The Toxicology of Mercury

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Mercury is a toxic heavy metal that is of significant concern as an environmental pollutant. Mercury and the other noble metals were the first elements to be discovered and utilized by humans because they exist in nature either in the free state or as easily decomposable compounds. In the 4th century B.C., Aristotle discussed the use of 'fluid silver' for religious ceremonies. Hippocrates was said to have used mercury for medicinal purposes. And the Romans used vermillion (the red-colored sulfur salt of mercury) extracted from the Almadén cinnabar mines as a cosmetic and decorative (Nriagu, 1979).

In the middle ages, Paracelsus popularized the use of mercury for the treatment of vermin, lice, and most notably syphilis; however, the predominant use of mercury in pre-industrial times was for the extraction and purification of gold and silver (Farrar & Williams, 1977). While gold mining remains a major use of the metal today, the unique chemical and physical properties of mercury are used widely in industry. For example, mercury-cathode electrolytic cells used for the production of chlorine and caustic soda have only recently diminished in popularity. The mercury dry-cell battery developed during World War II led to the extensive use of the metal in alkaline batteries until recently. Mercury was essential to the development of the incandescent lamp by Thomas Edison and remains a principal component of fluorescent light fixtures. The organo-mercury compounds have been used widely as fungicides in agriculture and paint manufacturing (Nriagu, 1979). And the United States government is currently debating the fate of vast stockpiles of mercury (~60% of the world's supply) originally set aside for use in the atomic energy program (Murdoch, 1996).

Mercury occurs in three valence states in nature: elemental (metallic, Hg°) mercury, monovalent (mercurous, Hg_2^{2+}) mercury and divalent (mercuric, Hg^{+2}) mercury. Elemental mercury has a significant vapor pressure under ambient conditions [~1.1 x 10^{-3} torr at 20° C (Phillips *et al.*, 1959)], and the saturated atmosphere concentration (~12 mg m^{-3} at 20°) is more than two orders of magnitude greater than the current threshold limit value for occupational exposure (WHO, 1991). Of the two ionized states, monovalent and divalent mercury, the latter is more stable and more common in the environment. In nature, divalent mercury is commonly associated with sulfur in the mineral cinnabar, but it may also be associated with inorganic molecules such as chlorine, oxygen and hydroxyl ions, or with organic molecules in compounds such as methyl mercury (MeHg).

Mercury is not essential to living cells and performs no known biological function (NAS, 1978). The toxicity of mercury is primarily associated with the cationic state (Hg^{+2}); however, absorption, tissue distribution and biotransformation are influenced significantly by the valence state of the metal (Berlin, 1986). Inorganic mercury is poorly absorbed through the gastro-intestinal tract (< 10%), however inhaled Hg° vapor is readily absorbed in the lungs and MeHg is almost completely absorbed (> 90%) upon ingestion (WHO, 1990; WHO 1991). Inhalation of Hg° vapor is associated with an acute, corrosive bronchitis or pneumonitis (Goyer, 1991). Chronic exposure to mercury vapor (or extreme acute dosing) results in toxicity of the central nervous system including tremors, increased excitability and delerium. The extensive use of mercury in the fur, felt and hat industry was the cause of 'mad hatters disease,' a condition characterized by delerium and hallucinations and inspiration for the Mad Hatter in Lewis Carroll's *Alice in Wonderland*. Elemental mercury is eventually oxidized to Hg^{+2} in the body by the hydrogen peroxidase-catalase pathway and is primarily excreted via the kidneys (however, a small portion may be exhaled) (Halbach & Clarkson, 1978).

Ingestion of inorganic, oxidized mercury can result in abdominal cramping, ulceration and renal toxicity. Mercury has a strong affinity for sulfur, and mercury's primary mode of toxic action in living organisms is thought to be the interference of enzyme function and protein synthesis by binding to sulfhydryl groups (Kark, 1979). Because it is a fundamental element, mercury is not metabolized by Phase I or II reactions, however excretion is associated with oxidation of mercury and mercury compounds to the water soluble divalent form. Renal excretion is the primary route of elimination of oxidized mercury, and because of its strong affinity for protein (including that in the epithelium of the nephrons) renal toxicity is commonly associated with mercury exposure. Proteinuria is one of the primary symptoms associated with mercury exposure to Hg^{+2}.

By comparison, organic mercury is highly lipophilic. Exposure occurs primarily via consumption of contaminated fish, however dermal exposure is not uncommon in laboratory settings and MeHg recently caused the death of Karen Wetterhahn, Ph.D., a Dartmouth University researcher exposed to a single drop of MeHg that passed through her protective latex glove (Associated Press, 1997). Both MeHg and Hg° cross the placental and blood-brain barrier where they can be oxidized (via the peroxidase-catalase pathway), trapped and accumulated in these tissues.

The nervous system is the critical organ for toxic exposure to both methyl and elemental mercury. Methyl mercury can react directly with important receptors in the nervous system, such as the acetycholine receptors in the peripheral nerves (WHO, 1990). The effects of mercury on the nervous system range from irritability, excitability and parasthesia (numbing of the extremities) at low levels of exposure, to tremors, violent muscle spasms and death in the extreme (WHO, 1991). While carcinogenicity and mutagenicity are not commonly associated with mercury exposure, mercury can cross the placental barrier where exposure can lead to spontaneous abortion, congenital malformations and severe neurological defects such as cerebral palsy (WHO, 1991). Mercury affects the developing fetus by interfering with normal neuronal development; it may also affect cell division (possibly through the inhibition of the microtubular system) during critical stages of formation of the central nervous system. The model emerging to explain the toxic effect of mercury is a continuous dose-effect relationship where low level exposure results in subtle changes in brain function as indicated by psychological tests (WHO, 1990). Recent research also suggests that low level exposure to mercury may potentiate the genetic damage associated with environmental mutagens, such as radionucleides (Sugg *et al.*, 1995).

Because of the extreme and pronounced toxicity of mercury, environmental contamination due to increased industrial use of the metal has resulted in many episodes of human poisonings. One of the earliest and best known examples of environmental mercury poisoning occurred in Japan in 1953 with the first reported cases of 'Minamata disease'. An international investigation revealed that inorganic mercury released to Minamata Bay from a nearby acetaldehyde plant had been converted to methyl mercury by microorganisms in the bay sediments. The MeHg formed was bioaccumulated by fish and shellfish, a staple of the nearby population. Symptoms of the 'disease' were typical of MeHg poisoning, ranging from parasthesia to severe birth defects and death.

Despite the recognition of the toxicity of mercury and mercury vapor in the 17th century in the Almadén mercury mines, Minamata was the first identified example of the *in situ* methylation and bioaccumulation of mercury in fish. Inorganic mercury released by the plant would have had little impact on human health because of its poor adsorption. Mercury methylation by naturally occurring benthic organisms, however, resulted in greatly increased exposure because MeHg is more readily absorbed by living organisms. Fish can bioaccumulate MeHg by a factor of $\sim 10^6$ (Gilmour & Henry, 1991) and are a significant source of mercury in the diets of humans and other piscivorous animals (U.S. EPA, 1984). Minimata demonstrated that fish and shellfish which accumulated concentrations of MeHg toxic to humans and wildlife showed no abnormality in many cases (Takizawa, 1979).

The environmental mercury cycle is further complicated because certain forms of mercury are volatile. Unlike most metal pollutants whose movement is limited to erosion or leaching pathways, Hg° is readily transported in the atmosphere (Carpi, 1997) and has an atmospheric half-life of approximately one year (Lindqvist & Rodhe, 1985). Elemental mercury is eventually removed from the atmosphere by oxidation to water soluble species and by dry deposition (Carpi, 1997). Although large-scale industrial releases of mercury have been controlled in the United States, atmospheric transport has implicated smaller environmental sources (i.e. the combustion of coal, municipal solid waste and sewage sludge) as the cause of widespread elevations of environmental mercury concentrations, even in remote ecosystems (Glass *et al.*, 1990; Carpi *et al.*, 1994). Because of widespread mercury contamination in the environment, more than 90% of all U.S. states have been forced to limit fishing or issue fish advisories for hundreds of valuable water resources (USGS, 1995; NJ DEPE, 1993; also see, for example, Smith, 1989; AP, 1994). In a recent study in New Jersey, for example, unsafe mercury levels were found in approximately 20% of more than 300 fish samples taken from 56 different water bodies throughout the state, prompting the state to issue fish advisories (Charlton & Johnson, 1994). The complexity of the environmental mercury cycle is illustrated in Figure 1.

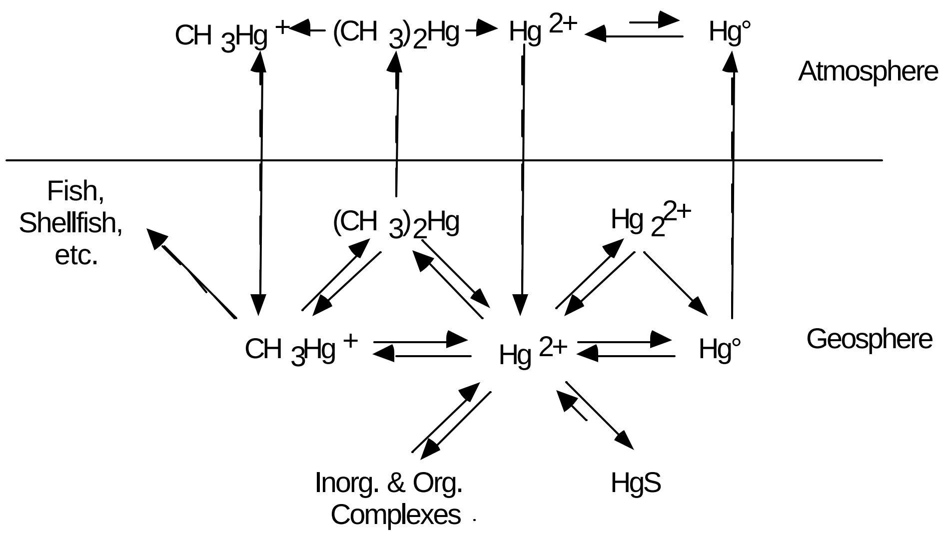

Figure 1. Major transformations of mercury in the environment [adapted from Beijer & Jernelöv (1979)].

There are a wide range of sources that emit mercury to the atmosphere. Approximately half of the atmospheric budget of vapor-phase mercury is attributed to anthropogenic sources and half to natural sources (Nriagu, 1989). Important anthropogenic sources of mercury include the combustion of coal, municipal solid waste and sewage sludge, mining and smelting of metals, and production of chloralkali. Natural sources of atmospheric mercury include volcanoes, degassing from mercury mineral deposits, emission from surface waters and natural terrestrial emission. Of these natural sources, aquatic and terrestrial emissions are of particular interest because of the large surface area with the potential for emission. In addition, water and soil are affected by atmospheric deposition and thus are integral to the continual global cycling of environmental mercury. Once mercury is deposited to surface waters it may be methylated by benthic organisms and accumulated in fish or it may undergo reemission to the atmosphere as Hg° or dimethylmercury, two forms of mercury with significant Henry’s law constants (Table 1).

Table 1. Experimentally-determined Henry's Law constants for some common mercury compounds (from Lindqvist and Rodhe, 1985)

Compound	**Temperature** (°C)	**H**= $\frac{[air]}{[water]}$
Hg°	20	0.29
$(CH_3)_2Hg$	25	0.31
CH_3HgCl	25	1.9×10^{-5}
$HgCl_2$	25	2.9×10^{-8}
$Hg(OH)_2$	25	3.2×10^{-6}

In summary, mercury is a significant environmental pollutant because of its complex environmental chemistry and extreme toxicity. While both the absorption and toxicity of mercury in biological systems vary considerably with the chemical complex of the metal, environmental pathways can result in transmutation between different species of mercury. Mercury is most problematic when present as an organic compound, such as the case with methyl or dimethyl mercury. Methyl mercury is formed from inorganic mercury by aquatic microorganisms and is biomagnified in the aquatic food web. Because of the potential for methylation and bioaccumulation, even trace amounts of mercury deposited from the atmosphere to surface waters remain a significant cause of concern across the United States and much of the rest of the world

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