EcoHealth 5, 456–459, 2008
DOI: 10.1007/s10393-008-0204-y

ECOHEALTH

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*Special Feature: Methylmercury*

*Forum*

# Mercury Toxicity and the Mitigating Role of Selenium

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**Abstract:** Mercury is a well-known environmental toxicant, particularly in its most common organic form, methylmercury. Consumption of fish and shellfish that contain methylmercury is a dominant source of mercury exposure in humans and piscivorous wildlife. Considerable efforts have focused on assessment of mercury and its attendant risks in the environment and food sources, including the studies reported in this issue. However, studies of mercury intoxication have frequently failed to consider the protective effects of the essential trace element, selenium. Mercury binds to selenium with extraordinarily high affinity, and high maternal exposures inhibit selenium-dependent enzyme activities in fetal brains. However, increased maternal dietary selenium intakes preserve these enzyme activities, thereby preventing the pathological effects that would otherwise arise in their absence. Recent evidence indicates that assessments of mercury exposure and tissue levels need to consider selenium intakes and tissue distributions in order to provide meaningful risk evaluations.

**Keywords:** mercury, selenium, toxicity, environment, heavy metals

Mercury is a naturally occurring element that originates from geological materials, but readily distributes into the air, water, soil, and biomass of the environment. The uncharged metallic mercury form ($Hg^0$) is highly volatile and enters the atmosphere where it can reside for extended periods. Substantial releases of $Hg^0$ from natural sources such as solar irradiation, combustion (grass and forest fires), and volcanism cannot be controlled. However, there is substantial concern regarding mercury releases caused by human activities. Regardless of the source, atmospheric $Hg^0$ eventually becomes charged and precipitates as inorganic mercury ($Hg^{2+}$) deposited on ground and water surfaces. Bacteria convert $Hg^{2+}$ to form methylmercury ($MeHg^+$) that is largely found in association with the sulfur of cysteine and similar thiomolecules in the aquatic biomass. As a result, the most common organic mercury compound found in the environment is MeHg-cysteine. The charge on the Hg moiety is satisfied by complex formation with sulfur, which although thermodynamically stable, is kinetically promiscuous. This is also the predominant form accumulated in the aquatic biomass that eventually became coal. Because many millennia of mercury deposition and bioaccumulation are stored in these organic materials, thousands of years' worth of mercury deposition is released back into the environment when coal is burned. As a result, coal-burning power plants are a dominant source of human-caused mercury emissions to the atmosphere.

Coal-fired power plants in the United States account for ~40% of domestic (~5% of global) human-caused mercury emission (Driscoll et al. 2007); the U.S. Environmental Protection Agency (EPA) estimates that ~25% of

Published online: February 6, 2009

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these domestic emissions are deposited within the conterminous United States, while the remainder enters the global biogeochemical cycle (http://www.epa.gov/mercury/about.htm). Although contributions from the United States continue to diminish as more advanced technologies for mercury capture are developed and employed, environmental mercury deposition may increase in coming years as the result of dramatically increasing inputs from overseas. Mercury releases from coal-fired power plants in Asia are major contributors to the global atmospheric pool (>50%) and are increasingly significant sources of atmospheric mercury deposition. Newly built, large, coal-fired power plants are coming on line in China and India at the rate of approximately one per week. Although these new plants burn coals that often have much higher mercury contents than those burned in North America, they are not being equipped with pollution control technologies that are mandatory in the United States. This is particularly worrisome since China currently burns more coal than the United States, European Union, and Japan combined, and its consumption rate is rapidly growing. Increasing mercury releases from these new power plants in Asia will inevitably result in increasing atmospheric mercury deposition in North America and throughout the Northern Hemisphere.

Atmospheric mercury deposited directly into water, or onto land where it can be washed into bodies of water, is rapidly incorporated into aquatic ecosystems and food webs. There, bacteria in the sediments and water column change it into $MeHg^+$. The transformation of $Hg^+$ to $MeHg^+$ is a critical step in this process, as $MeHg^+$ is the most readily assimilated form that bioaccumulates in all aquatic organisms and, ultimately, biomagnifies as it is transferred up the food web. Fish and shellfish consumption are the main sources of $MeHg^+$ exposure to wildlife and humans (http://www.epa.gov/mercury/about.htm), and there are particularly acute concerns regarding the effects of prenatal exposure on neurological development in children. Sixty percent of the fish and shellfish consumed by humans are from marine ecosystems, but most of the research on the fate of mercury has been conducted in upland terrestrial and freshwater ecosystems (Mergler et al. 2007; Sunderland 2007; Chen et al. 2008). Far less is known about mercury biogeochemistry in the coastal and open ocean systems.

Although initially difficult to understand, experimental animal and human exposure studies delineate the risks that accompany $MeHg^+$ exposures. In controlled feeding studies in fish, birds, and mammals, the consumption of diets that contained $MeHg^+$ at environmentally realistic concentrations resulted in a range of toxic effects including behavioral, neurochemical, hormonal, and reproductive changes. Limited field-based studies with wild piscivorous bird species demonstrated significant relations between $MeHg^+$ exposure and various indicators of toxicity, including reproductive impairment (Scheuhammer et al. 2007). The most extensive human exposure to $MeHg^+$ was caused by the dumping of mercury compounds into Minamata Bay, Japan. It has been estimated that 27 tons of mercury were dumped into Minamata Bay from 1932 to 1968. Thousands suffered severe mercury poisoning symptoms and many died from what became known as Minamata disease, caused by consumption of fish or shellfish contaminated with up to 50 ppm of mercury (Takeuchi et al. 1962). Of special concern, children that were highly exposed in utero often showed severe neurodevelopmental impairments, even when their mothers exhibited minimal or no clinical signs.

There is growing awareness that the toxicity of $MeHg^+$ is intimately linked with its high binding affinities with selenium. Selenium is a nutritionally essential element with particularly important roles in brain and endocrine tissues. This corresponds remarkably well with the recognition that the target tissues of $MeHg^+$ toxicity are the neuroendocrine and nervous systems. Virtually all forms of animal life that possess nervous systems also possess selenium-dependent enzymes that utilize selenocysteine to perform important antioxidant and redox control functions. These enzyme functions appear to be indispensable, especially in brain tissues where they are required to protect against oxidative damage from reactive oxygen metabolites. Since mercury is uniquely able to inhibit selenium-dependent enzyme activities in brain tissues (Watanabe et al. 1999), the risks of oxidative brain damage as a result of mercury toxicity directly correspond to Hg:Se molar ratios in tissues (Ralston et al. 2007, 2008). Converging evidence from cell culture studies indicates a progressive decrease in the activity of selenium-dependent glutathione peroxidase enzyme activities in cells exposed to mercury (Bulato et al. 2007).

In animal studies where mercury toxicity has been observed, mercury has consistently been present in substantial molar excess of selenium in the affected tissues (Cuvin-Aralar and Furness 1991; Chapman and Chan 2000). Since the binding affinity between mercury and selenium is a million times greater than the affinity between sulfur and mercury (Dyrssen and Wedborg 1991), it is easy to understand why Hg:Se molar ratios in excess of a 1:1

stoichiometry are increasingly toxic. Since fetal supplies of selenium are dependent upon ratios of selenium to mercury in the mother's food sources, inhibition of the biological functions of selenium plays a particularly significant role in the mechanism of prenatal mercury intoxication.

Selenium has been known to play a role in binding toxic metals and potentially reducing toxicity. Accumulation of mercury in tissues of marine mammals or mineworkers following exposure or ingestion is accompanied by increased accumulation or retention of selenium (Koelman et al. 1973; Kosta et al. 1975). The concentrations of mercury in brain tissues of these miners approached, but never exceeded a 1:1 molar ratio (Falnoga et al. 2006). Instead, the amount of "free" selenium in excess of mercury remained essentially constant, even though the amount of mercury rose to concentrations many times higher than the normal brain selenium content. Studies have demonstrated the binding of complexes of mercury–selenium, silver–selenium, and cadmium–selenium by plasma selenoprotein P (Yoneda and Suzuki 1997; Sasakura and Suzuki 1998), leading to the proposal that this protein may function to chelate heavy metals, reducing their toxicity. Binding of zinc (Yan and Barrett 1998), nickel (Mostert et al. 1998), and silver (Sasakura and Suzuki, 1998) by selenoprotein P has also been reported. In miners exposed to high concentrations of mercury, expression of both selenoprotein P protein and glutathione peroxidase activity was increased. These increments were accompanied by elevated selenium concentrations in serum. In addition, selenoprotein P bound more mercury at higher mercury exposure concentrations (Chen et al. 2006).

The ability of selenium compounds to decrease the toxicity of mercury has been established in all species of mammals, birds, and fish investigated (Cuvin-Aralar and Furness 1991; Chapman and Chan 2000; Raymond and Ralston 2004 [and references 16 and 17 therein]). Therefore, it is important to consider the molar relationships between mercury and selenium when investigating neurodevelopmental outcomes of maternal mercury exposure during pregnancy. Since free-ranging marine fish are rich sources of selenium in substantial molar excess of mercury, this may explain why the largest and most recent studies of effects of maternal seafood consumption (and associated $MeHg^{+}$ exposures) on child neurodevelopmental outcomes find substantial benefits ($\sim$5–10 IQ points) instead of harm.

Knowledge of selenium's influence on mercury's fate in aquatic ecosystems and on mercury exposure, bioaccumulation, and toxicity is substantial, but urgently requires increased attention. In order to perform accurate environmental and epidemiological mercury exposure risk assessments, future studies will need to simultaneously assess the amounts and forms of selenium that are also present. Otherwise, important beneficial effects of maternal seafood consumption will continue to be mistakenly associated with risk, while the actual risks of mercury exposure that may accompany consumption of freshwater fish will continue to go unrecognized.

## Acknowledgments

MJB is supported by the NIH. NVCR is supported by the EPA and NOAA.

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