Children's Exposure to Mercury Compounds

World Health Organization

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Abbreviations

Organizations and other entities

ATSDR	Agency for Toxic Substances and Disease Registry
FAO	Food and Agriculture Organization
FDA	United States Food and Drug Administration
EU	European Union
ILO	International Labour Organization
IPEC	International Programme for the Elimination of Child Labour
JECFA	United Nations Food and Agriculture Organization and World Health Organization Joint Expert Committee on Food Additives
UNEP	United Nations Environment Programme
UNIDO	United Nations Industrial Development Organization
US CDC	United States Centers for Disease Control and Prevention
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

Technical Terms

ADME	Absorption, Distribution, Metabolism, Excretion
ADI	Acceptable Daily Intake
ASGM	Artisanal and Small-Scale Gold Mining
BAF	Bioaccumulation factor
CFL	Compact Fluorescent Light Bulbs
$(CH_3)_2Hg$	Dimethyl mercury
CHD	Coronary Heart Disease
CPOX	Coproporphyrinogen Oxidase
CVD	Cardiovascular Disease

DHA	Docosahexaenoic Acid
EPA	Eicosapentaenoic Acid
GCL	Glutamate Cysteine Ligase
GSH	Glutathione
GST	Glutathione S-Transferase
GTT	Gamma-Glutamyl Transpeptidase
Hg^0	Elemental Mercury
Hg^{2+}	Inorganic Mercury
HgS	Cinnabar
KICP	Ketoisocoproporphyrin
LOAEC	Lowest Observed Adverse Effect Concentration
MeHg	Methylmercury
MT	Metallothionein
ppm	Parts per million
PTWI	Provisional Tolerable Weekly Intake
PUFAs	Poly-unsaturated Fatty Acids
RfD	Reference Dose
RGHg	Reactive gaseous mercury
SRB	Sulfur reducing bacteria

Preface

Human exposure to mercury and mercury compounds remains a serious concern to health professionals and public health scientists worldwide. The World Health Organization (WHO) has been specifically concerned with preventing the adverse human health effects of mercury exposures, particularly for the fetus and child.

Environmental Health Criteria 1: Mercury, published in 1976, examined the effects of mercury on human health; Environmental Health Criteria 101: Methylmercury was published in 1990 and Environmental Health Criteria 118: Inorganic mercury was published in 1991. The evaluation of human health risks from methylmercury in food has been carried out on numerous occasions by the United Nations Food and Agriculture Organization and World Health Organization Joint Expert Committee on Food Additives (JECFA). The most recent evaluation occurred at the sixty-seventh meeting in 2006. The Committee re-evaluated inorganic mercury in 2010. The WHO Environmental Burden of Disease Series (No. 16) assessed the effects of human exposures to mercury at local and national levels in 2008. During the past 10 years, a large body of knowledge on mercury exposure has accumulated. This document focuses on the sources and routes of childhood mercury exposure and methods of assessing mercury exposure.

Foreword

Dear Colleagues,

It is with great pleasure that I present to you this report on Children's Exposure to Mercury Compounds.

For centuries, human exposure to mercury has resulted in severe and often tragic health consequences, particularly for the world's children. Mercury intoxication, both chronic and acute, has been recognized worldwide as a significant contributor to environmental burden of disease. All forms of mercury are toxic, and children, as well as the developing fetus, are particularly sensitive to most, if not all of these forms. As a neurodevelopmental toxicant, mercury poses a specific threat to the developing fetus and to the child in early life. Fetal exposure to high levels of methylmercury has led to devastating congenital malformations, infantile cerebral palsy, and neurocognitive effects.

As an element with high atomic weight, mercury vapour settles close to the ground where young children are more likely to spend their time. At room temperature, elemental or liquid mercury forms a silvery, dense liquid that can coalesce into small, shiny droplets. This unique property increases children's attraction to the substance. Children also face disproportionate exposure to this toxicant in the occupational setting as mercury is widely used in the metal mining sector. Moreover, children can be directly exposed to methylmercury by eating contaminated fish and shellfish, and the developing fetus is exposed *in utero* by maternal consumption of fish with high mercury concentrations.

Regional and global actions, both immediate and long-term, are necessary to reduce the release of mercury into the environment, eliminate the use of mercury where possible, and promote the development of alternatives to the use of mercury. These three actions will be essential in order to reduce and some day eliminate childhood exposure to mercury and mercury compounds. As a bioaccumulative and persistent toxicant that pollutes across national boundaries, it remains our prerogative, as an interconnected, global society to ensure our children – our most vulnerable citizens – are protected. This document provides information

about childhood exposure and documents the most recent advances in evaluating biological exposures. It is intended to be used by public health scientists worldwide to understand the extent and complexity of childhood mercury exposures. I commend it to you.

Maria Neira
Director
Public Health and Environment
World Health Organization

Summary

This document presents the various sources and routes of childhood exposures to mercury and mercury compounds and reviews the specific vulnerabilities of children to the effects of this neurodevelopmental toxicant. The particular susceptibility of the developing fetus to *in utero* mercury exposures is highlighted.

Children's exposures to mercury pose a significant threat to their healthy development. The main sources of mercury in the environment result from anthropogenic activity.

The two major sources of mercury that result in childhood exposures are:

Industrial Processes

- The majority of mercury in the environment results from coal-fired power stations, residential heating systems, and waste incinerators. Mercury is also released into the environment in the process of mining gold and other metals.

Diet

- Consumption of contaminated fish, shellfish, and marine mammals is the main source of methylmercury exposure, especially for people who rely on predatory fish as their main source of protein.

The health effects of mercury in children vary widely, depending on the type of mercury or mercury compound to which the child is exposed, the age of the child, and the dose and duration of exposure. However, children are overall more vulnerable to mercury exposures and more susceptible to its health effects. The fetus is particularly vulnerable due to ongoing brain and organ development *in utero*. Neurodevelopmental effects of *in utero* mercury exposure include mental retardation, congenital malformations, vision and hearing loss, delayed development, and language disorders. Acrodynia, a syndrome characterized by rashes and swollen, painful extremities, may result from chronic exposure to mercury or mercury compounds.

WHO is committed to work with the health sector and with national, regional, and global health partners to reduce mercury exposure in children, eliminate the use of mercury wherever possible, and promote the

development of alternatives to the use of mercury. Both immediate and long-term policy actions are necessary to reduce the release of mercury and its compounds into the environment in order to protect our children from current and future exposure threats. Elimination of mercury exposures and subsequent disease requires strategic action (WHO, 2007) to:

- Conduct national assessments of mercury usage and disposal and implement educational activities for the health and the environmental sector
- Develop effective mercury clean-up, waste handling, and storage procedures. Promote management of health related waste containing mercury as set out in the UN Basel Convention on the Control of Trans-Boundary Movements of Hazardous Wastes and their Disposal
- Assist nations in preparing regulatory advisories and advice for pregnant women and children regarding mercury exposure, particularly in relation to fish consumption
- Encourage nations to implement legislation on mercury reduction campaigns
- Promote long term monitoring and programs to reduce childhood occupational exposures to mercury and mercury compounds
- Identify traditional practices and folk medicines involving mercury and disseminate educational information regarding routes of mercury exposures and its toxicity, especially for children and pregnant women
- Encourage international agencies to work with manufacturers to develop inexpensive mercury-free products, and facilitate their procurement worldwide.

The most important action that national, regional, and international agencies can take is the development and promotion of mercury-free alternatives in the industrial, medical, and occupational sector. This is especially true for the design and use of essential medical devices, such as thermometers and manometers. Until mercury-free alternatives are designed and marketed, policy actions should enforce that mercury-containing devices are taken back by manufacturers and safely disposed to reduce the risk of environmental release and human exposure.

The goal of this report is to inform public health scientists about the significance of childhood exposures to mercury and mercury compounds in order to reduce this environmental burden of disease for the next generation. This report emphasizes the importance of effective biological assessment of exposures and reviews recent toxicological advances in exposure evaluation.

Introduction

Between 1932 and 1968, a Japanese factory released industrial waste containing high levels of methylmercury into local waterways, resulting in widespread pollution of Minamata Bay and the contamination of fish and shellfish species in the region. In the 1950s, local residents became alarmed by the strange behaviors of animals and an increase in the incidence of developmental disorders in newborns. In 1959, epidemiological studies revealed that communities living near Minamata Bay, who traditionally depended on fish and shellfish for their diet, had been unknowingly exposed to high levels of methylmercury. The devastating health effects subsequently became known as Minamata disease – a developmental condition at high dose characterized by infantile cerebral palsy, congenital abnormalities, ataxia, paralysis, hearing and vision loss, and other symptoms related to acute methylmercury exposure. Since the identification of the disease, WHO estimates that at least 50,000 people have been affected and more than 2000 cases of Minamata disease have been certified as result of the incident.

Between 1971 and 1972 in Iraq, widespread consumption of grain coated with an organic mercurial fungicide caused the largest mercury poisoning epidemic ever recorded. A total of 6,530 individuals were diagnosed with mercury intoxication and hospitalized, of which 459 died. However, it is believed that this figure is severely underestimated. Infants exposed *in utero* by mothers who consumed the contaminated grain demonstrated developmental disorders similar to Minamata disease. Children exposed at lower doses experienced delays in neuro-cognitive development and ataxia.

Together, these tragic incidents demonstrated the toxic human health effects of mercury, which were particularly severe for infants exposed *in utero*. Mercury induces potent effects on the developing brain of the fetus. The early processes of brain development which include cell differentiation and migration are highly sensitive to the neurotoxic effects of mercury exposure.

Throughout the developed and developing world, children face mercury exposure risks from numerous different sources as well as multiple different species of mercury. In general, all forms of mercury are toxic, and children (as well as the developing fetus) are particularly sensitive to most, if not all of these forms.

This report draws its origins from an initial workshop held in Bonn, Germany in 2007 and further meetings held at the World Health Organization (WHO) Headquarters in Geneva, Switzerland. Additional material was added by an international working group to allow a more comprehensive understanding of children's exposures to mercury. The intent is to present material relevant to an international audience of public health scientists, and to indicate areas where further information is needed.

This document does not review every topic related to mercury exposures of children, nor does it serve as a guidance document for how to identify childhood exposures to mercury. Instead, it makes extensive use of published reports by WHO, UNEP, UNIDO, health institutions, academia, and national authorities. Persons seeking additional details on these topics are invited to access these materials.

The World Health Organization stresses the importance of utilizing an established risk paradigm to identify and assist specific subpopulations that may be at risk for chemical exposures, including childhood exposures to mercury. For more information regarding a risk assessment paradigm on how to identify populations at risk to mercury exposure, please reference the WHO/UNEP document entitled: Guidance for Identifying Populations at Risk from Mercury Exposure (2008), available at http://www.who.int/foodsafety/publications/chem/mercuryexposure.pdf.

For more general information related to human mercury exposure, please see the WHO document entitled: Exposure to Mercury, A Major Public Health Concern (2007), available at http://www.who.int/phe/news/Mercury-flyer.pdf.

Special vulnerability of children to mercury

Mercury is highly toxic to children and adults and all forms of mercury are associated with toxicity (Holmes et al., 2009). There are relatively few recent comprehensive reviews of this topic, specifically on children, and none on all mercury compounds (for example, Counter and Buchanan 2004, which focuses on methylmercury).

Methylmercury as a food contaminant was reviewed by the United Nations Food and Agriculture Organization and World Health Organization Joint Expert Committee on Food Additives (JECFA) in 2007 (http://whqlibdoc.who.int/publications/2007/9789241660587_eng.pdf). At this

meeting, the Provisional Tolerable Weekly Intake (PTWI) of 1.6 μg/kg was confirmed, based on review of epidemiological and toxicological studies published since the prior review in 2003. This review also considered the issue of critical windows of toxicity during pre- and postnatal development, and concluded that the epidemiological data support the conclusion that the prenatal period represents the period of greatest vulnerability for the neurodevelopmental effects of methylmercury. While it was noted that vulnerability to methylmercury extends through the postnatal period to at least adolescence, JEFCA noted there was insufficient evidence to conclude that these periods represent greater vulnerability than the prenatal period.

Some of the differences in vulnerability may be related to developmental differences in the metabolism of mercury compounds, as reviewed by JECFA (2007).

In addition to neurodevelopmental effects, JECFA evaluated evidence for cardiovascular effects of early methylmercury exposure in children. Data from studies in the Faroe Islands and in Japan indicate that prenatal exposures to methylmercury may decrease vagal modulation of cardiac autonomic function assessed in children aged 7 years and older. The Committee noted that these effects were observed at cord blood levels about six times lower than the value used to derive the PTWI in 2003 based on neurodevelopmental endpoints.

The health effects of mercury exposures in children are influenced by the species of mercury, route of exposure, dose, timing and duration of exposure. High dose exposures of fetuses and children are associated with increased risks of intrauterine death and increased risks of early childhood death. Exposures can occur *in utero*, as described in this document, due to the presence of mercury from pre-conception and to the ready passage of mercury compounds across the placenta, and throughout extra uterine early life via breast milk and during childhood and adolescence through direct exposure to mercury compounds in the environment, diet, and consumer products.

Mercury has important effects on developing systems, with evidence for cardiovascular, neurodevelopmental and immune system toxicity that may persist throughout later life (JECFA, 2007). Experimental studies confirm these modes of toxicity in children. Mercury compounds also affect multiple organ systems in addition to the nervous and immune system,

including the cardiovascular and respiratory systems, renal function, skin, and liver. In children, there is information on toxicities involving brain, cardiovascular system, renal function, and skin. There are no conclusive data on mercury as a carcinogen.

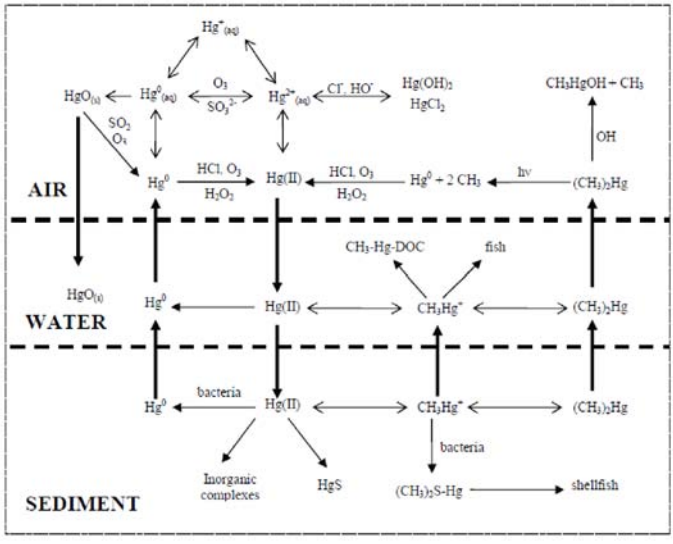
More information regarding the health effects of mercury, including those that are not exclusive to children, is available in the WHO Food Additive Series, 58, accessible at http://whqlibdoc.who.int/publications/2007/9789241660587_eng.pdf.

Geochemical cycling of mercury in the environment

Introduction

As a stable element, mercury (Hg) cannot be degraded or destroyed. However, it undergoes a variety of physical and chemical transformations that convert mercury compounds from one species to another (Figure 1). That speciation governs its partitioning and dispersion in the environment, as well as its bioavailability and toxicity to organisms including children. For this reason, the processes of speciation of mercury (elemental, inorganic, and organic) in the environment are summarized in this section.

Figure 1
Model of Mercury Speciation and Transformations in Air, Water and Sediments (Figure from Stein et al., 1996). *Reproduced with permission from Critical Review Environmental Science and Technology.*



Mercury in the Atmosphere

Elemental mercury (Hg^0) in its gaseous form is the predominant form of mercury in the atmosphere because it is volatile and relatively inert compared to other mercury species (UNEP, 2008). As a result, its atmospheric lifetime is approximately 6-24 months, which is relatively long compared to those of other mercury species that remain in the atmosphere for only a few weeks. The long atmospheric lifetime of Hg^0 also accounts for its dispersion to regions of the planet remote from sources and releases (Nguyen et al., 2009). Natural emissions and re-emissions of mercury (including outgassing of the Earth's mantle and crust; volcanic activity; geothermal processes; evapouration from soils and sediment, water bodies and vegetative surfaces; and release from forest fires and erosions) are estimated to be 4800 tonnes/year and anthropogenic emissions of mercury (including fossil fuel combustion; deforestation, small and large-scale mining; metal, cement, and chlor-alkali production; waste incineration; and cremation) are estimated to account for approximately 2200 tonnes/year (Selin et al., 2007). See Figures 2 and 3.

After Hg^0 enters the atmosphere, it is oxidized to inorganic mercury (Hg^{2+}),

Figure 2
Global atmospheric emissions of industrial mercury (from UNEP, 2008).
Reproduced with permission from UNEP.

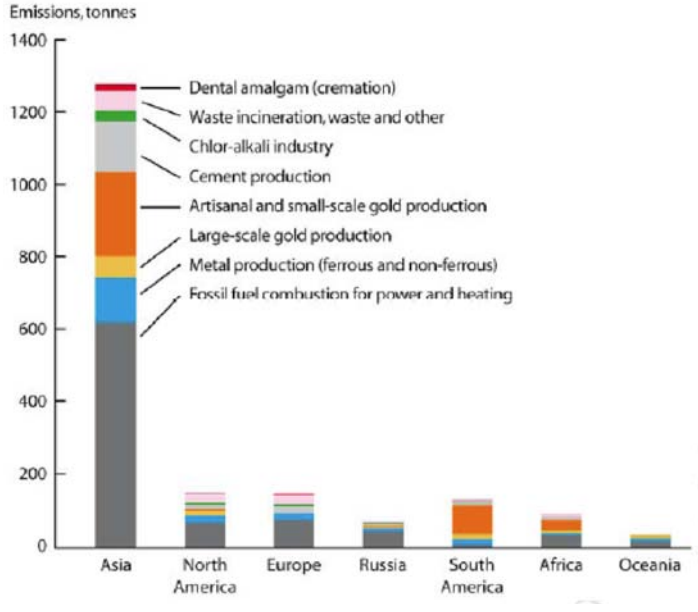
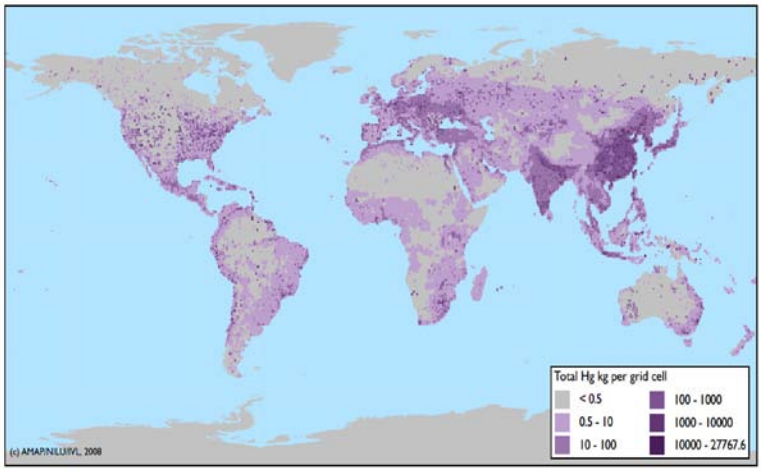


Figure 3
Map of estimated Global Atmospheric Emissions in 2005 (UNEP, 2008) –The darker purple areas have higher estimated global atmospheric mercury (Hg) emissions than regions indicated in light purple or grey. It is of note that children living in areas with the highest rates of emissions may not be at highest risk for negative health impacts associated with mercury exposure. Instead, regions with both high rates of mercury deposition and geochemical conversion between inorganic mercury (Hg2+) and methylmercury (MeHg) facilitate the highest rates of environmental exposure through fish consumption. In this sense, Hg exposure is not merely a function how much mercury is being emitted but where it is being emitted from.
Reproduced with permission from UNEP.



which is much less volatile, much more water soluble, and much more reactive than Hg^0. Consequently, Hg^{2+} is rapidly deposited to land and water surfaces by both wet and dry deposition. The transformation of Hg^0 to Hg^{2+} is an area of active research, though it is understood that this process is influenced by a variety of factors including the presence of oxidants (ozone and hydroxyl radicals), halides (bromine and chlorine), temperature, and the presence of ice crystals in the atmosphere (UNEP, 2008). These atmospheric characteristics, which are seasonally dependent, contribute to fluctuations in atmospheric mercury deposition throughout the year. This is particularly pronounced in certain regions. For example, following polar sunrise from March through June, there are large atmospheric depletion events in the Arctic which result from rapid conversion of gaseous Hg^0 to other mercury compounds which are rapidly deposited (Lindberg et al., 2002; Steffen et al., 2005). Another relatively small amount of mercury in precipitation is in the form of organic mercury, primarily CH_3Hg or methylmercury (Downs et al., 1998; Conway et al., 2010).

Following deposition, mercury can either be retained in the ecosystem, or alternatively converted to the reactive gaseous Hg^0 form and returned to the atmosphere. It is this process of repeated atmospheric deposition and re-emission which, in addition to the high vapour pressure of Hg, further contributes to the long-range distribution of Hg far from the point of emission. This process is referred to as the "grasshopper effect" (Poissaint et al., 2008; UNEP, 2008). Please see figure 4 for more information.

Figure 4
Global Mercury Transport (UNEP, 2008) – The deposition of compounds around the globe is dependent on many parameters; however, both vapour pressure and latitude are very important. Elements and compounds with high vapour pressure (purple), including elemental mercury (Hg^0), are transported over very long distances and are mostly deposited at the poles. Compounds with medium high vapour pressure (blue) may be deposited many times; however, they are easily volatilized and are transported farther away from the equator each time they are re-emitted to the atmosphere. Compounds with low vapour pressure (pink) are deposited over short ranges and are not as easily re-emitted into the atmosphere, thus having shorter ranges of atmospheric transport.
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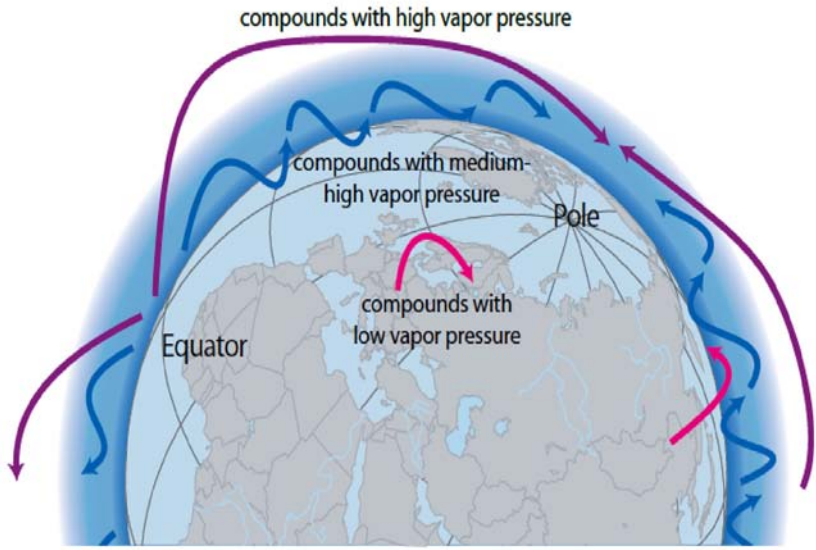


Mercury in the Hydrosphere

Due to the importance of the aquatic mercury cycle and its link to contamination of fish and seafood by methylmercury (MeHg), mercury in the hydrosphere remains a particularly important subject for discussion.

Freshwater systems

Atmospheric mercury reaches freshwater ecosystems through direct deposition to lake surface waters and through erosions of soils, runoff from watersheds, as well as discharges from anthropogenic sources such as waste water treatment plants, chlor-alkali and other industries utilizing mercury, and mine drainage (Balogh and Nollet, 2008; Suchanek et al., 2008; UNEP 2008). Wet and dry deposition of mercury to watersheds and lake surface waters, as in terrestrial systems, is predominantly as Hg^{2+}. Although most of the dissolved, colloidal, and particulate mercury in fresh water systems is inorganic, mercury in fresh water systems may be converted by certain types of sulfate and iron-reducing anaerobic bacteria to organic mercury species, including methylmercury and dimethyl mercury $(CH_3)_2Hg$), (Benoit et al., 2003; Kerin et al., 2006) that may be biomagnified to potentially toxic levels in aquatic food webs under specific physical and chemical circumstances.

Mercury is removed from aquatic systems through volatilization of Hg^0, aerosolization of Hg^{2+} and small amounts of methylmercury at the surface from freshwater aquatic systems. Additionally, there is partial removal of Hg from aquatic systems from the sequestration of methylmercury in biota that are removed from the ecosystem through the food web. In spite of this, there has been a net increase in mercury concentrations in freshwater systems in most regions of the world (Selin, 2009). The uneven rates of atmospheric deposition from one location to another, along with unequal efficiencies of conversion of inorganic mercury to methylmercury results in "hot spots" of methylmercury contamination, with important implications for the exposure of children and others through fish consumption.

Marine systems

Similar to freshwater systems, Hg^{2+} can be deposited to the ocean by dry or wet deposition, and Hg^0 by wet deposition. In contrast to freshwater systems, most inputs of mercury to the ocean are from atmospheric deposition, although specific instances of industrial or mining discharges into marine systems (such as the Minimata Bay in Japan) can have important consequences for human health (Storelli et al., 2003). Generally, Hg^{2+} deposited to the ocean can be reduced to Hg^0, adsorbed onto particles or colloids, or biomethylated. Reduction from aqueous Hg^{2+} to Hg^0 can be both biologically and photochemically mediated, and oxidation process

can also be significant (Selin, 2009). As a result, Hg^0, Hg^{2+}, methylmercury, and $(CH_3)_2Hg$, are all found in the ocean (Morel et al., 1998).

Exchange of mercury at the surface of the ocean is thought to be rapid (Strode et al., 2007). Measurements by Mason and Sheu (2002) have attested to the complexity of the cycling of mercury between the ocean and atmosphere, due to the enhanced oxidation of Hg^0 and the formation of reactive gaseous Hg (RGHg) in the marine boundary layer. These authors estimated that the dry deposition of RGHg to the ocean is 35% of the total mercury input to the ocean.

A further reevaluation of the global Hg cycle suggested that there is a net transfer of mercury from the terrestrial environment to the ocean and that the deep ocean mercury concentration has been increasing by a few percent per year. Similarly, anthropogenic inputs on land have increased mercury on the Earth's surface layer with accumulation in the terrestrial environment accounting for nearly 80% of the net input from human activities. Dry deposition of reactive gaseous mercury (RGHg) is important for the terrestrial realm but because of its relatively short residence time in the atmosphere, it is the oxidation of Hg^0 over the ocean, rather than RGHg transport offshore, which is primarily contributing to oceanic RGHg deposition (Mason and Sheu, 2002).

Mercury in Soils and Sediment

Mercury exists naturally in sediment and soil, with concentrations dependent on regional geological characteristics. The Earth's crust contains only trace amounts of mercury, with an average concentration of 0.08 parts per million (ppm). However, there are rich deposits of cinnabar (HgS) that contain 0.1-2.5% mercury, over 12,000 times the average crustal mercury abundance. Elevated concentrations of mercury in surface soils can also result from long term atmospheric deposition of Hg^{2+}, surface runoff, and industrial contamination. Once deposited in soil, Hg^{2+} is converted to mercury compounds that form complexes with organic anions in organic matter or clays. Because the majority of mercury in soil is bound in these organic and inorganic matrices, it is not highly mobile or susceptible to washout in runoff except in cases of extensive ecological disruption, such as deforestation. The sorption of mercury to those particulate matrices is dependent on pH, as well as the concentration of chloride and organic matter. Generally speaking, as pH

and Cl^- increase, the sorption of mercury to organic matter decreases. The strength of this relationship, however, is weakened under situations in which the soil contains high levels of organic matter (Barrow & Cox, 1992; Yin et al., 1996). Significant amounts of Hg^0 in soils are volatilized into the atmosphere, or removed though bacterial or botanic uptake. To an as of yet undetermined extent, mercury species can be taken up by foliage from which it can be incorporated into soil following leaf fall (Rea and Keeler, 1996). Studies have shown that certain plants are able to take up mercury species, such as the rice plant that effectively sequesters methylmercury found in rice paddy soil (Zhang et al., 2010).

Pathways from sources to fish: Biomethylation of mercury in environmental systems

Introduction

The dominant pathway of mercury exposure for many children is to methylmercury through eating contaminated fish and/or seafood, and for this reason understanding the cycling of mercury in aquatic systems is critical to understanding exposures and health risks for children as well as adults. Consumption of fish, shellfish, and marine mammals is the single most important source of human exposure to methylmercury for individuals around the world, accounting for approximately 75% of total methylmercury exposure. In the United States, consumption of marine fish and shellfish is estimated to account for over 90 percent of human mercury exposure, and tuna harvested in the Pacific Ocean account for 40 percent of this total exposure (Sunderland, 2007). For populations in many developing nations fish represent the main source of animal protein, as in coastal regions of China, south and southeast Asia, and Africa as well as indigenous populations in Amazonia, the Arctic, and northwestern coastal communities of North America. Depending upon the species of fish and marine mammals that are consumed, these populations who rely on subsistence fishing can experience a disproportionally higher risk of methylmercury exposure through the diet.

At the same time, it is important to recognize that these exposures to mercury can occur in the context of consuming foods that also contain important dietary constituents. In particular, consumption of fish, which

is predictive of methylmercury exposures in populations around the world, is also an important source of exposure to essential nutrients (omega-3 fatty acids and selenium). Fish is the primary dietary source for elongated omega-3 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which have been shown to lower triglyceride levels as well as the risk of heart attack when consumed through the diet (Lee et al., 2009). There is also strong evidence for a beneficial effect of fish consumption on early child neurodevelopment (Daniels et al., 2004).

Biomethylation in freshwater systems

Most methylmercury originates in aquatic systems where it is formed through the action of bacteria that appear to reside in water and sediments with limited available oxygen (Summers and Silver, 1978). There is evidence that some soils, particularly in wetlands, can convert deposited inorganic mercury to methylmercury where it is subject to uptake into terrestrial systems or runoff into aquatic systems and bioaccumulation in both non-aquatic and aquatic species (Rimmer et al., 2005). The extent to which this occurs in species consumed by humans is not known, although some insects can accumulate methylmercury in wetlands (Tsui et al., 2009).

After mercury is biomethylated, it is efficiently bioaccumulated and biomagnified in trophic webs up the food chain, resulting in elevated levels in organisms such as piscivorous fish and mammals. This process of bioaccumulation can result in methylmercury concentration in predatory fish greater than 10^6 times that of water (Engstrom, 2007). As discussed in this section, the process of biomethylation is affected by several environmental factors by influencing the supply of biovailable Hg^{2+} and/or the activity of methylating microbes.

In freshwater systems, methylation is predominantly attributed to sulfur-reducing and iron reducing bacteria (Benoit et al., 2003; Kerin et al., 2006), although abiotic methylation of mercury also occurs under certain conditions (Ullrich et al., 2001). Some bacteria also de-methylate mercury in response to relatively high organic mercury concentrations, which limits the total methylmercury in aquatic systems (Marvin-Dipasquale et al., 2000; Bailey et al., 2001). Since both methylation and demethylation processes occur, the total methylmercury concentrations in an ecosystem reflect net methylmercury production, rather than solely the rate of methylation.

There are differences in biomethylation in tropical regions as compared to

the northern hemisphere. In temperate zone lakes, most biomethylation takes places in the benthic zone (lowest level in body of water) and top sediments, whereas in tropical systems (such as the Amazon), the floating mass of plant biota is the richest zone of biomethylation as compared to sediments (Guimaraes et al., 2000). In polar regions, where mercury deposition rates are relatively high owing to the grasshopper effect (Poissaint et al., 2008), the biomethylation of mercury is also different from temperate zones (Barkay and Poulain, 2007). The differences in biomethylation processes in different parts of the world have not been fully evaluated, but are important given the fact that children in both the Amazon and polar regions consume relatively large amounts of fish (and, in the case of Arctic communities, fish-consuming marine mammals) (Fillion et al., 2006).

Biomethylation in marine systems

Less is known about the biomethylation process in marine systems as compared to freshwater systems. Several studies have postulated that methylmercury produced in coastal and estuarine sediments bioaccumulates in plankton and fish that are horizontally transported along water currents to open ocean regions, forming the primary methylmercury source for marine food webs (Hammerschmidt and Fitzgerald, 2006). In aquatic sediments, microbes convert a relatively small fraction of inorganic Hg^{2+} to methylmercury over time. However, other data indicate that there is active mercury methylation in the marine water column, such that the entry of methylmercury into marine food webs may occur independent of biomethylation by bacteria in sediments or benthos as previously hypothesized (Kraepiel et al., 2003). In addition, there is evidence for some abiotic methylation in the oceans (Celo et al., 2006).

Methylmercury accumulation in aquatic species

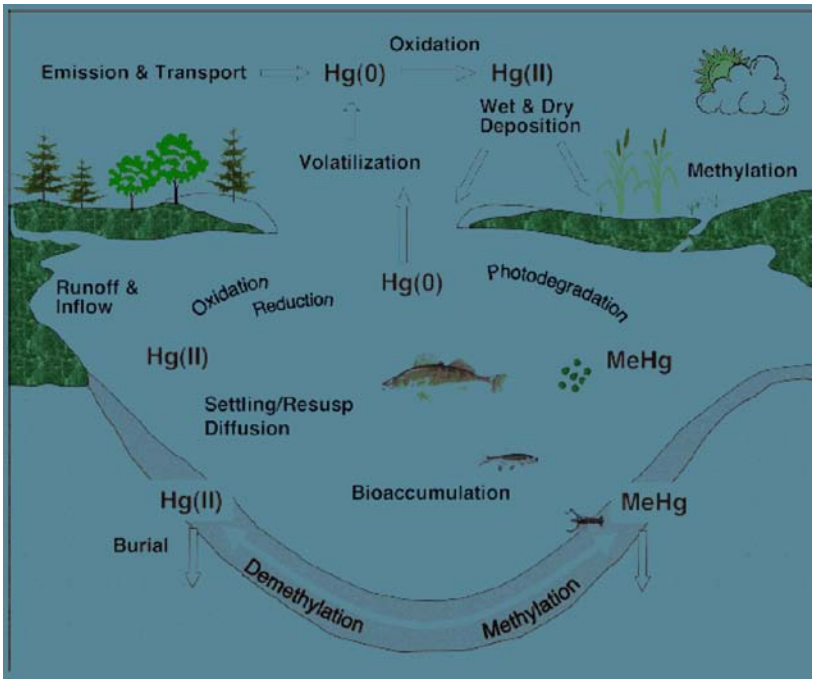
Bioaccumulation is defined as the ability of individual organisms to take up and retain a compound against an environmental or physiological gradient; biomagnification is defined as the integrated effect of bioaccumulative processes within a trophic web. In contrast to the importance of physical-chemical properties of lipophilicity in determining bioaccumulation for organic pollutants, methylmercury is retained in biological systems because of its affinity for sulfhydral groups, including those in the amino

acid cysteine. Because the cysteine-methylmercury complex is recognized as the amino acid methionine by the neutral amino acid carrier, it is readily transported across cell membranes and not readily eliminated (Kerper et al., 1992; Kajiwara et al., 1996; Clarkson et al., 2007). These biochemical mechanisms are highly conserved and thus bioaccumulation of methylmercury occurs in organisms throughout aquatic food chains. The commonality of these mechanisms across species, and the increase in energy demand with species size, results in biomagnification with movement up the food chain. The concentration of methylmercury in fish tissue is a function both of the trophic level of the species and of the age and size of the individual (Weis, 2004).

Biomagnification within aquatic food chains is often expressed in terms of a bioaccumulation factor (BAF), the ratio of the concentration of a chemical in a particular animal species to its concentration in the water. Thus this factor is influenced by both the behaviour and physiology of the organism as well as by the fact that levels of methylmercury in the water column are very low in most aquatic systems since much, if not most, of the methylmercury is bound to colloidal suspensions or incorporated into microbiota and thus, not free in the water column. For methylmercury, the BAF for fish at the top of fresh water food webs has been measured as greater than 5×10^6 (Paller et al., 2004).

Both freshwater and marine fish are subject to bioaccumulation and biomagnification of methylmercury and at the top of their respective food chains, mercury concentrations can exceed 1 ppm (1 μg/g). Notwithstanding their generally smaller size, however, top-trophic level freshwater fish can have mercury concentrations comparable to those in much larger top-trophic level marine fish. Thus, North American species of freshwater bass, pickerel and walleye, for instance, can have the same mercury concentrations as albacore tuna (US EPA, 2009). This is due to differences in diet and characteristics of freshwater and marine ecosystems. Freshwater bodies are more subject to the chemistry of the soils in the surrounding watershed and the underlying sediment than are deep oceans. Certain soil chemistries, including acidic soils, are effective at mobilizing mercury and facilitating methylation. Freshwater bodies are in some cases more directly impacted by mercury emissions and thus can receive a larger flux of mercury deposition from both the ambient air and the watershed. Also, freshwater systems are less open and thus less likely to dilute mercury inputs into the water column. These processes are shown schematically in Figure 5

Figure 5
Processes of bioaccumulation and biomagnification of methylmercury in freshwater ecosystems (Engstrom, 2007).
Reproduced with permission from the National Academy of Sciences.



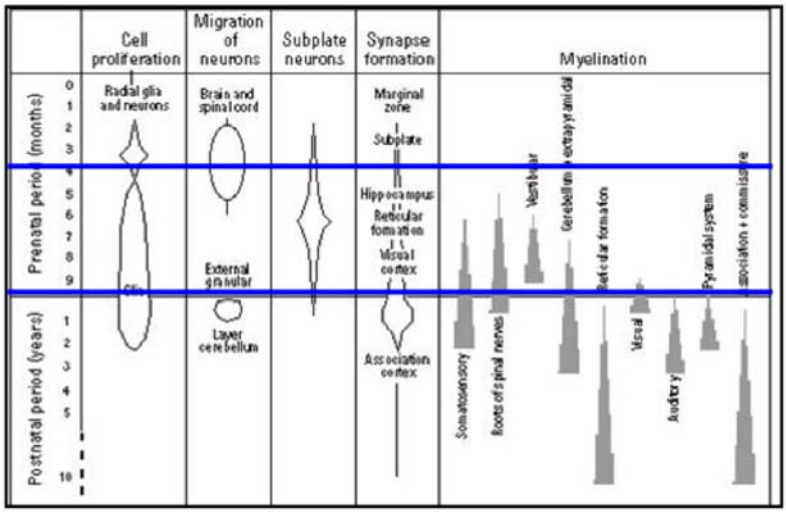
Exposures of children to mercury compounds

Introduction

Children may be particularly vulnerable to the health effects from mercury exposure because of their rapid growth and development. Children are different from adults in several respects, including differences in metabolism, diets, patterns of behaviour, growth and changes of organ systems and functions. All of these factors can affect the way in which children may be exposed to or react to mercury or other toxicants. Moreover, these factors change throughout the stages of childhood -- prenatal life, infancy, childhood, and adolescence (US EPA, 2007).

It is important to note that mercury is characterized as a developmental neurotoxicant, indicating its potent effects on the developing brain in the fetus and young child. The early processes of brain development, including cell differentiation and migration as well as the formation and pruning of synaptic connections, orderly axonal and synapse reduction, present biological stages that are highly sensitive to perturbation, often referred to known as "windows of susceptibility" (See Figure 6). Exposures to environmental contaminants during these critical periods of development may result in irreversible damage to the nervous system and other systems in which prolonged developmental processes are required such as the immune system and reproduction, behavioural and cognitive patterns and motor skills (Rice & Barone, 2000). For this reason, early childhood exposure to mercury poses a significant threat to health that may persistently impact the quality of life in adolescent and adult years.

Figure 6
Windows of Susceptibility and Neurodevelopment. (Rice and Barone, 2000).
Reproduced with permission from Environmental Health Perspectives.



Mercury exposures are not equally distributed among the world's children. As a result of the geospatial concentration of releases (as shown in Figure 3), mercury deposition is highly variable, and in addition, geographic and cultural factors (including but not limited to diet) influence environmental exposures. As a result, environmentally mediated exposures, especially to fish and seafood (as discussed in Section on special vulnerability of children to environmental exposures), are not

uniform for children and others worldwide. This is an important issue in developing effective strategies for protecting children in specific regions and communities.

Children's exposure to mercury should be considered in a holistic fashion, reflecting the cumulative complexity of both the sources and pathways by which children may be exposed. Mercury has multiple exposure sources, as described in this section, as well as multiple routes of exposure (e.g., inhalation, ingestion, dermal absorption). Moreover, it is important to consider all forms of mercury to which children may be exposed, including elemental, inorganic, and organic species. Historically, discussion of children's exposure to mercury has assumed that fish consumption is the most important exposure of concern and that methylmercury is the most important form of mercury in terms of hazard (WHO, 2007). As a consequence, research and public health policy particularly in industrialized nations is largely focused on the presence of methylmercury in fish and the extent to which different fish species are consumed by children and their mothers. However, throughout the developed and developing world, children face mercury exposure risks from numerous different sources as well to multiple different species of mercury. This fact is particularly evident in developing nations where children face additional mercury exposure risks via occupational settings (i.e., mining or scavenging), cultural or religious practices (i.e., Ayurveda or Santeria) as well as due to a subsistence diet of fish or marine mammals.

In general, all forms of mercury are toxic, and the developing fetus and child are particularly sensitive to most, if not all of these forms. While it is not clear whether, or to what extent, toxicity from the various forms of mercury is cumulative, it is prudent to consider total mercury exposure as well as exposure to the individual compounds and species of mercury. Additive exposures and additional health risks may have more appreciable impacts than previously recognized, especially for toxicants like mercury that may result in adverse health effects even at low exposure doses. Methods for addressing cumulative exposures through biomarker analyses are discussed in the Section on biomarkers (see page 20).

The focus on methylmercury has led to a relative lack of attention to the toxicity of the other forms of mercury. This can result in confusion between levels of exposure and severity of toxicity. As illustrated in this section, exposures to all forms of mercury – elemental, inorganic, and organic mercury species beyond methylmercury – have been associated

with significant intoxication events in children. Moreover, methylmercury is converted to inorganic mercury (inorganic Hg) and stored long term in the brain as inorganic Hg. Experimental studies have demonstrated that Hg vapour, inorganic Hg, ethyl as well as methylmercury are all toxic to the development of the brain and immune systems. The failure to examine exposures to mercury species in addition to methylmercury has resulted in proposals such as the use of bioremediation methods that reduce methylmercury, without consideration that inorganic mercury levels would be increased by demethylating methylmercury (Barkay et al., 2005).

Exposures over childhood

Prenatal exposures

Childhood exposures to mercury begin at the point of conception because of transfer of mercury from the mother to the embryo and fetus. Since exposures to pregnant women result in fetal exposure, sources of mercury exposure to adults are also a source of fetal exposure. There are several sources of mercury exposure that have been recognized of special significance during pregnancy, including dietary intake of fish and other food containing elevated levels of methylmercury (WHO, 2007). Mercury exposure during the course of pregnancy, particularly among women living in developing nations, may also occur in occupational settings, such as in gold mining communities. Mercury vapours released from maternal dental amalgams also represent a pathway of concern for pregnant women (Clarkson et al., 2003).

Prenatal exposures to methylmercury have been of particular concern since (see figure 6) the gestational period seems to be a critical "window of exposure" for a number of adverse developmental endpoints in multiple systems that have been associated with mercury. Some of the first reports of mercury toxicity in young children were the severe neurologic effects of intrauterine exposure to methylmercury observed in extensive poisonings such as Minimata, Iraq, and Niigata (WHO, 2007). Since that time a number of additional studies have reported measurable neurodevelopmental impacts following *in utero* exposures to lower doses of methylmercury, including reduced neonatal neurological function (Davidson et al., 2004; Harada et al., 1995) poorer cognition (Ekino et al., 2007; Kjellstrom et al., 1989) and altered brainstem auditory and/or visual evoked potentials (Grandjean et al., 1992; Grandjean et al., 1995; Grandjean et al., 1997). As

with the cardiovascular benefits of other constituents of fish diets, there is evidence for a beneficial effect of maternal intake of polyunsaturated fatty acids (PUFAs) from fish that may ameliorate the toxicity of methylmercury, although this has not consistently been found (Daniels et al., 2004; Strain et al., 2008; Budtz Jorgensen et al., 2007; Oken, 2010).

Exposures during infancy

Infants may be exposed to mercury compounds via breast milk consumption as well as exposures to specific practices and products. Infants can also be exposed to products used during early life, such as teething powders, soaps, and organo-mercurials used in medicines.

Mercury in breast milk

For optimal infant feeding, WHO recommends exclusive breastfeeding for 6 months (WHO, 2001). Breastfeeding is an important source of nutrients for an infant and numerous health benefits from breastfeeding have been documented (American Academy of Pediatrics, 2005).

Mercury concentrations in breast milk are lower than mercury concentrations in maternal blood. A study of Swedish women documented that breast milk mercury concentrations were 30% of corresponding maternal blood concentrations (Oskarsson, 1996). Breast milk mercury concentrations as well as the ratio of blood mercury to breast milk vary among different populations depending upon maternal exposures (Dorea, 2004). Time may also be a factor in breast milk mercury concentrations: there are several reports of mercury concentrations in breast milk (or colostrum) at or near birth being higher than several weeks after birth (Drexler, 1998; Dorea, 2004; Bjornberg, 2005).

In addition to diet, maternal exposures to mercury via occupational exposures or dental amalgams can also contribute to elevated levels of mercury in breast milk (Oskarsson, 1995; Drexler, 1998; Drasch et al., 1998; Sundberg, 1999; Bose-O'Reilly, 2008).

Both organic and inorganic mercury can contribute to mercury in breast milk, although more information is needed on the relative distribution of different forms of mercury into breast milk. Inorganic mercury seems to be more readily transferred from maternal blood to breast milk than methylmercury (Yoshida, 1994; Oskarsson, 1996). Several studies have reported that maternal dental amalgams are more closely correlated with breast milk mercury concentrations as compared to maternal

methylmercury or fish consumption (Björnberg, 2005, Oskarsson, 1996). Some animal studies also support the inference that inorganic mercury is more readily transferred to breast milk (Sakamoto, 2002). The preferential distribution of inorganic Hg to breast milk is consistent with the associations between plasma Hg and breast milk. As methylmercury is preferentially partitioned to erythrocytes rather than plasma, plasma is relatively enriched in inorganic Hg (Skerfving et al., 1988). Some data from studies of laboratory animals challenge the assumption that placental transfer of mercury and prenatal exposures are the dominant concern in terms of early exposures to mercury during development (Sundberg, 1998, Sundberg, 1999).

Nonetheless, WHO recommends exclusive breast feeding for the first six months of life for infants. As the natural first food for newborn babies, breast milk supplies essential energy and nutrients that are essential for healthy development. Exclusive breastfeeding has been shown to promote sensory and cognitive development, reduce infant mortality due to diarrhea or pneumonia, and promote quicker recovery from illness (WHO, 2001). Using formula instead of breast milk is not recommended, as formulas lack the species-specific nutrient and natural immunity that breast milk provides and are not completely free of pollutants (Dorea, 2004; LaKind, 2005).

Childhood exposures

Children can be exposed to mercury in a number of ways such that their exposures exceed those of most adults. For example, children consume relatively larger amounts of foods, including fish, on a body weight basis and this may result in greater protein and caloric intakes to support body weight and growth. Moreover, children may not have fully developed metabolic excretory pathways at the time of exposure, potentially signifying less effective detoxification and physiological elimination of contaminants. Children may be exposed to specific products such as certain medical preparations, amalgams used in dental restoration, mercury-containing paints, spills of Hg^0 from switches and gauges in the home and school, broken fluorescent light bulbs and thermometers, environmental contamination from nearby industrial sources, and through transfers of mercury from the workplace via their parents.

Puberty/adolescent exposures

Although more work needs to be done in this area, it is possible that critical windows of exposure may still be important influences for children entering puberty and adolescence, potentially through the continuing immaturity of the immune, neurological and gastrointestinal systems. Additionally, adolescents may engage in hobbies or work in environments that may result in increased mercury exposure. Among these, intentional misuses of mercury are discussed below.

Sources of children's exposure to mercury

This section reviews some of the more important and frequent sources of children's exposure to mercury compounds. Emphasis is placed on methylmercury in animal-derived products, but it is important to note that other sources have been associated with severe intoxications, namely, occupational exposures in the mining setting. Also, socio-cultural factors must be considered in assessing exposures for specific populations.

Methylmercury in diets of children: animal-derived food products

Children are directly and indirectly exposed to methylmercury in food derived from aquatic animals in amounts that depend upon region, culture, and socioeconomic variables. Indirectly, children are exposed to the methylmercury absorbed by their mothers pre- and postnatally. Directly, children consume fish as part of their diets and then throughout life in patterns usually similar to those of adults.

This topic was reviewed by JECFA in 2007, and additional information on concentrations of methylmercury in various foods are available, including summaries from dossiers submitted by several countries (JEFCA, 2007).

Fish

Both freshwater and marine finfish contain mercury in both inorganic and organic forms, mostly as methylmercury which generally constitutes 80->95% of total mercury in fish tissues (Bloom, 1992; Lasorsa & Allen-Gil, 1995; Andersen & Depledge, 1997). To date, there is no comprehensive worldwide database on mercury levels in commonly consumed fish. In recent years, a number of countries have carried out surveys of methylmercury in various edible aquatic species and some have

also estimated human exposure in terms of consumption patterns. It is important to note that comparison among studies is not always easy, as dietary habits vary across countries and even in regions within countries. As a result, the fish and seafood species included in these surveys differ and in some cases include both commercial products as well as wild species caught for sport fishing or subsistence purposes.

Exposure to mercury via fish consumption: the role of national registries

Many governmental agencies of nations around the world maintain databases on mercury concentrations in important fish species. The US Food and Drug Administration (US FDA) maintains a database of mean mercury concentrations in commercial fish sold in the US and the Environmental Protection Agency (US EPA) (along with the US Department of the Interior) maintains state-specific databases on mercury concentrations in wild caught species that are locally important for intake and exposure (http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115644.htm). Similar data are collected in Japan on fish commonly consumed in Japan. http://www.mhlw.go.jp/english/wp/other/councils/mercury/.

These databases support the general association between elevated biomarkers of methylmercury exposure and rates of consuming fish. In additional, regional analyses can reveal the importance of more specific information on fish consumption. In Japan, a study of several districts examined sex- and age-dependent differences in hair mercury levels among a total of 8665 persons. The study results proved that differences in hair mercury levels between the districts depended on the total amount of daily fish/shellfish consumption and on the preference for tuna consumption. Tuna is a major carnivorous fish with a high methylmercury level that is often consumed in Japan. The district with the highest hair mercury level was associated with very high fish/shellfish consumption and specifically high tuna consumption.

According to the US FDA database, many fish with wide consumption can be considered to have characteristically low levels of mercury (< 0.1 ppm). These include anchovies, farmed catfish, cod, flatfish (flounder, place, sole), haddock, herring, mackerel (but not king or Spanish mackerel), mullet, salmon (canned, farmed and wild), sardines, tilapia, freshwater trout, and whiting. While the characteristic mercury levels for these species can be considered low, individual fish can have mercury concentrations in the 0.3-1.0 ppm range. There are also many commonly consumed fish with mercury levels in the intermediate range (0.1-0.5 ppm). These include Chilean sea bass, bluefish, carp, halibut, Spanish mackerel, orange roughy, skate, snapper, and weakfish (sea trout). Several fish have been found to have mercury levels (0.5->1.0 ppm): shark, swordfish, Gulf of Mexico tilefish and king mackerel, while the lowest levels (<0.1 ppm) were found in clams, shrimp, tilapia, oyster, salmon, hake, and sardine among others. Since commercial fish sold in the US reflects a worldwide catch of marine fish, these data can provide some indication of mercury levels in species of fish that may be consumed in other countries as well the US (US FDA, 2000). However, the FDA data do not provide information on those species of near-shore and estuarine fish that are important sources of methylmercury in other countries.

Because of its popularity in many countries and cultures, tuna deserves special discussion. There are several distinct species of fish that are

commonly referred to as tuna. Tuna sold as canned light tuna is reported by the US FDA as having an average mercury concentration only slightly greater than 0.1 ppm, while canned albacore tuna (also called solid white tuna) as well as fresh albacore is reported to have an average mercury concentration of 0.4 ppm. Individual cans of albacore tuna, however, have been reported to have mercury concentrations approaching 1.0 ppm (Burger and Gochfeld, 2004). Some tuna used in high-end sushi (e.g., bigeye, 0.6 ppm) can have considerably higher mercury concentrations than other common species of tuna.

The effects of cooking processes on four toxic metals (including mercury) concentrations have been investigated in various foodstuffs (Perelló et al., 2008). All food samples were randomly acquired in local markets, big supermarkets, and grocery stores of Reus, Spain. Foods included also 3 fish species: sardine, hake and tuna. The highest mercury concentrations in raw and cooked samples were mainly found in the fish group, with a clear tendency, in general, to increase the concentrations after cooking (fried, grilled, roasted, and boiled samples), which may be due to the loss of water mass.

As noted earlier in this document, a fish diet is recommended for its beneficial effects (see also JECFA, 2007). Because of the complexity of understanding information on methylmercury in fish, a simple computer program has been designed to support quantitative estimations of the intake of methylmercury and other pollutants versus the benefits (Domingo et al., 2007). The computer program is available on a website as an easy tool to optimize fish consumption; that is to say, to know which are the most suitable species, the frequency of consumption, and the size of meals. It is useful not only for professionals (cardiologists, general physicians, nutritionists, toxicologists, etc.), but also for the general population.

RIBEPEIX and RIBEFOOD: Understanding the Risks and Benefits of Fish Consumption

In recent years, based on the importance of fish as a part of a healthy diet, there has been a notable promotion of fish and seafood consumption. However, a number of studies have shown that fish might also be a potential source of exposure to chemical pollutants with well-known adverse effects on human health. Mercury has been one of the most investigated chemical contaminants in edible marine species. Salonen et al. (1995) reported that dietary fish might be protective or harmful, depending on its contents of omega-3 fatty acids and mercury. Domingo et al. (2007) determined in 14 edible marine species the concentrations of EPA and DHA, as well as those of a number of chemical contaminants, including

total mercury. This has been a controversial issue, Yoshizama et al. (2002) did not find an association between total mercury exposure and the risk of coronary heart disease (CHD), but these authors remarked that a weak relation could not be ruled out. In contrast, Guallar et al. (2002) concluded that the risk of cardiovascular disease (CVD) in a population might depend on the balance between omega-3 fatty acids and methylmercury in the fish consumed. These authors reported that high mercury content could diminish the cardioprotective effect of fish intake, which was corroborated by Virtanen et al. (2005). These authors also noted that high content of mercury in hair might be a risk factor for acute coronary events and CVD, CHD, and all-cause mortality in middle-aged eastern Finnish men. For pregnant women, nursing mothers, women who may become pregnant, and young children, the US EPA and the US FDA have advised to continue eating fish, but avoiding those species that are higher in mercury (Crawford, 2004).

It is possible to quantitatively establish the intake of various environmental inorganic and organic pollutants (risks) versus that of the omega-3 fatty acids EPA and DHA (benefits) through the use of a simple computer program, RIBEPEIX (http://www.fmcs.urv.net/ribepeix/).
RIBEFOOD and RIBEPEIX are simple software programs that enable the quantitative determination of an individual's intake of many micro- and macronutrients contained in widely consumed foodstuffs and fish, respectively. Simultaneously, RIBEFOOD and RIBEPEIX can determine the dietary intake of a number of chemical contaminants (including total mercury). RIBEFOOD is available on line at an accessible website (http://www.fmcs.urv.cat/ribefood/) designed to optimize the dietary habits of any subject by increasing the intake of beneficial nutrients and by reducing that of toxic pollutants. The programs can be useful not only for professionals (general physicians, nutritionists, endocrinologists, toxicologists, etc.), but also for the general population. However, it must be taken into account that the level of chemical contaminants in the fish and seafood was based on an analysis of samples taken from the Catalonia region of Spain. It remains unknown where these chemical concentrations are representative of fish and seafood in different regions around the world.

Shellfish

In shellfish, the percentage of total mercury occurring as methylmercury is generally less than that in finfish and much more variable (Bloom, 1992; Lasorsa & Allen-Gil, 1995; Andersen & Depledge, 1997). Since these organisms are generally in prolonged contact with the sediment, their mercury levels and species may reflect the mercury characteristics of the sediment. Despite the lower trophic level of shellfish compared to most finfish and their resulting generally lower mercury concentration, the likely influence of local sediment makes generalization about worldwide levels of methylmercury in any given species of shellfish particularly uncertain.

Marine mammals

Marine mammals, particularly in the arctic and sub-arctic, are a significant aquatic food source particularly for indigenous populations. Associations between mercury exposures and whale consumption have been reported for children in the Faroe Islands (Grandjean et al., 1995) and in whaling

populations in Japan (Endo et al., 2008). As marine mammals are high-end and long-lived predators, they tend to accumulate significant concentrations of mercury. Depending on the particular species and location, mercury in aquatic mammal muscle tends to be almost entirely methylmercury and can exceed 5 ppm (Endo et al., 2008). However, aquatic mammals tend to sequester mercury in the liver because this organ is particularly efficient in de-methylating methylmercury (and/or sequestering inorganic mercury that has been de-methylated elsewhere in the body). Levels of liver total mercury can be 10-30 times that of liver methylmercury which, in turn is generally more than double the concentration of methylmercury in muscle (Wagemann et al., 1998). Consistent with the fact that methylmercury is not lipophilic, levels of mercury in blubber are much lower than those in muscle (Wagemann et al., 1998).

The Arctic Hotspot and Traditional Diets: Methylmercury in Marine Mammals

As explained in previous sections, mercury accumulates in greater concentrations throughout the colder, northern areas of the world, making the Arctic region specifically unique for harbouring increased levels of mercury (see section 2.2). Annually, approximately 200 tonnes of mercury are deposited in the Arctic Circle and bioaccumulate in the top level of regional predators, including seals, toothed whales, and polar bears. This poses a direct threat for dietary methylmercury exposure for populations dependent on these organisms to sustain traditional diets. Mercury levels in ringed seals and beluga whales have increased by 200-400% in the last 25 years in the Arctic Regions. In Northern Greenland, where seals represent a primary protein source, 80% of the indigenous population exceed the blood mercury concentration WHO considers acceptable for pregnant women, signifying a disproportionate health threat for the developing fetus within this sub-population. A Canadian Inuit health study revealed that over 50% of the Inuit people tested had blood levels that exceeded the Canadian "no risk" level of 20 ppb, with some members of the community demonstrating as much as six times the recommended risk levels for methylmercury blood levels (Chan et al., 1997). Due to global variations of mercury deposition, infants, children, and adolescents residing within indigenous Arctic communities thus face an elevated risk of dietary methylmercury exposure as well as placental transmission. The variability of global childhood exposures to mercury remains a central component in the development of effective prevention strategies.

Other foods

While a large portion of the global population is exposed to dietary methylmercury via fish and seafood consumption, other dietary components may also pose a risk to humans, particularly pregnant women. It was noted by JECFA (2007) that the use of fish-derived meal as a protein source in poultry and swine feeds may result in exposures to methylmercury from consumption of food products from these animals. More information on this topic is needed.

A recently conducted study by Zhang et. al (2010) found an elevated concentration of methylmercury in rice (9.3 μg/kg) throughout the Guizhou province of China. Rice paddy soil is a suitable environment for sulfur reducing bacteria (SRB) and thus supports the Hg-methylation processes (Stubner et al., 1998). Additionally, detoxifying peptides known as phytochelatins, can sequester Hg^{2+} but not methylmercury in the soil, suggesting that methylmercury in rice paddy soil can readily be taken up by the rice plant. The authors calculated the personal daily intake of methylmercury and determined that rice accounted for between 94% and 96% of total methylmercury intake within a rural population. The primary source of mercury pollution in this region was attributed to coal burning power plants (Zhang et al., 2010).

Mercury continues to be found in rice even in regions where mercury-based pesticides are no longer used. A study conducted in Saudi Arabia found that the concentration in rice was 3.18 μg/kg. The authors note that this value is for rice only and does not take into consideration other dietary sources of mercury exposure (Al-Saleh et al., 2001). In addition to past or ongoing fungicide use, mining and other industrial activities introduce another route of mercury exposure into the food chain through rice consumption in some regions of the world. Elevated methylmercury content in rice is particularly concerning for populations for whom rice is the primary dietary staple, particularly because it does not contain the same important micronutrients associated with neurodevelopment and cardiovascular health that are found in fish, such as DHA, arachidonic acid and iodine (Jacobson et al., 2008). For this reason, a more protective reference dose may be necessary to protect populations from adverse effects due to methylmercury exposure via a rice-based diet, particularly for pregnant women.

In other regions of the world, mercury has not been detected in rice despite inputs of mercury into the environment. For example, in Spain, irrigation from the Ebro River did not result in elevated concentrations of mercury in rice samples (Ferre-Huguet et al., 2008). As with most metals, methods of cooking may influence mercury concentrations in consumed food (Musaiger et al., 2008). However, there is not a great deal in the literature about rice – despite the fact that it is the dietary staple of more than half of the world's population. There is a need for further studies of mercury content in rice in heavily polluted regions and of the effect of different cooking methods. In 2010 the Food and Agriculture Organization and World Health Organization Joint Expert Committee on

Food Additives established a provisional tolerable weekly intake (PTWI) for inorganic mercury of 4 μg/kg body weight. The previous PTWI of 5 μg/kg bw for total mercury was withdrawn. The new PTWI for inorganic mercury is applicable to dietary exposure to total mercury from foods other than fish and shellfish (JEFCA, 2010).

Mercury in health care and children's exposure

Mercury has been used in medicine for centuries, as a treatment for diseases such as syphilis, as a disinfectant and preservative, and as a material for restorative dentistry. Despite recent regulation of mercury in the established pharmacopoeia, mercury remains in widespread use in traditional medicines and other health-related practices. Moreover, while many mercury-containing medicines have been banned or restricted in use to reduce or prevent paediatric and other exposures, mercury continues to be used in medicine and health care, including: elemental mercury in amalgams used in restorative dentistry, (up to 50% elemental mercury); traditional medicines, neutraceuticals, and homeopathic preparations (containing mostly inorganic mercury compounds); and use of thimerosal (an organo-mercurial) as a preservative in vaccines.

Medicinal agents

While mercury has largely been removed from the pharmacopoeia in developed countries as a direct agent and limits have been set on mercury contamination in these products (Gasser et al., 1980), mercury compounds are still found in other types of products used for medical purposes. The main health impact associated with use of these products in children is acrodynia. Acrodynia is characterized by severe pain in the extremities and swelling and pink discolouration and desquamation of the hands and feet. Exposures to elemental, inorganic and organic mercury compounds have been associated with acrodynia, including elemental mercury vapour, calomel-containing teething and diaper powders, fungicides in paint, repeated gamma-globulin injections containing thimerosal, anthelmintics, termite-protected wood (mercury bichloride), ingestion of watch batteries, laxative use, and ammoniated mercury ointments applied as antibacterial agents (Dathan, 1954; Dinehard et al., 1988; Agocs et al., 1990; Graeme & Pollak, 1998; Bose-O'Reilly et al., 2010). Calomel (mercuric/mercurous chloride) was removed from widespread use in conventional medicine in the 1940's when it was recognized that it was associated with acrodynia

among infants and children.

Mercury compounds are still common ingredients in many traditional medical preparations, mostly found in the developing world (Martena et al., 2010). The globalization of products and movement of peoples brings these sources of mercury into many developed countries as well. In an evaluation of Ayurvedic medicines (for ingested use) produced in the US and India, available in stores and over the internet in the US, mercury was detectable in as much as 21% of the products from one supplier, with a median of 104 ppm in all products and 20,800 ppm in the products from one supplier. If the recommendations on intake dosages of these products were to be followed, this was estimated to result in intakes exceeding the WHO recommended acceptable daily intake (ADI) by 100 to 1000 times (Saper et al., 2008).

Medical Agents and Mercury in the Developing World: Examples from South Asia and Mexico

Throughout the developing world, many cultures have historically attributed various healing powers to mercury. Some populations believe that the rapid and volatile movement of liquid mercury will enhance the power of other remedies for health ailments (UNEP, 2008). Due to the lack of regulation concerning traditional medicines in a significant portion of the world, specific mercury-containing agents may exceed safe levels (Martena et al., 2010). This poses a significant concern for childhood exposures and for pregnant women.

Ayurvedic medicine describes a traditional medical system practiced in India, China and other parts of South Asia. Some Ayurvedic medicines are composed of only herbal ingredients, while another class, known as *Rasa Shasta,* describes herbal mixtures combined with certain heavy metals, including mercury (Saper et al., 2008). *Rasa Shasta* is used widely for various medical ailments and is often given to infants and children. Marten and colleagues (2010) investigated the heavy metal content of traditional Chinese and Tibetan *Rasa Shasta* preparations. Of 59 *Rasa Shasta* samples tested, 50 traditional herbal preparations significantly exceeded the safety limit for mercury as established by WHO recommended ADI (Martena et al., 2010). In Mexico, liquid mercury is encapsulated and sold as a traditional remedy for indigestion and gastro-intestinal problems. Known as *azogue,* these capsules are thought to dislodge gastro-intestinal blockages, particularly in young children. While the extent of *azogue* use is largely unknown and unrecorded, the direct ingestion of liquid mercury may pose an exposure risk for children and pregnant women throughout Mexico (Geffner & Sandler, 1980).

Mercury is also a contaminant in so-called neutraceuticals (defined as foods or food products with health or medical properties); as reported in Croatia in 2003, more than 50% of neutraceuticals tested contained

mercury concentrations in excess of amounts allowed by standards of the European Union (Dragun et al., 2003). Mercury is also utilized in homeopathic medications available over the internet and counter in many countries (5 mercury containing preparations were listed on line at http://www.abchomeopathy.com/shop.php).

Exposure to Traditional Medicines in Canada

There are numerous case reports in the literature of clinically significant mercury poisoning in the developed world related to the use of traditional medicines from many different traditional medicine practices including Chinese, Ayurvedic, Caribbean and African cultures. This case study will summarize a report of twins in Canada who developed significant mercury toxicity related to the use of a "teething powder" that contained inorganic mercury (Weinstein et al., 2003).

The twins had been given a "teething powder" from India once or twice a week for four months. They presented with a one-month history of weakness, anorexia, a papular rash and swollen red and painful hands and feet. They had regressed developmentally and were unable to feed orally, sit or walk. On examination they were irritable, diaphoretic, apyrexial, tachycardic, hypertensive and had reduced muscle power and diminished reflexes. Their palms and soles were erythematous with desquamation consistent with acrodynia. They had markedly raised blood mercury concentrations of 176 and 209 μmol/l and they were treated with chelation therapy with DMSA (2,3-dimercaptosuccinic acid). Over the next 8 weeks they showed some improvement in their neurological function; unfortunately they were lost to long-term follow up and so the final outcome is unknown. This case illustrates the significant risk of mercury toxicity associated with these products.

Dental amalgams

Dental amalgams, used for restorative dentistry, usually contain 50% elemental mercury by weight in formulation with silver (Brownwell et al., 2005). There is clear evidence that Hg is released from amalgams mostly as a vapour. Ingestion may also be a route of exposure during installation of restoration. There is also clear evidence that biomarkers of absorbed Hg are increased in persons with amalgams, over the short term. At present, there is uncertainty regarding potential health risks associated with amalgams (Barregard et al., 2008; Lauterbach et al., 2008; Rasines et al., 2008), but because of continuing consumer concern, occupational exposures, and problems in ensuring proper management of mercury-containing wastes, some authorities have recommended the phase-out of mercury amalgams in dentistry. Some alternatives to mercury-containing amalgams have included composite resin, gold, porcelain, or glass fillings, though the safety of these alternative materials has not been established. (Pichay, 2004).

It is important to note that many developing nations depend on amalgam technology as a primary means of oral health management. The WHO Global Oral Health Programme asserts that access to affordable dental restorative materials is imperative for poor and disadvantaged populations and thus has reviewed and evaluated the use and safety of dental amalgam for many years. In 1997, a WHO Consultation on Dental Amalgams and Alternative Direct Restorative Materials unanimously approved a Consensus Statement on Dental Amalgam stating that there was no direct filling material that had the wide indications for use, ease of handling and good physical properties of dental amalgam. In most of the low- and middle-income countries, the use of dental amalgam remains the only appropriate material for dental fillings or build-up material, as the alternative materials are far too expensive. Moreover, WHO concluded that amalgam restorations are durable, cost-effective and generally considered safe for the patient, although adverse biological reactions to the materials have been known to occasionally occur (WHO, 1997; WHO, 2002).

Thimerosal or Thiomersal

Thimerosal is an organomercurial that contains 49.6% ethylmercury and has been used as a preservative in a range of medications, such as skin creams, eye drops, and vaccines since the 1930s. Uses of thimerosal in topically-applied preparations has largely been discontinued on the basis of reports associating these uses with contact dermatitis in as many as 10% of persons using these preparations (Van t'Veen, 2001). This compound is used to prevent bacterial and fungal growth in some vaccines during use of opened multi-dose vials and in situations lacking adequate resources for preservation, such as refrigeration. In 1999, concerns were raised about the mercury in infant immunization schedules. However, in 2006, WHO's Global Advisory Committee on Vaccine Safety found no evidence of toxicity to infants, children or adults exposed to thiomersal (containing ethylmercury) in vaccines. In addition, the committee concluded that there is no reason to change current immunization practices with thiomersal-containing vaccines, as the risks of the compound remain unproven (WHO, 2006; WHO, 2007).

Thermometers, switches, and gauges

The continued use of mercury in thermometers and other pressure gauges present opportunities for inadvertent exposures when this equipment

breaks as well as increased costs for proper disposal. When mercury-containing equipment breaks, the mercury can be dispersed throughout the surrounding environment and can pose a long-term, and often unnoticed, exposure threat. This may pose a particularly hazardous exposure in indoor environments that are not well ventilated. This has been a major impetus for replacement of these items in health care settings. Exposures of children to mercury used in these products are primarily associated with spills and also with deliberate misuse by children. Although unintended, exposures through misuse are frequent occurrences, with well-documented health impacts on children. Purposeful misuse is also an important aspect of children's exposures, specifically with respect to the attractiveness of elemental mercury in its liquid form.

Accidental exposures to mercury from equipment in health care settings

The use of mercury containing instruments in medical care has been associated with accidental exposures, increasing the pressure to remove mercury from these products. Mercury-containing thermometers, sphygmomanometers, some barometers, manometers, switches and gauges used in medical instruments, thermostats and some medical tubes are a concern in hospital environments because they can release elemental mercury vapours when broken. Breakage of mercury thermometers and improper mercury waste management has resulted in significant human exposure and contributed to environmental mercury contamination globally. The production and use of mercury thermometers is decreasing and some countries have restricted the use of mercury thermometers, but they are still in demand. Mercury-free thermometers are more and more accepted. The WHO recommends the use of mercury-free thermometers in health-care and domestic settings. Affordable alternatives are available, though some alternatives may require appropriate consumables (WHO, 2005).

Sphygmomanometers are the most serious source of mercury spills (they can contain about 10 ml) as they can easily be knocked off their holders and release mercury onto the floor. This represents a significant exposure hazard for health care personnel, patients, and the environment. The WHO recommends mercury sphygmomanometers be gradually phased out for affordable, mercury-free alternatives as more become available in low resource settings. The WHO has explored the possibility of an accurate and affordable alternative for low resource settings and have recently field

tested and validated a solar-powered, digital sphygmomanometer (WHO, 2005).

Some barometers, manometers and gauges utilized in medical instruments contain mercury to obtain precise readings of changes in air pressure. Some infrared heaters and ovens use a flame sensor/safety valve that may contain mercury (Wisconsin Department of Natural Resources, 2007). No data was found in the literature about the amount of these items present in medical devices. Mercury's high conductivity and its liquid state at room temperature make it a functional component of electrical switches such as thermostats. The US EPA estimates that 90% of the 70 million residential thermostats in the United States contain approximately 4 g of mercury (US EPA, 1994). A 1979 survey of infant incubators in the Special Care Nurseries of Los Angeles County, California, USA, showed 18 out of 42 units with detectable concentrations of mercury vapour. In 12 cases the air mercury concentrations in the thermometer holder exceeded 0.05 mg/m^3. In 16 incubators the contamination could be traced to broken mercury containing thermometers used to monitor incubator ambient temperatures. The highest mercury vapour levels were detected in the presence of broken glass irrespective of the release of elemental mercury. Finally, there was no difference in mercury levels between those incubators maintained at room temperature or at higher temperatures (Waffarn et al., 1979).

In 1980 the case of a healthy newborn contaminated by inhalation of mercury vapour from a broken mercury expansion switch in the heating system of the incubator was described. The infant was maintained in the incubator only for the first 19 hours of life. One day after, urine mercury concentration was reported to be 340 μg/l and then ten days later dropped to 4.0 μg/l (McLaughlin et al., 1980).

Consumer Goods

Mercury may be present in consumer products through deliberate addition or contamination. Children can be exposed to mercury compounds through direct use, accidental or purposeful misuse, and eventually through releases of mercury into the environment as a consequence of product disposal.

Soaps

Mercury continues to be used in soaps for antimicrobial and antifungal properties (usually as phenylmercury) and for cosmetic qualities (usually inorganic mercury). In a small study conducted in Tanzania, Harada et al. (2001) found that a widely used soap product contained over 1000 times the concentration of mercury (as high as 1.7%) as compared to a reference product, and that persons reporting use of this soap had elevated hair mercury and symptoms consistent with inorganic mercury poisoning, including tremor, lassitude, vertigo, neurosthenia, and black and white skin blots.

Cosmetic creams

Skin-lightening creams containing mercury are also in widespread use. An estimated 25-67% of women in sub-Saharan Africa use mercury-containing skin lightening creams daily (Del Giudice et al., 2003) and there are reports of this use among the African diaspora in other regions of the world including the Caribbean nations (Arsouze et al., 2008). These preparations can contain very high concentrations of mercury (up to 57,000 ppm based on an analyses conducted in Hong Kong), and mercury in these formulations was rapidly absorbed resulting in substantial elevations of urine and blood mercury concentrations (Sin et al., 2003).

Mercurial fungicides and pesticides

Mercurial compounds were widely used in pesticides – fungicides and insecticides – through much of the 20th century. One of the most significant outbreaks of acute human intoxication, affecting children as well as adults, involved a phenylmercury-based fungicide used to treat seed grain. This episode of unintended use, in which seed grain was used to make bread in Iraq, has been extensively reported (see WHO EHC Mercury 1990). Even after this tragic event, use of mercurial pesticides may still occur in certain regions or countries, as documented in a report from the Amur region in 2003 (Katola et al., 2003). An inventory of mercury production and use in Russia conducted by the Danish Environmental Agency reported that several mercurial pesticides were in use as of 2005, despite a ban on production of Granozan (containing mixtures with hexachlorobenzene (mercurbenzene) and hexachlorocyclohexane (mercurhexane)(http://www2.mst.dk/common/Udgivramme/Frame.asp?http://www2.mst.dk/udgiv/Publications/2005/87-7614-539-5/html/kap01_eng.htm)

In 2000 mercury-containing pesticides were still used in 15 regions and about 50 tonnes of Granozan were applied for a total of about 1 tonne of mercury (at average Hg concentration in Granozan equal to 2%). According to the US EPA, mercury based pesticides are also registered for use in Canada to prevent turf mould (http://www.epa.gov/glnpo/bnsdocs/hgsbook/agr.pdf accessed 2.2.2010). Application of mercury containing pesticides can contribute to ecosystem contamination (and transformation into methylmercury in aquatic systems) and to uptake by certain food products, notably rice (Peralta Videa et al., 2009; Islam et al., 2007). Mercurial pesticide contamination and uptake by specific plant species may occur in rice paddies (Ackerman et al., 2010). Similar to organochlorine insecticides and lead arsenate, soil contamination with mercury from former agricultural uses can persist for several decades. More information is needed on current uses of Hg-containing pesticides and fungicides.

Traditional practices

Some traditional practices employed for cultural and religious purposes can be associated with mercury exposures. A number of practices occur worldwide that utilize mercury, including Santeria (Afro-Hispanic tradition), Espiritsmo (Puerto Rican), Voodoo (Afro-Haitian), Palo Mayombe (Caribbean), Candomble (Afro-Brazilian), and various forms of Ayurvedic medicine (Dargan et al., 2008). Mercury is additionally employed in the Hindu practice of Parad, in which mercury is used as an amalgam to create religious relics (UNEP, 2005). For many ritual reasons, liquid mercury is scattered in a room or burned in a candle, or carried in a small container as a talisman (US EPA, 2002). These traditional practices may be specifically important for children as many practices using mercury are employed to protect youngsters from accidents or bad omens (UNEP, 2005). However, the exact extent of mercury use through these practices is largely unknown and it may be difficult to ascertain these exposures when children present with symptoms of mercury poisoning (Singhvi et al., 2005).

Intended and unintended uses of products containing mercury

Accidental mercury spills

In the US, elemental mercury was reported in the period 1993-1998 to be one of the 10 most frequently released hazardous substances, and 20% of

Table 1
Fixed-facility mercury events, by location type, HSEES, 1993-1998 (Zeitz et al., 2002).
Reproduced with permission from Environmental Health Perspectives

Location	Frequency	Percent
School/university	79	20.3
Private residence	65	16.7
Health care facility	64	16.5
Public utilities	49	12.6
Manufacturing	39	10.0
Public administration	19	4.9
Transportation[a]	13	3.3
Wholesale or retail trade	8	2.1
Agriculture/mining/construction	6	1.5
Entertainment and recreational services	6	1.5
Professional and related services[b]	6	1.5
Finance, insurance and real estate	5	1.3
Business and repair services	5	1.3
Active military duty	4	1.0
Lodging place	1	0.3
Unknown	20	5.1
Total[c]	389	99.9

[a]Includes warehousing/storage, postal service, and air transportation facilities. [b]Includes libraries, museums, and research and development facilities. [c]Percentages may not total 100% due to rounding.

these spills occurred in schools (Risher et al., 2003; Zeitz et al., 2002). See Table 1.

In terms of exposure risks to children, spills were frequently reported in educational settings. At colleges and universities, the major factor related to mercury spills was equipment malfunction (22%) followed by improper waste disposal (11%), while at elementary and secondary schools, the major factor involved children deliberately taking and playing with mercury (45%).

Deliberate misuse

As indicated above, younger children are often attracted to elemental mercury because of its unique physical properties including: silver appearance, density and tendency to form beads (MacLehose et al., 2001). The numerous sources of elemental mercury accessible to children include thermometers, old barometers and electrical switches as well as the liquid metal sometimes used in school laboratories (Goldman et al., 2001).

Mercury removal from school laboratories

Elemental mercury is aptly described as an "attractive nuisance" – that is, a material that is interesting or intriguing such that children or others engage in dangerous behaviours to obtain it and play with it. The availability of elemental mercury in school laboratories has been associated with a number of events involving children playing with mercury obtained through chance discovery, deliberate tampering with mercury-containing equipment or unauthorized removal. For example, one event in which children found liquid mercury in a waste container resulted in exposures of 24 persons (Sims et al., 2004). After one child removed mercury from a school laboratory; 23 additional persons were identified as having contact with mercury through that child (Tominack et al., 2002). Many of these persons had very high urine mercury levels, and 11 were symptomatic, including two children with severe dermatologic manifestations. Another event involved a child who took liquid mercury home from a school laboratory and handed it to a group of students on the school bus (Azziz-Baumgartner et al., 2007). Sixty-two students were identified as having direct contact with this mercury, and eventually 200 students were evaluated. Self-reported contact with mercury was associated with elevated biomarkers for mercury exposure; only nonspecific symptoms were reported. See Table 2.

Table 2

Urinary mercury levels of students according to self-reported risk behaviour, assessment of mercury exposure in a middle school, Nevada – 2004 (reproduced from Azziz-Baumgartner et al., 2007).

Reproduced with permission from Clinical Toxicology

Risk behavior	Yes µg/L (n)	No µg/L (n)	Two-sided p-Value
Saw mercury	0.43 (66)	0.31 (131)	0.003
Touched mercury	0.50 (36)	0.33 (159)	0.003
Got mercury in their clothes	0.49 (28)	0.33 (170)	0.02
Reported having mercury at home	0.80 (4)	0.34 (194)	0.46

µg/L (n) = mircrograms of total mercury per liter of urine.
(n) = number of participants who reported a specific risk behaviour.

Mercury contamination was found on the school bus and in many places at the school, including the boys' lavatory, school lockers, hallways, and the gymnasium. Mercury vapour levels >50 µg/m^3 were measured by the state EPA in the hallway near the lockers.

A similar event was investigated by the US CDC and EPA, involving a student who had taken mercury from a school laboratory and also from a dental office (Sims, 2004). By the time the event was discovered, significant exposures had occurred involving many students and contaminating extensive parts of the school as well as the student's home. Very high

levels of mercury were measured in air in the school cafeteria (between 5 and 36 μg/m^3) and in the urine and blood of several persons, including the student's family members. Dermatologic manifestations were reported, especially among younger children. Extensive cleanup was required; the mobile home in which the student lived had to be destroyed, along with a car owned by the family of another student reporting frequent "play" with mercury. From 1999 until the end of 2005, the state of Kentucky experienced a total of 15 mercury spills, 10 of which were associated with schools. In November 2004, a 15-year-old student brought a vial of liquid mercury onto a school bus and into a high school in Kentucky. Mercury had been in the student's possession for more than one year and large amounts had been spilled in multiple places, including the mobile home in which he lived with his family. Blood concentrations, obtained from this student and seven family members ranged from 32 to 72 μg/l and the 24-hour urine levels from 28 μg/l to 496 μg/l. Within the examined family, the student showed the highest mercury levels in both blood and urine. Urine mercury concentrations were directly associated with the amount of time spent in the mobile home (Sims, 2004). In October 2003 in Washington, DC, USA, students stole a container with 250 ml of liquid mercury from a science laboratory and spread it around the school and grounds. The school was shut down and decontaminated. More than 100 homes were found to be contaminated, city buses had to be cleaned because of the mercury contamination, and 1,300 students were evacuated in temporary classrooms. Due to the rapid intervention, only five people showed symptoms of mercury exposure, but the cleanup and investigation costs were in the millions of US dollars (Pike-Paris, 2004).

There are fewer data on these types of exposures outside the US. Mercury intoxication in three Turkish adolescent students with a history of exposure to Hg^0, the source being broken barometers taken from school laboratories 2-4 months previously, has been reported by Koyun et al. (2004). One of the students died; the others recovered over a period of 1-4 months.

Development of In-School Mercury Management Guidelines

Worldwide, many school systems lack proper chemical contamination management guidelines, particularly as it pertains to mercury spills and deliberate misuse. For example, in 2006, the National Poisons Management and Control Center at the Phillipine General Hospital in Manilla, Phillipines, received a 14 year old boy with symptoms of redness, numbness, and pain the extremities. The health effects signified elemental mercury exposure and an alleged mercury spill had occurred in the boy's classroom three days earlier, unknown to school authorities.

Reports from formal interviews indicated that a few children had played with two mercury filled beakers (containing an estimated 100-200 g each) and spilled approximately 326-408 g of elemental mercury in the room. The children applied the mercury to their hair, skin, and other body parts, while others took the mercury home with them. In total, approximately eighty students (13-14 years old) and the teacher were directly exposed to elemental mercury via dermal exposure and inhalation. Within 13 to 16 hours post exposure, ten students were admitted to the hospital with symptoms of chest pain, difficulty breathing, itchy rashes, fever, and body malaise. Additional symptoms included headache, muscle pain, nausea, numbness and redness of extremities.

The school was closed for clean-up and the Inter-Agency Committee on Environmental Health established regular meetings with 14 national agencies to open transparent dialogue on the issue of mercury exposure in the school setting. It became immediately evident that the nation lacked proper guidelines for in-school mercury management. The committee has since established a phase-out of mercury in schools, developed a disposition plan for existing mercury, and conducted a mercury inventory for schools nationwide.

Such exposure scenarios highlight the need for first response guidelines and management plans for mercury spills in school settings in order to protect vulnerable, school-age populations. Further, school curricula should emphasize the dangers of mercury exposure to increase awareness among students, teachers, and academic administrators to prevent human and environmental exposures. Coordinated efforts between school systems and national health departments are imperative in the implementation of strategies measures to reduce in-school mercury exposures.

Exposures to mercury in residential settings

There are several exposures to mercury not associated with specific products, which may be important to children in specific regions.

Mercury in paints

Phenylmercuric acetate has been used in interior latex paint formulations as an antifungal (anti-mildew) agent up to concentrations as high as 2000 ppm in latex paints (Buesterian et al., 1991). This use has been discontinued in the US since 1990 following reports that mercury could be released as a vapour from painted surfaces leading to exposures that were associated with acrodynia in young children (Agocs et al., 1990; Mielke & Gonzalez,

2008). Overall, there is very little information available on mercury use in paints around the world.

Exposure to mercury from coal burning in homes

Globally, coal is a major source of mercury emissions into the atmosphere through fossil fuel burning. There is no report on mercury exposures associated with coal burning in stoves or heaters in the home. However, Finkelmann et al. have raised concerns based on strong evidence for exposures to and toxic effects of arsenic, fluoride, and thallium associated with this practice, as well as the presence of high concentrations of mercury in coal used in some regions of China for this purpose (Finkelman et al., 2003).

Fluorescent light bulbs

Fluorescent light bulbs contain mercury as a ballast for regulating electrical current. While this does not result in releases during normal use, these light bulbs are fragile and easily broken. The use of compact fluorescent light bulbs (with an average mercury content of 2.4 mg of elemental mercury) has dramatically increased over the past few years. The appeal of compact fluorescent light bulbs (CFLs) is directly due to their significant increased energy efficiency (75%) as compared to incandescent light bulbs and their greater life span of use (Stemp-Morlock et al., 2008). After breakage, 30% of the mercury release occurs during the first 8 hours. In the hour immediately following the break of a CFL, mercury gas concentrations near the bulb shards are between 200 and 800 $\mu g/m^3$. The average 8-hour occupational exposure limit set by the US Occupational Safety and Health Administration (OSHA) is 100 $\mu g/m^3$. Because the use of CFLs will reduce demand for electricity (often generated through coal burning), there is no dispute over the lifecycle analysis in terms of a net reduction in overall mercury releases. However, there is a new public health issue of preventing direct exposure to children at home, specifically if not well-ventilated, if the bulb breaks in the household. The US EPA website lists the following actions to reduce exposure when a CFL breaks, including: opening a window, leaving the room for 15 minutes, and methods for the physical clean including sealing the bulb in a plastic bag up (US EPA, 2009). It is equally important to note the danger of exposure to individuals who work in waste management, specifically for pregnant women or in the case of a take-home exposure scenario. Recent findings indicate that once in municipal waste sites, broken CFLs continue to be a source of mercury exposure for several days (Southworth et al., 2005).

Antiques at home

Lesser known sources of elemental mercury include some antique or vintage objects and instruments kept in the home. The unique properties of the elemental mercury prompted, in fact, its use in wall-clocks with temperature-compensated pendulums made in the late 19th and early 20th centuries; in barometers constructed beginning from the mid 17th century in which liquid mercury (140-180 g) was used to replace air in the glass tube; and in mirrors made by layering a thin amalgam of approximately 75% tin and 25% mercury to a backing of flat plate glass during the 16th through the 19th centuries (Calvert, 2007). Finally, elemental mercury was used as a weight in some antique floor and desk lamps to assure better stability. As mercury-containing antiques become more fragile through aging there is an increasing risk of mercury exposure at home due to breakage. Additional potential exposure is possible during winter months, when heating systems are running in houses and there is less ventilation, and, consequently, the indoor mercury vapour concentrations may increase. Removal of mercury spills with a vacuum cleaner or vapourization from spill-contaminated surfaces such as carpets, floors, furniture, mops, or brooms can elevate mercury air concentrations (Agency for Toxic Substances and Disease Registry, 1999).

Exposures to mercury through residential building contamination

This is an uncommon source of children's exposure to mercury, but as former industrial buildings are recycled for living spaces in many cities around the world, these exposures can occur if the structure is not checked for mercury contamination on the basis of information on past uses.

The renovation of old industrial properties for residential purposes is increasingly popular in many cities in de-industrializing countries such as the US, many parts of the European Union, and in major Chinese cities. This can result in exposures to hazardous materials if insufficient information is available on past uses or if inadequate assessments are done prior to conversion from industrial to residential use. A pertinent instance occurred in New Jersey in the 1990s (Gochfeld et al., 2003; Orloff et al., 1997). A building that had been used for several commercial activities became contaminated by mercury during production of electric vapour lamps in the 1930s prior to its conversion to condominiums in 1994. When residents moved in, pools of mercury were observed, prompting them to

notify the city Board of Health. Investigations by the state of New Jersey and by the Agency for Toxic Substances and Disease Registry (ATSDR) revealed air mercury concentrations as high as 888 μg/m^3 (the US EPA's reference concentration is 0.3 μg/m^3). Urine mercury concentrations in 29 residents ranged from 10.5 to 127.6 μg/l, with a mean of 47.2 μg/l. Ninety percent had normalized mercury concentrations >20 μg/l (Gochfeld et al., 2003; Orloff et al., 1997). Several of these persons reported symptoms, and 37 residents were assessed by physicians (Fielder et al., 1999). In adults, impaired neurobehavioural performance was correlated with degree of exposure (by urine mercury measurement). A high level of psychological distress was also observed in the group. The building was first evacuated and later condemned by the US EPA.

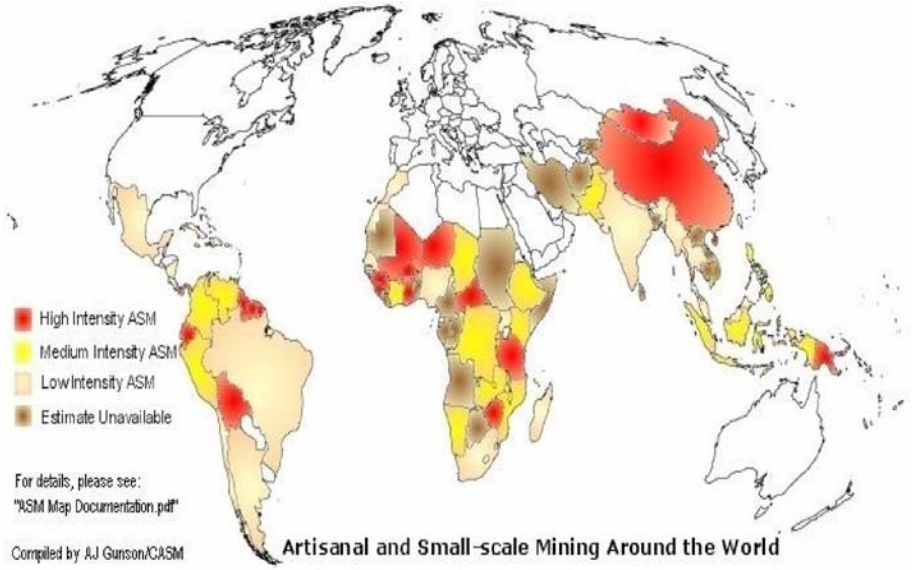
Occupational Exposure

Children are rarely employed in industries in which mercury exposures occur, but they are often exposed to mercury through work in the informal sector. Two important examples, involving significant numbers of children globally, are small scale or artisanal mining, and waste scavenging. Children may also face an increase risk for mercury exposure via take-home exposures from parents, siblings, and other family members engaged in these activities.

Children in mining

Children (and women) make up a significant portion of the world's population of artisanal gold miners. Artisanal and small-scale gold mining (ASGM) describes gold mining activities that utilize rudimentary techniques, labour intensive processes, and involve small groups of individuals. The activities are usually un-mechanized apart from perhaps a water pump or a compressor. As part of the informal sector, small-scale gold miners do not typically hold exploration or mining licenses. ASGM most commonly occurs in rural areas throughout the developing world where economic opportunities are extremely limited (ILO, 2004). See Figure 7.

Figure 7
Artisanal small scale mining intensity worldwide: Intensity of small-scale mining is shown based on estimates compiled by the Communities and Small Scale Mining (CASM) group at the World Bank. No distinction was made between ASGM and other small-scale mining in the collection of these data.
Reproduced with permission from Communities and Small Scale Mining.



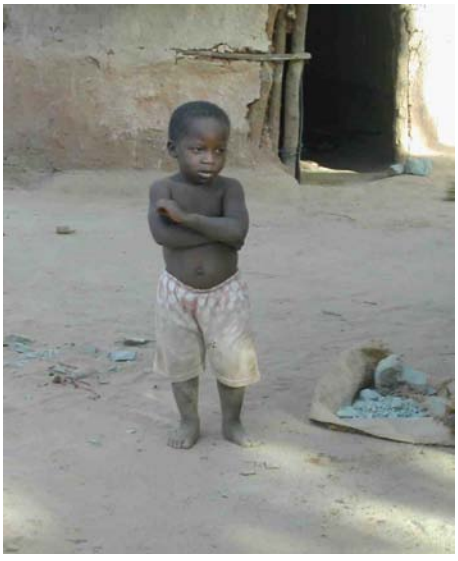
ASGM commonly involves the extensive use of mercury during gold extraction. When added to gold-laden silt pulverized rock, mercury forms an amalgam with gold particles. This amalgam is heated over a fire or by blowtorch to vapourize the mercury and isolate gold. Mercury amalgamation is the preferred method of extraction in ASGM due to mercury's availability, low capital cost, ease of use and transport, and absence of alternative technologies. These uses result in the release of an estimated 1000 tonnes of mercury per year, constituting approximately 30% of the world's anthropogenic mercury emissions and the greatest source of intentional mercury release into the environment. In a worst case scenario, as much as 95 percent of mercury used in ASGM can be released into the environment, constituting a danger to human health (Veiga, 2005).

While the exact number of people participating in ASGM is difficult to calculate, it is estimated that 10 to 15 million individuals directly participate worldwide (Veiga, 2004), including up to one million children (UNEP, 2008). An additional 100 million people in over 55 countries depend on ASGM for their income. The magnitude of ASGM is also difficult to

assess due to its illegal status and often transient character; however, it is estimated that ASGM produces approximately 20-30% of the world's gold, or approximately 500-800 tonnes per year (Navch, 2006).

Poverty and the lack of alternative economic opportunities are the driving force compelling children to become involved in ASGM. Many families transition their children from school to the mines when they reach 8–12 years of age. Younger children who do not directly participate in ASGM may be exposed to elevated levels of mercury by spending time close to ASGM locations where family members are working (Bose-O'Reilly, 2008). Child labour in ASGM is considered among the worst forms of child labour due to the extent and severity of the hazards and the risks of death, injury and disease (IPEC, 2005). The informal character, remoteness, and mobility of ASGM collectively pose a challenge to estimating the number of children involved; however, it is estimated that approximately one million children engage in ASGM worldwide (UNEP, 2008). In the Sahel Region of Burkina Faso and Niger, it is estimated that children constitute 30 to 50 per cent of the ASGM workforce, and approximately seventy per cent of these children are below the age of 15 (IPEC, 2006). In Ghana, an estimated 10,000 children are involved in ASGM, while 65,000 children are thought to participate in Bolivia, Ecuador and Peru (IPEC, 2006).

Figure 8
Child in Zimbabwe, mercury contaminated tailings in front of his home (® S. Bose-O'Reilly). Reproduced with permission from S. Bose-O'Reilly



While the division of labour involved in ASGM varies significantly from one site to another, children commonly play a major role in mercury amalgamation since it does not require immense strength. During the amalgamation process, metallic mercury may be absorbed through the skin. This route of exposure is common since use of personal protective equipment is rare. Children also are exposed to mercury through inhalation during the burning process. This exposure pathway can be magnified when burning is conducted in the home. Women are often involved in burning amalgam, which can result in very high exposures to mercury compounds. Children not actively participating in ASGM still face exposure to vapourized mercury from family members burning amalgam in the home or in their proximity. A study conducted in the Philippines found that 11% of children who were not active miners but lived in proximity to ASGM activities demonstrated mercury intoxication, while 27% of children who worked directly with mercury in the ASGM sector were classified as intoxicated (Bose-O'Reilly, 2005b).

Children who work in the ASGM sector or live in nearby communities may also be chronically exposed to mercury via ingestion of contaminated fish or rice or breast milk from their mothers, who may also work in or be secondarily exposed to mercury from this activity. Children whose parents work as miners may be exposed to mercury residue on the clothing, hair, and skin via "take home exposures" from the occupational setting. It is estimated that for every g of gold recovered in ASGM, 1 to 2 g of mercury is directly released into the ground (UNEP, 2008). This mercury can then be bio-transformed to methylmercury and integrated into the food chain through the processes described in previous sections. A study of Amazonian children living in an ASGM community demonstrated that 65% of children aged 2-6 years, and 50% of children aged 7–12 years surpassed the 10 μg/g limit (Pinheiro et al., 2007). Mercury is additionally excreted into breast milk. In a study of breast-feeding women in Indonesia, Tanzania, and Zimbabwe, fourteen of the 46 breast milk samples exceed 4 μg/l. Within this study population, twenty-two of the 46 children had a higher calculated total mercury uptake. One child's total mercury uptake was found to be 127 μg, a figure that greatly exceeds the recommended maximum uptake of inorganic mercury. A majority of infants in developing nations are breast-fed (Bose-O'Reilly, 2008a).

Children working in the ASGM sector or living in ASGM communities experience multiple routes of exposure to mercury (see Figure 8). Several

studies have found elevated blood mercury concentrations in children working in the ASGM sector. Children who do not directly participate in ASGM but live in, or in proximity to, ASGM communities have also been found to have elevated mercury loads in biological samples. A study that assessed childhood gold miners in Zimbabwe, Indonesia, and Tanzania discovered that concentrations of mercury in urine, blood, and hair were significantly higher than the control group, and that peak mercury concentrations of children were as high 941 μg/l in urine, 100 μg/l in blood, and 53 in μg/g hair. Children who did not work in ASGM but lived in the mining community also demonstrated statistically significant higher levels than the control group (Bose-O'Reilly, 2008b).

Table 3. Laboratory data from 166 children from Indonesia and Zimbabwe.

Data	Control group (CG)	Children living in Hg-exposed areas (EG)	Children working with Hg (WG)
Urine Hg (µg/l)###		***	***
N	50	36	80
Mean ± S.D.	0.58 ± 0.54	10.20 ± 12.40	47.35 ± 146.35
Median	0.40	6.49	10.05
Minimum	<0.20	0.35	0.29
Maximum	2.15	70.53	941.89
95% percentile	1.88	29.87	203.54
Urine Hg (µg/g creatinine)###		***	***
N	50	36	80
Mean ± S.D.	0.35 ± 0.26	9.16 ± 11.32	36.50 ± 93.06
Median	0.32	5.31	7.06
Minimum	<0.20	0.68	0.43
Maximum	0.98	56.41	666.87
95% percentile	0.88	38.60	175.92
Blood Hg (µg/l)###		***	***
N	50	36	80
Mean ± S.D.	2.95± 2.21	5.52 ± 2.39	12.40 ± 14.66
Median	3.47	5.25	7.75
Minimum	<0.20	1.28	1.00
Maximum	7.94	12.40	100.80
95% percentile	7.10	10.96	47.42
Total Hg hair (µg/g)###		***	***
N	42	33	75
Mean ± S.D.	1.23 ± 0.81	2.27 ± 0.83	4.08 ± 7.07
Median	1.08	2.31	2.34
Minimum	0.02	0.42	0.45
Maximum	3.46	4.16	52.96
95% percentile	2.62	4.02	16.08
Organic Hg hair (µg/g)			
N	27	31	70
Mean ± S.D.	1.25 ± 0.71	1.36 ± 0.72	1.55 ± 1.21
Median	1.10	1.34	1.21
Minimum	0.12	0.06	0.09
Maximum	3.25	2.86	5.86
95% percentile	2.96	2.69	4.15
Inorganic Hg hair (µg/g)###		***	***
N	27	31	70
Mean ± S.D.	0.17 ± 0.14	0.95 ± 0.79	2.66 ± 6.73
Median	0.11	0.66	0.87
Minimum	0.03	0.16	0.10
Maximum	0.61	4.02	49.04
95% percentile	0.57	2.85	12.55

***p<0.001: Mann-Whitney test (exposed groups versus control group).

###p<0.001: Kruskal-Wallis test.

Table adapted from Bose-O'Reilly (2008b)

In terms of health risks, the interactions between mercury-induced immunotoxicity (Silbergeld et al., 2005) and the inadequate hygienic conditions in many ASGM communities may place children at risk for infectious diseases. This has been specifically considered in the Amazon where exposure to mercury may increase risks of malaria infection in ASGM communities (Silbergeld et al., 2005).

Waste scavenging and recycling

Approximately 50 million tonnes of electrical and electronic waste (e-waste) is generated annually and is known to contain numerous environmental toxicants, including mercury. Children throughout the developing world are a major component of the informal workforce involved in waste scavenging or picking. Exposures of children to mercury through these activities are not well documented, because this occupation often involves the informal economy and street children. However, it is recognized as one of the "potential worst forms of child labour" by the International Labour Organisation (ILO, 2004). Because of this, there are relatively few studies of toxic exposures to children involved in these activities. Hunt (1996) reviewed studies of scavenger children and also studied exposures and health impacts among children in waste picking in Bangalore. No information was collected on types of waste or specific exposures. As compared to a group of children not employed in waste picking, there were significant differences in health indicators, including infections, abdominal pain, and fever, pallor, and lymph node enlargement. The International Program on the Elimination of Child Labour (IPEC) of the ILO undertook an examination of child waste pickers and scavengers in several countries in the world (ILO, 2004). No information was reported on details of these activities or potential exposures. The conclusions indicated a "significant lack of detailed information" and a low rate of success for interventions in terms of increased school enrollment and decreased participation in scavenging.

There is clearly a need for more information particularly in the context of increased disposal of hospital and e-wastes, which can be expected to present opportunities for exposure to mercury. The transfer of risks through uncontrolled transnational movement of wastes has been well documented and continues to grow, despite the adoption of the Basel Convention and other policies to constrain this practice (Robinson, 2009). Some of these wastes, particularly electronic wastes, have been directly

associated with significant exposures to mercury, among other heavy metals. (Tong & Wang, 2004). Globally, waste incineration and open air burning remain a common practice and significantly contribute to toxic chemical load in the atmosphere (Wong et al., 2007).

Parental exposures

Children face an increased risk of mercury exposure even if they are not actively participating in the aforementioned occupational sectors. For example, studies have shown that children who live in proximity to, but do not work in, mining areas that utilize mercury demonstrate higher levels of mercury biomarkers than children who do not live in proximity to these areas (Bose-O'Reilly, 2008). This fact reflects mercury's ubiquitous and persistent nature, as well as its ability to geospatially disperse once it enters the environment. Additionally, children may be exposed to mercury via take home exposures of their parents, siblings, or relatives who work with the metal as miners or scavengers. Mercury may settle on the hair, skin, and clothing and be transported back to the living environment where infants and young children are likely to spend a majority of their time. Mercury may settle within the home and present a chronic low-dose exposure scenario for children. In addition, maternal occupational exposures present a significant mercury exposure risk for the unborn fetus.

Toxicokinetics of mercury in children

Understanding the toxicity of mercury exposures as well as interpreting biomarkers of exposure requires an understanding of the toxicokinetics of specific mercury compounds, particularly in children. This topic is described in this section.

In terms of toxicokinetics, much is known about the processes that regulate ADME (absorption, distribution, metabolism and excretion) of different mercury compounds. Methylmercury can rapidly cross biological barriers, including the gut epithelium, the blood-brain barrier, and the placental barrier, by complexing with the amino acid cysteine to form a structure that closely resembles the amino acid methionine. This complex is transported via the large neutral amino acid transporter across biological membranes, including the blood-brain-barrier and the placental barrier (Leaner and Mason, 2002). Within cells, methylmercury has a strong affinity for sulfhydryl groups. In liver cells, methylmercury forms soluble complexes with cysteine and glutathione (GSH), which are then secreted in bile and can be reabsorbed from the gastrointestinal tract, though the major route for methylmercury excretion is the fecal route. Methylmercury is demethylated to inorganic mercury (Hg^{2+}) in situ in mammalian tissues such as liver, brain, and phagocytic cell populations by an unknown mechanism (Suda and Hirayama, 1992). However, for humans and most other mammals (aquatic mammals being an exception), this is not a very efficient process and this lack of efficiency contributes to the prolonged half-life of methylmercury in the body. Once metabolized, the presence of inorganic mercury in brain and other body tissues is extremely persistent (Suda and Hirayama, 1992; Vahter, Mottet et al., 1994).

Inorganic mercury salts are not well absorbed in the GI tract, with less than 10% of the ingested dose being retained. Of the mercurous mercury that is absorbed, the Hg-Hg^{2+} ion quickly dissociates to the mercuric ion (Hg^{2+}) and an atom of uncharged mercury (Hg^{0}), which is then oxidized to Hg^{2+} (Hand, Edwards et al., 1943). Hg^{2+} is complexed with reduced GSH in the liver and transported to the kidney, where it is secreted by proximal tubular cells into the tubular lumen. The enzyme gamma-glutamyl transpeptidase (GTT) degrades GSH, releasing cysteine-mercury complex that is reabsorbed by renal cells (Tanaka et al., 1990; Tanaka-Kagawa et al., 1993; Wei et al., 1999). This cycle leads to the accumulation of mercury in, and the potential for subsequent damage to, the kidneys.

Urinary excretion of mercury reflects direct release of mercury from the kidney tissues and the kidney's burden of inorganic mercury, as opposed to directly reflecting blood plasma levels. Inorganic mercury can also be excreted via the fecal route.

Metallothionein (MT) is a small molecular-weight, cysteine-rich protein that plays a role in the metabolism, transport, and storage of metals such as zinc and copper, and has been shown to bind to mercury within cells, in addition to glutathione. Mercury species are not potent inducers of MT. High concentrations of mercury have been shown to induce heat shock proteins and cellular stress pathways within cells, which could potentially affect mercury protein binding and transport. These effects have only been shown at high concentration in experimental settings that may not reflect the reality of human exposure and biological responses (Noda et al., 2003; Walker et al., 2006; Brkljacic et al., 2007).

As mentioned above, excretion of mercury is partially based on the activity of endogenous proteins and enzymes, including GSH. Once GSH has bound mercury, the complex is transported for excretion from the body. Glutathione synthesis is mediated by glutamyl-cysteine ligase (GCL), which is the rate-limiting enzyme for this reaction; and conjugation of mercury to glutathione is mediated by glutathione S-transferase (GST).

Many of these processes are characterized by age-dependent differences, which may influence age-dependent toxicity. For example, differences in gut flora between infants and children may affect the methylation status of Hg compounds (JECFA, 2007).

Placental transmission

The placenta plays a major role in the transfer of oxygen and essential nutrients from the mother to the fetus and also in protecting the fetus from toxic substances. In the placenta, maternal and fetal capillaries are situated in close proximity, allowing the diffusion of substances from the mother to the fetus. The ease with which a substance passes through the placental barrier depends on many factors, including molecular size, polarity, and interaction with other compounds. Both methylmercury and Hg^0 readily pass across the placental barrier; inorganic mercury is also transferred from mother to fetus across the placenta, but at a much lower rate than methylmercury and Hg^0 (WHO, 2007).

Blood mercury concentrations among human maternal-infant cohorts were summarized in the 1990 WHO report; more recent data are summarized below. There is a consistent trend for higher mercury levels in the fetus compared to the mother (Stern and Smith, 2003). While the overall mean ratio of approximately 1.7 appears to vary little across populations, there is some variability in the ratio that may be population dependent. Even though total Hg levels are reported, most of these data have been collected on populations exposed to methylmercury via fish consumption. Thus there is relatively little data on the cord-maternal blood ratio for inorganic mercury. As inorganic mercury does not cross the placenta as well as organic mercury, it is possible this ratio could be lower than 1.7, but more data are needed. See Table 4 for more information regarding the concentration of mercury in maternal blood, umbilical cord blood, and their ratio from various reports.

Table 4. Concentration of mercury in maternal blood, umbilical cord blood, and their ratio from various reports.

Location	Measure	Maternal blood	Cord blood	Cord: maternal ratio	Reference
Canada	THg (all), µg/L	2.96 (1.66)	5.8 (2.7)	1.49 (1.40)	Butler-Walker 2006[1]
	Methylmercury (all), µg/L	2.20	4.9	1.86	
	Inorganic Hg (all)), µg/L	0.78	0.83	1.01	
	THg (Inuit), µg/L	5.41	10.96	1.73	
	Methylmercury (Inuit), µg/L	4.32	9.73	2.11	
	Inorganic Hg (Inuit), µg/L	1.09	1.23	1.10	
Spain	THg, µg/L	6.23	6.43	1.03	Soria 1992[2]
	Methylmercury	4.97	5.25	1.06	
Singapore	THg, ug/L	15.8	18.8	1.19	Ong 1993[2]
	Methylmercury, µg/L	5.46	8.82	1.62	
Sweden	Inorganic Hg, µg/L	0.32	0.34	1.06	Ask 2002[3]
	Methylmercury, µg/L	0.73	1.4	1.36	
Taiwan	THg, µg/L	8.3	9.1	1.10	Hsu 2007[3]
Brazil	THg, µg/L	11.53	16.68	1.45	Santos 2007
Hong Kong	THg, nmol/L	24.0	44.0	1.83	Fok 2007[3]
Poland	THg, µg/L	0.6	0.9	1.5	Jedrychowski 2007[3]
Turkey	THg, µg/L	0.38	0.5	1.31	Unuvar 2007
Brazil	THg, µg/L	6.03	10.54	1.75	Marques 2008
Slovakia	THg, µg/L	0.63	0.80	1.27	Palkovicova 2008[3]

USA	THg, µg/L (all)	1.7	4.3	2.52	Lederman 2008[3]
	THg, µg/L (China-born Asian)	4.0	15.8	3.95	
Japan	THg, ng/g	9.41	15.3	1.63	Sakamoto 2010[4]

Concentrations are arithmetic mean, except where noted.

1. Methylmercury calculated as THg-Inorganic Hg; ratios calculated using paired samples.
2. Ratio not presented in original paper; calculated from summary concentrations.
3. Medians are presented instead of arithmetic mean.
4. Measured in red blood cells; authors calculated ratio.

Elemental mercury

Major routes for exposure to Hg^0 are inhalation of airbone Hg^0 vapour and inhalation of Hg^0 vapour from dental amalgams (WHO, 2007). Liquid Hg^0 is poorly absorbed via the gastrointestinal tract. However, humans who accidently ingested several grams of Hg^0 showed increased blood levels of mercury (WHO, 2007). Following inhalation exposure, the absorption of Hg^0 vapour occurs efficiently and rapidly through the lungs. The lung tissues absorb about 80% of inhaled vapours. The general picture of disposition of mercury following inhalation of the vapour involves two sequential processes. First, the inhaled vapour dissolved in tissue fluids and bloodstream moves rapidly throughout the body. It readily crosses the blood-brain and placental barriers. The second process is the oxidation of dissolved vapour to mercuric mercury, by the catalase-hydrogen peroxide pathway. It would appear that some of the vapour generated by reduction of mercuric mercury is reoxidized by the catalase pathway; thus, a cycle of oxidation and reduction of inorganic mercury exists inside the cell (Clarkson et al., 2007).

Two recent studies looked at the connection between maternal dental amalgam fillings and fetal mercury levels. In the first study, mercury levels in the placenta increased with an increasing number of maternal fillings ($p < 0.001$). Although there was noticeable accumulation of mercury in the placenta of the 119 female subjects (median, 1.3 µg/kg; range, 0.18-6.7 µg/kg wet weight), a substantial fraction of maternal blood mercury still reached the fetus (Ask et al., 2002). Similarly, Palkovicova and colleagues found among a Slovakian cohort of 99 mother-infant pairs that mercury in umbilical cord blood was significantly associated with both the number of maternal dental amalgams, but also with the time since the most recent filling (Palkovicova et al., 2008). In this study, median values of mercury

concentrations were 0.63 μg/l (range 0.14-2.9 μg/l) and 0.80 μg/l (range 0.15-2.54 μg/l) for maternal and cord blood, respectively.

Inorganic mercury

Most of the information on maternal-fetal transfers of inorganic mercury arises from animal studies, since most human exposures studies involve male workers. Inorganic mercury exposure may arise through direct maternal exposure to inorganic mercury, and there is some evidence in animal studies that methylmercury can be demethylated into an inorganic mercury form within the body; some inorganic mercury in fetuses is the result of maternal demethylation of methylmercury to inorganic mercury, and then transfer of inorganic mercury across the placenta (Dock, 1994; Nordenhall, 1995). As previously stated, Hg^{2+} could also result from oxidation of inhaled Hg vapour. After Hg^{2+} enters the blood, a very small fraction is found after 24 hours. This pattern contrasts with inhaled Hg vapour and methylmercury clearance, but seems to be similar to ethylmercury (thimerosal exposure). Inorganic mercury is much less readily transferred across the placenta than methylmercury or mercury vapour (Yang, 1996).

However, even though inorganic mercury is not readily transferred across the placental barrier, it is possible that the amount that is transported may pose a health risk. Additional research needs to be conducted in order to determine whether these small amounts pose a health risk.

Methylmercury

Following exposure via ingestion such as fish consumption, roughly 95% of methylmercury is rapidly and extensively absorbed through the gastrointestinal tract, and easily penetrates the placental barrier. An excellent review describes how methylmercury is found in higher concentrations within the fetus compared to the mother (Stern & Smith, 2003).

Transport and distribution of methylmercury in the body is affected by the presence of cysteine. Within the body, methylmercury combines with cysteine, an amino acid found in most proteins that appears to be form of a methylmercury-cysteine conjugate, which is transported across the placenta via a neutral amino acid transporter (Kajiwara et al., 1996).

Selenium is considered to be a possible factor modulating distribution and toxicity of methylmercury. Selenium compounds have been shown

to reduce mercury toxicity in animal studies (Watanabe, 1999; Beyrouty and Chan, 2006). However, whether this can be replicated in humans is unclear. A human study among Swedish mothers found that significant associations between methylmercury and selenium were present in both maternal and umbilical cord blood, but not in the placenta. In this same study, no correlations between inorganic mercury and selenium were present (Ask et al., 2002). This was confirmed in a study in the Brazilian Amazon by Fillion et al. (2009). A more recent study among the Faroe Island cohort explicitly looked at the potential interaction between mercury and selenium levels using statistical models, and found no evidence that selenium was a significant protective factor against mercury toxicity (Choi, 2008). The impact of selenium on mercury transfer and toxicity needs to be explored further.

Toxicokinetics of ethylmercury in infants

Thimerosal (containing ethylmercury) is more chemically similar to methylmercury than inorganic or elemental mercury. Based on this similarity, it is likely that ethylmercury can also be transferred via the placenta. Before the removal of thimerosol from most vaccines, it was estimated that infants following a vaccination schedule recommended by the US CDC may have been exposed to 12.5 μg ethylmercury at birth, 62.5 μg ethylmercury at 2 months, 50 μg ethylmercury at 4 months, 62.5 μg ethylmercury at 6 months, and 50 μg ethylmercury at approximately 18 months, for a total of 237.5 μg ethylmercury during the first 18 months of life, if all thimerosal-containing vaccines were administered (Redwood, 2001). Mercury exposure ranged from 4.2 to 21.1 μg Hg/kg body weight for those receiving thimerosal-containing vaccines with the highest thimerosal concentration (Dórea, 2009).

However, these concentrations cannot be directly compared to what is known about methylmercury because the blood half-life of intramuscular ethylmercury from thimerosal in vaccines given to premature infants is substantially shorter than that of oral methylmercury in adults (Pichichero, 2008, 2009). A population-based pharmacokinetic study to assess blood levels and elimination of mercury after vaccination of premature infants born at and <37 weeks of gestation and with birth weight 2000 but <3000 g was conducted. The mean ±standard deviation (SD) birth weight was 2.4±0.3 kg for the study population. Maximal mean ± SD blood mercury level was 3.6±2.1 ng/mL, occurring at 1 day after vaccination; maximal

mean ± SD stool mercury level was 35.4± 38.0 ng/g, occurring on day 5 after vaccination; and urine mercury levels were mostly nondetectable. The blood mercury half-life was calculated to be 6.3 (95% CI, 3.85 to 8.77) days, and mercury levels returned to prevaccination levels by day 30. Ethylmercury has a shorter half-life than methylmercury, and risks of ethylmercury are not accurately predicted by using models designed for methylmercury (ATSDR, 1999).

In 2006, WHO's Global Advisory Committee on Vaccine Safety (GACVS) found no evidence of toxicity to infants, children or adults exposed to thimerosal (containing ethylmercury) in vaccines. In addition, the committee concluded that there is no reason to change current immunization practices with thimerosal-containing vaccines, as the risks of the compound are not established (WHO, 2007).

Application of toxicokinetics to biomarkers of Hg exposures

Introduction

Biomarkers are important tools in evaluating exposures and early outcomes in populations at risk for mercury exposure and toxicity (Aardema and McGregor, 2002). Over the past 20 years, there has been great development in Hg biomarkers and their validation (NRC 2000). In this section, research and application on biomarkers are discussed in the context of children's exposures and health risks. An imprecise exposure assessment will tend to underestimate the true effect of the exposure and may also complicate confounder adjustment. Validation of exposure biomarkers, therefore, is a key to environmental epidemiology studies. This is distinct from a high level of replicability in laboratory results, which alone does not substantiate the validity of a biomarker in regard to the causal associations between exposure and a health risk. A valid exposure marker must reflect the actual exposure, which usually requires other sources of information in addition to biomarker measurement.

A number of biomarkers have been utilized in epidemiological studies of mercury exposure (primarily methylmercury). JECFA (2007) reviewed studies investigating correlations among these biomarkers. See Table 5.

Table 5 Correlations among biomarkers for methylmercury in mothers, infants and children (JECFA 2007).

Sample	Concentration [a]	Comparison (corrected for different units) [b]	Mean ratio	Reference
Maternal blood at delivery [c]	0.45 µg/l	—		Björnberg et al. (2005)
Cord blood [c]	0.99 µg/l	Maternal blood at delivery	2.2	Björnberg et al. (2005)
Infant blood at age 4 days	1.10 µg/l	Maternal blood at delivery	2.4	Björnberg et al. (2005)
Milk at age 4 days (total mercury) [d]	0.29 µg/l	Maternal blood at delivery	0.64	Björnberg et al. (2005)
Cord blood	22.6 µgll	—	5.4	Budtz-Jorgensen et al. (2004)
Maternal hair (full length) (total Hg)	4.22 µg/g	Cord blood	187 [e]	Budtz-Jorgensen et al. (2004)
Blood at age 7 years (total Hg)	1.93 µg/l	—	—	Budtz-Jorgensen et al. (2004)
Hair at age 7 years (total Hg)	0.6 µg/g	Blood at age 7 years	310 [f]	Budtz-Jorgensen et al. (2004)
Blood at age 14 years (total Hg)	3.81 µg/l	—	—	Budtz-Jorgensen et al. (2004)
Hair at age 14 years (total Hg)	0.96 µg/g	Blood at age 14 years	252[g]	Budtz-Jorgensen et al. (2004)
Cord blood (total Hg)	22.4 µg/l	—	—	Grandjean et al. (2005)
Maternal hair (full length) (total Hg)	4.17 µg/g	Cord blood	187	Grandjean et al. (2005)
Cord tissue (wet weight) (total Hg)	0.025 µg/g	Cord blood	1.1	Grandjean et al. (2005)
Cord tissue (dry weight) (total Hg)	0.21 µg/g	Cord blood	9.4	Grandjean et al. (2005)
Maternal blood (total Hg)	0.52 µg/l	—	—	Jedrychowski et al. (2005)
Cord blood (total Hg)	0.85 µg/l	Maternal blood	1.6	Jedrychowski et al. (2005)

Hg: mercury.

[a] Mean or median as reported.

[b] Assumes that 1 l of blood or milk = 1 kg.

[c] The corresponding concentrations of inorganic mercury were 0.09 µg/l in both maternal and neonatal infant blood

[d] The concentrations in milk correlated with maternal blood inorganic mercury concentrations; other data have shown a correlation between the concentrations in milk and the number of maternal amalgam fillings (Da Costa et al., 2005).

[e] The published mean ratio based on paired data was 370.

[f] The published mean ratio based on paired data was 370.

[g] The published mean ratio based on paired data was 264.

Biomarkers of exposure

Biomonitoring for human exposure to mercury reflects an individual's current body burden, which is a function of recent and/or past exposure. Thus, the appropriate selection and measurement of biomarkers of mercury exposure is based upon the purpose of exposure assessment. Interpretation of mercury exposure biomarkers requires knowledge of exposure scenarios for the group under study. In assessing the appropriateness of a particular biomarker of exposure, it is important to consider three factors: (1) how well the biomarker of internal dose (i.e., the concentration of mercury in hair, blood, etc) correlates with the external exposure, which may vary with the route of exposure as well as the specific mercury compound; (2) how well the internal dose biomarker correlates with dose at the site of toxic action, such as the mercury concentration in the target tissue; and (3) how informative the biomarker is related to variations in external exposure as well as changes in dose at the site of toxic action.

Hair mercury

Hair is a biological specimen that is easily and noninvasively collected, with minimal cost, and it is easily stored and transported to the laboratory for analysis. However, considerable attention to laboratory quality assurance and quality control is required to produce reliable analytic results. These attributes make hair an attractive biomonitoring compartment for epidemiological studies. The growth rate of hair (~1 cm per month) and the tendency of toxicants such as mercury to accumulate in hair make it possible to estimate exposure history as well as long-term exposure. Mercury concentration in hair is most often used to estimate exposure to methylmercury, since the predominant form of mercury in hair is methylmercury among persons exposed to methylmercury. Hair mercury is not an indicating biomarker for ethylmercury exposure assessment. After ethylmercury enters the blood a considerable fraction is rapidly converted to inorganic mercury and probably totally converted before it gets to the hair (Rodrigues et al., 2010).

Hair mercury concentration as a biomarker of methylmercury exposure can provide information over a definable period of time, based upon sequential analyses of hair segments, to represent both the magnitude and timing of past exposure. The ability to obtain such information from hair is predicated on two assumptions: that growing hair shafts incorporate

mercury from the circulating blood in proportion to the concentration of mercury in the blood at the time of hair growth, and that hair shafts grow at a constant rate that does not vary significantly among individuals. The first of these assumptions is necessary to establish a quantitative relationship between hair mercury concentration and methylmercury intake (with blood mercury concentration assumed to be an intermediate kinetic compartment). The second assumption is necessary to establish a relationship between location along the hair strand and time of exposure (Cernichiari et al., 2007; National Research Council, 2000).

Maternal hair is also used as a biomarker of fetal exposure, based upon its assumed relationship to maternal blood mercury levels and the correlations between maternal and cord blood mercury levels (see Section 5.1). Several attempts have been undertaken to determine guidance based on hair mercury levels. Benchmark doses were determined on the basis of studies in New Zealand, and the Faroe and Seychelles Islands; these indicate that a level of 4–25 μg Hg/g measured in maternal hair may carry a risk to the infant (Van Wijngaarden et al., 2006). However, there are sources of uncertainty that could affect the derivation of benchmark doses, including assumptions about the shape of the dose–response curve (e.g. linear versus nonlinear), the choice of the cut-off for an abnormal response as a benchmark response, and decisions regarding the critical endpoints to measure (Rice, 2004). A recent calculation of the lowest observable adverse effect hair concentration was undertaken on the basis of a systematic review of the published literature (Schoeman et al., 2009). A total of 48 independent studies from 315 reports accessed by a systematic search of the literature were included in this analysis of associations between maternal hair mercury concentrations and neurodevelopmental decrements in children exposed *in utero*. The LOAEC was determined to be 0.3 μg/g hair, which was calculated to correspond to a concentration of 0.75 μg/l in cord blood. However, since this estimate was based upon hair:blood ratios in adults, this may not hold for cord blood as Hg in cord blood is generally higher than in maternal blood (Table 4).

Blood mercury

Total blood mercury has been used as a biomarker of mercury exposure, and its interpretation depends upon knowledge of the exposure sources for children being assessed (ATSDR, 1999). It is generally considered the appropriate indicator of the absorbed dose and the amount systemically

available. Unlike hair, total blood mercury levels also include inorganic mercury, which may be of importance in certain contexts. Analyses of data collected as part of the US National Health and Nutrition Examination Survey in 2005 and 2006 showed that the 95th percentile for mercury in blood was 1.43 μg/l for children 1-5 years of age (n=968) (Caldwell et al., 2009).

Compared to methylmercury exposure, ethylmercury exposure from thimerosal is reported to have different kinetics in the human blood. According to Pichichero et al. (2008) the blood mercury half-life in children after thimerosal exposure (vaccination) was calculated to be 3.7 days, which is considerably shorter than the half-life of methylmercury. Moreover, blood Hg may be not an appropriate biomarker for either inorganic or ethylmercury exposure in terms of estimating internal doses in the central nervous system. In a recent study, Björkman et al. (2007) found that mercury in blood is a useful biomarker for methylmercury in brain, but it is not a good biomarker for inorganic mercury in brain, probably the main form of mercury in this tissue after thimerosal exposure.

The main limitation on blood mercury as a biomarker is that, without additional information on duration and timing of exposure, it is not possible to obtain clear information about the magnitude or timing of the exposures that have contributed to total mercury concentration observed in a given sample collected at a specific time. As with hair mercury, blood mercury is also subject to possible variation. Mercury's high affinity to fetal hemoglobin is one factor that results in higher mercury concentration in cord blood as compared to maternal blood (Sakamoto et al. 2004). Methylmercury binds to hemoglobin, so that hematocrit affects whole blood mercury concentrations as in the case of lead. Some researchers therefore prefer to measure the mercury concentration in erythrocytes (Sakamoto et al., 2004), although this procedure is more difficult. There are no studies on mercury levels in plasma at present (2010).

Hair and blood mercury compared

There are important public health reasons for integrating data from studies utilizing hair or blood mercury biomarkers in order to utilize the full set of relevant information. However, there are no well accepted methods for accomplishing this, as reviewed by the National Research Council (2000). Studies that have attempted to define the relationship between different biological indices have produced inconsistent and somewhat wide-ranging

results, and conversion from one set of values to another appears to involve a number of incompletely validated assumptions. Other difficulties in the interpretation of the data set arise as a result of the use of different units of measurement and a lack of clarity in some studies about whether the measure is intended to denote organic, inorganic, or total mercury concentrations (Spurgeon, 2006). Additional elements of the debate about hair versus blood samples are linked to unanswered questions surrounding the appropriate methods of measuring prenatal exposure, including the relative importance of exposure at different periods of gestation, and the relative importance of average or peak exposures (NRC, 2000; Spurgeon, 2006). Thus, there are continuing uncertainties about the association between elements of the diet and concentrations in child hair, maternal hair, cord blood, and maternal blood, as well as uncertainty about the strength of any relationship between each of these elements and the relationship between any of these biomarkers and the actual exposure of the fetus. The ideal exposure biomarker should show a clear-cut relationship to the degree of exposure (Grandjean et al., 1993), but the reality is often that up to several imprecise measures may be available, none of them necessarily an accurate indicator of the true exposure.

In regard to methylmercury, substantial information is now available on daily intake levels and experimental studies in human volunteers have demonstrated how the dietary intakes may be translated into mercury concentrations in blood or hair (Sherlock et al., 1984). However, these two commonly used exposure biomarkers show only scattered associations (Budtz-Jørgensen et al., 2004), suggesting that their total imprecision significantly exceeds routine laboratory errors. Grandjean et al. (2005) employed different statistical strategies to explore this issue. The results show that analysis of cord blood or cord tissue is likely to provide better precision than does maternal hair mercury, considering both analytic variability and pre-analytic factors (including specimen sampling, storage and transport, toxicokinetic variability and other issues) (Grandjean and Budtz-Jørgensen, 2007). The same group also showed with the use of structural equation models that the imprecision in hair mercury analyses is substantial and can produce underestimations of the neurotoxic impacts of methylmercury on exposed children.

The relationship between maternal hair mercury concentration and fetal or maternal blood mercury concentration depends on the type and frequency of fish consumption as well as potential inter-individual variability in

methylmercury toxicokinetics. In a Swedish study for a population mostly not representing frequent fish consumers, the relationship between total mercury (THg) concentration in hair (μg/g) and total mercury concentration in blood (μg/l) was (hair-THg = 0.169 + 0.254 blood-THg; (r^2 = 0.62) (Berglund et al., 2005). Based on this relationship, a hair concentration of 1.0 μ/g would correspond to a blood concentration of 3.3 μ/l. In a Swedish population selected on the basis of frequent fish consumption (approximately 4 times per week) the ratio of THg blood concentration (μg/l) to THg hair concentration (μg/g) was 2.7 (Björnberg et al., 2005).

Typical background levels of mercury in hair in non-exposed children or pregnant women are lower than 1.0 μg/g. For example, non-exposed pregnant British women have been found to have total mercury concentration in hair of 0.39 μg/g (Razagui and Haswell, 2001). In the US, the mean hair mercury concentration among women 16-49 years old in a statistically representative sample of the national population in that category was reported to be 0.47 μg/g. The 10th percentile of the distribution was 0.04 μg/g (McDowell et al., 2004). The 10th percentile provides an estimate of the population with little or no fish consumption.

Analyses of data from the Faroe Islands indicate that a doubling of the proportion of children in the lowest 5% of performance in several tests of neuropsychological performance occurred at fetal blood mercury concentration (from methylmercury exposure) of 58 μg Hg/l (NRC, 2000). In order to convert this to a daily maternal intake, it is necessary to apply a pharmacologic model that takes into account variability in maternal metabolism and placental transport (Stern, 2005). There is considerable variability in this relationship. The mean value predicted by this model is that a concentration of 58 μg Hg/l in fetal cord blood would result from a daily maternal intake of 1.0 μg methylmercury/kg-maternal body weight/day. However, in this model, if 95% of the variability is accounted for, the corresponding maternal intake is 0.3 μg/kg/day. Taking this into account and including additional adjustment to account for uncertainties relating to other potential adverse health effects, the US EPA estimated the corresponding maternal daily intake at 0.1 μg/kg/day. Overall, in comparing maternal hair and cord blood as possible biomarkers of *in utero* methylmercury exposure, each has significant advantages and disadvantages. At least conceptually, cord blood is kinetically more closely linked to the fetal brain-target and could, therefore, yield a more precise dose-response

relationship if the critical period for toxicity coincides with the time period reflected in the cord-blood mercury measurement. However, the cord blood mercury measurement is not capable of providing information about the specific patterns of exposure during gestation and does not reflect exposure over a clearly delineated period of gestation (NRC 2000). In addition, cord blood is not capable of providing information about variability in exposure, even for the time period it most directly reflects. Maternal hair analysis can provide information about average exposure over the entire period of gestation but provides no information about variability in exposure during that period (NRC, 2000). Identification of the specific portion of a hair strand corresponding to all of gestation is uncertain and is a potential source of exposure misclassification. In addition, maternal hair mercury concentration is kinetically more distant from the fetal brain than is cord blood mercury. Segmental hair analysis has the potential to provide information about exposure during specific portions (e.g., trimesters) of gestation, but uncertainties related to hair growth rate make the identification of segments corresponding to periods as short as a single trimester uncertain. Although segmental hair analysis can provide some information about variability in exposure during different periods of gestation, it is of limited use in identifying either the magnitude or the duration of peak exposures. Continuous single strand hair analysis, on the other hand, can provide precise information on peak exposures and thus permits the investigation of several different dose metrics in dose-response assessment (NRC, 2000).

Tissue mercury levels

Tissue levels of mercury are measured at autopsy and in biopsies, but these are relatively rare events and unlikely to be available for application in epidemiological studies. Because of concerns over precision of hair mercury as a biomarker as discussed in the section on hair mercury and the challenges in sampling cord blood, there has been use of umbilical tissue. The umbilical cord offers advantages because it is easy to sample by noninvasive means, the tissue otherwise being discarded after parturition (Yorifuji et al., 2009). The cord is formed mainly during the second and third trimesters, and it reaches two-thirds of its full length by the end of the second trimester. Assuming a biologic half-life of about 45 days for methylmercury in tissues (Smith and Farris, 1996), cord mercury may be a measure of the average mercury exposure during the third trimester.

It will likely be less sensitive to short-term changes than will the cord blood mercury concentration (Grandjean et al., 2005). However, certain caveats must be considered in regard to the variability of cord tissue. The appearance of the umbilical cord varies substantially and is mainly due to differences in water content retained by the gelatinous Wharton's jelly that surrounds the blood vessels (Grandjean et al., 2005). The mean water content decreases with increasing duration of gestation, and the fetal end of the cord has higher water content than does the placental end. Because of these considerations, the dry weight–based mercury concentration may be a more precise parameter than the level expressed on a wet weight basis.

Urinary mercury

Urinary mercury concentrations are widely used as a biomarker of mercury exposure from elemental or inorganic mercury. In persons not exposed to these forms of mercury, urine concentrations rarely exceed 5.0 μg/g creatinine. A case study of a four-year-old child with acrodynia found urinary mercury concentrations to be as high as 324 nmol of mercury per liter (reference value <100 nmol/l). This urinary mercury concentration followed acute indoor exposure to latex paint containing phenylmercuric acetate (Agocs et al., 1990). There are many children exposed to elemental and inorganic mercury in small scale gold mining, and for these groups, measurement of urinary mercury may be an appropriate biomarker.

Nails

In most epidemiologic and exposure studies, mercury exposure is assessed by analysis of hair, blood, or urine, most commonly in occupational contexts (Bose O'Reilly et al., 2010). However, there has been extensive use of nail analyses to assess body burdens of metals, often in the context of nutritional epidemiology (Guallar et al., 2002). The methodologies available for nail mercury analysis include instrumental neutron activation analysis (Bode et al., 1997) as well the as digestion-cold vapour atomic absorption methods also applied to hair and blood. The ability to assess past exposures in stored samples and to evaluate the effects of mercury in the context of other factors (such as essential trace elements) has increased interest in this technique. However, there is less information on the physiological and kinetic relationships between body burden and toenail levels, as compared to hair (Björkman et al., 2007). The advantages

of nail mercury as a biomarker are: ability to measure multiple elements in one sample, ease of collection, stability in storage, and relevance to chronic exposure.

Toenail mercury has not been used in studies of children but it has been applied as a biomarker of exposure in studies of mercury exposures related to cardiovascular endpoints in adults (Guallar et al., 2002). There have been relatively few direct comparisons of the informational value of results by compartment. Nail mercury content was reported to be the best discriminator for exposure among dental workers (Morton et al., 2004). A relatively small study of 59 women in Japan compared correlations among biomarkers of mercury exposure (Ohno et al., 2007). Anttolainen (1997) evaluated the correlation between mercury levels in nails with those levels in hair and blood in Finnish population. Blood, hair and toenail total mercury concentrations were determined simultaneously in a southern urban sea ($n = 35$) and an eastern rural lake ($n = 37$) group and separately in a central Finnish rural lake ($n = 39$) group. In the combined southern and eastern groups ($n = 72$) sampled simultaneously, the correlations between blood and hair mercury were $r = 0.92$ and that of blood and toenails $r = 0.78$ ($p < 0.0001$).

Rees et al. (2007) measured the mercury content in toenails of 27 individuals in New Hampshire, USA who participated as controls in a health study in 1994–95. The mean total toenail mercury concentration was 0.27 μg/g (median 0.16; SD 0.27; range 0.04–1.15 μg/g). The best predictor of toenail mercury levels was the mean combined fish and shellfish consumption measured using four simple questions from a validated food frequency questionnaire. Toenail total mercury content was significantly correlated with the mean average weekly consumption of finfish and shellfish (Spearman correlation coefficient 0.48, $p=0.012$). Multivariate models confirmed that toenail total mercury concentration was best predicted by total finfish and shellfish consumption.

Biomarkers of susceptibility

Nutritional background can influence the uptake and distribution of mercury species (Chapman & Chan, 2000), while sex and genetic background have been shown to influence the overall body burden of mercury in both epidemiological and experimental studies. Assessments of risk may be improved by information on different levels of individual

susceptibility to mercury exposure. When this information is not available, uncertainty or safety factors are used to account for inter-individual differences in exposure and susceptibility.

There is considerable interest in understanding genetic determinants of susceptibility to mercury toxicity among children and others. This research has focused on toxicokinetic and toxicodynamic factors, that is, genes encoding proteins involved in mercury metabolism as well as potential molecular targets.

Glutathione-related genes as biomarkers of susceptibility

The glutathione S-transferases (GST) are a super gene family of dimeric, enzymes that catalyse the conjugation of glutathione (GSH) to a variety of electrophiles including arene oxides, unsaturated carbonyls, organic halides and other substrates. In humans, polymorphism in GST genes has been associated with susceptibility to various diseases though some recent data indicate that these genotypes can also modify disease phenotype (Strange et al., 2000).

As discussed above mercury detoxification involves the glutathione (GSH) system. This is indicated by the up regulation of the system-related enzymes glutathione-S-transferase (GST) and glutamate cysteine ligase (GCL), and by increased GSH synthesis following mercury exposure in animal models (Brambila et al., 2002). The mercury GSH conjugation complex is the preferred transport vehicle excreted via the bile and the kidneys, the major excretion pathways of mercury (Clarkson and Magos, 2006). The formation of the tripeptide GSH is catalyzed by the enzyme GCL. It consists of two subunits, the catalytic subunit GCLC and the modifier subunit GCLM. Polymorphism of human GCLC is functionally significant; the effects on expression and protein levels, however, depended on the type of variant allele and the allelic dose. Six cytosolic GST subclasses with different issue distributions catalyze the conjugation reaction between the glutathione molecule and various electrophilic substrates, among them mercury. The GST genes show single-nucleotide exchange and gene deletions resulting in reduced expression and/or enzyme activity. In the case of mercury toxicokinetics, there is evidence for the impact of GST and GCL polymorphisms on mercury body burdens (Custodio et al., 2004, 2005) and for enhanced susceptibility in the case of ethylmercury exposure (Westphal et al., 2000).

Custodio et al. (2004) observed associations between GCLC-129 or

GSTP1-114 variant alleles and increased mercury contents in erythrocytes (i.e. indicator of methylmercury exposure). In accordance, Gundacker et al. (2009) observed higher hair mercury levels in GSTP1-114 variant carriers than in the homozygous wild type. However, Schläwicke-Engström et al. (2008) and Gundacker et al. (2009) found no evidence for effects of GCLC-129 polymorphism on mercury body burdens. Gundaker et al. (2009) also observed synergistic effects of the variant combinations GSTP1-114/GSTT1 and GSTP1-105/GCLC. The authors assumed that GSTP1 variants play a more important role in mercury toxicokinetics than the other investigated GST polymorphisms.

MT polymorphisms

The impact of metallothionein (MT) gene polymorphisms on metal metabolism apart from cadmium is less well investigated. Many questions remain on the evolutionary role of MT, the relatively high presence of MT genes in the human genome as a result of duplication events, and the functional relevance of MT polymorphisms with regard to storage, homeostasis, and detoxification of metals. The four mammalian MTs (MT1–MT4) are often characterized as multipurpose proteins. Due to structural characteristics, i.e. unusually high cysteine content, they are potent metal-binding proteins with high redox capabilities. They are involved in metal regulation, protection against oxidative stress, and adaptation to chemical, physical, and psychological stress (Hidalgo et al., 2001).

Heme biosynthetic pathway enzymes

Heme proteins, including hemoglobin, are involved in Hg toxicokinetics and toxicodynamics. Woods et. al (1995) described a porphyrinogenic response to low level mercury exposure among a majority (85%) of human subjects, characterized by predictable dose- and time-related increases in the concentrations of coproporphyrin, 5-carboxyl porphyrin and the atypical, ketoisocoproporphyrin (KICP), in the urine, and this response has been proposed as a biomarker of mercury exposure and potential toxicity (Woods, 1995). Notably, the remaining 12–16% of human subjects have been found in several population-based studies to manifest an atypical response to Hg exposure, characterized by excretion of highly elevated concentrations of coproporphyrin, 5-carboxyl porphyrin and KICP in the urine, exceeding the population mean (39.37, SD 28.74 Hg/g creatinine) by more than 4-fold, well above the 80 Hg/g creatinine upper

95% confidence limit (Woods, 2005).

Recently, urinary porphyrin concentrations in children 8 to 18 yr of age, with and without dental amalgam fillings, were determined over the course of a recently completed clinical trial that was designed to evaluate the potential health consequences of prolonged exposure to Hg from dental amalgam fillings (Woods et al., 2009). These authors found no significant differences between treatment groups (amalgam versus composite) when comparing all subjects for any of the porphyrins of interest. However, incipent amalgam treatment-specific increases were observed in the mean concentrations of penta-, precopro- and coproporphyrins especially when the analyses were restricted to younger subjects (8 to 9 years old at baseline), and these increases were most apparent during year 2 through 3 of follow-up, the period of highest mercury exposure from amalgam treatment. According to the authors, based on the mean number of amalgam fillings received by children in this group (17.8), the renal mercury concentration associated with incipient increases in urinary porphyrins was estimated to be approximately 2.7 μg/g renal cortex. This value corresponds to an observed mean urinary mercury concentration of 3.2 μg/g creatinine, which is approximately fivefold less than that at which renal damage from mercury exposure is estimated to occur in children.

Coproporphyrinogen oxidase (CPOX) catalyzes the two-step decarboxylation of coproporphyrinogen-III to protoporphyrinogen-IX in the heme biosynthetic pathway. The CPOX protein contains a number of reduced thiol residues that render it potentially susceptible to inhibition by thiol binding agents including mercury. A polymorphism in this enzyme, characterized by an A814C substitution in exon 4 encoding an asparagine-tohistidine change at amino acid 272 (N272H) in a population of dental professionals has been described (Woods, 2005). Within this population, the frequencies of the homozygous common A/A allele genotype, the heterozygous (A/C) genotype, and the homozygous (C/C) genotype were 0.72, 0.25 and 0.03, respectively, and were equally prevalent in males and females. This polymorphism in exon 4 of the coproporphyrinogen oxidase gene (CPOX4) was found to be predominant (>60% prevalent) among subjects manifesting this atypical response to mercury (Woods, 2005).

The CPOX4 polymorphism may affect susceptibility for specific neurobehavioural functions associated with mercury exposure in human subjects (Echeverria et al., 2006). Neuropsychiatric disturbances associated

with prolonged mercury exposure seem to be similar to those observed in the form of porphyria (hereditary coproporphyria) that is associated with inherited CPOX deficiencies (Grandchamp et al., 1995) and include increased irritability, depression, and anxiety (or affective disorders) coupled with neurologic declines in central and peripheral nervous system functions manifested in both cognition and sensory function. Of note, these conditions can be more strongly induced in females by endocrine factors (Schuurmans et al., 2001).

Co-exposures as susceptibility factors

Mercury compounds can induce a lupus-like systemic autoimmune disease in rodents (Abedi-Valugerdi & Moller, 2000; Haggqvist & Hultman, 2001; Pollard et al., 2001; Nielsen & Hultman, 2002; Via et al., 2003; Silbergeld et al., 2005). However, it is unlikely that mercury is solely responsible for the development of autoimmune disease in humans or for interacting with the immune system of children in such a way as to predispose them to developing autoimmune disease in early adulthood. Therefore, consideration of interactions between mercury and "triggers" for autoimmune disease, such as infection and antigen exposure (Via et al., 2003; Silva et al., 2004) are relevant.

Biomarkers of effect

At present, there are no validated or widely used biomarkers of mercury effects. Given the range of systems affected in children by mercury (see Section on special vulnerability of children to mercury exposure), it is unlikely that a biomarker will be uniformly useful. Assessment of effect usually requires specific testing for organ specific function. Recent studies on mercury-associated immunotoxicity in adults may provide a basis for using cytokine measurements as biomarkers (Gardner et al., 2010).

Conclusion

In the last decades, increasing evidence has demonstrated the significant adverse health effects of heavy metals exposure for the developing fetus, infant, child, and adolescent. Exposure to mercury, a neurodevelopment toxicant, represents a growing health problem of particular concern for children in the developed and developing world. Children are particularly susceptible to the health effects of mercury exposure during specific periods of rapid growth and development.

The health effects of mercury exposures in children are influenced by the species of mercury, route of exposure, dose, and timing of exposure, indicating significant variability in health effects and symptoms of exposure. Mercury exposures are not equally distributed among the world's children as a result of the spatial deposition of mercury, and the geographic, economic and cultural factors related to traditional practices, lifestyle habits, and diets of global populations. For these reasons, children's exposure to mercury should be considered in a holistic fashion, reflecting the cumulative complexity of both the sources and pathways by which children may be exposed. The ubiquitous and persistent nature of mercury and mercury compounds poses a threat for the healthy development of the world's children.

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