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Chapter 4

MERCURY EXPOSURE CONSIDERATIONS: EVALUATING THE CHEMICAL FORM AND ACTIVITIES OF THE INDIVIDUAL

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ABSTRACT

Evaluation of exposure to mercury in an environmental or an occupational context is more complex than that for many other substances, insofar as it requires consideration of a combination of factors including the form of mercury present and the associated toxicology (e.g., elemental vs. organic vs. inorganic), as well as characteristics of the individual/exposure being evaluated (e.g., route, frequency, duration, and magnitude of exposure). Given the major differences in absorption of mercury forms by route, it is not sufficient to discuss simply "mercury exposure", as often occurs in media reports. Methods for addressing each of these characteristics are discussed, and specific case studies are presented to illustrate the practical significance of differences in contact with several common mercury forms that may be encountered under variable exposure circumstances. In addition, a discussion is presented of the variability of responses between adults and children to selected mercury forms, with attention to similarities or differences in observed effects. Finally, common sources of mercury exposure to the general population are discussed, for purposes of comparison with potential exposures in the workplace.

Keywords: Mercury, exposure, environmental, workplace, health, adults, children, toxicology

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1. INTRODUCTION & HISTORICAL PERSPECTIVE

Mercury often is listed as a primary environmental pollutant by the U.S. Environmental Protection Agency (USEPA), as well as other local, state, federal and international entities. Although it is an element found naturally in the earth's crust, an estimated 50-75% of environmental mercury comes from anthropogenic sources (USGS, 2009; Davidson et al., 2004), resulting from increased mercury mobilization and atmospheric release since the 1800s (USEPA, 2001).

Mercury is found in air, water, soil and sediments existing as one of three forms: elemental (metallic) mercury, inorganic mercury compounds, and organic mercury compounds. Elemental mercury is evident as a shiny, silver/white liquid at room temperature, displays some unique properties (e.g., significant vapor pressure, high surface tension, toxic to certain microorganisms, conducts electricity), and in its stable elemental form cannot be destroyed. Mercury cycles between the atmosphere, land, and water while undergoing complex chemical reactions, many of which are not entirely understood (USEPA, 2001; Figure 1). Mercury released to the air may deposit in water or on land where it can be washed into neighboring waterbodies (Zahir et al., 2005). Over 95% of the mercury in the atmosphere exists in the gaseous elemental state, while mercury found in water, sediments and soils is mainly found in the oxidized, divalent state. A small fraction of the divalent form may be converted to methylmercury via microbes in aquatic environments. Methylmercury is the highly toxic form of mercury that can accumulate in fish, shellfish and subsequent elements of the food web.

Ambient air mercury concentrations in the U.S. have been reported to be between 10 and 20 ng/m^3 in nonindustrialized areas (WHO, 2003). Due to industrial activities and other anthropogenic sources, current average levels in the atmosphere are estimated to be on the order of 3 to 6 times greater than preindustrial conditions (WHO, 2003). Because mercury is persistent and travels in the atmosphere for long periods (Zahir et al., 2005), sources of mercury detected in fish in U.S. surface waters are believed to originate from a combination of local, regional and global sources. National Pollutant Discharge Elimination System (NPDES) permits regulate point sources of mercury discharge to waterbodies, while nonpoint sources of mercury contamination are not specifically regulated. However, if shown to cause water quality exceedences, states will be required to develop Total Maximum Daily Load (TMDL) estimates that include potential nonpoint sources. Domestic sources influence mercury deposition in the eastern U.S., while in the West, where fewer domestic sources exist, global sources contribute proportionally more to mercury deposition.

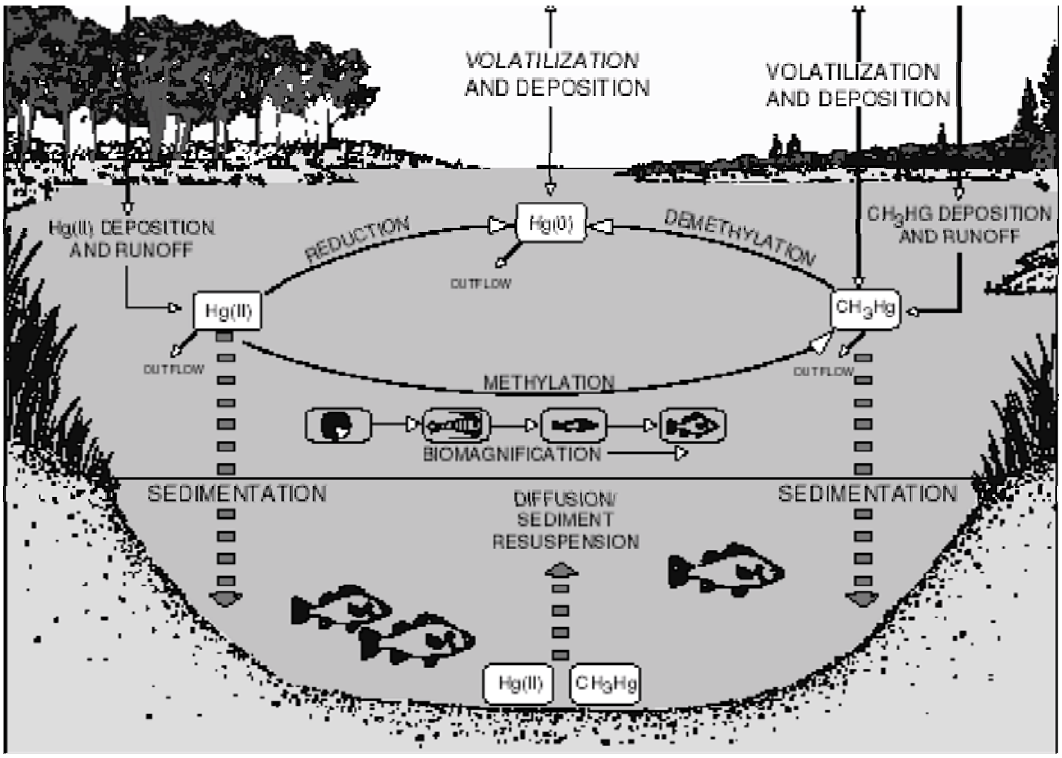

Figure 1. Aquatic mercury cycle. Source: Mercury Pollution: Integration and Synthesis. Copyright Lewis Publishers, an imprint of CRC Press.

Natural sources of mercury include emissions from volcanoes and crystal degassing in the deep ocean (Rasmussen, 1994; UNEP, 2002; Castoldi et al., 2003; Poulin and Gibb, 2008). The largest single U.S. source of airborne anthropogenic mercury is coal-fired power plant emissions (Zahir et al., 2005). Other potential releases from U.S. activities include combustion facilities (e.g., utility boilers, municipal waste combustors, commercial/industrial boilers, hospital incinerators), mining, and manufacturing. There are about 100 facilities in 44 countries that have some mercury cell production capacity (UNEP, 2010). While chloralkali facilities are no longer a major concern in the U.S., problems at former sites in Albania, China and Peru have been identified (Bose-O'Reilly et al., 2010). Over the past decade as international gold prices have risen, more attention has been focused on small-scale gold mining communities, in developing countries such as Ghana (Paruchuri et al., 2010), Mongolia (Steckling et al., 2011), Burkina Faso (Tomicic et al., 2011), Indonesia and Zimbabwe (Bose-O'Reilly et al., 2008), and Tanzania (Spiegel, 2009), where exposure to mercury can occur during traditional extraction operations. At the turn of the 21st

century, approximately 13 million people were engaged in small scale mining worldwide, and 80 to 100 million people eventually may depend on the practice for their livelihood (ILO, 1999). Because these often are communities dependent upon fish consumption, they may also be exposed to methylmercury in the diet.

In 2003, the United Nations initiated the Global Mercury Project (GMP), to educate and promote cleaner, more efficient gold mining/extraction technologies for these impoverished communities (Purwana, 2003). The Amazon basin has been extensively studied with regard to miners being exposed to mercury. It was determined that deforestation and erosion that accompanies mining activities were major sources of mercury release to waterways (Passos and Mergler, 2008).

Mercury can be found in common household products such as thermometers, switches, medicines, skin creams and some light bulbs. Disposal of these items is a potential source of environmental impact when placed in landfills or burned in waste combustors, as opposed to recycling (Goldman and Shannon, 2001). There may also be exposures in food products, such as fish, citric acid, sodium benzoate, and high fructose corn syrup (Dufault et al., 2009; Bose-O'Reilly et al., 2010). Use of mercury in fungicides was discontinued in the U.S. in the 1970's based on concern regarding persistence and potential toxicity. Thimerosal, a preservative containing approximately 50% mercury by weight (ethylmercury), has been used since the 1930's as a preservative in vaccines. Apprehensions about the preservative were raised concerning association with autism in children but the American Academy of Pediatrics and the U.S. Public Health Service have concluded that there is insufficient evidence that exposure to these vaccines containing thimerosal could result in developmental neurotoxicity. Both organizations nevertheless recommend use of alternative preservatives (Davidson et al., 2004).

USEPA and other agencies are working to reduce environmental mercury and to limit human exposure. Since the Clean Air Act in 1990, U.S. releases of mercury to the air declined ~58% through 2005 and continue to do so (USEPA, 2009d). Reducing mercury-containing items in trash (e.g., batteries, light bulbs) has resulted in reductions related to waste combustion. The Mercury-Containing and Rechargeable Act (the Battery Act) signed in 1996 was one of the first efforts to reduce mercury containing batteries in landfill and incinerator ash by encouraging recycling (USEPA, 1997).

In March 2005, USEPA issued the Clean Air Mercury Rule (CAMR) which created performance standards and established declining caps for power plant mercury emissions. That rule was vacated in February 2008, causing USEPA to propose the Mercury and Air Toxics Standards (MATS) in March 2011, which is designed to replace CAMR. Comments were accepted on MATS through August 4, 2011 (USEPA, 2011a). The Mercury Export Ban of 2008 prohibits export of

mercury beginning in 2013, with the intent to reduce availability of elemental mercury on the global market. The ban does not include mercury compounds (USEPA, 2009a). In 2009, United Nations Environment Programme (UNEP) entered into Global Mercury Partnership program to protect human health and the global environment from release of mercury into the environment (UNEP, 2009).

2. EXPOSURE TO DIFFERENT MERCURY CHEMICAL SPECIES

Mercury can be associated with a variety of effects on health depending on factors such as mercury form, level of exposure, route of exposure, duration/frequency of exposure, and age of the person being exposed. Mercury speciation influences environmental behavior, availability of mercury for possible exposure, transport in the body, as well as the spectrum of toxicity, accumulation, excretion, biomagnification, and ability to transport between environmental compartments (UNEP, 2002; WHO, 2010). Speciation of airborne mercury influences transport and deposition. Most atmospheric mercury is elemental mercury vapor, while mercury in the water, soil, sediments, plants and animals is either inorganic mercury salts or organic mercury (e.g., methylmercury).

Absorption varies among different species of mercury (See Table 1). While the major exposure route to methylmercury typically is ingestion of contaminated fish, the primary exposure route for metallic and inorganic mercury is inhalation. Methylmercury is readily absorbed by the GI tract (~95%), as compared with limited GI absorption of mercury salts (~10 to 30%), and negligible GI absorption of elemental mercury (ATSDR, 1999; WHO, 2010). Various metabolic changes can occur once mercury is absorbed, and it may accumulate in brain or fetal tissues, but subsequently become sequestered as a result of conversion to inorganic divalent cations (ATSDR, 1999). Factors such as nutritional status, drug interactions, temperature, intestinal flora, genetics and age all play a role in metabolic processes following mercury absorption. Mercury elimination is generally slow (Smith et al., 1970; Sallsten et al., 1994). Elimination of elemental mercury occurs primarily via urine and feces, with expired air, sweat, and saliva contributing nominally. Methylmercury is excreted >90% in the feces (ATSDR, 1999; Goldman and Shannon, 2001; Clarkson and Magos, 2006).

Medical monitoring via mercury measurement in hair, blood and urine can be used to provide information regarding chemical form, duration of exposure, and degree of exposure (Mahaffey, 2005; ACGIH, 2001; Risher and De Rosa, 2007).

Table 1. Relative Absorption Efficiencies of Mercury Species.

Route	**Elemental**	**Inorganic***	**Methylmercury**
Inhalation	*High*	*Low*	*Low*
Oral	*Low*	*Low-Moderate*	*High*
Dermal	*Low*	*Low*	*Low*

*Inorganic group includes mercuric chloride, mercurous chloride, mercuric sulfide, mercuric acetate

2.1 Elemental mercury

Elemental mercury vapor is colorless and odorless, and can circulate in the atmosphere for months or years, traveling thousands of miles from a source before settling in water or on land (USEPA, 2001). It is volatile, exhibiting a vapor pressure of 0.2 to 0.3 Pa at 25°C (~0.002 torr; WHO, 2003; ATSDR, 1999). Elemental mercury is lipophilic, can distribute widely in the body and is able to cross blood-brain and placental barriers. About 80% of inhaled elemental mercury is absorbed through the lungs (UNEP, 2002) while only ~0.01% is absorbed via the GI tract after ingestion. The difference is attributed to enterogastric conversion to divalent mercury which binds to sulfhydryl groups, favoring excretion following ingestion (WHO, 2003). Exposure to elemental mercury typically is related to occupational, accidental or self-inflicted events. The brain and kidney are particularly susceptible to effects of metallic mercury poisoning. Elemental mercury is not classifiable as to carcinogenicity in humans [International Agency for Research on Cancer (IARC) Group 3].

Acute, high dose elemental mercury exposure may lead to acute pneumonitis. At lesser exposures, symptoms such as tremor, gingivitis, neurocognitive or behavioral disturbances, irritability, depression, fatigue, memory loss and sleep disturbances may occur, though not always (CDC, 2009). Barboni et al. (2009) reported that chronic low level mercury exposure in workers from mercury recycling plants in San Paulo, Brazil, was associated with visual disturbances but not neuropsychological changes. Although association between exposure of dentists and prevalence of intoxication symptoms has been reported (Neghab et al., 2011), exposure to dental amalgams has not shown consistent association with neurotoxicity. The U.S. Public Health Service concluded that insufficient evidence exists to show that dental amalgams pose a human health threat

(USPHS, 1993; Clarkson and Magos, 2006). Renal dysfunction following elemental mercury exposure has been reported in the workplace. If low level exposure ceases and mercury is excreted, most effects are reversible (ATSDR, 2001).

Occupational guidelines set by Occupational Safety and Health Administration (OSHA), The National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) and the Agency for Toxic Substance and Disease Registry (ATSDR) are listed in Table 2. The USEPA has also established a reference concentration (RfC) value of 0.0003 mg/m^3, which is an estimate of continuous inhalation exposure concentration that is likely to be without risk of deleterious effects during a lifetime.

Table 2. Toxicological, Environmental and Occupational Guidelines for Different Mercury Species

Elemental	
OSHA PEL (ceiling)	0.1 mg/m^3
NIOSH REL	0.05 mg/m^3
ACGIH TLV	0.025 mg/m^3
ATSDR MRL	0.0002 mg/m^3
USEPA RfC	0.0003 mg/m^3
Inorganic	
USEPA RfD (mercuric chloride)	0.0003 mg/kg•day
USEPA MCL	0.002 mg/L
Methylmercury	
USEPA RfD	0.0001 mg/kg•day
USEPA Fish Tissue Criterion	0.3 mg MeHg / kg fish tissue

2.2 Inorganic mercury compounds

Examples of inorganic mercury compounds (or salts) include mercuric chloride, mercurous chloride, mercuric sulfide and mercuric acetate. Most inorganic compounds are white powders/crystals, except for red mercuric sulfide which turns black following exposure to light and air (ATSDR, 1999). These compounds are not very lipophilic, but are water soluble and, thus, less easily absorbed through the skin but more readily absorbed after ingestion. Ingestion of one gram of mercuric chloride may cause shock and kidney function collapse, likely due to corrosive damage to the GI tract (Clarkson and Magos, 2006). The dermal route is usually not an issue, although a skin notation often is given, and absorption after inhalation is low. Inorganic mercury compounds can reach most organs, primarily the kidneys, where prominent effects occur (ATSDR, 1999; CDC, 2009). Mercurous chloride use occurred until the mid-1900s in laxatives and teething powder (Clarkson and Magos, 2006). Inorganic mercury compounds are not classifiable by IARC as to human carcinogenicity (IARC Group 3). The RfD for mercuric chloride and maximum contaminant level (MCL) for inorganic mercury are listed in Table 2. The MCL is an enforceable standard, considering health and technical feasibility, and for inorganic mercury the MCL is the same as the maximum contaminant level goal (MCLG), the health-based guideline for drinking water below which there is no expected risk to health.

2.3 Methylmercury

Significant worldwide populations have potential exposure to organic mercury, of which methylmercury is the most common threat to human health, principally through consumption of contaminated fish and shellfish. Widespread historical use of methylmercury for seed dressings and fungicides in paper mills reportedly has caused impacts to global waterways (Grandjean et al., 2010). Methylmercury is absorbed readily via the GI tract (ATSDR, 1999; WHO, 2010). At sufficient dosage, it is a well-known neurotoxin which can pass placental and blood-brain barriers and effect the developing brain (Zahir et al., 2005; WHO, 2010). IARC has classified methylmercury as possibly carcinogenic to humans (Group 2B), though no quantitative potency is available. The National Research Council (NRC) and others (e.g., Mahaffey, 2005) have concluded that the most sensitive endpoint in assessing human exposure to methylmercury is neurodevelopmental effects, and the RfD should be based on that endpoint (NRC, 2000). The RfD for methylmercury is listed in Table 2, along with the fish tissue criterion.

Formation of methylmercury is enhanced at low environmental pH and high sediment mercury levels (WHO, 2003). Methylmercury elimination in fish is

slow, and longterm reductions in concentrations are unlikely except for "growth dilution" (e.g., stable mercury mass diluted by increased body size; USEPA, 2001). Size, age, community structure, feeding habits, and food chain position influence fish methylmercury concentration (USGS, 2009). The U.S. Food and Drug Administration (USFDA) and the American Medical Association (AMA) recommend that women who are pregnant, may become pregnant, or nursing mothers and young children should follow local, state and federal fish advisory guidance particularly for swordfish, king mackerel and tilefish, which have been found to contain elevated levels of methylmercury in edible tissues (USFDA, 2001; AMA, 2004; USFDA/USEPA, 2004; Bose-O'Reilly et al., 2010).

Methylmercury is readily absorbed and stored, but inefficiently and slowly demethylated to inorganic mercury in mammalian tissues, yielding a prolonged half-life (WHO, 2010). Following methylmercury exposure, there can be an unexplained long latency period prior to rapid onset of symptoms (USEPA, 2001; Clarkson and Magos, 2006; Grandjean et al., 2010). Selenium is an important micronutrient, deficiency of which can lead to enhanced mercury sensitivity (Clarkson and Magos, 2006; Dufault et al., 2009).

3. VARIABILITY IN RESPONSE

Common recognition of toxic effects from mercury dates to 18th and 19th century England where the phrase "mad as a hatter" was coined. Mercury was used in felt production, and hat factory workers experienced regular mercury exposure, resulting in neurotoxicity (e.g., paraesthesias, slurred speech, anxiety, vision/hearing impairment, hallucinations, depression, lack of coordination, tremors). Other mercury poisoning reports in the early- to mid-1900s included childhood teething powders and ointments. In the 1950s, a well-known chemical plant release of inorganic and methylmercury into Minamata Bay, Japan contaminated fish and shellfish that were consumed by local fishermen and families (Clarkson and Magos, 2006). Devastating health effects were termed Minamata Disease, characterized by infantile cerebral palsy, congenital abnormalities, ataxia, paralysis, hearing/vision loss and other effects of acute and chronic methylmercury toxicity (WHO, 2010). Another famous exposure episode in Iraq in the 1970s involved seed grain coated with a methylmercury fungicide, where the grain subsequently was used in making bread. In that case, official estimates suggested that over 6,500 individuals sustained mercury intoxication, although the actual number may have approached 100,000 (WHO, 2010). Peak methylmercury exposure appears to be the determining factor in assessing response (Clarkson and Magos, 2006).

Signs of mercury toxicity may include tremors, emotional instability, irritability, peripheral neuropathy, gingivitis, vision changes, hearing loss and renal impairment. These effects have been observed in humans exposed to mercury in elemental, inorganic, and organic form (ACGIH, 2001; WHO, 2010). Children are more susceptible to adverse health effects following mercury exposure than adults, and the fetus is particularly vulnerable, due to development of the brain and other systems (WHO, 2010). Differences in metabolic rates, diets, patterns of behavior, growth, and changes of organ systems/functions seen in adults and children, influence the different responses observed (WHO, 2010).

As noted, exposures can occur *in utero* by placental passage of mercury, during early life via breast milk, and during childhood/adolescence via exposure to mercury in the environment, diet and consumer products (WHO, 2010; ATSDR, 1999). In children, toxicity can involve the brain, cardiovascular system, and kidneys, as well as skin (Torres et al., 2000; WHO, 2010). It is important to consider total exposure to different mercury species. Historical home exposures have included teething powders, soaps, medicines, paints (discontinued in the US in 1990), mercury from home coal burning stoves or heaters, fluorescent lightbulbs, antiques, and vintage objects in the home (e.g., thermometers, barometers). Acrodynia, or "pink disease", is a skin condition that can develop in children, but not adults, following exposure to mercury vapor, usually associated with urine mercury levels >100 ug/L (ATSDR, 2001), and characterized by severe pain, swelling and discoloration in the extremities. Beck et al. (2004) presented a case of a three-year old boy who presented with severe hypertension along with other classical mercury signs. Hypertension was found to accompany acrodynia in some case studies (Beck et al., 2004). The rarity and observed wide variability in this skin condition makes a dose-response relationship difficult to develop.

Adequate nutrition is important for maintaining neuronal integrity and learning capacity, and mercury may adversely effect learning if either metallothionein or glutathione metabolic systems are not functioning properly (Dufault et al., 2009). One of the earliest signs of mercury toxicity is “intentional tremor”, indicating cerebellar impairment, the area of the brain involved in coordination and voluntary movements (Wastensson et al., 2008). Motor performance has been described in children following low level mercury exposure.

Complicating diagnosis and assessment processes, clinical signs of mercury intoxication mimic those that can be observed in undiagnosed neurological diseases, pharmacotherapy, vitamin/mineral deficiencies, and psychological stress (Risher and Amler, 2005). Physicians must carefully evaluate relevant biological

markers along with symptoms in order to make a complete and accurate diagnosis.

Chelation therapy can be used on patients with evidence of large mercury burden and clinical signs. Agents such as succimer, dimercaptopropanesulfonate, and d-penicillamine have been used to increase mercury elimination, though removal of methylmercury often is difficult (Goldman and Shannon, 2001). Further, chelation can mobilize significant mercury concentrations and can be associated with subsequent renal disease associated with kidney accumulation.

4. COMMON EXPOSURE VS OCCUPATIONAL EXPOSURE

A number or organizations, including USEPA, are involved on national and international fronts to reduce mercury releases to the environment and to limit human exposure (USEPA, 2009a). The World Health Organization (WHO) also is working with national, regional and global health partners to reduce mercury exposure in children by eliminating uses of mercury products where alternatives are available in industrial, medical and occupational sectors (WHO, 2010). As noted, the most important source of mercury exposure in the general U.S. population is consumption of contaminated fish (USEPA, 2008). Occupational exposure is much less common in recent years. Humans also can be exposed to elemental mercury vapors through inhalation and eye/skin contact following breakage of products in poorly-ventilated indoor spaces. Other non-occupational exposures include contaminated soils, as well as playing with liquid mercury from broken electrical switches, thermometers and barometers. Mercury vapors are heavier than air so at significant concentrations they may remain near the floor and may get into ventilation systems where they can spread through the house (ATSDR, 2001). Exposures from ambient air and drinking water typically are minor. Fish consumption advisories involving mercury accounted for 80% of all such advisories in 2008, involving nearly 17 million lake acres (USEPA, 2009b).

In 2001, instead of a water concentration-based criterion, USEPA developed a fish tissue-based criterion for methylmercury of 0.3 mg per kg (0.3 parts per million, ppm) of wet weight fish tissue (USEPA, 2001). This value was obtained by assuming a 17.5 gram/day fish ingestion rate, a 70 kg body weight, and a target reference dose (RfD) of 0.0001 mg/kg•day (= 0.1 ug/kg•day). The RfD is the level of exposure without expectation of adverse effects when exposure is encountered daily for a lifetime. The derivation of the reference dose by USEPA is explained in detail elsewhere (Rice et al., 2003; USEPA, 2011c). While neurotoxicity to the developing fetus was used to calculate the RfD, it is not specific to children and often is used for the general population, though quite conservative for adults. Equivalent guidelines set by USFDA and ATSDR are 0.5

ug/kg•day and 0.3 ug/kg•day, respectively (Clarkson, 2002). If additional states, tribes and territories adopt EPA's recommended fish tissue criterion, the number of water bodies listed under Section 303(d) of the Clean Water Act as "impaired" will increase (USEPA, 2010). Nearly 2,100 U.S. waterbodies are listed as impaired for mercury (USEPA, 2011b). A National Study of Chemical Residues in Lake Fish Tissue found that mercury concentrations in predators exceeded the human health screening value (0.3 ppm) in 36,422 U.S. lakes (USEPA, 2009c).

In occupational settings, elemental mercury typically is the primary source of exposure. Historical occupations of interest include workers in lightbulb manufacturing, chemical laboratories, mines, industrial manufacturing, and thermometer production (Mahaffey, 2005; UNEP, 2010). In some instances, as with other chemicals, workers may bring mercury home with them on clothing and shoes.

Medical monitoring (e.g., baseline and periodic exams) is common in the workplace where mercury exposure may occur. Routine air and biological monitoring are available to assess exposure levels in comparison to those tied to adverse effects (NJDOH, 2004). Measurements typically should be carried out several times per year in potentially exposed workers and evaluated on individual and group bases. Early nonspecific signs of mercury exposure may, but not always, include personality changes, weight loss, irritability, nervousness, memory loss, tremor, coordination loss, indecision and intellectual decline (NJDOH, 2004). Potential sensitive target organs for workplace mercury exposure are CNS and kidneys (Holmes et al., 2009). Cardiovascular effects of low level methylmercury exposure are uncertain (Holmes et al., 2009; Lim et al., 2010; Mozaffarian et al., 2011).

Neurobehavioral tests are available to detect early changes in nervous system effects of mercury exposure. A 24-hour urine collection to evaluate mercury in urine is ideal, but is often not feasible. In other cases, a regular sample should be taken at the same time of day near the end of the work week after several months of steady exposure. The results should be corrected for grams of creatinine in the urine (ug Hg/gm creatinine). Many reports dealing with exposure to mercury have not accounted for the creatinine level, rendering it difficult to compare results across studies.

The most reliable biomarker for longterm mercury exposure is considered to be urine samples (Holmes et al., 2009). The urine mercury levels are also a good indicator of kidney load because the kidneys tend to be the main site of mercury deposition, and this may also be a rough indicator of total body burden (Clarkson and Magos, 2006). Blood samples can be utilized for shortterm high level exposures but do not reflect body burden over long periods of time because mercury has a relatively short blood half-life. Blood concentrations decline with

a half-life of 1 to 3 weeks (CDC, 2009). Inorganic forms of mercury are not excreted in significant amounts in hair, making it an unreliable biomarker for occupational exposure, though it has been used to assess methylmercury exposure.

The toxicological literature is not conclusive in determining a relationship between urinary levels of mercury, airborne levels of mercury and observed symptoms (Tsuji et al., 2003; WHO, 2003). The variability in each of these measurements presents a challenge for epidemiologic studies (Symanski et al., 2000). Several studies concur that average exposure to elemental mercury at a concentration of 20 ug/m^3 may yield subtle CNS effects in occupationally exposed workers (WHO, 2003). A meta-analysis performed by Meyer-Baron et al. (2002) reported evidence for neurobehavioral impairments associated with urinary concentrations at or below 100 ug Hg/g creatinine, while older work (e.g., Mattiusssi et al., 1982) was focused on correlations between mercury air concentrations and urine concentrations of exposed workers. Concentrations of urinary mercury over 10 ug/L suggest that a person has some exposure (ATSDR, 2001), while neurological signs may be evident at levels greater than 100 ug/L (Goldman and Shannon, 2001). However, "Finding a measureable amount of mercury in blood or urine does not mean that the level of mercury causes an adverse health effect." (CDC, 2009).

WHO concluded a high probability of developing tremor, erethism, and proteinuria at urinary mercury levels $\geq$100 ug/g creatinine (Poulin and Gibb, 2008). Mercury blood levels reflect exposure to organic mercury, inorganic mercury and the metallic form thus the blood test is not recommended for assessing exposure to occupational mercury. Urinary mercury consists primarily of inorganic mercury, though if not specified in testing, it cannot be segregated from the other possible forms. Laboratory analytical practices typically will reduce all of the mercury present in a biological sample to its elemental state prior to analysis, although this is not acceptable when speciation is desired (Holmes et al., 2009). Being relatively volatile, mercury can be lost during sample preparation, requiring precautions.

5. SELECTED CASE EXAMPLES

5.1 Fish Consumption

Results of three large epidemiologic cohort studies from Seychelles, Faroe Islands, and New Zealand, have enhanced our level of knowledge, but have also increased the ambiguity associated with mercury exposure and the potential for adverse health effects. Studies conducted in the Faroe Islands and New Zealand

reported associations between mercury in maternal hair and several neurotoxic endpoints, whereas work conducted in the Seychelles did not show an association.

Myers et al. (2003a) investigated 779 mother-infant pairs living in the Seychelles in which the mother consumed large amounts of fish per week. Prenatal exposure was determined by maternal hair concentration during pregnancy. The authors in that study did not detect an association between neurodevelopmental risk and prenatal methylmercury exposure from fish consumption. This conclusion was controversial, as illustrated by author exchanges in scientific journals (Myers et al., 2003b; Lyketsos, 2003; Keiding, 2003; Stern, 2004). Several years later the same authors (Myers et al., 2009) reiterated that there was no consistent association.

In contrast, a cohort study of 1,022 single births in the Faroe Islands reported that several aspects of brain function may be affected by prenatal mercury exposure and that study, coupled with an integrative analysis of all three mentioned epidemiologic studies, was used by USEPA as rationale for keeping the RfD derived in 1995 the same in 2001 (Grandjean et al., 1997; Rice et al., 2003). Qualitatively similar results were reported in earlier studies by Kjellstrom et al. in 1986 and 1989 (as cited in Rice et al., 2003) from New Zealand.

A current detailed review of the three principal cohorts is found elsewhere (Bose-O'Reilly et al., 2010).

5.2 Chloralkali facilities

A Canadian cross-sectional study of 241 people living near a closed chloralkali facility found that 33.8 % of the participants had blood mercury levels above Health Canada's 20 ug/L guideline. Significantly higher blood mercury levels in participants with elevated local fish and seafood consumption, showing that dietary intake, not air, was the major exposure route (Chang et al., 2008).

Another cross-sectional study carried out in Sweden, Italy and Poland followed subjects living near chloralkali plants, as well as occupationally exposed men, to biomarkers of early kidney damage (Jarosinska et al., 2008). Limited statistical associations were found, although there were limitations to the study.

Wastensson et al. (2008) studied 43 mercury-exposed workers from two different chloralkali plants located in similar regions of Sweden. Only 12 exposed subjects showed any deviations in neurological testing, 10 of which presented with tremor. Overall, the study did not show any significant adverse health effects associated with low level exposure to mercury in that circumstance.

5.3 Other cases

One unusual case study involved a pregnant women with extremely elevated levels of blood mercury and urinary mercury who was able to deliver a healthy infant with no early signs of adverse health effects noted up through 8 months (Pugach and Clarkson, 2009). The mercury levels detected in the infant fell from 190 ng Hg/mL in the cord blood to 17 ng Hg/mL in infant blood at 4 months of age. The child continues to be monitored for signs of developmental delays.

Accidental household poisonings have been reported from mercury being brought home from school. Tezer et al. (2011) described a six-member family being exposed to mercury brought home by an elder child. Symptoms originally were diagnosed as a *Brucella* infection. It later was learned that the children played with the mercury and actually spilled some on the carpet and surrounding furniture. The 12 year old presented with the classic signs of acrodynia ("pink disease") following approximately two months of exposure, including joint and muscle pain, tremors, chills, weight loss and fever with dark pink appearance of the hands. Six weeks later her urine mercury was elevated at 73 ug/L and succimer treatment (chelation) was given, resulting in decreased urine mercury levels. The other two children (11 year old boy, 16 year old girl) presented with symptoms a little over a week after her first sign, while the other brother and parents, who slept in different rooms, were not affected. The 11 year old brother had initial urine mercury of 74 ug/L and following chelation therapy his complaints decreased yet his urine mercury increased to 118 ug/L. Following a second course of treatment urine levels returned to normal and the patient's complaints resolved. A 16 year old sister had initial urine mercury of 573 ug/L. Following first round of chelation, this remained high at 210 ug/L. She then consulted with the psychiatric department with complaints of behavior problems.

Home mercury poisoning occurred when a 36-year old woman became ill and her 14-month old child died as a result of inhalation and skin exposure to elemental mercury brought home and heated by an older child (Sarikaya et al., 2010). The child had fever and died before hospital admission. The autopsy listed possible mercury poisoning leading to likely cardiorespiratory death. The woman complained of abdominal pain, diarrhea and fever on admission to the emergency department. Neurological exam did not show tremor, paresthesia, ataxia, spasticity, hearing or vision loss and no other laboratory findings of disease were found. On the seventh day of admission the patient had a blood mercury level of 30 ug/dL. At follow-up two weeks later, the patient was asymptomatic.

6. CONCLUSION

There are many pieces to the puzzle that are essential when evaluating mercury exposure and potential risk to human health. Not only must the species of mercury be known, but the route of exposure, age of person at exposure, and the length of exposure are critical. The three major areas of interest related to mercury exposure are contaminated fish consumption, accidental or intentional exposure, and occupational exposures. Children generally are much more susceptible to effects of all mercury forms, though the precise extent and nature of sensitivities are poorly understood. Several studies have shown pregnant women exposed to methylmercury exhibit few or no symptoms, yet their offspring showed neurotoxic effects. Other studies have shown similar impacts to mothers and children. Fish are a lean low-calorie source of protein, with many benefits balancing risks, causing USEPA to develop a fish advisories website and other sources to help consumers to select fish that are low in mercury and to limit intake of fish known to be high in mercury. Caution should be taken at home to avoid accidental exposure to elemental or inorganic mercury in both adults and children.

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