation of ambient air near mercury refineries, mines, and industrial plants, or where mercury-containing fungicides have been applied (i.e. environmental "hotspots");
- ingestion of mercury-contaminated food or drinking water;
- use of traditional, folk, or herbal medicines (e.g. antiseptics, diuretics, laxatives);
- application of mercury-containing skin lightening creams and soaps;
- exposure during religious and cultural practices.

Occupational exposure

Mercury vapour inhalation is the primary route of occupational exposure, but mercury can also be absorbed through the skin. Mercury-related health effects have been observed in dental personnel, gold and silver miners, florescent light bulb manufacturers, and workers in the chlor-alkali and thermometer industries, among others. In developing countries, mercury vapour exposure through artisanal and small-

scale gold mining can reach very high levels due to uncontrolled working conditions. As many as 10–15 million people in over 50 countries are engaged in these activities, which are estimated to release between 800 and 1000 tons of mercury into the environment each year (Veiga and Baker, 2004).

2.2 Organic mercury

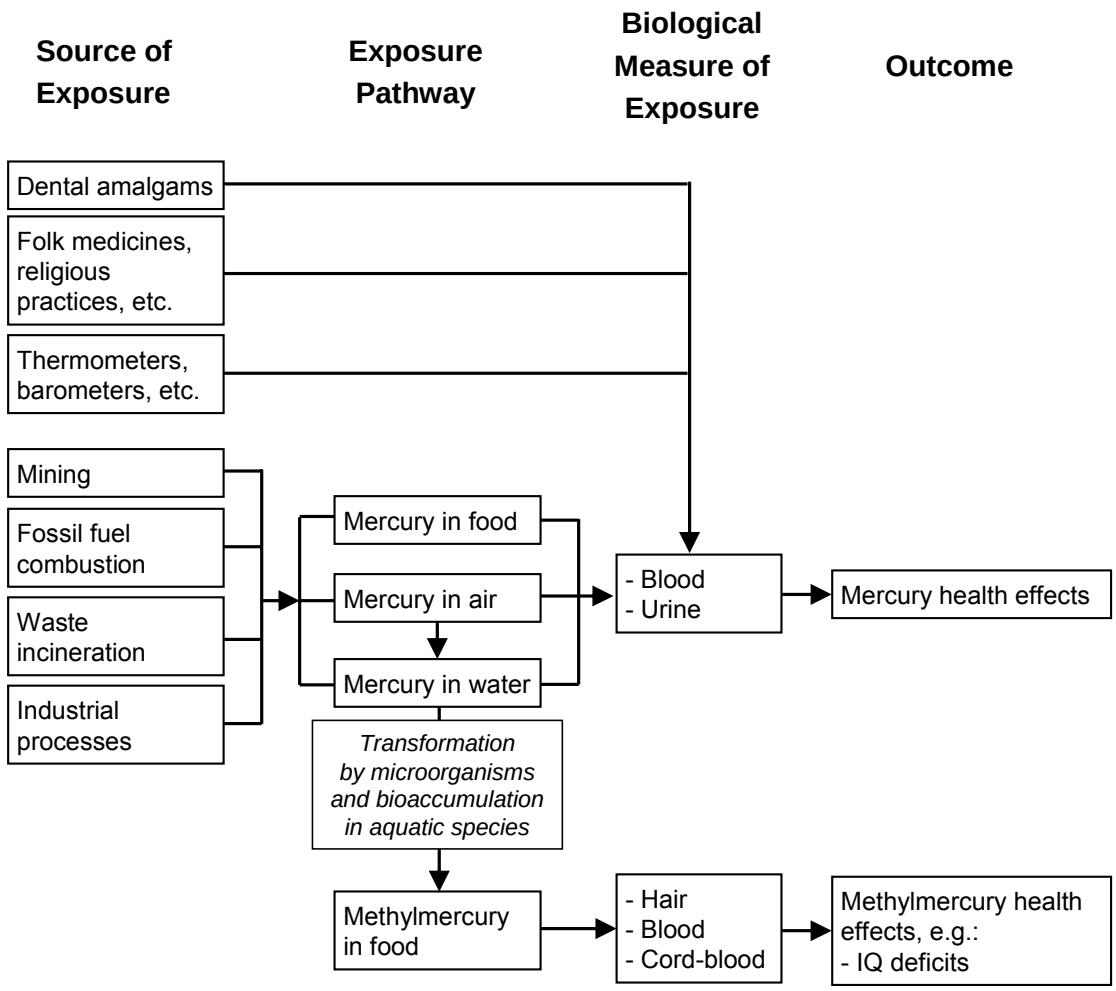
The most common form of organic mercury is methylmercury, which is formed when mercury in oceans, lakes, and rivers is biotransformed by aquatic microorganisms. Methylmercury is present in most aquatic species and bioaccumulates in the aquatic food-chain, which may lead to high concentrations in fish, shellfish, and marine mammals. Mercury content is highest in large carnivorous species and older fish. The major source of human exposure to methylmercury is ingestion of contaminated fish and seafood (seafood includes shellfish and marine mammals, such as whales). High exposures can occur among populations with high fish consumption (e.g. subsistence fishers, sport fishers). Environmental hotspots can occur near industrial and mining activities, where pollution of local water bodies may result in elevated levels of methylmercury in fish.

Other organic forms of mercury, such as ethyl mercury and phenyl mercury, have been used in paints, fungicides, antiseptics, preservatives, and topical disinfectants. Although these uses have been largely discontinued, they may be a source of exposure in some parts of the world. Other forms of mercury (i.e. dialkyl mercurials) are extremely toxic and not commonly used outside of limited occupational applications. Thimerosal is a preservative in vaccines that contains ethyl mercury. While there has been much debate over the possible toxicity of ethyl mercury in thimerosal (i.e. autism), the WHO Global Advisory Committee on Vaccine Safety concluded that there is “no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines” (WHO, 2006). Data on health effects and exposure-response for organic forms other than methylmercury are not well characterized and are thus not evaluated in this assessment.

2.3 Mercury exposure framework

It is important to identify all sources of mercury as they may be significant among exposed individuals. Common routes of mercury exposure are summarized in Fig. 1.

Figure 1 Framework for mercury exposure



3. Mercury toxicity

This section outlines the main health effects resulting from exposure to elemental mercury, inorganic mercury compounds, and methylmercury. The data provided below are based on reviews, which are available for additional information on mercury toxicity (ATSDR, 1999; NRC, 2000; WHO/IPCS, 1990; WHO/IPCS, 1991; WHO, 2003; WHO/IPCS, 2004). The weight of evidence for these endpoints and their usefulness in the burden of disease evaluation are discussed in Section 4.

3.1 Elemental and inorganic mercury

Nervous system effects

The nervous system is the most sensitive target for mercury exposure. A variety of neurological and behavioural disorders have been reported, including tremors, erethism (abnormal irritability or responsiveness to stimulation), emotional lability, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy, and deficits in cognitive and motor function tests. Effects are similar at varying durations but can become more severe (sometimes irreversible) as duration and concentration increase. Studies of workers in florescent tube manufacturing, wood processing, chlor-alkali, and thermometer plants have demonstrated subtle central nervous system toxicity at mercury vapour concentrations in air as low as 20 $\mu g/m^3$.

Renal effects

The kidneys are another major target of mercury vapour toxicity, though effects occur at higher levels than neurological problems. Inhalation of high mercury vapour concentrations can cause gross or mild transient proteinuria, changes in urinary acid excretion, hematuria, oliguria, and acute renal failure. Chronic oral exposure to inorganic mercury compounds also results in renal damage, and renal failure has been reported in several cases following mercuric chloride ingestion.

Cardiovascular effects

Increased blood pressure, palpitations, and increased heart rate have been observed in cases of acute high level mercury exposure. Studies of chronic exposure in chlor-alkali workers and mercury miners have also been suggestive of cardiovascular toxicity (Barregard et al., 1990; Boffetta et al., 2001; Kobal et al., 2004).

Skin effects

Rashes, hives, and dermatitis have been observed following occupational and accidental contact with inorganic mercury compounds. Inhalation of mercury vapours and contact with mercurous chloride in teething powders and ointments can cause acrodynia, a pink discolouration of the hands and feet usually accompanied by insomnia, irritability, and light sensitivity.

Respiratory effects

Acute high-level exposure to mercury vapours causes respiratory effects such as cough, dyspnea, and chest tightness or burning. Effects of chronic occupational exposure include similar symptoms and more severe effects such as pneumonitis, reduced pulmonary function, airway obstruction, hyperinflation, decreased vital capacity, respiratory distress, pulmonary oedema, and lobar pneumonia fibrosis.

3.2 Methylmercury

Nervous system effects

Methylmercury poisoning can cause a variety of central nervous system effects in adults. Neurological effects in adults with Minimata disease include sensory and motor impairment, such as paresthesia, peripheral neuropathy, tremor, dysarthria, cerebellar ataxia, gait and equilibrium disturbance, opthalmological and audiological impairment, and subjective symptoms (e.g. headache, muscle and joint pain, forgetfulness, fatigue). Some of these effects may be reversible with removal from exposure. It is unclear whether low dose methylmercury exposure from fish is toxic in adults; several cross-sectional studies have reported varying results (Auger et al., 2005; Johansson et al., 2002; Lebel et al., 1998; Yokoo et al., 2003; Weil et al., 2005).

Developmental neurotoxicity

Neurodevelopmental toxicity is the most sensitive endpoint for methylmercury (WHO/IPCS, 2004). Methylmercury can pass through the placental barrier and affect the nervous system of developing foetuses. Prenatal exposure can result in irreversible damage to the fetal central nervous system, which is more sensitive to methylmercury toxicity than that of adults. Severe neurodevelopmental toxicity was demonstrated in children exposed to high methylmercury concentrations in utero during poisoning episodes in Japan and Iraq. Effects included mental retardation, impaired mental development, dysarthria, sensory impairment (blindness and deafness), paralysis, hyperactive or primitive reflexes, cerebellar ataxia, cerebral palsy, physical growth disturbance, and limb deformities (NRC, 2000).

Developmental neurotoxicity has also been observed following prenatal exposure of children to methylmercury from maternal fish consumption. Prenatal methylmercury exposure from fish and seafood has been investigated in three prospective long-term cohort studies conducted in the Faroe Islands, New Zealand, and the Republic of Seychelles. Maternal hair mercury concentrations in these three studies were 4.3 μg/g (geometric mean), 8.3 μg/g (mean), and 5.8 μg/g (median), respectively (Cohen et al., 2005a). The Faroe Islands study reported an inverse dose response relationship between children's performance on standardized neurobehavioural tests and consumption of methylmercury-contaminated seafood (primarily pilot whale) by their mothers during pregnancy. Deficits were observed in tests of attention, fine-motor function, visual-spatial abilities, and verbal memory (NRC, 2000). The New Zealand study found similar associations between fish consumption by pregnant women and neurodevelopmental effects in their children, but the Seychelles Island study did not.

Evaluations by WHO and NRC provide thorough descriptions and analyses of these studies (WHO/IPCS, 2004; NRC, 2000).

Cardiovascular effects

Several studies have found associations between low level methylmercury exposure and cardiac outcomes in adults. Prospective studies of a cohort of Finnish males have shown that mercury exposure increases risk of acute myocardial infarction and death from coronary heart disease and cardiovascular disease, as well as increased intima-media thickness (an indicator of atherosclerosis) (Salonen et al., 1995; Salonen et al., 2000; Rissanen et al., 2000; Virtanen et al., 2005). Rissanen et al. and Virtanen et al. also reported that the cardio-protective effect of fatty acids in fish was attenuated by elevated hair mercury levels. A case-control study found a dose-related association between toenail mercury concentrations and myocardial infarction in European and Israeli men, which increased when adjusted for the omega-3 fatty acid docosahexaenoic acid (DHA) (Guallar et al., 2002). Yoshizawa et al. (2002) conducted a nested case-control study of American male health professionals and did not find an association between toenail mercury levels and cardiovascular disease. However, the study included a large number of dentists, who are exposed to elemental mercury vapour from dental amalgams rather than methylmercury from seafood. Since the two forms of mercury may affect the cardiovascular system differently, a second analysis was conducted that excluded dentists and controlled for the omega-3 fatty acids eicosapentaenoic acid (EPA) and DHA. The results showed an elevated risk of cardiovascular disease (RR = 1.70) that was non-significant, likely due to a lack of power from the reduced sample size (Yoshizawa et al., 2002). A study of non-indigenous fish consumers in the Brazilian Amazon reported that hair mercury levels above 10 μg/g were associated with increased systolic blood pressure (OR: 2.91, 95% CI: 1.26–7.28) (Fillion et al., 2006).

Cardiovascular effects have also been observed in children. A study of Faroese children exposed to methylmercury in utero, as measured by cord-blood mercury, reported significantly increased systolic and diastolic blood pressure at age 7 (Sørensen et al., 1999). However, when this cohort was followed to age 14, increased blood pressure was no longer associated with cord-blood mercury concentrations (Grandjean et al. 2004). Heart rate variability was 47% lower in boys at age 7 and remained decreased at the 14 year follow-up, but the degree to which decreased childhood heart rate variability can be associated with risk of future disease is uncertain (Stern, 2005).

4. Exposure-risk relationships

Methods for quantifying disease burden are provided only for selected health effects. This determination is based on:

- the strength of the evidence demonstrating the health effect;
- whether the effects are well defined health outcomes or can be converted into such;
- the availability of quantitative information on the association between the mercury biomarker and the health effect.

Only publicly available, peer-reviewed literature was used in the preparation of this document. A systematic literature search was conducted to obtain quantitative exposure-response data on mercury outcomes. A search of online databases including PubMed, MEDLINE, and TOXLINE was conducted using mercury and methylmercury as search terms and limiting the results to studies in humans. All references were downloaded into a reference management database and abstracts were reviewed. All studies with exposure-response data were obtained. ATSDR, EPA, NAS, and WHO documents on mercury were also reviewed for relevant information and further studies were obtained for consideration.

4.1 Endpoints not included in the assessment

For most of the outcomes described in Section 3, no exposure-response data are available. Case reports indicate ranges of exposure for some endpoints but do not provide sufficient quantitative information to estimate risk. In addition, many effects are subtle and/or transient and can not be related to quantifiable health outcomes for which disability weights have been determined. Data on exposure-response for inorganic mercury compounds are particularly sparse. Specific data limitations are discussed below.

Elemental Mercury

General assessments have attempted to determine exposure-response relationships between elemental mercury and health effects. Clarkson and Magos (2006) summarized data from twelve occupational studies where the mercury concentrations were less than 50 µg/L in urine and reported that while there are effects on the nervous, immune, and renal systems, "One cannot see any consistent relation between urinary levels and effect findings." WHO determined that there is a "high probability" of developing tremor, erethism, and proteinuria at levels of 100 µg/g creatinine in urine (80 $\mu g/m^3$ in air), but a quantitative definition of "high probability" was not provided (WHO/IPCS, 1991).

Neuropsychological effects

Neuropsychological deficits in workers and other adults are difficult to quantify because they are subtle and vary from study to study (e.g. tremor, irritability, negative self-concept, anxiety, psychoticism, hysteria, schizoid and psycho-asthenia, decreased

logical memory and total retention score). Two meta-analyses failed to identify a dose–response relationship. A study by Meyer-Baron et al. (2004) found general exposure-response associations between inorganic mercury exposure and neurobehavioural tests, but was unable to estimate specific dose–response relationships. A meta-analysis by Rohling and Demakis (2006) reported that "the prevalence of neuropsychological deficits due to occupational exposure to mercury is small and difficult to detect on an individual case-by-case basis." Additionally, many neuropsychological effects recover with removal from exposure.

Renal effects

No exposure-response information was identified for renal outcomes. Effects such as renal failure occur following high exposure such as in uncontrolled occupational settings.

Cardiovascular effects

Silberud (1990) found an association between blood pressure and mercury and Boffetta et al. (2001) reported "a possible association between employment in mercury mining and refining and risk in some groups of cardiovascular diseases." However, both studies had methodological problems such as limited exposure data, confounding, and disease misclassification. Although they are suggestive of a relationship between inorganic mercury exposure and cardiovascular risk, more studies are needed.

Skin effects

Children who inhale mercury vapour can develop a skin condition known as acrodynia. Although there may be a threshold for development of the disease, there is wide individual variability. A dose–response relationship has not been determined and there is no disability weight for this condition.

Methylmercury

Adult nervous system effects

As discussed in Section 3.2, several studies have noted effects of methylmercury on the adult nervous system. However, the health significance of these outcomes are difficult to quantify as they may be reversible. No quantitative estimates of exposure-response in the adult nervous system were identified in the literature.

Cardiovascular effects

The Institute of Medicine (IOM) reviewed the risks and benefits of fish consumption and concluded that, "increased methylmercury exposure might be a risk factor for adult cardiovascular toxicity, although the data available are not extensive and uncertainties remain" (IOM, 2006). The IOM report also reported that "increased seafood consumption is associated with a decreased risk of cardiovascular deaths and cardiovascular events in the general population" (IOM, 2006). Similarly, a US EPA review stated that "the science on the impact of methylmercury on the risk of cardiovascular events remains uncertain, and the weight of the evidence, in fact,

supports a positive association between fish consumption and potential cardiovascular benefits" (US EPA, 2005). Therefore, the evidence for cardiovascular effects was not deemed adequate for use in the burden of disease analysis.

4.2 Methylmercury-induced IQ deficits

The neurodevelopmental deficits caused by prenatal methylmercury exposure are well documented and can be used to determine health impacts in a population. In a safety evaluation of methylmercury in food, WHO stated that "neurodevelopment was considered to be the most sensitive health outcome, and in utero the most sensitive period of exposure" (WHO/IPCS, 2004).

Dose–response studies

Three studies were identified that calculated a dose–response relationship between prenatal methylmercury exposure and IQ deficits in infants.

Budtz-Jorgensen et al. (2004a)
Using data from the Faroe Islands 7-year follow-up study, Budtz-Jorgensen et al. estimated the association between maternal hair mercury concentration and observed test performance deficits in infants expressed as IQ points. Since there is no standardized Faroese IQ test, structural equation analyses were conducted using four tests as indicators of motor function and seven tests as indicators for verbally mediated function. Doubling of maternal hair mercury concentration was estimated to result in a test performance deficit of 9.74% of the test standard deviation for motor function and 10.45% of the standard deviation for verbally mediated function. Since a 10% reduction of the IQ scale standard deviation is 1.5 points, doubling of maternal hair mercury was estimated to be associated with a 1.5 point IQ deficit.

Cohen et al. (2005a)
Cohen et al. modelled the relationship between IQ and methylmercury exposure using data from all three major cohort studies (Faroe Islands, the Republic of Seychelles, and New Zealand). For each cohort, regression coefficients were calculated for each test in seven functional domains: motor, attention, visuospatial/visuomotor, language, memory, intelligence, and learning/achievement. Neurological tests were weighted according to known or judged correlation with IQ scores, relevance to the US population, and study quality. The log regression coefficients reported in the Faroe Islands were linearized over the lowest quartile of exposure for comparison with the linear coefficients of the other studies. This portion of the curve, which is supra-linear, was deemed most applicable to US exposures. The average cognitive performance decrease was 0.043 SDs per μg/g increase in maternal hair methylmercury concentration. Based on the IQ test standard deviation of 15 points, the authors concluded that every 1 μg/g increase in maternal hair methylmercury concentration is associated with an IQ decrease of 0.7 points. In a sensitivity analysis, the Faroe Islands data were linearized over the mid-range of exposure where the dose–response curve is linear. This analysis was conducted due to the NRC (2000) conclusion that a linear relationship is more biologically plausible than a supra-linear one. This model resulted in a mean deficit of 0.2 IQ points per 1 μg/g increase in maternal hair mercury. An

integrated sensitivity analysis determined that the plausible values for the association ranged from 0 to 1.5 IQ points lost per 1 μg/g increase in maternal hair methylmercury.

Axelrad et al. (2007)
This analysis incorporated dose–response coefficients for neurological outcomes from the three major cohort studies in a Bayesian hierarchical model assuming a linear non-threshold association. The relevance of each neurodevelopmental test to IQ scores was evaluated and the following tests were included in the model: full-scale IQ (all three cohorts), performance IQ (New Zealand), California Verbal Learning Test (Faroes and Seychelles), Bender-Gestalt Test (Faroes), Boston Naming Test (Faroes and Seychelles), McCarthy Scales of Children's Abilities (New Zealand), Test of Language Development (New Zealand), Developmental Test of Visual-Motor Integration (Seychelles), and Wide Rage Assessment of Memory and Learning (Seychelles). The Wechsler Intelligence Scales for Children (WISC) test of full-scale IQ was administered to the Seychelles and New Zealand cohorts; the WISC dose–response coefficient for the Faroe Islands cohort was estimated in a structural equation model based on three subtests. Although the Seychelles study used WISC-R and the New Zealand and Faroe Islands studies used WISC-III, the two versions correlate well ($r = 0.89$). A Bayesian hierarchical random effects approach was used to treat all model parameters as random variables and control for within and between study variability. The coefficient for each test was rescaled based on the standard deviation and expressed as IQ. The authors obtained a central estimate of –0.18 IQ points (95% CI –0.387, –0.012) per each 1 μg/g increase in maternal hair mercury. Estimates from sensitivity analyses ranged from –0.125 to –0.25 IQ points per 1 μg/g increase in maternal hair mercury.

Evaluation of the literature

The Axelrad et al. (2007) paper is the most recent meta-analysis describing the relationship between methylmercury and IQ. It incorporates data from all three of the large prospective cohort studies on prenatal methylmercury exposure and neurological outcomes. It uses a sophisticated Bayesian hierarchical model approach and considers several measures of cognitive performance. As an update of a prior study by Ryan (2005), which was conducted for the US EPA's Clean Air Mercury Rule, the methods of Axelrad et al. have undergone extensive scientific peer-review and comment. In a discussion of the Ryan study, the IOM stated, "although the findings of the Seychelles study appear discrepant from those of the Faroe Islands and New Zealand studies if one focuses only on the p-values of the reported analyses, at a deeper, quantitative level that focuses on the rates of decline in scores as mercury burden increases, the findings of the three studies are remarkably concordant" (IOM, 2006). The relationship described by Axelrad et al. is also similar to the results of the Cohen et al. (2005a) sensitivity analysis, and the studies share a primary author (David C. Bellinger). For these reasons the dose–response relationship described by Axelrad et al. is deemed the most reliable for use in burden of disease calculations. For a discussion of model uncertainties, see Section 9.2.

4.3 Summary

Table 1 summarizes the quantitative relationship developed by Axelrad et al. (2007).

Table 1 Health effects of prenatal exposure to methylmercury

Outcome	Group	Biomarker	Threshold	Relationship
IQ reduction	Infants	Maternal hair	None	Linear relationship between 1 μg/g increase in maternal hair mercury concentration and 0.18 point decrease in IQ (Axelrad et al., 2007)

5. Exposure assessment

5.1 Measuring methylmercury levels

Many techniques are available to assess mercury exposure. While proximal estimates of methylmercury intake from food can be useful, pathophysiological measurements that assess the body burden of mercury (e.g. hair, blood, cord-blood) are preferred. When conducting burden of disease calculations, it may be necessary to convert blood, cord-blood, or dietary levels into hair mercury concentrations. Although relationships between biomarkers are described below, these correlations are subject to individual and population variability and using hair mercury concentrations is suggested.

Hair

Maternal hair concentrations correlate well with dietary methylmercury intake and hair sample collection is simple and non-invasive. Concentrations at increasing distances from the root can also provide information on exposure over time, including magnitude and peak levels (NRC, 2000). Determining past exposure using concentrations in hair further from the root may be particularly beneficial for populations with seasonal variability in fish consumption (NRC, 2000). For populations without significant elemental mercury exposure, total hair mercury can be used as a measure of methylmercury exposure: "the use of total hair Hg concentration in fish-consuming populations as a surrogate for hair MeHg concentration in fish-consuming populations should not lead to significant exposure misclassification" (NRC, 2000). Information on assessing hair mercury concentrations is provided in Annex 2.

Blood

Blood mercury levels indicate recent or current exposure and can reflect both elemental and methylmercury exposure. In populations exposed to mercury mainly through fish consumption, a high fraction of total blood mercury is organic and can therefore be used as a measure of methylmercury exposure. However, blood samples from populations with concomitant elemental mercury exposure must be analysed specifically for methylmercury. WHO determined that "the concentration of mercury in hair is approximately 250 times the concentration in blood"; however, this relationship varies between populations and ratios from 140 to 370 have been reported (WHO/IPCS, 2004). If blood and hair mercury measurements are available for the study population, a population-specific blood to hair ratio should be used to convert mercury levels. In the absence of these data, burden of disease calculations use the average ratio of 250 to estimate mercury levels in hair from blood values.

Cord-blood

Umbilical cord-blood mercury levels are representative of prenatal methylmercury exposure during late pregnancy. Mercury concentrations in cord-blood correlate well with fetal-brain mercury concentrations during the third trimester, but not as well with maternal dietary intake (NRC, 2000). Mercury concentrates in cord-blood; thus mercury levels cord-blood are higher than in maternal blood. A meta-analysis of studies that collected cord-blood and maternal blood mercury levels determined that

the central tendency for the ratio of total mercury in cord-blood (μg/L) to total mercury in maternal blood (μg/L) is 1.7 (Stern and Smith, 2003). This ratio can be used in burden of disease calculations to convert mercury cord-blood levels to blood levels and subsequently to hair mercury concentrations. However, relationships between biomarkers differ between populations and ratios computed from levels observed in the study population are preferred. For example, Axelrad et al. (2007) converted Faroe Island cord-blood levels to hair concentrations using a ratio of 200, which was the value observed in the Faroes' population.

Dietary records

Quantitative, prospectively collected data on dietary intake including the frequency, amount, and species of seafood consumed can provide valuable information on methylmercury exposure (NRC, 2000). Supplementing direct measurements with dietary intake data can provide key information on the variability, magnitude, and timing of exposure. Knowledge of the type and amount of fish consumed is particularly valuable for developing policy recommendations and advisories (see Section 11). WHO modelled the following relationship between dietary intake and blood mercury levels (WHO/IPCS, 2004):

$$d = \frac{C \cdot b \cdot v}{A \cdot f \cdot bw}$$

where:

d =	dose (μg/kg bw/day)
C =	concentration in blood (μg/L)
b =	elimination rate constant (0.014 per day^{-1})
v =	blood volume (9% of bw - pregnant female)
A =	fraction of the dose absorbed (0.95)
f =	absorbed fraction distributed to blood (0.05)
bw =	body weight (65 kg for pregnant female)

This relationship may not be an accurate indicator of population hair levels due to individual variability in absorption and elimination rates (Canuel et al., 2006). However, if direct measurements are not available, the dietary intake model can be used to estimate blood mercury levels and then convert from blood to hair concentrations.

Nails

Fingernail and toenail mercury levels have also been used to measure the body burden of mercury. As with blood mercury measurements, using nail mercury levels may be problematic for populations with concomitant elemental mercury exposure. In addition, the extent to which finger and toenail levels correlate with methylmercury exposure has not been established (NRC, 2000). For these reasons, this document does not include methods for estimating the disease burden using mercury concentrations in nails.

Summary

The National Research Council states that “the most useful and powerful approach to exposure and dose assessment for methylmercury is the collection of comparable dietary, cord-blood and single-strand hair data” (NRC, 2000). However, the majority

of existing studies on mercury exposure report only hair mercury concentrations. In addition, the dose–response relationship between methylmercury exposure and IQ deficits in infants developed by Axelrad et al. (2007) is based on hair mercury measurements. Therefore, this guide uses maternal hair mercury concentrations (or hair mercury concentrations of women of childbearing age) as a surrogate measure for prenatal exposure. If necessary, the blood, cord-blood, and dietary intake conversions described above can be used to estimate hair mercury concentrations. These conversions are based on the best available estimates; however, the use of these ratios introduces additional uncertainty. In addition, they are based on populations solely exposed to methylmercury and may not be accurate for populations with appreciable elemental mercury exposure.

5.2 Determining population mercury levels

The mercury-related burden of disease in a population can be estimated using the population mean and standard deviation mercury levels. Mercury exposure information can be obtained from many sources (described below). Population studies are also needed to determine the number of infants born in the study year. Information on hair sampling and analysis techniques are provided in Annex 2.

Mercury surveys

Ideally, the burden of disease estimate would use hair mercury concentration data from one or more population-based studies. Population-based studies of this sort have not been conducted in many countries; often, only sparse data on mercury levels or fish consumption are available for highly exposed subgroups.

Focused sampling of populations believed to have high methylmercury exposure can be useful for estimating the burden of disease among groups with the greatest risk. This requires careful consideration of sites to be studied and how the results can be applied to non-sampled areas. There are many factors to account for since mercury sources and fish consumption behaviours vary among sections of the population. Subsistence fishing, location near environmental hotspots, and differences in other relevant behaviours and exposures throughout the region must be considered.

If a representative burden of disease estimate for a country or large region is desired, studies should be conducted using a probability sample from the entire population. These studies are expensive to mount; however, hair sample collection is generally a small fraction of the total cost since it does not require medical personnel or invasive procedures. One way to minimize the expense of conducting a population-based study is to add mercury testing to an established survey. In the United States for example, mercury sampling in hair and blood was added to the National Health and Nutrition Examination Survey in 1999.

Although mercury concentration data in children and males may be useful for other public health purposes, they are not required to estimate the burden of disease using the methods provided in this guide. Therefore, if resources are limited, mercury samples may be collected from women of childbearing age only.

Data from the literature

A literature search can provide data on mercury levels collected from existing studies when a new survey can not be conducted. Information may be available from national institutes, universities, administrations, government authorities, or other research bodies. In addition, databases searches (e.g. MEDLINE, PubMed, TOXLINE) can provide data from the peer-reviewed literature (use keywords such as methylmercury, women, pregnancy, blood, cord-blood, hair, diet, exposure, fish, seafood, neurological deficit, cognitive function). Table A4–1 in Annex 4 of this document contains mercury exposure data from many peer-reviewed studies conducted throughout the world. While this table can be helpful as a starting point for a literature review, additional data may be available and should be sought.

Studies obtained from the literature search must be evaluated to determine whether they are of sufficient quality for use in the burden of disease study and to ensure the data are representative of the target population. Factors to consider include the characteristics of the study population, the type of exposure (occupational, hotspot, general population); whether the study measured dietary intake or a biomarker; what type of biomarker (i.e. blood, cord-blood, hair); if the biomarker measured total mercury or methylmercury; the applicability of the study (e.g. is the population also exposed to elemental mercury?); and quality control. In addition, it is important to note whether a fish advisory has been issued since the data were collected, as it might have had a significant influence on current exposure levels.

5.3 Summary

Regardless of whether data are collected from the literature or surveys, the population mean hair mercury concentration and its standard deviation are required to estimate the burden of disease.

6. Disease burden methodology

6.1 Incidence of methylmercury-induced MMR

This guide uses the dose–response relationship described in Table 1 to quantitatively estimate the burden of disease from methylmercury-induced IQ loss. Because IQ loss is not considered a disease, the adverse health outcome is defined as IQ loss that results in mild mental retardation. Intelligence in human populations approximates a normal distribution with a mean of 100 IQ points and a standard deviation of 15 IQ points (NRC, 2000). Mild mental retardation (MMR) occurs when IQ is between 50 and 70 points.

The number of infants that would be shifted into the MMR range with a given methylmercury exposure is estimated from the mean and standard deviation maternal hair mercury levels of the population. The loss of IQ points is quantified assuming a linear no threshold relationship between each μg/g increase in maternal hair mercury concentration and a 0.18 point decrease in IQ (Axelrad et al., 2007).

The method implements an incremental approach for associating hair mercury levels with IQ deficits. Maternal hair mercury concentrations are divided into 2 μg/g intervals from 0 to 100 μg/g and an IQ point deficit is assigned to each interval based on the midpoint of the interval. For example, the IQ deficit for 2–4 μg/g is based on 3 μg/g, which is associated with a 0.54 point IQ deficit ($3 \times 0.18 = 0.54$). An 18 point IQ deficit is assigned to exposures greater than 100 μg/g. IQ deficits were not calculated above this exposure because it is unknown if the relationship holds at such high levels, which are uncommon even in populations with substantial methylmercury exposure. Because this approach is based on a no threshold dose–response relationship, any exposure above 0 μg/g results in at least a 0.18 IQ point loss, essentially shifting the population IQ down by 0.18 points.

Table 2 illustrates how the IQ deficit associated with each hair mercury increment is combined with the normal distribution of IQ to estimate the percent of the population within each IQ range that would be shifted to MMR given mercury exposure in each interval.

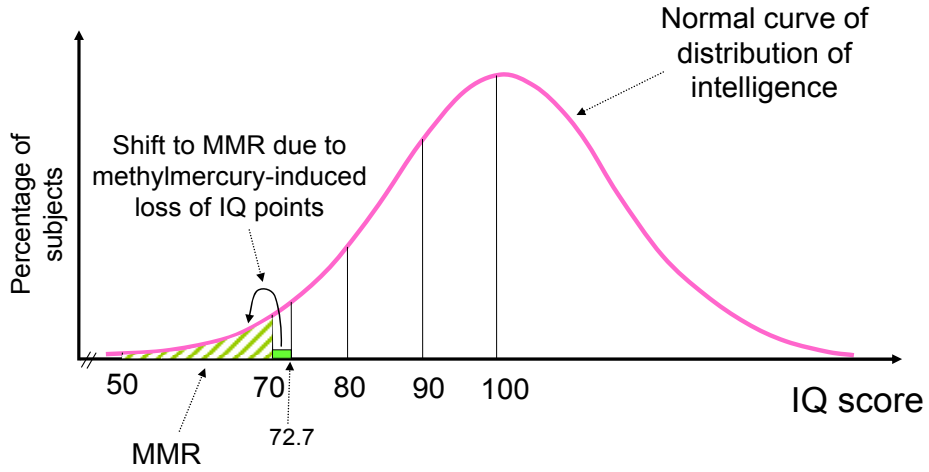
Table 2 Incremental IQ loss and percent of population shifted to MMR

Hair mercury interval (μg/g)	IQ point loss from exposure	IQ range for which exposure would result in MMR	Percent of population shifted to MMR
0–2	0.18	70.00 - 70.18	0.05
2–4	0.54	70.00 - 70.54	0.22
4–6	0.90	70.00 - 70.90	0.34
6–8	1.26	70.00 - 71.26	0.46
8–10	1.62	70.00 - 71.62	0.66
10–12	1.98	70.00 - 71.98	0.79
12–14	2.34	70.00 - 72.34	1.01
14–16	2.70	70.00 - 72.70	1.16
16–18	3.06	70.00 - 73.06	1.31
18–20	3.42	70.00 - 73.42	1.56

[a] Based on a normal distribution

For example, prenatal exposure to 15 µg/g maternal hair mercury falls into the 14–16 µg/g exposure interval, which results in a 2.7 point IQ loss (Table 2). A 2.7 point IQ loss would shift 1.16% of the infants in the IQ range of 70 - 72.7 points into the MMR range. This shift to MMR is illustrated in Fig. 2.

Figure 2 Shift to MMR as a result of methylmercury-induced IQ loss



Adapted from: Fewtrell et al. 2003

To estimate the incidence of the MMR shift in a population, the proportion of the population with mercury exposure in each interval must be estimated from the population mean and standard deviation. A brief discussion of these methods is provided below. The Mercury Spreadsheet (available by request, see Annex 5) includes a datasheet programmed to estimate the incidence rate of MMR with only the population mean and standard deviation hair mercury concentrations as input.

In populations with high mercury exposure, hair mercury levels are assumed to be normally distributed. The Microsoft Excel function NORMDIST[1] (Microsoft Corporation, Redmond, Washington, U.S.A) is used to determine the proportion of the population above a given hair mercury concentration. The syntax for this function is **NORMDIST (*x*, µ, σ, cumulative)**. The function returns the probability that the observed value of a normal random variable with a mean of mu (µ) and a standard deviation of sigma (σ) will be less than or equal to *x*. The last argument in the function is set to true, or 1, to obtain the cumulative probability. Thus, 1 - NORMDIST (*x*, µ, σ, 1) calculates the cumulative proportion of a population above the lower bound (*x*) of a given mercury interval.

[1] Additional information can be obtained from the "Help" function in Microsoft Excel.

For example, in a population with a mean hair mercury concentration of 2.5 μg/g and a standard deviation of 3.5 μg/g, the proportion with hair mercury concentrations above 6 μg/g can be calculated using the NORMDIST function:

$$n = 1 - \text{NORMDIST}(6, 2.5, 3.5, 1)$$

The output of this function is 0.1586, meaning that 15.86% of the population have hair mercury levels above 6 μg/g. (This method is also used to calculate the proportion of the population with mercury levels greater than 10 μg/g, at which there is a 1.98 point IQ loss. This proportion is an output of the Mercury Spreadsheet.)

To determine the percentage of the population in the 6–8 μg/g mercury exposure interval, the formula is repeated using the upper bound ($x = 8$). The output of this calculation, 0.0580, reveals that 5.80% of the population has mercury levels greater than 8 μg/g. Subtracting the proportion of the population with mercury levels greater than the upper bound from the proportion with mercury levels greater than the lower bound reveals that about 10% of the population is exposed to mercury levels between 6 and 8 μg/g ($0.1586 - 0.0580 = 0.1006$).

The 6–8 μg/g mercury exposure interval is associated with an IQ deficit of 1.26 IQ points (Table 2). Thus, the rate of a 1.26 IQ point deficit per 1000 infants is calculated by multiplying the proportion of the population in the interval by 1000 ($0.1006 \times 1000 = 100.6$). This rate is then multiplied by the proportion of the population that would be shifted to MMR given an IQ deficit of 1.26 points, which was determined to be 0.46% (Table 2). This calculation, $0.1006 \times 0.0046 = 0.4628$, reveals that the incidence rate for MMR among infants in the 6–8 μg/g exposure interval is 0.4628 per 1000 infants. The total MMR incidence rate is estimated by summing the rates for each interval.

6.2 Disease burden in DALYs

The incidence rate can be used to estimate disability-adjusted life years (DALYs) lost due to methylmercury-induced MMR. DALYs are defined as "a health gap measure that combines both time lost due to premature mortality and non-fatal conditions" (WHO, 2001a). Because methylmercury-induced MMR is not associated with premature mortality, DALYs for this outcome are based solely on healthy years lost due to disability (YLDs). This section briefly describes the parameters required to calculate DALYs; detailed information on DALY methodology is available elsewhere (WHO, 2001a).

The following parameters are used to calculate DALYs lost due to methylmercury-induced MMR (described in further detail below). Values used in this analysis are in parentheses:

- age weight (full age weights);
- discount rate (3%);
- MMR incidence rate (calculated using the methods described above);

- disability weight (0.361):
- disease duration, equivalent to life expectancy (80 years for males, 82.5 years for females);
- number of infants born in the year of interest.

Age weighting reflects societal preferences for years of healthy life lived at different ages and assigns less value to years lived at younger and older ages than to other ages. Age weights range from 0 (no age weights) to 1 (full age weights). This report uses full age weights, but DALYs can be computed with other age weights or none at all.

The DALYs reported in this study are calculated using a 3% discount rate per year for years of life lost in the future. Discounting, often used in economic analyses, assigns less value to future years lost than to years lost in the present. WHO is currently re-evaluating the standard discount rate of 3% and whether discount rating should be applied at all. If preferred, other discount weights can be used or DALYs can be calculated without age discounting.

Disability weights quantify societal preferences for different health states as compared to optimal health. Because no disability weight has been developed for methylmercury-induced MMR, this document uses the disability weight for lead-induced MMR (0.361) (Mathers et al., 2003).

Since an infant born with an IQ below 70 will always be in the MMR range, the disease duration for MMR is equal to average life expectancy. Persons with moderate or severe mental retardation are known to have decreased life expectancy (Bittles et al., 2002; Eyman et al., 1990; Patja et al., 2000; Whalley and Deary, 2001), but studies are conflicted on whether MMR is associated with shorter lifespan. A longitudinal cohort study reported that Scottish students with a 15 point lower IQ at age 11 had decreased survival 65 years later (RR = 0.79, 95% CI: 0.75–0.84) (Whalley and Deary, 2001). A prospective cohort study in Finland found that life expectancy for people with mild intellectual disabilities did not differ from the general population at the 35-year follow-up (Patja et al., 2000). Western Australians with mild intellectual disability had an average life expectancy of 74.0 years compared to 67.6 and 58.6 years for moderate and severe forms, but there was no comparison group without intellectual disability (Bittles et al., 2002). Even in studies for which MMR has been associated with decreased life expectancy, it is unknown whether the reduction is due to MMR itself or to a condition associated with MMR. Furthermore, the studies referenced above were conducted in developed countries; less is known about the survival of persons with MMR in developing countries. Because the effect of methylmercury-induced MMR on lifespan is uncertain, this guide calculates DALYs with the standard expectancies of 80 years for males and 82.5 years for females.

DALY calculations also require population size data to determine the number of DALYs lost. For methylmercury-induced MMR, the population data required is the number of infants born in the year of interest. Caution should be taken in applying the incidence rate to years distant from the year that the exposure information was determined, since many factors may lead to changes in mercury levels over time (e.g. consumption advisories or recommendations, seafood availability, industrial activity, environmental contamination).

The Mercury Spreadsheet is programmed with the functions needed to derive the incidence rate, the number of DALYs lost, and rate of DALYs per 1000 attributable to methylmercury-induced MMR (see Annex 5).

7. Example disease burden estimate

This section provides an example of how to combine exposure information with data on methylmercury-related IQ deficits to obtain the population incidence rate for MMR and the disease burden in DALYs.

The steps to determine the MMR incidence rate are summarized as follows:

1. collect data (mean and standard deviation) on mercury concentrations in the population;
2. convert blood, cord-blood, and dietary measurements into hair concentrations;
3. determine the proportion of the population within each mercury exposure interval (from Table 2);
4. for each interval, multiply the rate of IQ loss per 1000 infants by the percent of a normal population that would be shifted to MMR (from Table 2);
5. sum the results to obtain the incidence rate for MMR.

These steps are illustrated in the example below and the calculations are shown in the Mercury Spreadsheet (see Annex 5).

7.1 Biomarker conversions

To estimate disease burden, it may be necessary to convert blood, cord-blood, or dietary mercury levels into hair mercury concentrations. Section 5.1 discusses the relationships between these biomarkers and provides a dietary intake model and ratios for converting blood and cord-blood levels into hair concentrations. Formulas for these calculations are provided in the Mercury Spreadsheet (see Annex 5).

7.2 Calculating the population at risk

The first step in estimating incidence of MMR is to use the mean and standard deviation hair mercury concentrations to determine the proportion of the population at risk. Consider a hypothetical population of subsistence fishers, population X, with a mean hair mercury concentration of 4.6 μg/g and a standard deviation of 2.25 μg/g.

As mentioned earlier, hair mercury concentrations are normally distributed in a population. The mean mercury concentrations and standard deviation are entered in the 1 – NORMDIST function described in Section 6.1, and the proportion of the population with mercury levels greater than the lower bound of each given interval is calculated (Table 3).

Table 3 Proportion above lower bound of each hair mercury interval

Hair mercury concentration (μg/g)	Proportion
0 μg/g	1.0000[a]
2 μg/g	0.8761
4 μg/g	0.6051
6 μg/g	0.2669
8 μg/g	0.0654
10 μg/g	0.0082
12 μg/g	0.0005
14 μg/g	0.0000
16 μg/g	0.0000
18 μg/g	0.0000
20 μg/g	0.0000

[a] 100% of the population is assumed to have levels greater than 0

The table shows that 0.82% of the population has mercury levels greater than 10 μg/g, the level at which infants will sustain approximately a 2 point IQ deficit.

To determine the proportion of women within each mercury exposure interval (0–2 μg/g, 2–4 μg/g, etc.), the proportion corresponding to the upper bound of each interval is subtracted from the lower one. Since IQ deficits in infants are based on the hair mercury concentrations of their mothers, the proportions of women within each hair mercury interval represent the proportion of infants at risk. Thus, the proportions in each interval are multiplied by 1000 to give the rate of IQ loss per 1000 infants.

For example, the proportion of women who have hair mercury concentrations in the 0–2 μg/g exposure interval is 1.0000 – 0.8761 = 0.1239. Multiplying this proportion by 1000 gives the rate of IQ loss, which is 123.93 per 1000 infants in the 0–2 μg/g interval. The IQ loss associated with prenatal exposure to 0–2 μg/g is 0.18 IQ points (from Table 2). The number of IQ points lost and the rate of IQ loss per 1000 infants are presented for each exposure interval in Table 4.

Table 4 Rate of IQ loss per 1000 infants in each exposure interval

Hair mercury interval (μg/g)	IQ loss (points)	Rate of IQ loss per 1 000 infants
0–2	0.18	123.93
2–4	0.54	270.93
4–6	0.90	338.24
6–8	1.26	201.52
8–10	1.62	57.18
10–12	1.98	7.69
12–14	2.34	0.49
14–16	2.70	0.01
16–18	3.06	0.00
18–20	3.42	0.00

7.3 Estimating MMR incidence

The final step in the MMR incidence calculation is converting IQ loss into a rate of MMR per 1000 infants. The rate of IQ loss in each exposure interval is multiplied by the percent of a normal population that would be shifted into the MMR range (from Table 2). Summing the values for each exposure interval yields the total rate of MMR per 1000 infants.

For example, the incidence rate of methylmercury-induced MMR in population X is calculated as:

I(MMR) = (123.93 infants/1000 × 0.0005) + (270.93 infants/1000 × 0.0022) + (338.24 infants/1000 × 0.0034) + (201.52 infants/1000 × 0.0046) + (57.18 infants/1000 × 0.0066) + (7.69 infants/1000 × 0.0079) + (0.49 infants/1000 × 0.0101) + (0.1 infants/1000 × 0.0116)

= 3.18 infants per 1000 infants in population X

Exposure to methylmercury is therefore expected to result in 3.18 cases of MMR for every 1000 infants born each year in population X. The MMR incidence rate can also be calculated by entering the population mean and standard deviation into the Mercury Spreadsheet (see Annex 5).

7.4 Estimating DALYs

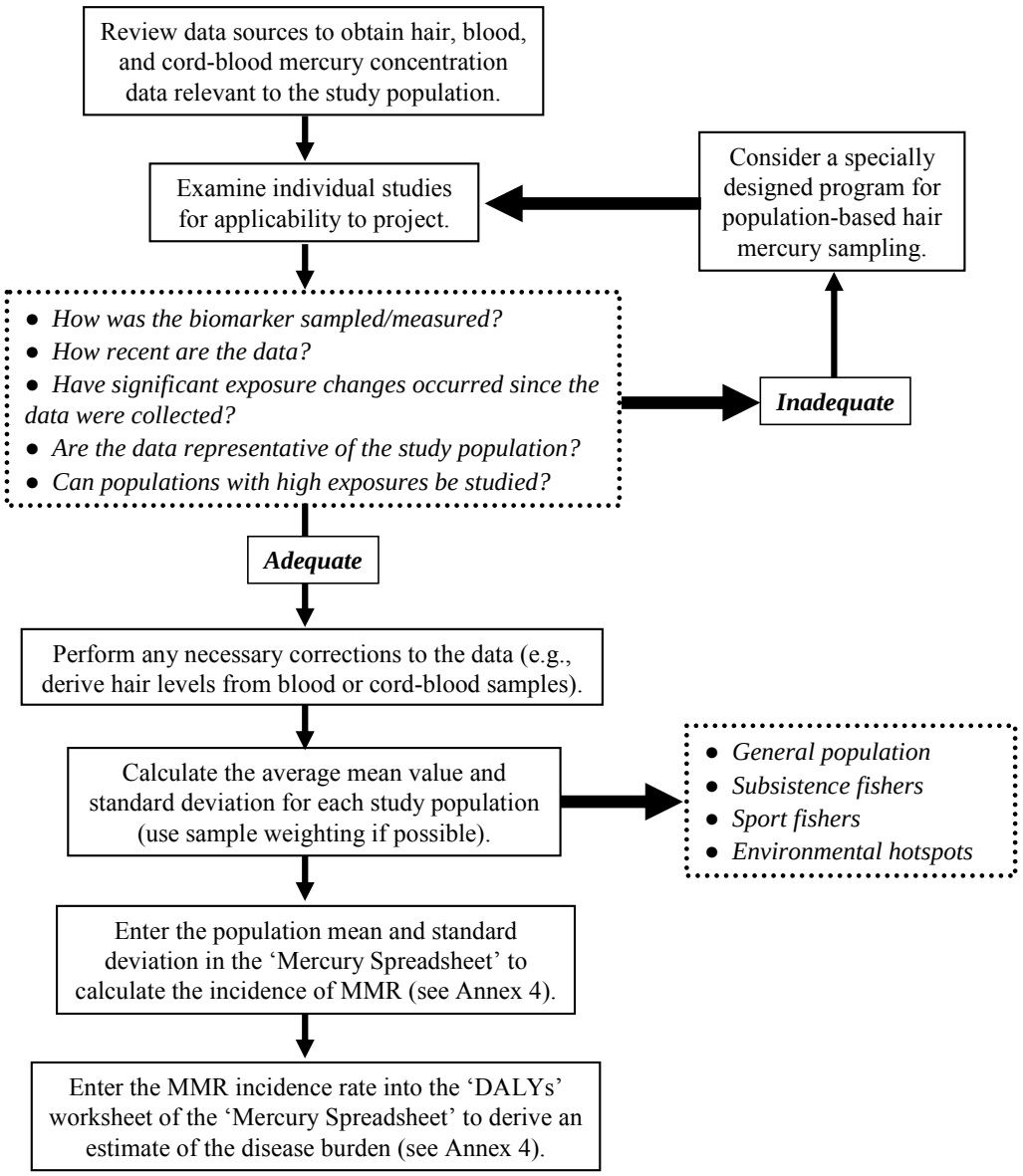
The disease burden can also be quantified using disability-adjusted life years, which take into account the severity and length of the illness. The disease burden in DALYs can be estimated by entering the MMR incidence rate and the number of infants born in the year of interest into the 'DALYs' worksheet of the Mercury Spreadsheet (see Annex 5).

In population X, 100 000 infants were born in year Y. Inputting these data and the incidence rate from Section 7.4 into the Mercury Spreadsheet reveals that 3794 DALYs were lost due to methylmercury-induced MMR in population X in year Y. If the mercury exposure observed during year Y continues over a five-year period and the number of births per year remains stable, methylmercury exposure would result in a loss of 18 971 DALYs.

7.5 Summary of steps for estimating disease burden

The process for estimating disease burden is summarized as a flowchart in Fig. 3.

Figure 3 Flowchart for estimating the disease burden of methylmercury



8. Burden of disease estimates for selected populations

Methylmercury-induced IQ loss is greatest among populations with high fish or seafood consumption such as subsistence fishing populations. This is particularly true in areas with high environmental mercury exposure such as from industrial or mining operations.

A literature review was conducted to identify studies which measured the distribution of mercury levels in blood, cord-blood, and hair (see Annex 4). For studies that measured mercury in blood or cord-blood, the levels were converted to hair mercury concentrations using the conversion factors provided in Section 5.1. Table 5 provides compiled data on exposure, proportion of infants losing approximately 2 or more IQ points, MMR incidence, and DALYs per 1000 infants for selected populations (i.e. populations with studies on mercury exposure levels in pregnant women or women of childbearing age). See Section 6 for assumptions used in the incidence rate and DALY calculations. The total number of DALYs lost is not reported because the number of infants born per year could not be determined for these population subgroups.

Table 5 Methylmercury exposure, MMR incidence, and DALYs for selected populations

Population (reference)	Mean (SD) hair mercury levels (μg/g)	% of infants losing ≥ 2 IQ points	Incidence of MMR per 1 000 infants	DALYs per 1 000 infants
Brazilian subsistence fishing population near the Tapajós River in a gold mining region of the Amazon (Santos et al., 2002)	16.0 (18.92)	62.44	17.37	202.8
Chinese fish consumers in Wujiazhan, downstream of a methylmercury-polluted river (Zhang and Wang, 2006)	2.92 (11.8)	27.43	5.16	60.6
Columbian fishing village in the San Jorge River basin near local gold mining activities (Olivero et al., 2002)	5.78 (1.21)	0.02	3.89	45.7
Canadian subsistence fishing Nunavik Inuits in the arctic (Muckle et al., 2001)	4.5 (1.9)	0.19	3.09	36.8
Greenland subsistence fishing Inuits in the Disko Bay (Bjerregaard and Hansen, 2000)	3.2 (3.4)	2.28	2.52	29.9
Canadian fish consumers of Asian-Canadian descent in the Great Lakes 'Area of Concern' (Cole et al., 2004)	2.35 (0.55)	0.00	1.76	20.9
Japanese fish consumers in the Akita prefecture (Iwasaki et al., 2003)	2.10 (0.98)	0.00	1.45	17.3
Canadian sport fishers in the Lake St. Pierre region of Quebec (Stamler et al., 2006)	0.68 (0.85)	0.00	0.60	7.2

SD = standard deviation

It is evident from Table 5 that subsistence fishing populations and seafood consuming populations near gold mining activities or industrial pollution sites may have a

significant disease burden due to methylmercury exposure. The estimated incidence rates for mild mental retardation were as high as 17.37 per 1000 infants born, resulting in a loss of 202.8 disability-adjusted life years per 1000 infants. When combined with population data and summed over the years that mercury exposure has occurred, the neurodevelopmental effects of mercury exposure may have a considerable health impact.

9. Uncertainties

Burden of disease estimates derived using the methods provided in this guide are subject to several sources of uncertainty, which are discussed in the following sections.

9.1 Other outcomes

The burden of disease methods provide an estimate based solely on neurodevelopmental effects of methylmercury in prenatally-exposed infants. All health effects of elemental mercury were excluded from the analysis, as were the cardiovascular and neurological effects of methylmercury exposure in adults, for which data were insufficient to quantify relationships between exposure and effect. The combined total health impact of mercury and methylmercury exposure is likely to be greater than that which would be estimated with the methods provided in this document.

9.2 Model parameters

Health outcome

IQ is a useful measure for assessing the effects of methylmercury exposure because methods have been established to estimate the educational, occupational, economic, and societal impact of IQ deficits. While lowered IQ is not considered a disease in the traditional sense, it has been associated with diminished academic performance and occupational success. In the case of methylmercury, however, IQ may not reflect the full range of cognitive effects. Axelrad et al. (2007) noted that IQ tests do not assess word retrieval, verbal learning ability, motor skills, and attention/behaviour effects that are impacted by methylmercury exposure. Thus, using IQ as a measure of cognitive deficits may underestimate the true neurodevelopmental impact of exposure.

Background rate of MMR

The susceptibility of individuals and populations to IQ loss is variable and individuals may suffer effects at different levels of mercury exposure. One source of uncertainty in the burden of disease methodology is that not all populations follow the standard IQ distribution. For example, regions differ in several risk factors and diseases that affect the rate of MMR, such as anaemia, meningitis, pertussis, Japanese encephalitis, ascariasis, trichuriasis, hookworm infection, cretinoidism, and cretinism due to iodine deficiencies (WHO, 2001b). In populations where the rate of MMR is already high due to endemic diseases, the impact of methylmercury could be substantially greater than estimated in this guide. If a population-specific distribution of IQ is available, this can be applied instead of the standard curve to obtain a more accurate estimate.

Mercury measurements

Hair mercury collection is subject to a variety of procedural and analytical errors that can introduce substantial uncertainty. The techniques described in Annex 2 should be followed to minimize imprecision when collecting new data. Measurements derived from the literature should be reviewed for quality; when sampling and quality-control

procedures are not described the associated uncertainty may be significant. Using sound study design, sampling diverse populations, and implementing quality-control procedures will help make the estimate more accurate and representative.

Conversion factors

Central estimates of the ratios between blood and hair and blood and cord-blood are provided to convert blood and cord-blood levels into hair mercury concentrations. However, relationships between these biomarkers have been shown to vary widely between individuals and populations. The recommended conversion factor for converting blood to hair is 250, but values ranging from 140 to 370 have been observed. Similarly, the cord-blood to blood mercury relationship is based on a meta-analysis that incorporated ratios ranging from 1.09 to 2.32. There is also considerable uncertainty in the relationship between dietary intake and blood mercury levels. Canuel et al. (2006) constructed a model using pharmacokinetic parameters from NRC (2000), which are similar to those in the WHO model, and found that actual hair mercury concentrations were as much as 14 times less than predicted. Therefore, it is emphasized that the application of these conversion factors may not result in an accurate representation of the hair concentrations in the sampled population and direct sampling of hair levels is recommended.

Dose–response

The dose–response relationship between methylmercury and IQ is based on a meta-analysis of various cognitive test results from the three major prospective epidemiologic cohort studies on methylmercury and neurodevelopment (Axelrad et al., 2007). While the Faroe Islands data suggest that the dose–response curve may be supra-linear at low exposure, the NRC concluded that "an additive (linear) or perhaps sublinear model is the most justifiable from a biological perspective" (NRC, 2000). In addition, the New Zealand and Seychelles data have linear dose–response curves. Based on this information, Axelrad et al. chose a linear model. If in fact there is a supra-linear effect at low doses, the Axelrad et al. dose–response relationship would underestimate the effect of methylmercury on IQ.

Threshold

The burden of disease estimate in this guide is based on the linear non-threshold approach described by Axelrad et al. (2007). Axelrad et al. chose a no threshold approach based on the US EPA's statement that "no evidence of a threshold arose for methylmercury-related neurotoxicity within the range of exposures in the Faroe Islands study" (US EPA, 2002). However, the minimum maternal hair mercury concentration in the Faroes study was 0.2 μg/g (Budtz-Jorgensen et al., 2004b) and it is unknown if effects occur below this level. In the methods used to estimate burden of disease, any exposure above 0 μg/g results in at least a 0.18 IQ point loss, essentially shifting the population IQ down by 0.18 points and resulting in a minimum incidence rate of 0.5 cases of MMR per 1000 infants. The US EPA reference dose (RfD) of 0.1 μg/kg/day and the WHO provisional tolerable weekly intake (PTWI) of 1.6 μg/kg bw indicate that there is a level of exposure below which adverse effects are unlikely (US EPA, 2002; WHO/IPCS, 2004). If indeed there is a threshold, the methods in this guide may

overestimate the burden of disease from methylmercury-induced MMR in populations with low mercury exposure.

Incremental approach

Another source of uncertainty is the use of exposure intervals to estimate IQ deficits. The approach provided in this document assumes a uniform distribution of hair mercury concentrations across the exposure interval. If the hair mercury concentrations tend to be at the lower end of each exposure interval, the estimated disease burden would be an overestimate of the true burden. Conversely, the estimated disease burden would be an overestimate if the hair mercury concentrations tend to be at the upper end of each exposure interval.

DALYs

The strengths and limitations of using DALYs in burden of disease estimates have been discussed elsewhere (Cohen, 2000; Barker and Green, 1996; Murray and Lopez, 1997; WHO, 2001a). While DALYs have been criticized for being based on social and economic value judgments (e.g. age-weighting, age discounting, disability weights), DALYs have also been recognized as a useful and effective decision-making tool, especially in the absence of other data. A benefit of using DALYs in burden of disease estimates is that, in contrast to mortality-based measures, DALYs incorporate the impact of morbidity in the population. This is particularly relevant in the case of methylmercury-induced MMR, which is not associated with excess mortality.

Disability weight

Because no disability weight has been developed for methylmercury-induced MMR, this guide calculates DALYs using the disability weight for lead-induced MMR. It is reasonable to expect that the social preference for methylmercury-induced MMR does not differ substantially from social preference for lead-induced MMR.

Life expectancy

Disease duration for MMR is defined as the average life expectancy since the effects of MMR are life long. There is conflicting evidence on whether persons with MMR have reduced life expectancy and it is unknown if methylmercury-induced MMR has an effect on lifespan. Although this guide calculates DALYs with standard life expectancies, it may be appropriate to use reduced life expectancies if data become available.

9.3 Quantitative estimation of uncertainty

The methods in this guide provide a best estimate of methylmercury-related burden of disease; however, there are uncertainties in the estimate as described above. Monte Carlo analysis is a systematic approach for addressing uncertainty and is defined as "a repeated random sampling from the distribution of values for each of the parameters in a calculation (e.g., lifetime average daily exposure), to derive a distribution of estimates (of exposures) in the population" (US EPA, 1992). If the available data do

not contain the necessary input parameters for Monte-Carlo analysis, the alternative values in Table 6 can be used in the Mercury Spreadsheet to provide a less systematic indication of the uncertainty of disease burden estimate.

Table 6 Values for uncertainty analyses

Parameter	Best estimate	Alternative values
Mean IQ	100	Population-specific mean IQ
Exposure	Mean	95% confidence limits of the mean
Dose–response relationship	0.18	0.012 IQ points per μg/g (lower 95% CI) 0.387 IQ points per μg/g (upper 95% CI)
Blood: hair ratio	250	140–370, or value indicated by population data
Cord-blood: blood ratio	1.7	1–2.3, or value indicated by population data
Relationship between dietary intake and blood	Dietary intake model	Divide dietary intake model output by 14
Threshold	None	US EPA RfD (~0.94 μg/g in hair) WHO PTWI (~2.15 μg/g in hair)

* US EPA RfD and WHO PTWI were estimated as levels in hair using the dietary intake model described in WHO/IPCS, 2004 and assuming a hair to blood mercury ratio of 250

9.4 Beneficial nutrients in fish and seafood

Another source of uncertainty in the burden of disease estimate for methylmercury is concomitant exposure to nutrients in fish and shellfish. Because uptake of methylmercury is almost exclusively through consumption of seafood, the health benefits of protein, vitamin D, selenium, omega-3 polyunsaturated fatty acids, and other micronutrients should also be considered. Developmental exposure to the omega-3 fatty acids DHA and EPA have been associated with lengthened gestation time, improved visual function, and increased cognition in infants (IOM, 2006). A pooled analysis that quantified the benefit of DHA in terms of IQ estimated that every 100 mg/day increase in maternal DHA consumption increases child IQ by 0.13 points (Cohen et al., 2005b). Thus, the effects of fish consumption on IQ depend on the fat content of the fish consumed, with non-fatty, carnivorous fish posing a greater risk than oily or fatty fish high in omega-3 fatty acids and low in mercury. The disease burden methodology is based on dose–response data from studies of infants exposed to methylmercury from seafood consumption. Although these studies may inherently account for some beneficial effects of omega-3 fatty acids, effects on IQ may be influenced by species differences in omega-3 content. Furthermore, seafood species consumed by the mothers in those studies, such as pilot whale, may differ from those consumed by populations for which the disease burden is being estimated. More research is needed to characterize the relationship between the effects of omega-3 fatty acids and methylmercury on IQ before it can be incorporated into a burden of disease study.

10. Research needs and recommendations

Elemental mercury exposure is known to be toxic at high doses, but more data are needed to develop methods to quantify the disease burden. The probability of developing tremor, erethism, and proteinuria is "high" at urinary mercury levels of 100 µg/g creatinine, but exposure-response relationships and disability weights for these outcomes are not available (WHO/IPCS, 1991). Development of disability weights for such conditions and additional, high-quality studies are necessary to conduct a quantitative assessment of the health impact of elemental mercury in high risk populations (e.g. small scale mining communities).

Although this assessment focused on methylmercury-induced IQ deficits in infants, methylmercury has also been associated with neurological and cardiovascular effects in adults. More studies are needed to investigate these effects. If methylmercury is associated with cardiac toxicity, the relationship between concomitant exposure to methylmercury and omega-3 fatty acids must also be evaluated.

While the body of evidence is strongest for the neurodevelopmental toxicity of methylmercury, uncertainties regarding this association remain, particularly at low doses. Evidence that omega-3 fatty acids in fish promote cognitive development was not considered in this analysis. The relationship between the cognitive effects of omega-3 fatty acids and methylmercury must be further characterized to create a burden of disease estimate that considers the risks and benefits of fish consumption rather than the risks of methylmercury exposure alone.

Large data gaps exist regarding the omega-3 fatty acid and methylmercury content of fish and shellfish species throughout the world. Data on the frequency, amount, and species of seafood consumed in different regions is also needed. These data are critical for determining the specific risks and benefits of fish consumption in local populations.

Global or national environmental burden of disease estimates may be difficult to conduct due to the lack of representative exposure data for countries and regions. Most of the data on mercury levels pertain to populations with elevated exposure. While these data are essential for estimating the disease burden for high risk groups, information on general population exposure is lacking and studies that measure general population mercury levels, particularly among women of childbearing-age, are needed.

Finally, the use of DALYs to estimate the burden of disease of environmental chemicals is limited by the lack of disability weights for relevant health outcomes. Disability weights must be determined for additional diseases and symptoms to fully characterize the disease burden from mercury.

11. Disease burden and policy

Creating policy decisions based on burden of disease estimates requires careful consideration of the complex balance between the risks of mercury exposure and the benefits of fish consumption within the target population.

Methylmercury exposure is almost exclusively from fish and seafood, which also contain protein, vitamin D, selenium, and other micronutrients. Fish and shellfish are also major sources of omega-3 fatty acids such as DHA and EPA. Although the benefit of omega-3s in adults is as yet uncertain, they may decrease the risk of coronary heart disease, and there is evidence that adults who eat fish have reduced risk of heart disease (IOM, 2006). DHA and EPA are more strongly associated with health benefits in developing infants, including lengthened gestation, improved visual acuity, and increased cognitive development (IOM, 2006). It is therefore necessary to consider the alternative impacts of recommendations made based on the methylmercury burden of disease estimate. Reducing mercury levels in subsistence fishing populations is also complicated by the reliance of such groups on fish as a primary source of protein. Therefore, recommendations should be tailored to the risk profile of the target population to ensure the greatest health gain.

The risks and benefits of fish consumption depend greatly on the species and amount of fish consumed. Women of childbearing age and children should avoid large predatory, non-fatty fish (e.g. shark, swordfish, tilefish, king mackerel) (IOM, 2006). On the other hand, it may be prudent to encourage consumption of fish high in omega-3 fatty acids and low in methylmercury (e.g. salmon, oysters). If available, country- or region-specific data on the mercury and omega-3 fatty acid levels in fish should be used to develop recommendations. Mercury concentrations in some seafood species are available for several countries (UNEP, 2002). In the absence of national data, information compiled in the United States may be helpful to guide consumers in some regions (see Annex 3 for mercury and omega-3 fatty acid levels in US seafood).

Ideally, the burden of disease from mercury should be reduced by lowering the amount of mercury in the environment rather than by managing fish consumption. This would generate the greatest health benefit by eliminating contaminants in fish and increasing their overall benefit to human health. While global partnerships are working towards this goal, nations can minimize the impact of methylmercury toxicity by helping high risk populations make informed choices on the type and amount of fish they eat.

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Annex 1 List of meeting participants

The following is a list of participants in the Informal preparatory meeting for the Chemical Task Force of the Foodborne Disease Epidemiology Reference Group (FERG), held in Geneva on 29 June 2007.

- Dr Janis BAINES, Food Standards Australia and New Zealand.
- Dr David BELLINGER, Neuroepidemiology Unit, Children's Hospital, Farley Basement, USA.
- Dr Diane BENFORD, Food Standards Agency, London, UK.
- Dr Mike BOLGER, Division of Risk Assessment, Food and Drug Administration (FDA), USA.
- Dr Herman GIBB, Sciences International Inc., Alexandria, USA.
- Dr John LARSEN, National Food Institute, Technical University of Denmark.
- Professor Rolaf van LEEUWEN, Centre for Substances and Integrated Risk Assessment, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands.
- Dr Andrew RENWICK, Clinical Pharmacology Group, University of Southampton, UK.
- Dr Josef SCHLATTER, Food Toxicology Section, Swiss Federal Office of Public Health, Zürich, Switzerland.

Observers

- Dr Robert BLACK, John Hopkins University, Baltimore, USA.
- Ms Jessie POULIN, Sciences International Inc., Alexandria, USA.

WHO Secretariat

- Dr James BARTRAM, Water, Sanitation and Health.
- Dr Cynthia BOSCHI PINTO, Newborn and Child Health and Development.
- Dr Tanya KUCHENMÜLLER, Food Safety, Zoonoses and Foodborne Diseases.
- Dr Gerry MOY, Food Safety, Zoonoses and Foodborne Diseases.
- Dr Claudia STEIN, Food Safety, Zoonoses and Foodborne Diseases.
- Dr Kurt STRAIF, International Agency for Cancer Research (IARC), Lyon.
- Dr Angelika TRITSCHER, International Programme on Chemical Safety.

Annex 2 Measuring hair mercury concentrations

Hair sampling is the preferred method for measuring methylmercury concentrations, as obtaining hair samples is minimally invasive, reduces the risk of disease transmission, and does not require medical supervision (NRC, 2000). There are also fewer cultural issues in obtaining hair samples, although in some regions of Africa and Latin America hair may be of superstitious or magical significance (Veiga and Baker, 2004). Other factors to consider include sampling of persons who are bald or have short hair, and the use of certain hair treatments (artificial waving may reduce mercury content while mercury-containing soaps may increase it).

Before conducting hair sampling, describe the goal of the research to each donor and obtain informed consent. Stress that the samples will only be used for this purpose and that there is no consequence for choosing not to participate. Be sure to follow any other local guidelines on research ethics. Administer a questionnaire to gather demographic and exposure information (e.g. age; sex; species, amount, and frequency of fish consumption; possible sources of elemental mercury exposure).

Samples should be collected from the occipital region of the head and hair should be cut with scissors as close to the hair root as possible. The National Institute for Minamata Disease of Japan recommends cutting at least twenty 10 cm long strands; if hair is longer than 10 cm, the portion of the hair furthest from the root can be discarded (Nakamura, 2003). If hair is shorter than 10 cm, more strands are required for laboratory analysis. One end of the hair sample should be tied, stapled, or knotted to differentiate the proximal and distal ends, especially if time sequencing is to be conducted (Veiga and Baker, 2004). The sample should then be placed in a sealed envelope or plastic bag until laboratory analysis.

If the population is primarily exposed to mercury through fish consumption, laboratory analyses for total mercury are acceptable. Samples from populations exposed to mercury vapour should be analysed specifically for methylmercury content due to external contamination. A variety of techniques have been used to analyse mercury in hair and there is no international standard. Common methods include gas-liquid chromatography (Veiga and Baker, 2004), flameless atomic absorption spectrometry (Nakamura, 2003), cold vapour atomic absorption spectroscopy (NRC, 2000), and cold vapour atomic fluorescence spectrometry (CDC, 2006). If one of the preceding techniques is chosen, segmental analysis can be conducted to obtain exposure levels over time. This is done by cutting the hair samples into 1.1 cm segments, which correspond to about a month of hair growth (NRC, 2000). A non-segmental method of time sequencing analysis is X-ray fluorescence (XRF), which continuously measures mercury levels along a single strand of hair. The NRC suggests using XRF analysis because it provides the most detailed information on magnitude and timing of exposure (NRC, 2000).

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Annex 3 Mercury and omega-3 fatty acid content of seafood

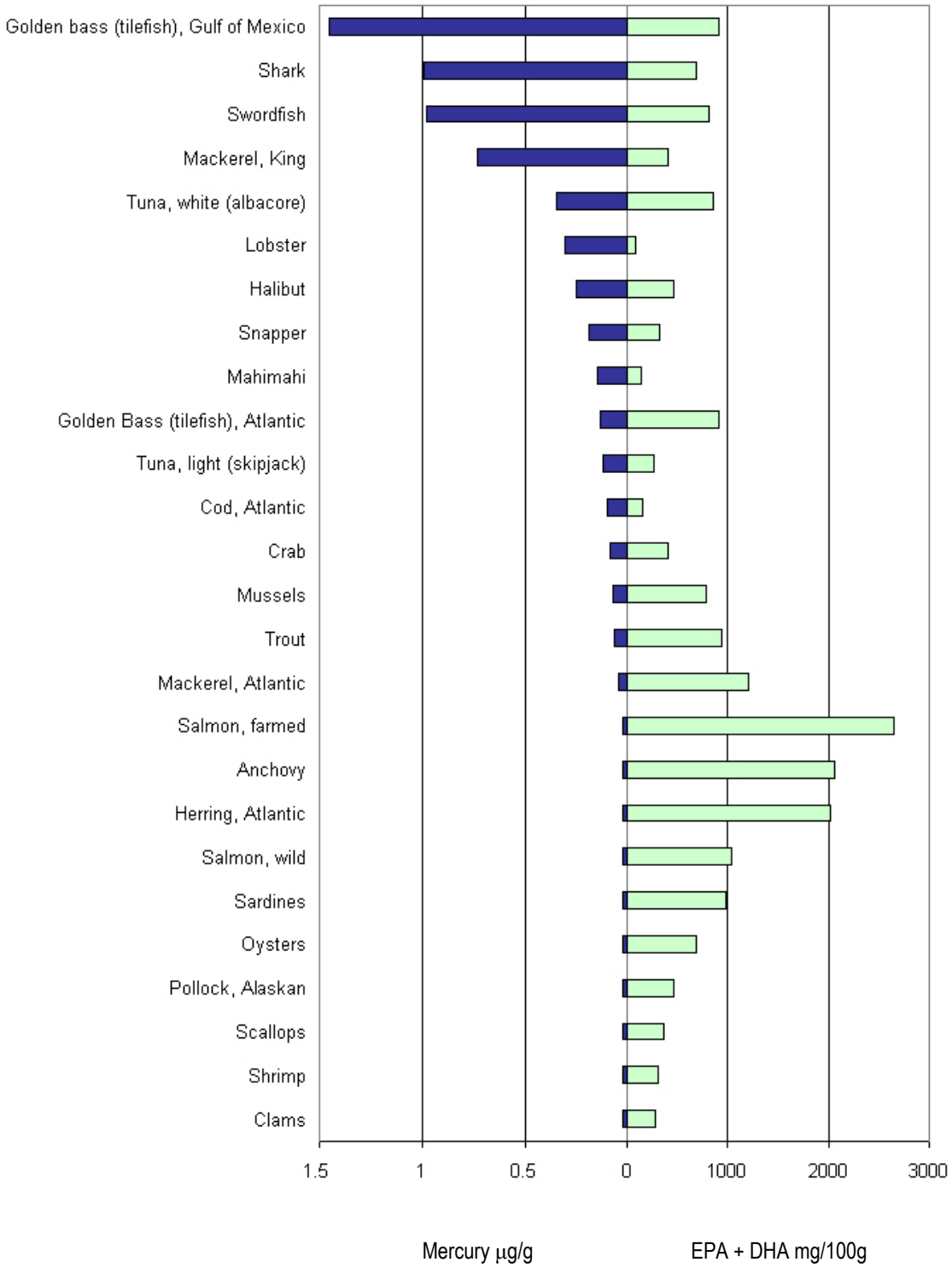
The simplest way to minimize the burden of disease from methylmercury is to consume seafood low in mercury. However, it is also wise to consume fish and shellfish that contain high levels of omega-3 fatty acids. The table below provides the mercury and combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) content of several seafood species. While these data are based on levels in US seafood, they may be helpful to guide recommendations if local data are unavailable. This table is also represented graphically in Fig. A3–1, with mercury levels of < 0.05 and < 0.15 represented as half the detection limit.

Table A3 –1 Mercury and omega-3 fatty acid (DHA + EPA) content of seafood

Species	Mercury µg/g (ppm)	EPA + DHA mg/100 g (3.5 oz)
Anchovy	< 0.05	2055
Catfish, farmed	< 0.05	177
Cod, Atlantic	0.1	158
Golden bass (tilefish), Gulf of Mexico	1.45	905
Golden Bass (tilefish), Atlantic	0.14	905
Halibut	0.25	465
Herring, Atlantic	< 0.05	2014
Mackerel, Atlantic	0.05	1 203
Mackerel, King	0.73	401
Mahimahi	0.15	139
Pollock, Alaskan	< 0.05	468
Salmon, farmed	< 0.05	2 648
Salmon, wild	< 0.05	1 043
Sardines	< 0.05	982
Shark	0.99	689
Snapper	0.19	321
Swordfish	0.98	819
Trout	0.07	935
Tuna, light (skipjack)	0.12	270
Tuna, white (albacore)	0.35	862
Clams	< 0.05	284
Crab	0.09	413
Lobster	0.31	84
Mussels	< 0.15	782
Oysters	< 0.05	688
Scallops	< 0.05	365
Shrimp	< 0.05	315

(from Mozaffarian and Rimm, 2006)

Figure A3 –1 Mercury and omega-3 fatty acid (DHA + EPA) content of seafood



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Annex 4 Subpopulation mercury levels

Table A4–1 summarizes available methylmercury exposure data from peer-reviewed studies. The table includes surveys of high exposure subpopulations as well as information on general population exposure in countries where data were identified. For areas where mercury data are lacking, the table may be useful to indicate exposure levels in nearby regions or in populations with similar characteristics.

The table is divided by WHO global region (see Table A4–2) and by country. Studies published in English from 1990 forward are included if they contained mean hair, blood, or cord-blood mercury levels. Populations exposed primarily to elemental mercury (i.e. dental amalgam, occupational) are not included. Studies that did not include women are excluded except for countries where only male exposure data were available. All data are represented as hair mercury concentrations using the conversions provided in Section 5.1 [blood mercury levels given in nmol/L were divided by 5 to convert to μg/L, as described in Grandjean et al. (1997)]. Blood mercury levels are reported in addition to hair concentrations when elemental mercury may have contributed significantly to exposure. Because total hair mercury correlates well with methylmercury exposure, all reported levels are total mercury unless otherwise noted (i.e. methylmercury concentrations are used when there is substantial elemental exposure).

Table A4–1 Review of mercury levels by region and country, represented as concentrations in hair (μg/g)

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
AfrD									
Ghana	NR	12–18				X	X	South-west Ghana; small- and large-scale gold mining	Adimado and Baah, 2002
			50	1.61 ± 1.33	0.15–5.86	X	X	Anwiaso, upstream of Ankobra river basin	
			50	0.62 ± 0.41	0.32–2.19	X	X	Sahuma, downstream of Ankobra river basin	
			51	4.27 ± 6.26	0.06–28.3	X	X	Tanoso, upstream of Tano river basin	
			66	1.21 ± 0.65	0.07–3.19	X	X	Elubo, downstream of Tano river basin	
Seychelles	F	P	711	6.8 ± 4.5	0.5–26.7	X		Mothers enrolled in Seychelles Child Development Study	Davidson et al., 1998
AfrE									
Kenya								Lake Victoria region; number of volunteers using European-made mercury-containing skin whitening soaps in parentheses	Harada et al., 2001
	M/F (2)	20–39 (30)	9	1.44 ± 0.95	0.67–3.5		X	Kamuango (0)	
	M/F (4)	7–64 (40)	12	2.09 ± 1.56	0.73–5.6	X		Sori Beach (12)	
	M/F (8)	19–45 (28)	13	4.50 ± 11.5	0.61–42.8	X		Homa Bay (1)	
	M/F (9)	18–87 (39)	19	48.5 ± 206	0.27–900	X		Dunga Beach (1)	
	F	16–39 (28)	12	145 ± 219	1.1–603			Kisumu (city) (6)	
	M/F (27)	7–87	57	1.57 ± 1.30	0.27–6.2			Total not using European skin whitening soaps (weighted mean and SD calculated from reported values)	
South Africa	M	10–34	14			X		KwaZulu-Natal; Zulu speaking fish consumers near mercury processing plant; no subjects or controls were above the limit of detection (0.5 μg/g)	Oosthuizen and Ehrlich, 2001
United Republic of Tanzania	M/F (11)	6–65	29	0.947	0.156–5.433	X	X	Nungwe Bay area of the Lake Victoria goldfields; fish in bay had low methylmercury concentrations	Ikingura and Akagi, 1996
AmrA									
Canada		I	1 109	0.126†	0.029–1.971			Infants born in 10 hospital in Southern Quebec	Rhainds et al., 1999
		I	48	0.27†	0.03–1.62	X		St. Lawrence River; subsistence fishers recruited at delivery from the Sept-Îles regional hospital	Belles-Isles et al., 2002
		I	60	0.13†	0.03–0.59			Sept-Îles and Port-Cartier; recruited at delivery from the Sept-Îles regional hospital	

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	F	P (26.7)	101	0.15		X		South-west Quebec near the St. François and St. Louis lakes; women recruited from prenatal clinics within the Quebec Public Health System, some local fish consumption	Morrissette et al., 2004
	M/F	NR	130	0.83 ± 0.97		X		Quebec near Lake St. Pierre; sport and subsistence fishers	Canuel et al., 2006
	M/F	NR	146	1.20 ± 1.40		X		Quebec; Abitibi, sport and subsistence fishers	
	M/F	NR	118	0.40 ± 0.36		X		Labrador; First Nations people of the Innu community, samples taken during "camp" season when they rely on country foods	
	M/F (23)	> 17	52	0.42 ± 0.15				Bay of Fundy; St. Andrews/St. Stephen	Legrand et al., 2005
	M/F (54)	> 17	91	0.70 ± 0.55		X		Bay of Fundy; Grand Manan, fishing and lobstering community	
	F	P (24.6)	123	4.5 ± 1.9	0.3–14.0	X		Nunavik; Inuit subsistence fishers	Muckle et al., 2001
								Human tissue monitoring program in the North-west Territories	Butler Walker et al., 2006
	F	P (31.5)	134	0.22 ± 0.49	ND-1.05			Caucasian	
	F	P (26.9)	92	0.34 ± 0.40	ND-1.51	X		Dene/Métis	
	F	P (23.6)	31	1.68 ± 4.42	ND-8.48	X		Baffin (Inuit)	
	F	P (23.0)	31	0.53 ± 1.26	0.60–6.07	X		Inuvik (Inuit)	
	F	P (24.9)	17	0.92 ± 1.44	0.60–2.88	X		Kivalliq (Inuit)	
	F	P (26.4)	63	0.86 ± 1.47	ND-3.19	X		Kitikmeot (Inuit)	
	F	18–24	67	2.70	0.50–16.80	X		Arctic Quebec; Randomly selected Inuit households in Nunavik	Dewailly et al., 2001
	F	25–44	131	3.89	0.65–19.85	X			
	F	45–75	85	6.76	2.25–28.00	X			
	M/F (12%)	(45)	60	0.82 ± 2.54		X		Montreal area; eat sport caught fish from the St. Lawrence River ≥ once per week	Kosatsky et al., 2000
	M/F (11%)	(48)	72	0.38 ± 2.28		X		Montreal area; eat sport caught fish from the St. Lawrence River < once per week	
	F	17–64	26	0.33 ± 0.53				Ontario; licensed anglers, non-fish eaters	Cole et al., 2004
	F	17–64	60	0.48 ± 0.45		X		Ontario; licensed anglers in Ontario, fish eaters	
	F	17–64	27	2.35 ± 0.55		X		Ontario; fish consumers in the Great Lakes Area of Concern of Asian-Canadian decent	

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	F	17–64	15	0.55 ± 0.48		X		Ontario; fish consumers in the Great Lakes Area of Concern of Euro-Canadian decent	
	F	20–49	97	0.07 ± 0.01		X		Quebec; consumers of fish from Upper St. Lawrence River Basin lakes	Mahaffey and Mergler, 1998
	F	> 18	52	0.68 ± 0.85		X		Quebec; sport fishers who consume fish from Lake St. Pierre	Stamler et al., 2006
United States of America	F	C, 16–49	1 726	0.20† ± 0.02[se]				National Health and Nutrition Examination Survey (NHANES) 1999–2000	McDowell et al., 2004
	F	C (29.9)	45	0.40				Puerto Rico, north-east	Ortiz-Roque and López-Rivera, 2004
	F	C (31.8)	41	4.40		X		Puerto Rico, island of Vieques where fish is relied on for protein	
	F	P	135	0.55	0.02–2.38			Eastern Massachusetts; women recruited for Project Viva, a prospective pregnancy and child cohort study	Oken et al., 2005
	F	18–92	1 050	0.525	0.012–15.2			Wisconsin; volunteers (ate more fish and had a higher SES than general Wisconsin pop)	Knobeloch et al., in press
	F	P, > 14	1 024	0.29	0.01–2.50			Michigan; women recruited for the Pregnancy Outcome and Community Health study	Xue et al., in press
	M/F	> 5	63	0.64 ± 0.43		X	X	California; Native Americans near an inactive mercury mine; some participants consume fish from local lake	Harnly et al., 1997
	F	P (25.7)	189	0.53 ± 0.07[se]	< 0.2–9.1			New Jersey; women recruited from hospitals, clinics, and physicians offices state-wide	Stern et al., 2001
	M/F (65%)	(41)	311	0.4	NR-2.95	X		Wisconsin, Michigan, and Minnesota; tribal members in Great Lakes region	Dellinger, 2004
	M/F (68.57%)	50–70 (59.32)	474	0.69 ± 0.59	0.0–4.0			Maryland; recruited for the Baltimore Memory Study	Weil et al., 2005
		I	188	0.71 ± 0.50	0.0–2.94			Hawaii; recruited deliveries at Kapiolani Medical Center for Women and Children in Honolulu	Sato et al., 2006
AmrB									
Brazil[4]	F	P, 14–45	75	1.12 ± 1.17	0.05–8.2	X	X	Alta Floresta; near the Teles Pires River in the Southern part of the Amazon Basin	Hacon et al., 2000
	M/F (192)		324	16.0 ± 18.92	4.50–90.40	X	X	Para; Munduruku Indians near the Tapajós River (women aged 14–44 had a mean concentration of 15.7)	Santos et al., 2002
	F	C (26.6)	21	9.39†	5.25–21.00	X	X	Tapajós River; riverside communities	Pinheiro et al., 2005

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	F	P (23.8)	19	8.25†	1.51–19.43	X	X	Tapajós River; riverside communities	
	F	15–40	100	7.4	0.16–62.4	X	X	Porto Velho; urban mothers	Marques et al., in press
Colombia	F	15–69	38	5.78 ± 1.21	NR	X	X	San Jorge River basin; fishing village of Caimito	Olivero et al., 2002
Suriname	M	(26)	16	6.70 ± 3.65	NR	X	X	Djumu; non-mining control group near the Boven Suriname River (study measured blood THg)	de Kom et al., 1998
	M	(27)	25	4.53 ± 2.75	NR	X	X	Sillakreek mining area; small scale miners (study measured blood THg)	
AmrD									
Peru	F	P	131	7.1† ± 2.1	0.9–28.5	X		Máncora; prospective study of Peruvian fish eating population	Marsh et al., 1995 (cited in NRC, 2000)
EmrB									
Islamic Republic of Iran (Islamic Republic of)	F	P (26.9)	348	0.34 ± 0.30	0.0–3.3			Tehran; controls from case-control study of trace metals and preeclampsia	Vigeh et al., 2006
	NR	NR	23	0.99 ± 0.89	0.196–4.27			Postmortem samples collected at random; no information on age, sex, or location	Raie, 1996
Kuwait	M	25–60 (34.9)	100	4.18 ± 3.22	0.025–17.79	X		Fishermen of Egyptian origin in the Doha fishing village	Al-Majed and Preston, 2000
	M	26–35 (30.4)	35	2.62 ± 1.40	0.75–5.21			Controls of Egyptian nationality working at a nearby construction company	
	M/F	2–57	106	4.6 ± 4.8	0.80–25.0			Kuwait residents	Al-Yakoob and Bou-Oyalan, 1994 (cited in Al-Majed, 2000)
EmrD									
Egypt	M/F (25)	28–40 (34.4)	68	0.23 ± 0.06	0.11–0.41			Mansoura; randomly selected hospital staff members	Mortada et al., 2002
Morocco	M/F (80)	> 18 (38.8)	377	2.4 ± 3.5				Rabat; randomly selected from Rabat Transfusion Center (no statistically significant difference between levels in men and women)	Khassouani et al., 2000

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
EurA									
Austria	F	18–65 (42.9)	78	0.63 ± 0.42	0.09–9.97			Vienna; blood donors recruited at the Red Cross, range for males and females combined	Gundacker et al., in press
Croatia	M/F (45)	2–83						Vis; over-sampled the island fishing population	Buzina et al., 1995
			51	4.91 ± 3.15	0.33–16.30	X		Fish consumption < 1 000 g / wk	
			23	6.56 ± 4.67	0.84–19.30	X		Fish consumption 1 000–1500 g / wk	
			17	6.39 ± 3.51	1.30–12.10	X		Fish consumption > 1 500 g / wk	
Denmark	M/F (21)	20–60 (43)	41	0.6‡				Denmark; Danes consuming European food	Pedersen et al., 2005
	M/F (32)	20–60 (43)	53	1.2‡				Denmark; Greenlanders consuming European food	
	M/F (30)	20–60 (39)	45	2.7‡				Greenland; Greenlanders consuming European food	
	M/F (23)	20–60 (42)	47	6.2‡		X		Greenland; Greenlanders consuming traditional foods	
	F	P	180	3.2 ± 3.4	0.5–18.9	X		Greenland; Inuits of five municipalities in the Disko Bay region	Bjerregaard and Hansen, 2000
	F	P	914	4.27		X		Faroe Islands	Grandjean et al., 1997
Finland	M/F (9%)	(48)	11	0.98‡	0.29–1.55			Riihimäki; Workers at hazardous waste treatment plant (increase of 0.35 μg/g since treatment plant opened)	Kurttio et al., 1998
	M/F (64%)	(51)	55	0.40‡	0.09–5.11			Hämeenlinna; controls living 30km from plant	
France	F	> 18	62	0.85 ± 0.50	NR-1.9			Angers; randomly selected from the University Hospital Center of Angers	Khassouani et al., 2000
Germany	M/F	18–69	4 645	0.22				German Environmental Survey 1998 (GerES III); probability sample of 120 locations throughout East and West Germany	Becker et al., 2002
Iceland	NR	NR	62	6.38 ± 8.69	0.88–51.1			Postmortem samples collected at random; no information on age, sex, or location	Raie, 1996
Portugal	F	P	181	10.39	NR-42.61	X		Medeira; coastal village of Camara de Lobos (37% of women had hair Hg concentrations > 10 μg/g)	Renzoni et al., 1998
Sweden	F	P (27‡)	127	0.35‡	0.07–1.5			Uppsala County; recruited at antenatal care clinics	Björnberg et al., 2003

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	F		43	.327‡	0.086–0.960			Southern Sweden; alkaline region	Rosborg et al., 2003
	F		47	.376‡	0.012–3.503			Southern Sweden; acid region	
	F	P (31‡)	112	0.18‡	0.0–0.7			Solna; recruited at first antenatal visit (measured concentrations of MeHg in blood)	Vahter et al., 2000; Ask et al., 2002
	F	19–97	51	1.1		X		Hagfors; angling households near lakes and rivers with mercury (only 12 women were aged < 50)	Johnsson et al., 2004
	F	P (30)	30	0.28 ± 0.16	0.07–0.71			Västerbotten county	Oskarrson et al., 1996
United Kingdom	M/F (53%)	21–63 (32.1)	161	0.57 ± 0.48	0.04–3.86			Scotland; staff and postgraduate students at the University of Glasgow (controls for dentist study)	Ritchie et al., 2002
			70	5.52 ± 5.21				Scotland; postmortem samples collected at random; no information on age, sex, or location	Raie, 1996
	F	P (22.6)	14	0.05 ± 0.03				Mothers delivering at North of England Maternity Hospital who did not have dental amalgams	Lindow et al., 2002
EurB									
Albania	M/F	20–56	25	0.405 ± 0.3	0.195–1.698			Durres and Tirana; controls from study of dental clinic workers	Babi et al., 2000
Poland	M/F (8)	17–90	46	0.379 ± 0.315				Gdańsk region; postmortem samples from people who died suddenly	Hac et al., 2000
EurC									
SearB									
Indonesia	M/F (61.8%)	1–65 (14.7)	68	5.59	0.78–60.86	X		Two islands off Batam; randomly selected indigenous islanders, predominantly fishermen	Foo et al., 1998
	M	40–49	55	3.133 ± 4.697	0.203–19.888			Medan; industrial centre ~30 km from the coast (MeHg concentrations were lower: 0.779 ± 0.498, range: 0.143–2.762)	Feng et al., 1998

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
SearD									
Bangladesh	M	16–69 (34)	219	0.44 ± 0.19	0.02–0.95	X		Cox's Bazar, Chittagon, Dhaka, Mymensingh, Khulna, and Bogra; means for all regions and occupational groups were well below 1 μg/g; fishermen (*n* = 26) had the highest mean (0.63 ± 0.12)	Holsbeek et al., 1996
India	F	20–25	5	0.08 ± 0.03				Central India; controls living > 100 km away from an integrated steel plant in Bhilai who had given birth < 1 week before sample collection. Inorganic mercury contributed to elevated total blood mercury levels in women who had recently given birth and lived in Bhilai (highest mean was 6.3 ± 5.3 μg/L for 35–40 year olds) or worked in the steel plant (highest mean was 31.5 ± 20.2 μg/L for 40–45 year olds)	Sharma and Pervez, 2005
	F	25–30	6	BDL					
	F	30–35	10	BDL					
	F	35–40	9	0.20 ± 0.05					
	F	40–45	5	0.23 ± 0.03					
WprA									
Japan	F	P (30.0)	115	1.624†				All participants	Sakamoto et al., in press
			30	1.453†				Tsushima Islands in Nagasaki Prefecture	
			68	1.954†				Fukuoka City in Fukuoka Prefecture	
			18	2.120†				Katsushika ward of metropolitan Tokyo	
	F	19–20 (19.9)	59	1.51 ± 0.91				Akita; women born in the Akita Prefecture applying for a dietician's license	Ohno et al., in press
	F	0–95	1 666	1.43†	0.00–25.75			Total of 5 districts; samples collected at beauty salons, barbershops, and primary schools; 588 (35%) of the women were between the ages of 16 and 49	Yatsutake et al., 2003
			594	1.23†	0.09–7.33			Minimata	
			327	1.33†	0.14–6.20			Kumamoto	
			209	1.40†	0.26–12.52			Tottori	
			303	1.46†	0.00–8.09			Wakayama	
			233	2.30†	0.14–25.75			Chiba	
	F	32–82	108	2.1 ± 1.1		X		Shiranui Sea, near Minimata Bay; fishermen and their families [men had significantly higher levels (5.0 ± 3.4)]	Harada et al., 1998
	M/F (73)	32–82 (59)	138	3.7 ± 3.0	0.5–22.5	X		Goshonoura	
	M/F (10)	43–75 (59)	19	3.3 ± 2.3	0.9–11.0	X		Ashikita	

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	M/F (4)	54–70 (62)	6	3.0 ± 1.1	2.2–5.1	X		Tanoura	
	M/F (9)	36–78 (62)	11	2.0 ± 1.3	0.7–5.6	X		Tsunagi	
	M/F (12)	33–77 (61)	17	1.9 ± 0.8	0.9–3.8	X		Minimata	
	M	40–49	243	4.624 ± 2.753	0.626–24.644			Tokushima prefecture; methylmercury correlated well with total mercury	Feng et al., 1998
			39	2.758 ± 1.0	1.309–5.642			Mountainous	
			126	4.069 ± 1.533	0.626–9.994			Middle	
			78	6.245 ± 3.717	1.742–24.644	X		Coastal	
	F	25–48 (35.7)	107	2.1 ± 0.98	0.49–5.82	X		Akita Prefecture; women recruited for the Akita cross-sectional study on the effects of prenatal methylmercury exposure on child development (results are presented for women without artificial hair waving)	Iwasaki et al., 2003
	F	12–82 (26.5)	284	2.02				Tokyo and surrounding area (Ibaragi, Chiba, Yokohama, Gunma, and Saitama); volunteer university students and their families	Nakagawa, 1995
	M/F (14)	0–82	35	5.6 ± 3.8				Tokyo; autopsy samples	Suzuki et al., 1993
Singapore	M/F (76.6)	2–77 (20.9)	85	5.92	1.14–35.52			Singaporean Chinese randomly selected from persons living at a housing estate	Foo et al., 1998
WprB									
Cambodia	M/F (50)	1–76	94	7.3 ± 22	0.54–190			Phnom Penh, Kien Svay, Tomnup Rolork, and Batrong; no information on donor selection	Agusa et al., 2005
	M/F (24)	10–49 (25.1)	40	11 ± 31	0.69–190			Phnom Penh	
	M/F (12)	1–76 (25.4)	20	8.2 ± 16	0.54–70			Kien Svay, only region where sex was significant mean for females was 5.1 μg/g	
	M/F (8)	6–14 (11.3)	12	2.4 ± 0.73	1.5–3.8			Tomnup Rolork	
	M/F (6)	8–62 (24.3)	22	3.2 ± 1.7	1.1–7.5			Batrong; near Sihanoukville industrial waste dumping site	
China	F	P (29‡)	96	1.7‡	1.4–2.4 IQR			Hong Kong Special Administrative Region; consecutive births	Fok et al., in press

Region / Country[1]	Sex[2]	Age[3]	N	Mean ± SD	Range	Local Fish Consumers	Nearby Mining	Population Description	Reference
	M	40–49	64	1.694 ± 4.979	0.112–36.356			Harbing; industrial centre 600 km from the coast, low fish consumption (MeHg concentrations were lower: 0.416 ± 0.244, range: 0.111–1.271)	Feng et al., 1998
	F	P (31)	26	0.88† ± 0.11				Hong Kong Special Administrative Region; controls with normal fertility recruited at the Prince of Wales Hospital	Choy et al., 2002
	F	18–77	69	0.474 ± 1.321	0.092–10.463			Changchun; urban population samples were collected from schools, barber shops and through personal contacts	Li et al., 2006
	F	5–73	40	2.92 ± 11.8	0.16–74			Wujiazhan, Jilin Province; downstream of the Di'er Songhua river, which was polluted with MeHg in the 60s and 70s	Zhang et al., 2006
Papua New Guinea	M	Adult	13	0.75 ± 0.4			X	Siuhamason; non-fish eating population from village near the upper Strickland River	Abe et al., 1995
	M	111 adults	134	21.9 ± 11.2		X	X	Buseki, Usukof, Miwa, Kusikina, Manda Kavienanga, and Levame; fish eating populations near Lake Murray, Fly River, and Strickland River (downstream of copper and gold mine, Ok Tedi)	
Philippines	M/F	Adult	48		0.13–13.0		X	Eastern Mindanao; near artisanal gold mining, includes 11 workers, 17 people living near a carbon-in-pulp (CIP) cyanidation plant, and 19 people living in communities within 3 km of a main gold processing plant	Appleton et al., 1999
	M/F		316	4.14	0.03–37.76	X	X	Diwalwal; people living near a gold mine and occupationally-exposed ball-millers and amalgam-smelters	Drasch et al., 2001
	F	P	78					Tagum; Recruited from consecutive births for Tagum Study I, a prospective cohort study evaluating the long-term effects of Hg exposure in Tagum; only five mothers had blood Hg > the detection limit of 2 μg/L (≈0.5 μg/g in hair)	Ramirez et al., 2000
Republic of Korea	F	5–67	104	1.1 ± 0.15[se]	0.2–5.8			Seoul; sample representative of urban background concentrations, age was not a significant factor (MeHg concentration was 0.5 ± 0.14)	Lee et al., 2000

[1] Grouped according to WHO Region and mortality strata (World Health Report. Geneva, World Health Organization, 2001), see Table A4–2.
[2] Parentheses show the number or percent of subjects who are female.
[3] Age is represented as the range with the mean in parentheses.
[4] Due to the number of investigations in the Brazilian Amazon, only studies conducted after 1999 that reported hair mercury concentrations in women of child-bearing age are included.
† Geometric mean
‡ Median

N	Study population size
SD	Standard deviation
NR	Not reported
F	Female
M	Male
P	Pregnant
C	Child-bearing age
I	Infants (data from cord-blood)
SE	Standard error
IQR	Inter quartile range
MeHg	Methylmercury
THg	Total mercury

Table A4–2 Countries in WHO regional groups

Region[1]	WHO Member States
AfrD	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
AfrE	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
AmrA	Canada, Cuba, United States of America
AmrB	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
AmrD	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
EmrB	Bahrain, Cyprus, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
EmrD	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
EurA	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
EurB	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Serbia and Montenegro
EurC	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
SearB	Indonesia, Sri Lanka, Thailand
SearD	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
WprA	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
WprB	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

[1] Grouped according to WHO Region and mortality strata (WHO, 2001).

Afr = Africa; Amr = Americas; Emr = Eastern Mediterranean; Eur = Europe; Sear = South-East Asia; Wpr = Western Pacific. A: very low child, very low adult mortality; B: low child, low adult mortality; C: low child, high adult mortality; D: high child, high adult mortality; E: high child, very high adult mortality.

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Annex 5 Calculation spreadsheet for mercury

A Microsoft Excel spreadsheet, referred to throughout this document as the Mercury Spreadsheet, is available to assist in calculating the burden of disease from methylmercury exposure. The worksheets in this file provide methods for estimating the incidence of MMR due to methylmercury and using the incidence rate to estimate DALYs lost due to MMR. The spreadsheet is available by request from ebdassessment@who.int. The parameters required to estimate disease burden using the Mercury Spreadsheet are briefly described below.

Required input parameters for the Mercury Spreadsheet

- target population mercury exposure data for pregnant women or women of childbearing age, preferably measured as hair concentrations:
    - mean
    - standard deviation
    - sample size
    - number of infants born per year.

Output parameters of the Mercury Spreadsheet

- incidence rate per 1000 infants for methylmercury-induced MMR;
- proportion of the population losing greater than 2 IQ points;
- methylmercury burden of disease from MMR expressed as DALYs and DALYs per 1000 infants.