Human Health Effects of Methylmercury Exposure

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Sergi Díez

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1 Introduction

Mercury (Hg) has caused a variety of significant and documented adverse effects on human health and the environment throughout the world. Mercury and the compounds with which it combines are highly toxic, particularly to the developing nervous system. The toxicity mercury imposes on humans and other organisms is dependent on the chemical form, the amount, the pathway of exposure and the vulnerability of the person exposed. Human exposure to mercury may occur via a variety of pathways, including consumption of fish, occupational and household uses, dental amalgams and mercury-containing vaccines.

Mercury has received special attention because it has proven toxic effects on multiple species. In particular, methylmercury (MeHg), the most toxic form of mercury, can cause severe neurological damage to humans and wildlife (Clarkson

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et al. 2003; Grandjean et al. 1999). The primary means by which humans are exposed to mercury are through contact with dental amalgams (mercury vapor, Hg^0) and fish consumption (MeHg). Recently, increasing concern has been expressed by pediatricians regarding the safety of many vaccine preparations routinely administered to infants, which contain an ethyl mercury compound (thimerosal). Although patterns of human usage of mercury have changed over the centuries, occupational exposure to it still occurs; significant sources include exposure to Hg vapor during mining (gold, etc.) operations (Grandjean et al. 1999; Malm 1998), Hg use in the chlor-alkali industry (Calasans and Malm 1997; Montuori et al. 2006) and Hg use in dentistry (Harakeh et al. 2002; Morton et al. 2004).

Today, the general population is primarily exposed to three different forms of mercury: mercury vapors emitted by dental amalgam fillings (Goering et al. 1992; Hansen et al. 2004; Razagui and Haswell 2001), MeHg naturally bioaccumulated in fish (Bjornberg et al. 2003; Canuel et al. 2006; Hightower and Moore 2003), and an ethyl mercury compound, thimerosal, which is employed as a preservative in certain commonly used childhood vaccines (Bernard et al. 2004; Halsey 1999; Sager 2006).

2 Sources and Cycling of Mercury in the Global Environment

Mercury is a natural element in the earth's crust; it is a silver-colored, shiny, liquid metal found in a variety of chemical forms in rocks, soil, water, air, plants and animals. Mercury usually combines with other elements to form various inorganic (e.g., the mineral cinnabar, a combination of mercury and sulfur), or organic (e.g., MeHg) compounds, although Hg occasionally also occurs in its elemental, relatively pure form, as a liquid or vapor.

The global cycling of mercury begins when Hg vapor rises from land and sea surfaces. Most atmospheric mercury exists as elemental mercury vapor, a chemically stable monatomic gas, which circulates in the atmosphere for up to 1 yr; mercury vapor may be widely dispersed and may be transported thousands of miles from original points of emission. Hg vapor is oxidized in the upper atmosphere to water-soluble ionic mercury, which is returned to the earth's surface in rainwater. Wet deposition during rainfall is the primary mechanism by which mercury is transported from the atmosphere to surface waters and land. After deposition, mercury commonly is emitted back to the atmosphere, either as a gas or associated with particles, to be re-deposited, elsewhere. As Hg cycles between environmental compartments (atmosphere, land, and water), mercury undergoes a series of complex chemical and physical transformations, many of which are not completely understood. In fact, about 90% of the total Hg input to oceans is recycled to the atmosphere, and less then 10% reaches sediments. However, a small percentage (about 2%) is methylated in biota and is accumulated in the food-chain; only a small fraction of MeHg is lost to the atmosphere, mainly as highly volatile dimethyl mercury (Fitzgerald et al. 1998). Mercury accumulates most efficiently in the aquatic food web, where predatory organisms at the top trophic levels have the highest mercury

concentrations. Almost all of the mercury that accumulates in fish tissue is MeHg; inorganic mercury is less efficiently absorbed, and more readily eliminated from the body than is MeHg, and it does not tend to bioaccumulate.

The sources from which mercury is released to the environment can be grouped into four categories: (1) natural sources; (2) current anthropogenic releases from mobilization of mercury impurities in raw materials; (3) current anthropogenic releases resulting from mercury used intentionally in products and processes; and (4) re-mobilization of historically-deposited anthropogenic mercury releases worldwide.

Natural sources include volcanoes, evaporation from soil and water surfaces, degradation of minerals and forest fires. Available information indicates that natural sources account for less than 50% of total releases. There are indications that current global anthropogenic emissions of mercury have resulted in deposition rates that are 1.5–3 times higher than those of pre-industrial times. In the vicinity of industrial areas, the deposition rates have increased by 2–10 times during the last 200 yr (Bergan et al. 1999; USEPA 1997). In 1994, global natural Hg emissions were estimated to be ~1,650 metric t/yr (Mason et al. 1994); in a later update, 1,400 t/yr constituted the best estimate (Lamborg et al. 2002). The Programme for Monitoring and Evaluation of the Long-Range Transmission of Air Pollutants in Europe (European Model and Evaluation Program; EMEP) estimated the global natural emission at about 2,400 metric t/yr, of which 1,320 was emitted from land and 1,100 was emitted from oceans (Bergan and Rodhe 2001). Emission inventories indicate that Asian sources account for more than 50% of the global anthropogenic emissions of total Hg (Jaffe et al. 2005). In the coming decades, it is expected that the rapid economic and industrial development in Asia will result in a significant increase in anthropogenic Hg emissions, unless drastic measures are taken to prevent it (Wong et al. 2006).

Among the more important *anthropogenic processes* that mobilize mercury impurities are the following: coal-fired power plants and coal burning for heat generation; cement production; and mining and other metallurgic activities involving the extraction and processing of minerals (production of iron and steel, zinc and gold). Important sources of anthropogenic releases that occur from the intentional extraction and use of mercury include the following: mercury mining; small-scale gold and silver mining; chlor-alkali production; breakage of fluorescent lamps, auto headlamps, manometers, thermostats, thermometers, and other instruments; dental amalgam fillings; manufacturing of products containing mercury; waste treatment and incineration of products containing mercury; landfills; and cremation.

The atmospheric residence time of elemental mercury is in the range of mon to ~1 yr. The environmental residence time for atmospheric mercury makes transport, on a hemispherical scale, possible; emissions on any continent may, therefore, contribute to the deposition on other continents. For example, based on modeling of the intercontinental mercury transport performed by the EMEP at the Meteorological Synthesizing Centre-East (EMEP/MSC-E) (Travnikov 2005), up to 67% of total depositions to the continent are from external anthropogenic and natural sources. Among these, ~24% are from Asian sources, and 14% from European ones.

In Europe, about 40% of annual mercury depositions result from intercontinental transport, including 15% from Asia and 5% from North America. The Arctic region has no significant local sources of mercury emission. However, about half of the mercury deposition in the Arctic results from atmospheric transport from foreign anthropogenic emission sources; the greatest contribution is from Asian (33%) and European sources (22%).

Speciation influences the transport of mercury within and between environmental compartments. Mercury adsorbed onto particles, and ionic (e.g., divalent) mercury compounds are normally deposited on land and in water, primarily near their sources of origin; in contrast, elemental mercury vapor is transported on a hemispherical or global scale portending global concern for such vapor emissions. Another concern is the so-called "polar sunrise mercury depletion incidence," a special phenomenon that has been shown to influence the deposition of mercury in Polar regions. It has also been termed "the mercury sunrise," because deposition of high amounts of mercury is taking place during the first few mon of the Polar sunrise. It appears that solar activity and the presence of ice crystals influence the atmospheric transformation of elemental gaseous mercury to divalent mercury, which is more rapidly deposited. Mercury depletion, from this effect, has now been observed in Alert, Canada (Schroeder et al. 1998), in Barrow, Alaska, USA (Lindberg et al. 2002), Svalbard, Norway (Berg et al. 2003), in Greenland (Ferrari et al. 2004), as well as in the Antarctic (Ebinghaus et al. 2002).

3 Methylmercury

3.1 Pathways of Human Exposure

As a result of the previously-described global cycling of mercury, inorganic mercury reaches the aquatic environment and is transformed to MeHg via methylation by microbial communities in aquatic sediments. Microbial conversion to MeHg is believed to be a protective mechanism, because inorganic (mercuric) mercury is more toxic to them. In aquatic systems, the microorganisms primarily responsible for methylation of mercury are the sulfate-reducing bacteria (Acha et al. 2005; King et al. 2000; Watras et al. 2005). This MeHg produced by microbial action enters the aquatic food chain. Accordingly, when human exposure occurs, it is almost exclusively from consumption of fish and marine mammals contaminated with MeHg.

The mercury concentrations that exist in various fish species generally range between 0.01 and 4 mg/kg, depending on factors such as pH and redox potential of the water, and species, age and size of the fish. Because mercury biomagnifies in the aquatic food web, fish and other higher trophic level organisms, tend to have higher levels of mercury. Hence, large predatory fish, such as king mackerel, pike, shark, swordfish, walleye, barracuda, large tuna, scabbard and marlin, as well as seals and toothed whales, contain the highest mercury concentrations. Available

data indicate that mercury is present around the globe in concentrations that may adversely affect humans and wildlife. These levels have led to advisories in a number of countries (for fish, and sometimes marine mammals) to limit or avoid consumption of certain fish taken from mercury-contaminated water bodies; warnings have been issued particularly for sensitive subgroups (pregnant women and young children). Moderate consumption of fish (with low mercury levels) is not likely to result in exposures that compromise health. However, people who consume larger quantities of fish or marine mammals may face health risks from overexposure to mercury (Hightower and Moore 2003). Although MeHg naturally accumulates in fish through the food chain, consumption of farmed fish may also result in MeHg exposures. Fish-consumption advisories issued to protect human health do not usually extend to fish by-products fed to farmed animals. Future guidelines designed to decrease exposure to MeHg must address farming practices that use fish by-products (Dorea 2006). Previous studies have shown that the meat of animals fed fish meal, or other fish products, is likely to contribute to MeHg exposure (Choi and Cech 1998; Lindberg et al. 2004). Nevertheless, results from studies have shown no significant difference in MeHg levels in wild vs. farmed salmon (Easton et al. 2002; Foran et al. 2004).

The most dramatic case of severe MeHg poisoning, which resulted from fish consumption by fisherman and their families, was the Minamata Bay, Japan incident of the 1950s. The source of contamination, in this incident, was an acetaldehyde manufacturing plant in which inorganic mercury was used as a catalyst. The amount of mercury discharged to water ways from this plant, between 1932 and 1968, was large, and was estimated at 456 t. As a result of these discharges, and subsequent consumption by the local population of MeHg contaminated-fish from the polluted water ways, hundreds of people died, and thousands were affected, many permanently (Akagi et al. 1998; Harada 1995). The medical disorders associated with this epidemic became known as “Minamata disease.” A similar fish-mediated epidemic of MeHg poisoning occurred in riverside villages along the Agano River in Niigata, Japan, in 1964–1965 (Tsubaki and Irukayama 1977).

Japan is not the only country, however, in which such events have occurred. Recently, a population resident in the Brazilian Amazon showed evidence of increased exposure to MeHg, which resulted from their consumption of fish contaminated by upstream gold-mining activities (Dolbec et al. 2000; Grandjean et al. 1999; Lebel et al. 1998).

Methyl- and ethyl-mercury poisonings occurred in Iraq following consumption of seed grain that had been treated with fungicides containing these alkylmercury compounds (Bakir et al. 1973). The first outbreaks were caused by ethylmercury, and occurred in 1956 and, again in 1959–1960; ~1,000 people were adversely affected. The second outbreak was caused by MeHg, and occurred in 1972. The imported mercury-treated seed grains were subsequently ground into flour that was used to prepare homemade bread throughout rural areas of Iraq. The latent period after exposure to MeHg, before toxicity appeared, contributed to this disaster; farmers fed contaminated grain to their livestock without observing any immediate effects. Such observations probably led farmers to conclude that

the grain was safe for them to consume, as well. Subsequent human consumption of contaminated bread resulted in insidious and irreversible neurological symptoms. The victims experienced no ill effects during the intake period. After consumption had stopped, no neurological symptoms appeared for more than 1 mon. This relatively long latent period is a dangerous property of MeHg. In the Iraq incident, the first symptom to appear was paresthesia and later, but in a rapid sequence, more severe signs appeared such as ataxia, dysarthria and loss of vision. Unlike the long-term exposures in Japan, the epidemic of MeHg poisoning in Iraq had a short duration, although, the magnitude of the exposure was high. It was reported that as many as 50,000 persons may have been exposed, and neurological impairments in children were evident (Myers et al. 2000). Tragically, more than 6,500 individuals were hospitalized, and 459 died from consumption of Hg-contaminated bread.

3.2 Reports of Exposure

Estimation of the magnitude of MeHg exposure to the general population has only been made in few countries such as the United States (Mahaffey et al. 2004; McDowell et al. 2004), Japan (Yasutake et al. 2004) and Germany (Becker et al. 2002, 2003). Apart from those populations known to have high fish consumption, mean Hg levels in hair generally range from >0.1 to 1.0 mg/kg (Bjornberg et al. 2003; Knobeloch et al. 2005; Montuori et al. 2006; Stern et al. 2001); mean blood levels of Hg are generally in the range of 1.0–5.0 μg/L, although, worldwide, there are more Hg residue data for hair, than for blood.

Higher levels of Hg exposure occur in populations that live near oceans, lakes and rivers, because these populations consume more freshwater fish. In the Faroe and Seychelles islands, the median Hg concentration found in maternal hair is 4.5 mg/kg (Grandjean et al. 1992), and 5.8 mg/kg (Cernichiari et al. 1995a), respectively. In the river basins of the Amazon, median hair Hg levels typically range between 5 and 15 mg/kg (Akagi et al. 1995; Barbosa et al. 2001; de Campos et al. 2002; Dolbec et al. 2001; Dorea et al. 2003; Kehrig et al. 1997; Santos et al. 2002a). Table 1 presents the Hg concentrations found in human hair for residents of various countries. It can be seen from these results, that gold mining, together with chlor-alkali plants, constitute the most important sources of mercury contamination that affect people, in the world.

3.3 Toxicokinetics

Several recent reviews have addressed the absorption, disposition, and excretion of MeHg in the body (ATSDR 1999; Clarkson and Magos 2006; USEPA 2001). It is well known that about 95% of MeHg ingested in fish is absorbed in the

Table 1 Comparison of mercury (Hg) concentrations (mg/kg dry wt) in human hair collected at various worldwide locations

Location	Mean	Range	Remarks	References
Faroe Islands	4.27	2.6–7.7	Mother at parturition	Grandjean et al.1997
	1.12	0.69–1.88	Child, 12 mon	
	2.99	1.7–6.1	Child, 7 yr	
Minamata, Japan		2.46–705	Patients of Minamata disease	Harada 1995
Tokyo	2.98		Male	Nakagawa 1995
	2.02		Female	
Wau-Bulolo, Papua, New Guinea	0.55	0.19–1.1	Background	Saeki et al. 1996
	1.20	0.39–3.0	Gold-mining area	
Bangladesh	0.44	0.02–0.95	Fish consumption	Holsbeek et al. 1996
Tarragona, Spain	0.77	0.18–2.44	School children	Batista et al. 1996
California, USA	0.64	0.3–1.8	Tribal members	Harnly et al. 1997
	1.60	0.3–2.3	Non-tribal members	
Shiranui Bay, Japan	5.00		Male	Harada et al. 1998
	2.10		Female	
Tokushima, Japan	4.62	0.626–24.6		Feng et al. 1998
Harbin, China	1.69	0.112–36.4		
Medan, Indonesia	3.13	0.203–19.9		
Hong Kong, China	3.33		Fertile male	Dickman et al. 1998
	4.23		Subfertile male	
New Zealand		3–6	Maternal hair	Crump et al. 1998
Madeira, Portugal	10.39	1.93–42.61	Pregnant woman	Renzoni et al. 1998
Lake Victoria, Tanzania		0.29–953	Gold mine	Harada et al. 1999
		0.29–416	Fishing village	
		0.48–474	City	
Seoul, Korea	1.70		Male	Lee et al. 2000
	1.10		Female	
Doha, Kuwait	4.18		Fisherman	Al-Majed and Preston 2000
	2.62		Control	
Gdansk, Poland	0.38		Person who died suddenly	Hac et al. 2000
Montreal, Canada	0.82	<0.20–6.59	Frequent fish consumers	Kosatsky et al. 2000
	0.38	<0.20–3.38	Infrequent fish consumers	
Seychelles Islands	6.80	0.5–26.7	Maternal hair	Myers et al. 2000
	6.5	0.9–25.8	5–6-yr-old children	
Diwalwal, Philippines	2.65	0.03–34.71	Control	Drasch et al. 2001
	2.77	0.03–13.17	Downstream of gold mine	
	1.71	0.03–8.91	Gold mine, non-occupational	
	3.62	0.03–37.76	Gold mine, occupational	
Kamuango, Kenya	1.44	0.67–3.5	Gold mine	Harada et al. 2001
Sori Beach, Kenya	2.09	0.73–5.6	Fishing village	
Homa Bay, Kenya	4.50	0.61–42.8	Fishing village, with Hg-containing soap user	
Dunga Beach, Kenya	48.50	0.27–900	Fishing village, with Hg-containing soap user	
Kisumu, Kenya	145	1.1–603	City, with Hg-containing soap user	
Tapajos River, Brazil		1.8–53.8	Gold-mining area	
Negro river basin, Brazil	12.65	0–44.53	<15-yr-old children	Barbosa et al. 2001
Wayana, French Guiana	11.40			Frery et al. 2001
Upper Maroni, French Guiana	12.7 (10.2)		Maternal (children) hair	Cordier et al. 2002
Camopi, French Guiana	6.7 (6.5)			
Awala, French Guiana	2.8 (1.4)			
Mansoura, Egypt	0.23	0.11–0.41	Urban area	Mortada et al. 2002
Anwiaso, Ghana	1.61	0.15–5.86	Children in gold-mining area	Adimado and Baah 2002

(continued)

Table 1 (continued)

Location	Mean	Range	Remarks	References
Sahuma, Ghana	0.62	0.32–2.19	Children in gold-mining area	
Tanoso, Ghana	4.27	0.06–28.3	Children in gold-mining area	
Elubo, Ghana	1.21	0.07–3.19	Children in gold-mining area	
Camito, Colombia	4.91		Fisherman	Olivero et al. 2002
Sai Cinza, Brazil	16.00	4.50–90.4	Gold-mining area	Santos et al. 2002b
Santana do Ituqyi, Brazil	4.33	0.40–11.60		
Aldeia do Lago Grande, Brazil	3.98	0.40–11.76		
Tabatinga, Brazil	5.37	0.37–16.96		
Caxiuana, Brazil	8.58	0.61–45.59		
Madeira Island	4.09	0.38–25.95	7-yr-old children	Murata et al. 2002
Germany	0.23	0.06–1.7	8–10-yr-old children	Pesch et al. 2002
Minamata, Japan	1.76	0.09–10.56		Yasutake et al. 2003
Kumamoto, Japan	1.57	0.14–19.18		
Tottori, Japan	2.04	0.00–12.52		
Wakayama, Japan	2.04	0.00–20.66		
Chiba, Japan	3.37	0.14–26.76		
Japan	1.64	0.45–6.32	7-yr-old children	Murata et al. 2004
Japan	2.42		Male	Yasutake et al. 2004
	1.37		Female	
USA	0.22	0.18–0.25	1–5-yr-old children	McDowell et al. 2004
	0.47	0.35–0.58	16–49-yr-old women	
Cambodia	3.10	0.54–190		Agusa et al. 2005
Kayabi, eastern Amazonia, Brazil	16.55		Children fish consumers in gold-mining area	Dorea et al. 2005
Cururu, eastern Amazonia, Brazil	4.76		Children fish consumers in gold-mining area	
Kaburua, eastern Amazonia, Brazil	2.87		Children fish consumers in gold-mining area	
Spain	0.94	0.19–5.63	4-yr-old children	Montuori et al. 2006
Menorca, Spain	0.72	0.23–3.83	4–yr-old children, diffuse source	
Flix, Spain	1.26	0.19–5.63	4-yr-old children, chlor-alkali source	
Mediterranean coast, Morocco	1.79	0.22–9.56	Frequent fish consumers	Elhamri et al. 2007
Zhoushan City, China	1.25	0.93–1.69	Maternal urban	Gao et al. 2007
Naples, Italy	0.64	0.22–3.40	Urban area	Díez et al. 2008a
Madrid and Sabadell, Spain	1.68	0.13–8.43	Neonates	Díez et al. 2008b

gastrointestinal tract, although the exact site of absorption is unknown. After consumption, MeHg is accumulated in liver and kidney, but is distributed to all tissues, a process that takes some 30–40 hr. Approximately 5% of MeHg is found in the blood and 10% in brain; in the blood, most mercury is bound to the hemoglobin in red cells, with a concentration of about 20 times the plasma concentration. The concentration in brain is about 5 times, and in scalp hair about 250 times the corresponding concentration in blood. Hair levels closely follow blood

levels. MeHg crosses the blood brain and placental barriers. Moreover, levels in cord blood are proportional to, but slightly higher than, levels in maternal blood. Levels in the fetal brain are about five to seven times higher than levels in maternal blood (Cernichiari et al. 1995a).

MeHg is slowly metabolized to inorganic mercury by microflora in the intestines; the biochemical mechanisms that accomplish this are not known. Although MeHg is the predominant form of mercury at the time of exposure, inorganic mercury slowly accumulates in the body and resides for long periods in the central nervous system. Inorganic mercury is believed to be in an inert form, perhaps existing as insoluble mercury selenide (Clarkson et al. 2003).

The half-life of MeHg in the body is about 50 d, with a range of 20–70 d; the half-life in hair averages about 65 d, with a range of about 35–100 d (Clarkson 1993), indicating that MeHg leaves the body slowly. Urinary excretion is negligible: 10% or less of total elimination from the body. Most MeHg is eliminated from the body by demethylation, and excretion of the inorganic form in feces. Biliary excretion and demethylation by microflora do not occur in suckling animals. The failure of neonates to excrete MeHg may be associated with the inability of suckling infants to perform these two metabolic processes (Ballatori and Clarkson 1982; Rowland et al. 1977).

The high mobility of MeHg in the body does not result from lipid solubility, as claimed in some textbooks; rather, it results from the formation of small molecular weight thiol complexes that are readily transported across cell membranes. MeHg is present in the body as water-soluble complexes, mainly, if not exclusively, attached to the sulfur atom of thiol ligands. It enters the endothelial cells of the blood–brain barrier as a complex with L-cysteine. The attachment of MeHg to the thiol ligand in the amino acid cysteine results in a complex, the structure of which mimics that of the large neutral amino acid, L-methionine. The process is so specific, that the complex with the optical isomer D-cysteine is not transported. Thus, MeHg transport into tissues appears to be mediated by the formation of a MeHg-cysteine complex. This L-complex is structurally similar to methionine, and is transported into cells via a widely distributed neutral amino acid carrier protein (Kajiwara et al. 1996, 1997; Kerper et al. 1992). Although MeHg is distributed throughout the organs of the body, it has its most devastating effect on the developing brain.

3.4 Toxicity and Effects on Humans

Once MeHg is dispersed throughout the body by blood flow, and enters the brain, it may cause structural damage. The critical target for MeHg toxicity is the central nervous system. Physical lesions may be manifested as tingling and numbness in fingers and toes, loss of coordination, difficulty in walking, generalized weakness, impairment of hearing and vision, tremors, and finally loss of consciousness leading to death. The developing fetus may be at particular risk from

MeHg exposure. Infants, born to mothers exposed to MeHg during pregnancy, have exhibited a variety of developmental neurological abnormalities, including the following: delayed onset of walking and talking, cerebral palsy, altered muscle tone and deep tendon reflexes, and reduced neurological test scores. Maternal toxicity may or may not have been present during pregnancy for those offspring to exhibit adverse effects. The critical effects observed following MeHg exposure to the general population are multiple central nervous system effects including ataxia and paresthesia.

3.5 Risk Evaluations

The general population is primarily exposed to MeHg through the diet, especially fish and other seafood. Authorities in several countries and international organizations have used risk evaluation tools to establish prospective safe levels (RfD: Reference Dose; PTWI: Provisional Tolerable Weekly Intake), limits, advisories or guidelines for consumption of fish or other foods contaminated by mercury compounds. The RfD is defined by the United States Environmental Protection Agency (US EPA) as an estimate (with an uncertainty of approximately tenfold) of the daily exposure to humans (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during an entire lifetime. In contrast, the PTWI represents the maximum acceptable level of a contaminant in the diet; the goal should be to limit exposure to the extent feasible, consistent with the PTWI.

Some studies have demonstrated the neurological injuries caused by low-level MeHg exposure (Mendola et al. 2002; Grandjean et al. 2004). Recent prospective epidemiologic studies from the Faroe Islands, the Seychelles Islands and New Zealand have reported on the developmental effects of low-level maternal and fetal MeHg exposure in fish-consuming populations (Cernichiari et al. 1995b; Grandjean et al. 1997; Crump et al. 1998).

The US EPA relied on the Faroe Islands study (USEPA 1997) to establish a benchmark dose that was converted into a maternal intake of 1.1 μg Hg/kg body weight (bw) per d. After applying a safety factor of 10, an RfD of 0.1 μg/kg bw/d was recommended. The reference dose will be exceeded if a substantial amount of mercury contaminated fish is ingested. For example, if the weekly intake of fish (having residues >0.4 mg/kg) is about 100 g (one typical fish meal per week), the RfD will be exceeded. Therefore, fish mercury levels should be kept below this limit.

The 67th meeting of the Joint FAO/ WHO Expert Committee on Food Additives (JECFA) was held in 2006 to evaluate certain food additives and contaminants. During this meeting a PTWI of 1.6 μg MeHg/kg bw/week (equal to 0.23 μg MeHg/kg bw/d) for the general population (JECFA 2006) was confirmed. The JECFA established this PTWI using the most sensitive toxicological end-point, i.e., developmental neurotoxicity, in the most susceptible species (humans). However, the

JECFA noted that life-stages other than the embryo and fetus may be less sensitive to the adverse effects of MeHg.

The risks from mercury in fish and shellfish depend on the amount of fish and shellfish eaten and the levels of mercury they contain. Therefore, the US Food and Drug Administration (FDA) and the EPA are advising women who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and eat fish and shellfish that are lower in mercury. Both recommend that these sensitive individuals avoid eating shark, swordfish, king mackerel, or tilefish, because they contain high levels of mercury; in addition, these sensitive groups should not eat more than 12 ounces (two average meals) a week of a variety of fish and shellfish that have lower mercury levels.

Shrimp, canned light tuna (not albacore tuna), salmon, pollock, and catfish are all regarded to have rather low concentrations of Hg. If advice for local consumption of contaminated fish is unavailable, it was recommended that people eat no more than two fish meals per week. Following a request from the European Commission, the European Food Safety Authority's (EFSA) Scientific Panel on Contaminants in the Food Chain (CONTAM) evaluated the possible risks to human health from consumption of foods contaminated with mercury, in particular MeHg; CONTAM used intake estimates for Europe. The Panel also considered the PTWI recently established by JECFA and the intake limits established by the U.S. National Research Council (US-NRC).

3.6 Risks and Benefits of Fish Consumption

It is well known that most human exposure to MeHg is through consumption of fish and shellfish. The levels of MeHg that reach human hair is dependent on the both the amount and the species of fish or other seafood consumed and the degree of their Hg contamination (Díez and Bayona 2002; Díez et al. 2007; Díez et al. 2008a, 2008b; Montuori et al. 2004, 2006). Several papers have recently dealt with the relative benefits and risks of fish consumption (Bouzan et al. 2005; Cohen et al. 2005a, b, c; Konig et al. 2005; McMichael and Butler 2005; Teutsch and Cohen 2005; Willett 2005). These articles address the quantity of fish people can consume relative to their corresponding risks and benefits. During late gestation, the developing brain is most vulnerable to neurochemical disruption from Hg exposure. Fetuses are known to face high-risks from MeHg exposure (Choi 1989; IPCS 1990) because of the susceptibility of the developing brain (IPCS 1990; Sakamoto et al. 2002); higher amounts of MeHg accumulate in cord blood than in maternal blood (Stern and Smith 2003; Vahter et al. 2000). Therefore, efforts must be made to protect fetuses from risks associated with MeHg exposure, particularly in populations such as the Japanese and other Asians, who consume large amounts of fish and other seafood (Agusa et al. 2005; Feng et al. 1998; Yasutake et al. 2004). Other populations that may face higher risks because they consume higher amounts of seafood are people in the Arctic region (Muckle et al. 2001;Van Oostdam et al.

1999), and others that dwell along rivers, lakes and coasts (Campbell et al. 2003; Dellinger 2004; Myers et al. 1997) such as Brazilians in the Tapajos River basin in the Amazon (Akagi et al. 1995; Lebel et al. 1997; Malm et al. 1995).

Fish constitute an important source of energy, protein and other nutrients (Clarkson and Strain 2003) and are low in saturated fats; they also contain essential nutrients such as heart healthy omega-3 fatty acids. Indeed, human intake of the n-3, longer chain polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid and docosahexaenoic acid (DHA), is also known to occur mainly from fish consumption. Both of these fatty acids are very beneficial for human health (Skerrett and Hennekens 2003), particularly DHA, which is known to be important for normal brain function and development (Makrides et al. 1995; Yavin et al. 2001). A recent study of over 7,000 children revealed that when fish is not contaminated, moderate fish intake by the mother during pregnancy, and by the infant postnatally, may benefit brain development (Daniels et al. 2004). One study of neurodevelopment in infants suggested that maternal mercury exposure, and fish intake, had opposing effects on visually-mediated neurobehavioral tests (Oken et al. 2005). In a small Faroese birth cohort (Steuerwald et al. 2000), it was found that prenatal MeHg exposure adversely affected neonatal neurologic function, and, selenium and n-3 fatty acid status did not affect this outcome. Recently, Sakamoto et al. (2004) have reported a significant positive correlation between MeHg and DHA concentrations in fetal circulation. These last results confirm that both MeHg and DHA, which originated from fish consumption, transferred from maternal to fetal circulation to impart its positive effects on the fetus. This finding confirms that a decrease in fish consumption may cause decreases in MeHg and DHA levels. Pregnant women, in particular, should not give up eating fish at the risk of loosing such benefits. However, they would do well to consume smaller fish, which contain lower MeHg levels, thereby balancing the risks and benefits from fish consumption.

Fortunately, fish with a high content of beneficial fatty acids do not necessarily contain high mercury levels, and a prudent choice may therefore be possible (Budtz-Jørgensen et al. 2007). Nevertheless, an increase of omega-3 fatty acids in the diet has been promoted by the American Heart Association (AHA); AHA encourages consumption of omega-3 fatty acids from a variety of sources such as fatty fish (salmon) or plant sources. The AHA recommends a minimum of two servings of fatty fish per week to confer cardio protective effects (Krauss et al. 2001). Table 2 presents average Hg concentrations found in fish species popular with American consumers. As previously described, the health benefits of eating fish high in omega fatty acids are important for cardiovascular health and fetal development, in particular. Table 2 also provides the relative fatty acid content of fish popular with consumers.

3.7 Biomarkers and Exposure Evaluation

To determine the effect of MeHg on humans, it is preferred to use a biological indicator in the body that reflects the MeHg concentration in the major target organ, the brain (Cernichiari et al. 1995a). Blood and hair Hg concentrations are

Table 2 Relative fatty acid content and Hg concentration in popular fish

Species	Average Hg wt/wt (mg/kg)	Relative fatty acid content
Catfish	0.05	Low (channel) moderate (brown bullhead)
Clams	<0.01*	Low
Cod	0.095	Low
Crab (blue, king, snow)	0.06	Moderate
Flatfish (flounder, sole, plaice)	0.045	Low
Halibut	0.252	Moderate
Mackerel king	0.730	High
Pollock	0.041	Moderate
Salmon	0.014*	High
Scallop	0.05	Low
Shark	0.988	Low
Shrimp	<0.01*	Moderate
Swordfish	0.976	Low
Trout	0.072	Moderate (Rainbow) High (Lake)
Tuna, (canned, light)	0.118	Moderate
Tuna (canned, albacore)	0.353	High
Tuna (fresh/frozen, albacore)	0.357	Moderate
Tuna (fresh/frozen, bigeye)	0.639	Moderate
Tuna (fresh/frozen, skipjack)	0.205	Moderate
Tuna (fresh/frozen, yellowfin)	0.325	Moderate

Italics indicate freshwater fish. All other fish are marine species.
Mercury was measured as total mercury (THg), except for species (*), when only MeHg was analyzed
Source of data: FDA1990–2004, "National Marine Fisheries Service Survey of Trace Elements in the Fishery Resource" Report 1978, "The Occurrence of Mercury in the Fishery Resources of the Gulf of Mexico" Report 2000. http://www.cfsan.fda.gov/~frf/sea-mehg.html

used as valid biomarkers for MeHg in both the adult and fetal brain (in the latter case, cord blood or maternal hair), although each provides a somewhat different reflection of exposure (NRC 2000). Blood gives an estimate of exposure over the most recent 100–140 d, whereas, hair reflects the average exposure over the growth period of the segment. Whether hair or blood is a better indicator of fetal brain exposure has been debated for several yr. Some researchers argue that MeHg residues in cord blood is in closer contact with the fetal brain than is mercury in maternal hair; they also argue that hair is potentially subject to external contamination (Budtz-Jorgensen et al. 2004). Moreover, various types of hair treatments may reduce mercury levels in hair (Dakeishi et al. 2005). In contrast, proponents for using maternal hair argue that cord blood levels are only relevant at the time of delivery, whereas, hair recapitulates mercury levels throughout pregnancy. Moreover, because at least 80% of the MeHg blood is associated with the RBC (red blood cells), cord blood levels will be influenced by the hematocrit. Depending on the method used to collect cord blood, the hematocrit may vary widely (Clarkson and Magos 2006). With respect to hair treatment, a recent

comprehensive study of mercury levels in human hair found no effects on hair mercury levels (McDowell et al. 2004). The mercury concentration in hair reflects the MeHg concentration in the blood during hair formation, and is frequently used as biomarker for evaluating MeHg exposure.

The mechanisms of MeHg transport have implications for the choice of indicator media. Because MeHg is highly mobile, and with continued exposures soon attains a steady state distribution in the body, levels of mercury in virtually any tissue or biological fluid may yield results useful in determining MeHg exposure. Biomarkers commonly used to assess MeHg exposure to the fetal brain include cord blood, placental tissue, and maternal blood and scalp hair.

Because of its proximity to the fetal brain, cord blood is generally the biomarker of first choice, however, based on what is known about the mechanisms of transport and disposition of MeHg, maternal scalp hair offers the best functional index of fetal brain levels. As mentioned, the MeHg-cysteine complex is responsible for MeHg transport into cells via the large neutral amino acid carrier. However, during its formation, the hair follicle has a high demand for amino acids as substrates for proteins, especially keratin. The large neutral amino-acid carriers will be highly active, not only in transporting its normal substrates, but also in transporting the MeHg–cysteine complex. Once transported into the hair follicular cells, keratin proteins synthesized in these cells have a high cysteine content that provides ample binding and stable storage for the transported MeHg. In fact, MeHg is incorporated into hair follicles in proportion to its content in blood. The hair-to-plasma ratio is about 2,500:1, whereas, the hair-to-blood ratio in humans is estimated to be ~250:1 expressed as mg/g hair to mg Hg/L blood (IPCS 1990). Once incorporated into hair, the mercury is stable, and can provide a history of exposure (Phelps et al. 1980; IPCS 1990). Hair grows at an approximate rate of about 1 cm/mon, and studies can be performed to determine past exposures if the length of the hair permits it. Because the half-life of MeHg in the body is about 1.5–2 mon (Smith and Farris 1996), the hair nearest the scalp best reflects current exposures and recent blood concentrations. A population that regularly and frequently consumes fish will show a clear correlation between total mercury (THg) content of hair and blood MeHg levels. Furthermore, MeHg levels in hair and THg are linearly related, with MeHg accounting for the 70–80% of hair THg (Cernichiari et al. 1995a; Dolbec et al. 2001). Finally, if the mechanisms of transport strongly suggest that the hair follicle accumulates the same transportable species of mercury as that which enters the brain, the levels of mercury in maternal hair, in a population of fish consumers, correlate highly with levels in the brain of newborn infants (Cernichiari et al. 1995a). The convenience of sampling and storing scalp hair is advantageous for monitoring and field studies and it has been extensively demonstrated that the THg concentration in hair reflects the average MeHg concentrations circulating in blood.

The growth rate of hair, generally estimated at 1 cm/mon, can have both inter- and intra-individual variability. Recent advances in analysis of a single hair strands (Duford et al. 2007; Legrand et al. 2004, 2007; Toribara 2001) should yield more information on the relationship between Hg uptake and Hg deposition in hair.

4 Summary

Mercury (Hg), and the organometallic compounds formed from it, are among the most toxic of substances to the global environment. Mercury is environmentally ubiquitous, and both wildlife and humans are exposed to the toxic effects of its environmental residues, primarily elemental mercury (Hg^0), divalent mercury (Hg^{2+}) and methylmercury (MeHg). Humans are exposed to different forms of Hg, and potential health risks have been reported from such exposures; examples of Hg exposure include mercury vapor from dental amalgams, occupational exposures and exposures during artisan and small-scale gold mining operations. Despite the significance of these foregoing Hg exposures, of particular concern is human and wildlife exposure to MeHg, a potent neurotoxicant. Once incorporated into the body, MeHg easily penetrates the blood-brain barrier and causes damage to the central nervous system, particularly in fetuses. It bioaccumulates and biomagnifies in the aquatic food chain; consequently, fish and seafood consumption is the major pathway by which humans are exposed to MeHg.

MeHg is the focus of this review. It adversely affects humans and is currently the subject of intense public health interest and worldwide concern. In this review, I summarize the sources and cycling of global mercury in the environment, pathways of exposure, toxicity and exposure evaluation, toxicokinetics, the common biomarkers to evaluate exposure and effects in populations, and finally review the nutritional risks and benefits from fish consumption.

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