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Environmental Mercury and Its Toxic Effects

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Mercury exists naturally and as a man-made contaminant. The release of processed mercury can lead to a progressive increase in the amount of atmospheric mercury, which enters the atmospheric-soil-water distribution cycles where it can remain in circulation for years. Mercury poisoning is the result of exposure to mercury or mercury compounds resulting in various toxic effects depend on its chemical form and route of exposure. The major route of human exposure to methylmercury (MeHg) is largely through eating contaminated fish, seafood, and wildlife which have been exposed to mercury through ingestion of contaminated lower organisms. MeHg toxicity is associated with nervous system damage in adults and impaired neurological development in infants and children. Ingested mercury may undergo bioaccumulation leading to progressive increases in body burdens. This review addresses the systemic pathophysiology of individual organ systems associated with mercury poisoning. Mercury has profound cellular, cardiovascular, hematological, pulmonary, renal, immunological, neurological, endocrine, reproductive, and embryonic toxicological effects.

Key words: Mercury, Toxicity, Environment

INTRODUCTION

Mercury is ranked third by the US Government Agency for Toxic Substances and Disease Registry of the most toxic elements or substances on the planet to arsenic and lead that continues to be dumped into our waterways and soil, spilled into our atmosphere, and consumed in our food and water [1,2]. Human activities have nearly tripled the amount of mercury in the atmosphere and the atmospheric burden is increasing 1.5 percent per year [1]. Soil contaminated by mercury or the redistribution of contaminated water has the potential to enter the food chain through plant and livestock [3-5]. Once in

the food chain mercury can bioaccumulate causing adverse effects to human health [6]. The exact mechanism(s) by which mercury enters the food chain remains largely unknown, and probably varies among ecosystems. Figure 1 presents multiple routes through which humans are exposed to mercury.

Environmental mercury can exist in its elemental form, as inorganic mercury or as organic mercury. In its elemental form mercury exists as liquid metal, which in spite of its low vapor pressure (2 $\mu\text{m Hg}$), can be converted to a vapor at room temperature due to its low latent heat of evaporation (295 kJ/kg) and its relative absence from ambient air. Current sources of human exposure to elemental mercury included dental amalgam, thermometers, sphygmomanometer, barometers, fossil fuel emissions, incandescent lights, batteries, ritualistic practices using mercury, and the incineration of medical waste [7]. Toxic vapors formed from mercury vaporization or the burning of mercury containing materials can enter the respiratory system and pass readily into the circulation. The average whole body biological half-life of inhaled mercury is approximately 60 days [8]. Because mercury vapor can become lipid soluble

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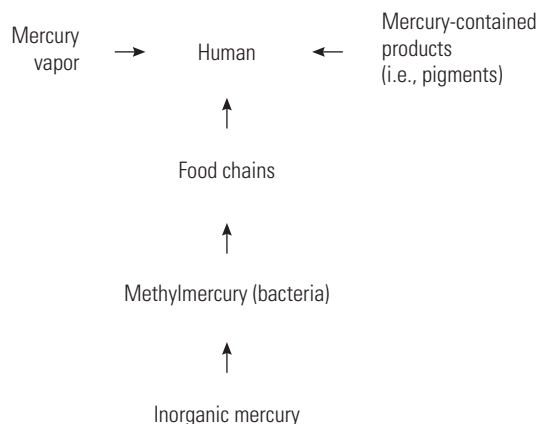


Figure 1. Routes of mercury exposure in humans.

once oxidized the potential exist for bioaccumulation in the renal cortex, liver, and especially the brain. It is estimated that the half-life of mercury in the brain can be as long as 20 years [9].

STATES OF MERCURY

Inorganic mercury exists in either the mercurous and mercuric form. Like oxidized elemental mercury, mercuric salts are more water soluble and toxic than elemental mercury. Mercuric salts are also easily absorbed by the gastrointestinal tract [10]. The average whole body half-life of inorganic mercury is about 40 days [11].

The most common form of organic mercury is methylmercury (MeHg), which is the major source of organic mercury found in the ecosystems [12]. MeHg is readily transported by water into the aquatic ecosystems. Because of its low water solubility it is considered to be relatively lipid soluble. MeHg is easily taken up by lower organisms, tends to work its way up the food chain and exhibits a proclivity to bioaccumulate in fish [13]. Fish appear to be the primary source of MeHg poisoning in humans. Through mechanisms which are not yet known, various species of fish tend to have higher rates of MeHg bioaccumulation (Table 1) [14]. The gastrointestinal tract absorbs approximately ninety five percent of ingested MeHg where it can then enter the red blood cells and the brain by binding covalently to glutathione and cysteine protein groups [15,16]. Because urinary excretion of MeHg is negligible, MeHg is primarily eliminated from the body in an inorganic form through the action of the biliary system at the rate of 1% of the body burden per day. The biological half-life of MeHg is 39 to 70 days depending on body burden. Potential sources of organic mercury included exposure to fossil fuel

Table 1. Mercury content of different seafoods [14]

Species	Mercury content (ppm)	Safety
Anchovies	0.043 ¹	Eco-good
Butterfish	0.058 ¹	Eco-good
Catfish	0.049 ± 0.084	Eco-good
Crab (blue, king, and snow)	0.060 ± 0.112	Eco-good
Crawfish	0.033 ± 0.012	Eco-good
Flatfish (flounder, plaice, and sole)	0.045 ± 0.049	Eco-good
Haddock	0.031 ± 0.021	Eco-good
Herring	0.044 ¹	Eco-good
Mackerel, Atlantic	0.050 ¹	Eco-good
Mullet	0.046 ¹	Eco-good
Oysters (farmed)	0.013 ± 0.042	Eco-good
Pollock	0.041 ± 0.106	Eco-good
Salmon, wild (Alaska)	0.014 ± 0.041	Eco-good
Sardines, Pacific (US)	0.016 ± 0.007	Eco-good
Scallops	0.050 ¹	Eco-good
Squid	0.070 ¹	Eco-good
Tilapia	0.010 ¹	Eco-good
Trout, rainbow (farmed, freshwater)	0.072 ± 0.143	Eco-good
Tuna, albacore (US, Canada)	0.353 ± 0.126	Eco-bad
Atlantic cod (also known as gadus morhua, rock cod, codling, scrod cod)	0.095 ± 0.080	Eco-bad
Bigeye/yellowfin tuna (imported long-line)	0.325 ± 0.220	Eco-bad
Bluefish	0.337 ± 0.127	Eco-bad
Chilean sea bass	0.386 ± 0.384	Eco-bad
Carp	0.140 ¹	Eco-bad
Grouper	0.465 ± 0.293	Eco-bad
Halibut	0.252 ± 0.233	Eco-bad
Imported swordfish	0.976 ± 0.510	Eco-bad
King mackerel	0.730 ¹	Eco-bad
Marlin	0.485 ± 0.237	Eco-bad
Monkfish	0.180 ¹	Eco-bad
Orange roughy	0.554 ± 0.148	Eco-bad
Sablefish (Alaska, Canada)	0.220 ¹	Eco-bad
Shark (<i>Carcharhinus limbatus</i>) or short-fin mako (<i>Isurus oxyrinchus</i>)	0.988 ± 0.631	Eco-bad
Snapper	0.189 ± 0.274	Eco-bad
Tilefish (golden bass, Atlantic)	1.450 ± 0.122	Eco-bad

Values are presented as mean ± SD.

Maximum allowable concentration in seafood is 1 ppm according to US Food and Drug Administration.

Mercury levels in commercial fish and shellfish US Food and Drug Administration and US EPA Advisory EPA-823-F-04-009 (March 2004).

¹No SD given.

emissions, the incineration of medical waste, dental amalgam, and various commercial products including skin creams, germicidal soaps, various medications, teething powders, analge-

Table 2. Some characteristics methylmercury toxic signs and symptoms are associated with the following mnemonic: DEADLY METHYLMERCURIALS

Letter	Definition
D	Dental problems and amalgam release of mercury
E	Endocrine toxicity and dysfunction
A	Affects adrenal function and hormone production (inhibiting of 21 α -hydroxylase)
D	Diabetes may be associated or caused
L	Likely inhibits myelin synthesis in developing feti and children
Y	Young's syndrome (Azoospermia sinopulmonary infections)
M	Methylation of inorganic mercury in body
E	Environmental accumulation (soil, water, air)
T	Toxic to GI, liver, and pancreas
H	Hypertension due to epinephrine excess (inhibits catecholamine metabolism)
Y	Young women should avoid some fish
L	Long biological half-life (may be >90 days)
M	Microorganisms (sulfate processors) synthesize from inorganic mercury
E	Enters food chain, bio accumulates, and biomagnifies
R	Red blood cell accumulation (competes with iron for hemoglobin binding)
C	Crosses blood-brain barrier and produces central nervous system toxicity
U	Uterine fetal toxicity
R	Renal toxicity, especially to renal tubules
I	Immune, enzyme, and genetic alterations
A	Association with many neurodegenerative diseases
L	Long-term toxicity on many organs and systems
S	Special senses affected

Developed by Walker EM Jr, 2008.

sics, diaper treatments, vaccinations, thermometers, sphygmomanometer, barometers, incandescent lights, and batteries [5,7]. Other sources for organic mercury include phenyl mercury compounds and ethyl mercury compounds, which were components of latex paints that were used before 1990s [12] and thimerosal which has been used as a preservative in vaccines [7]. Among the most dangerous mercury compound is dimethylmercury ((CH₃)₂Hg) which is toxic enough to cause death if only a few microliters is spilled on the skin, or even latex gloves [17]. Mercury poisoning can result in death, mental retardation, dysarthria, blindness, neurological deficits, loss of hearing, developmental defects, and abnormal muscle tone [7]. Table 2 presents a helpful mnemonic that practitioners can use when examining possible MeHg toxicity.

SYSTEMIC TOXICOLOGICAL EFFECTS OF MERCURY

Mercury exposure has been associated with the induction of over 250 symptoms which can complicate accurate diagnosis. Differential diagnosis begins with a patient history and physical examination consistent with mercury exposure. Laboratory testing typically includes 1) blood analysis; 2) urinalysis, with a 24-hour urine analysis, and a urine challenge test with a “chelating” agent; 3) hair analysis; and (d) tissue biopsy if warranted [10,18]. Because mercury can be quickly removed from the blood, redistributed and sequestered into different tissues it is important to note that there may not be a direct correlation between blood mercury concentration and the severity of mercury poisoning. Indeed, it is thought that shortly after entering the body that mercury quickly becomes tightly bound in the brain, spinal cord, ganglia, autonomic ganglia, and peripheral motor neurons. Nonetheless although the nervous system is the primary repository for mercury exposure, the transient and residual systemic distribution of mercury has the potential to cause symptoms in a number of different organ systems. In addition reports indicate that individual genetic background may play a role in mercury toxicokinetics [19].

CELLULAR EFFECTS OF MERCURY

At the cellular level mercury exposure is associated with alterations in membrane permeability, changes in macromolecular structure due to its affinity for sulfhydryl and thiol groups, and DNA damage [20-22]. Mercury has also been shown to induce oxidative stress and mitochondrial dysfunction [23] which can result in alterations in calcium homeostasis and increased lipid peroxidation [24]. In addition, mercury may also increase radical oxygen species levels because of its ability to act as a catalyst for Fenton-type reactions [24].

CARDIOVASCULAR, HEMATOLOGICAL, AND PULMONARY EFFECTS

Mercury accumulation in the heart is thought to contribute to cardiomyopathy. Indeed, mercury levels in the heart tissue of individuals who died from idiopathic dilated cardiomyopathy were found to be on average 22 000 times higher than in individuals who died of other forms of heart disease [25,26]. Mercury poisoning may also cause chest pain or angina, espe-

cially in individuals under age 45 [26]. *In vitro* studies have indicated that MeHg can inhibit the cardioprotective activity of paraoxonase 1 [27]. There is also good evidence linking mercury with anemia including hemolytic anemia and aplastic anemia as mercury is thought to compete with iron for binding to hemoglobin which can result in impaired hemoglobin formation [28]. In addition to anemia, additional data has also suggested that mercury may be a causative factor in mononucleosis and involved in leukemia, and Hodgkin's disease [29-31].

Toxic vapors formed from mercury vaporization or the burning of mercury containing materials can enter the respiratory system and pass readily into the circulation. Case control studies have demonstrated that the chronic inhalation of even low concentrations of mercury (0.7 to 42 $\mu\text{g}/\text{m}^3$) can produce tremors, sleep disturbances, and impaired cognitive skills in workers [12,32,33]. Mercury poisoning is associated with several different pulmonary conditions including Young's syndrome [34], bronchitis and pulmonary fibrosis [35,36].

EFFECTS ON THE DIGESTIVE AND RENAL SYSTEMS

Mercury is absorbed through the epithelial cells when ingested. This absorbed mercury can cause various digestive disturbances as it can inhibit the production of the digestive trypsin, chymotrypsin, and pepsin along with the function of xanthine oxidase and dipeptyl peptidase IV [37]. The effects of mercury on the gastrointestinal system typically present as abdominal pain, indigestion, inflammatory bowel disease, ulcers and bloody diarrhea. Mercury ingestion has also been associated with the destruction of intestinal flora which can increase the amount of undigested food products in the blood stream causing immune mediated reactions and reduced resistance to pathogenic infection [38].

Mercury can cause kidney damage and evidence suggests a linkage between mercury exposure and acute tubular necrosis, glomerulonephritis, chronic renal disease, renal cancer and nephrotic syndrome [35,39-41]. Various reports have shown mercury exposure can lead to various kidney injuries including: subacute-onset nephrotic syndrome, tubular dysfunction, secondary focal segmental glomerulosclerosis, syncretic nephrotic syndrome, nephritic syndrome, nephrotic-range proteinuria, glomerular disease, and membranous glomerulonephritis [42].

EFFECTS ON THE IMMUNE SYSTEM

Klinghardt's axiom states that "Most, if not all, chronic infectious diseases are not caused by a failure of the immune system, but are a conscious adaptation of the immune system to an otherwise lethal heavy metal environment". It has been known for many years that mercury impairs immune system function most likely via its deleterious effects on the polymorphonuclear leukocytes (PMNs). Mercury through suppression of adrenocorticosteroids production prevents normal stimulation of PMNs production and also affects PMN function by inhibiting their ability to destroy foreign substances [43]. Mercury-sensitive individuals are more likely to have allergies, asthma, and autoimmune-like symptoms, especially rheumatoid-like ones. Mercury can produce an immune response in the central nervous system, induce alterations in immune cell production and function, and modulate the production of interferon gamma and interleukin-2 [44]. With impairment comes a chronically susceptible to infections, if not chronic sickness.

Interestingly, the ingestion of mercury is oftentimes associated with increased levels of yeasts, bacteria, and molds which are thought to function in a protective manner to absorb excess mercury from the body. Indiscriminant and rapid destruction of the *Candida albicans* and other pathogens by antibiotics in adults with a significant body burden of toxic metals, including mercury, may cause the sudden release of large amounts of toxic metals contained within them and be potentially very dangerous. Mercury body burden has also been associated with or implicated in a number of immune or autoimmune conditions including allergic disease, amyotrophic lateral sclerosis, arthritis, autoimmune thyroiditis, autism/attention deficit hyperactivity disorder, eczema, epilepsy, psoriasis, multiple sclerosis, rheumatoid arthritis, schizophrenia, scleroderma, and systemic lupus erythematosus [45-51].

EFFECTS ON THE NERVOUS SYSTEM

It is clear that mercury is accumulated in nervous tissues all through the body [52]. The most devastating effect of mercury in the nervous system is interference with the production of energy which can impair cellular detoxification processes causing the cell to either die or live in a state of chronic malnutrition. It is thought that mercury causes neuronal problems through blockage of the P-450 enzymatic process [26]. Mercury is associated with increased tissue oxidative damage, and

children with autism had significantly higher urinary levels of lipid peroxidation when compared to controls. In the peripheral nervous system, circulating inorganic mercury can be taken up into the nerve terminals where it can impair the synthesis of tubulin and actin which are important constituents of neuronal cell structure and detoxification processes [53]. Primary sensory neuropathy is a hallmark of MeHg poisoning.

In the central nervous system mercury can damage the blood brain barrier and it facilitates penetration of the brain by other toxic metals and substances. The effects of mercury poisoning effects in the central nervous system include depression, paranoia, extreme irritability, hallucinations, an inability to concentrate, memory loss, tremors of the hands, head, lips, tongue, jaw and eyelids, weight loss, perpetually low body temperature, drowsiness, headaches, insomnia, and fatigue. Along with nervous system effects, mercury has also shown to have various effects on other special sensory systems including blindness, retinopathy, optic neuropathy, hearing loss, a reduced sense of smell, and abnormal touch sensation [54]. Autism is a syndrome characterized by impairments in social relatedness, language and communication, a need for routine and sameness, abnormal movements, and sensory dysfunction [55]. Mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism [56] leading some to suggest that many cases of autism may be a form of mercury poisoning [55].

EFFECTS ON THE ENDOCRINE SYSTEM

Low exposure levels of mercury may affect the endocrine system in animals and people by disruption of the pituitary, thyroid, adrenal glands and pancreas [57]. It is thought that mercury might impair endocrine function through its ability to reduce hormone-receptor binding or through the inhibition of one or more key enzymes or steps in hormone biosynthesis as is seen in the case of adrenal steroid biosynthesis and the inhibition of 21 α -hydroxylase [58]. Hormones that appear to be the most affected by mercury are insulin, estrogen, testosterone, and adrenaline.

Mercury can also inhibit catecholamine degradation through inactivation of S-adenosyl-methionine which can cause the accumulation of epinephrine and hyperhidrosis, tachycardia, ptyalism (hyper salivation) and hypertension [1]. In the adrenal cortex, mercury exposure has been found to be associated with lowered plasma levels of corticosterone [58]. Reduced cortisol

production causes a compensatory rise in adrenocorticotrophic hormone leading to adrenal hyperplasia. Mercury-induced adrenal hyperplasia may eventually stress the adrenal to a point at which there is adrenal atrophy and may be a causative factor in the development of Addison's disease [43].

Autopsy studies in 1975 revealed that the thyroid and pituitary retain and accumulate more inorganic mercury than the kidneys [59]. Mercury levels in the pituitary gland ranged from 6.3 to 77 ppb in one study, while another found the mean levels to be 28 ppb, levels found to be neurotoxic and cytotoxic [60]. Low levels of pituitary function are associated with depression and suicidal thoughts, and appear to be a major factor in suicide of teenagers and other vulnerable groups. Because of its effect on the pituitary, mercury is known to cause frequent urination as well as high blood pressure [61].

The thyroid is one of the largest endocrine glands in the body. The thyroid controls how quickly the body burns energy, makes proteins, and how sensitive the body should be to other hormones. Like the pituitary, the thyroid displays an affinity for accumulating mercury. Mercury blocks thyroid hormone production by occupying iodine-binding sites and inhibiting or altering hormone action leading to the impairment of body temperature control, hypothyroidism, thyroid inflammation and depression [43,61].

Like the thyroid, the pancreas is also susceptible to the toxic effects of mercury. Insulin, the molecule involved in diabetes, has three sulfur-binding sites which can be bound by mercury causing the interference with normal biological function and a dysregulation of blood glucose levels [62].

EFFECTS ON THE REPRODUCTIVE SYSTEM

Mercury can precipitate pathophysiological changes along the hypothalamus-pituitary-adrenal and gonadal axis that may affect reproductive function by altering the circulating of levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin, estrogen, progesterone, and the androgens [63,64]. Reduced fertility among dental assistants with occupational exposure to mercury has been noted [65,66]. Studies in Hong Kong demonstrated that increased mercury levels were associated with infertility in both men and women [67]. In males, mercury can have adverse effects on spermatogenesis [68], epididymal sperm count, and testicular weight. Evidence also exists linking mercury with erectile dysfunction [64]. In females, mercury has been shown to inhibit the release of

FSH and LH from the anterior pituitary which in turn can effect estrogen and progesterone levels leading to ovarian dysfunction, painful or irregular menstruation, premature menopause, and tipped uterus [62]. There is good evidence linking mercury with menstrual disorders including abnormal bleeding, short, long, irregular cycles, and painful periods [63].

FETOTOXICITY

In addition to reproductive issues, mercury is also associated with the fetotoxicity which can present as miscarriage, spontaneous abortions, stillbirth, and low birth weights [69]. In the neonate, mercury exposure during pregnancy has been linked to neural tube defects, craniofacial malformations, delayed growth, and others [69]. Mercury is known to cross the placenta where it can inhibit fetal brain development resulting in cerebral palsy and psychomotor retardation in the latter stages of development [70,71]. In primates maternal MeHg blood levels were moderately related to increased abortion rates and decreased pregnancy rates [72]. Embryopathic effects of MeHg in humans have also been reported. Fetal autopsies indicated a generalized hypoplasia of the cerebellum, decreased number of nerve cells in the cerebral cortex, marked decrease in total brain weight, abnormal neuron migration, and brain centers and layer deranged organization [73-76]. MeHg easily enters through the placenta and damages the brain of the fetus. Many exposed fetuses go on to develop infantile cerebral palsy and there may be a relation with the development of Minamata disease. Babies may be born with a variety of birth defects. A study of 64 children exposed in utero to mercury and showing mercury associated damage included the following signs and symptoms: mental retardation (100%), primitive reflexes (100%), strabismus (77%), cerebellar ataxia (100%), dysarthria (100%), chorea and athetosis (95%), deformed limbs (100%), hyper salivation (95%), epileptic attacks (82%), and growth disorders (100%) [6]. Mercury inhibits the trans membrane transport of nutrients including selenium in the placenta. In animal experiments it has also been shown that there is a much higher accumulation of mercury in the fetal brain tissue than in the maternal brain tissue [77].

CONCLUSION

It is evident by the number of organ systems and cellular functions affected by mercury that exposure to the various

form of mercury is detrimental to public health. Evaluation of the epidemiological consequences of mercury toxicity over the years has added greatly to the understanding of mercury toxicity and its human impact. History has left us with a wide array of information regarding the effects of mercury toxicity: the earliest recorded death by mercury of the Qin Shi Huang first emperor to unify China [78], the "Mad Hatter disease" among milliners in the 18th and 19th centuries [79], the mercury spill on board the two British ships the Her Majesty's ship (HMS) *Triumph* and HMS *Philpps* in 1810 [80,81], the apparent death of approximately 60 men during the construction of Saint Isaac's Cathedral in Russia between 1818 to 1858 from the gold amalgam used for gilding [82], the mysterious death of actress Olive Thomas in 1920 from ingestion of her husband's mercury pill used at the time to treat syphilis [83,84], the event at the Norwich England seed packing facility in the 1930s where the term "Hunter-Russell syndrome" originates [85], the 1950s industrial spill in Minamata and Niigata Japan where it was defined as "Minamata disease" [4], the rural poisoning in Iraq in 1971 to 1972 from MeHg-based fungicide [86], Karen Wetterhahn's death at Dartmouth College in 1996 from a drop of dimethylmercury of her latex gloves [87], Tony Winneet's accidental death from using liquid mercury to extract gold from old computer parts [88], the current finding of mercury in 6.0% of skin-lightening products tested in one study [89] and 47% of products tested in a Somali community contained mercury [90], the long term effects of the California Gold mining impact on mercury redistribution and potential impact on human health [91], and the numerous links to human consumption of mercury laden fish [92,93]. All of these events have left us with an indelible account of the detrimental effects of mercury on human health. In light of these historic events and the toxicological evidence presenting in this review regarding the systemic effects of mercury on cellular, cardiovascular, hematological, pulmonary, renal, immunological, neurological, endocrine, reproductive, and embryonic development, efforts should be made to insure adequate steps are taken in public health and prevention to reduce the occurrence of mercury exposure and raise public awareness.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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