

Human Exposure and Health Effects of Inorganic and Elemental Mercury

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Mercury is a toxic and non-essential metal in the human body. Mercury is ubiquitously distributed in the environment, present in natural products, and exists extensively in items encountered in daily life. There are three forms of mercury, i.e., elemental (or metallic) mercury, inorganic mercury compounds, and organic mercury compounds. This review examines the toxicity of elemental mercury and inorganic mercury compounds. Inorganic mercury compounds are water soluble with a bioavailability of 7% to 15% after ingestion; they are also irritants and cause gastrointestinal symptoms. Upon entering the body, inorganic mercury compounds are accumulated mainly in the kidneys and produce kidney damage. In contrast, human exposure to elemental mercury is mainly by inhalation, followed by rapid absorption and distribution in all major organs. Elemental mercury from ingestion is poorly absorbed with a bioavailability of less than 0.01%. The primary target organs of elemental mercury are the brain and kidney. Elemental mercury is lipid soluble and can cross the blood-brain barrier, while inorganic mercury compounds are not lipid soluble, rendering them unable to cross the blood-brain barrier. Elemental mercury may also enter the brain from the nasal cavity through the olfactory pathway. The blood mercury is a useful biomarker after short-term and high-level exposure, whereas the urine mercury is the ideal biomarker for long-term exposure to both elemental and inorganic mercury, and also as a good indicator of body burden. This review discusses the common sources of mercury exposure, skin lightening products containing mercury and mercury release from dental amalgam filling, two issues that happen in daily life, bear significant public health importance, and yet undergo extensive debate on their safety.

Key words: Elemental mercury, Inorganic mercury compounds, Kidney, Brain, Biomarkers, Public health

INTRODUCTION

Mercury (Hg) is ubiquitously distributed in the environment and is non-essential and toxic to the human body. Mercury is

considered to be one of the major environmental pollutants, is widely used in industry, agriculture, and medicine, and circulates in ecosystems, but is never destroyed. Chemically, mercury exists in various forms as elemental (or metallic, Hg⁰) mercury, inorganic mercury compounds, and organic mercury compounds. Elemental mercury is liquid at room temperature, and it can be released easily into the atmosphere as mercury vapor because of its high vapor pressure. Inorganic mercury compounds exist in two oxidative states (mercurous, Hg⁺; mercuric, Hg⁺⁺), which are generally in solid states as mercurous or mercuric salts and mercury compounds with chlorine, sulfur, or oxygen. Methylmercury and ethylmercury are common organic forms of mercury combined with carbon. Methylmercury

Received: September 12, 2012; **Accepted:** October 17, 2012

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is also formed from methylation of inorganic mercury by microorganisms in the environment [1]. The main forms of mercury exposure in the general population are methylmercury (MeHg) from seafood, inorganic mercury (I-Hg) from food, and mercury vapor (Hg^0) from dental amalgam restorations [2]. Often, the different mercury forms determine the route of exposure, absorption, distribution, and target organ toxicity. Hence, a thorough understanding of mercury based on the various chemical forms is critical to studying mercury toxicity and developing an effective and efficient means to control mercury intoxication.

In this review, we focus on the human exposure and health effects of elemental mercury and inorganic mercury compounds based on their chemical characteristics. The human uses and exposure are first discussed, followed by reviewing metabolism and toxicity. Exposure assessment and management are also addressed. Furthermore, the mechanisms whereby elemental and inorganic mercury compounds are transported to the target organs and the relations between early exposure to mercury and late onset of neurodegenerative diseases, such as Alzheimer's disease, are briefly discussed. Finally, two public health issues relevant to mercury exposure, skin lightening products containing mercury and mercury released from dental amalgam fillings, are examined.

USES AND HUMAN EXPOSURE

Humans are usually exposed to mercury in a chronic and low dose fashion. High dose mercury exposure can occur in industrial accidents for very short periods. Human exposure to mercury has a very long history. Several thousand years ago in China, an inorganic mercury compound (mercury sulfide) was used to prepare red dye pigment vermilion, which is a brilliant red ore, namely cinnabar. Inorganic mercury compounds have also been used in medical applications since ancient Egypt. In modern history, almost all of those applications have gradually disappeared. However, mercury compounds have been used as skin ointments to treat skin infection, and in developing countries, they have been applied to the treatment of skin sores from syphilis. Mercury compounds have been used as laxatives and also added to teething powders as calomel (mercurous chloride). Historical industrial mercury poisoning, "hatter's shake" or "mad hatter" was a result of the use of mercuric nitrate to treat the fur used in production of high quality felt hats. Inorganic mercuric compounds were also used world-

wide as antiseptic preservatives, mercurochrome (dibromohydroxymercurifluorescein), and preservative antibacterial agents as phenylmercury compounds. More recently, young women have used skin lightening products and cosmetics, which contain inorganic mercury compounds (discussed later) [3-5].

Mercury in its elemental state is the only metal that is liquid at room temperature, and has the properties of low viscosity, high density, high electrical conductance, and a reflective surface, for which it is used widely in scientific devices, electrical equipment, and industry, including in thermometers, barometers, batteries, electrical switches and relays, mercury lamps, solders, semiconductor solar cells, catalysts, preservatives, electroplating, pharmaceuticals, and chloroalkali production [1,3].

Liquid mercury forms a stable amalgam with silver and gold; thus it has been used to extract pure gold and silver from gold and silver ores. The mercury in amalgamation with gold or silver is evaporated by heating and becomes purified gold and silver. Miners can be exposed to mercury vapor by inhalation. Mercury released from such practices contaminates the soil, underground water, and rivers and lakes, eventually contributing to the bioconcentration of methylmercury through methylation and food chains [6]. This purification practice also can be performed at jewelry stores or at home, which may subject people performing such purification, along with their families, to exposure to elemental mercury by inhalation [7]. Occasionally, exposure of children to mercury can take place in the homes of workers in mercury industries if care is not taken to decontaminate the workers' clothes and shoes [8]. Mercury has been used widely in amalgam dental filling, which may also cause elemental mercury exposure to patients, dental practitioners, or both (discussed later).

In Korea, human exposure to mercury from various sources has also been reported in industry and in the general population. Several cases of chronic mercury poisoning in a fluorescent lamp manufacturing factory and high exposure to mercury at a silver refining plant were reported in occupational exposure settings [9,10]. In the general population, mercury exposure were reported as inhalation of mercury vapor in a family while burning charms [11], ingestion of herbal medication for vertigo treatment [12], inhalation of mercury vapor for pain relief of arthralgia [13], inhalation of mercury vapor for hemorrhoid treatment [14], intravenous injection of metallic mercury for suicide [15], dermal applications of inorganic mercury compounds [16], and children's exposure from house paints and lacquer [17].

METABOLISM

Inorganic Mercury Compounds

Approximately 7% to 15% of doses of inorganic mercury compounds are absorbed in the gastrointestinal tract after ingestion [18]. Dermal absorption of inorganic mercury salts is likely, based on the clinical case of mercury intoxication reported following dermal application of ointments containing inorganic mercury salts. Chan [19] suggested that inorganic mercury may be absorbed through the skin by the transport of mercury across the epidermis and via the sweat glands, sebaceous glands, and hair follicles. Mercury salts are usually non-volatile solids, so poisoning by inhalation is rare. Mercurous chloride is probably slowly absorbed due to its relatively low solubility compared to mercuric chloride. The tissue distribution of mercurous and mercuric mercury compounds appears quite similar.

The highest concentration of inorganic mercury is found in the kidney, which is a major target organ of inorganic mercury. The proximal tubule is the primary target site of mercuric ions where mercury salts are taken up and accumulated. It is known that two pathways mediate mercury salts in the renal proximal tubule, one by luminal uptake of Cys-S-Hg-S-Cys through amino acid transporters and the other by basolateral uptake through organic anion transporters (OAT1 and OAT3) [20].

Inorganic mercury salts are not lipid soluble; hence, they do not readily cross the blood-brain barrier or blood-placenta barrier. Inorganic mercury salts are mainly excreted in the urine and feces. The excretion rate is biphasic and dose-dependent, with an initial rapid excretion phase followed by a slow excretion later. The biological half-life is estimated to be about 60 days [4].

Elemental Mercury

Elemental mercury from ingestion is poorly absorbed, at less than 0.01% of the dose, in the gastrointestinal tract. In the case of accidental swallowing of elemental mercury such as from breakage of a thermometer, systemic toxicity is rare and generally not expected [3]. However, a defect on the gastrointestinal tract may alter the mucosal barrier and allow for increased bioavailability. Dermal absorption of elemental mercury is also limited.

Inhalation is a major exposure route of elemental mercury in the form of mercury vapor. Inhaled mercury vapor is readily absorbed, at a rate of approximately 80%, in the lungs, and

quickly diffused into the blood and distributed into all of the organs of the body [1]. Absorbed elemental mercury is oxidized to the mercuric form (Hg^{++}) in the red blood cells and tissues, a process that takes several minutes. However, inhaled mercury vapor, in contrast to inorganic mercury salts, accumulates in the central nervous system. Elemental mercury is in an uncharged monoatomic form, which is highly diffusible and lipid soluble. Elemental mercury can cross the blood-brain barrier and blood-placenta barrier as well as the lipid bilayers of cellular and intracellular organellar membranes. Though elemental mercury vapor is rapidly oxidized to ionic mercury, it remains as vapor in the blood for a short time, which is long enough for a significant amount of mercury vapor to penetrate the blood-brain barrier before it is oxidized. Mercury molecules can then be oxidized and accumulate in the brain [21]. The oxidized form will not effectively cross the blood-brain barrier. Notably, elemental mercury can pass through the mucosa and connective tissue of the nasal cavity, and from there it can be transported to the brain via the nerve cells of the olfactory system, namely the olfactory pathway. Henriksson and Tjälve [22] proposed that mercury from dental amalgam fillings may be transported to the brain through the olfactory pathway in a pattern of transport similar to manganese particles from the nasal cavity to the brain directly through the olfactory pathway, as suggested by several studies [23,24].

The primary organs of mercury deposition following inhalation exposure to elemental mercury vapor are the brain and kidney. With time after exposure, the greater proportion of the body burden of mercury is found in the kidney, which occurs similarly to inorganic mercury compound ingestion. Urine and feces are the main pathways of excretion, although a small amount of inhaled mercury can be eliminated in the breath, sweat, and saliva. The excretion of elemental mercury is dose-dependent and biphasic: initially rapid, then followed by slow excretion. The biological half-life of mercury is estimated to be approximately 30 to 60 days in the body [4]. The half-life of mercury in the brain is not entirely clear, but is estimated to be as long as approximately 20 years. Elemental mercury is bound strongly to selenium or SH-groups after oxidation in the brain, which may contribute to remaining brain deposits for a long time [21]. Methyl mercury also exposed through fish consumption transformed to inorganic mercury in the brain and retained.

TOXICITY

Inorganic Mercury Compounds

The toxicity of mercury salts depends on their solubility. Generally, mercurous compounds are less toxic than mercuric compounds because they are less soluble in water.

Acute

Oral exposure to mercury salts presents relatively greater acute health effects than elemental mercury. Approximately 1 to 4 g of mercuric chloride is fatal in adults [25]. Mercury salts are more corrosive than elemental mercury, which enhance gastrointestinal permeability and absorption. An acute high dose exposure of mercuric salts primarily causes burning chest pain, darkened discoloration of the oral mucous membrane and severe gastrointestinal symptoms due to extensive corrosive damage to the gastrointestinal tract, and following symptoms and signs of mercurial stomatitis and impaired kidney function. Mercury salts are generally irritants on the skin that cause dermatitis, discoloration of the nails, and corrosion of the mucous membranes, and may also cause corrosive burns. However, it is rare to be exposed to mercury salts through inhalation because of their generally solid and non-volatile state at room temperature [1,3,25].

Chronic

Chronic inorganic mercury poisoning, which is rare and happens only with pure inorganic mercury salts, often occurs with elemental mercury poisoning. The target organ toxicity of inorganic mercury is kidney damage, mainly in the proximal convoluted tubules. Clinical symptoms and signs of inorganic mercury poisoning are polyuria and proteinuria (especially low molecular proteinuria), which can develop into nephritic syndrome in severe cases, with hematuria and anuria [3,5].

However, inorganic mercury poisoning in children who used teething powders containing mercury compound (i.e., calomel), which was described as acrodynia or pink disease by Warkany and Hubbard [26], was characterized as profuse sweating and erythematous rash of the palms and soles, desquamating and painful sensitivity to touch, anorexia, fatigue, irritability, apathy, photophobia and polydipsia. Though the mechanism of toxicity has not been fully investigated, it is considered a type of hypersensitivity reaction. Acrodynia is probably caused by the deposit of mercuric chloride in the tissues. Exposure to elemental mercury vapor can produce pink

disease in children [27]. In Korea, a case of acrodynia in a 3-year-old boy was reported after exposure to house paints and lacquer for 2 months [17]. Inorganic mercury salts are not lipid soluble, so they generally do not cross the blood-brain barrier to induce neurotoxicity or cross the blood-placenta barrier to cause developmental toxicity.

Elemental Mercury

Acute

No significant toxicological effects of elemental mercury after ingestion have been observed in a healthy person because the metal species is poorly absorbed in the gastrointestinal tract, at less than 0.01%. The oral LD₁₀ is approximately 100 g for a 70 kg adult [25]. Acute exposure to elemental mercury can produce dermatitis. Local and systemic effects of mercury are caused by parental exposure to elemental mercury. Subcutaneous granuloma formation was reported following elemental mercury self-injection in the antecubital fossa and mercury embolism following intravenous injection of mercury [15,28]. Acute exposure to high levels of mercury vapor can lead to severe lung damage, even death due to hypoxia. Acute poisoning by mercury vapor inhalation usually occurs accidentally in industrial workers who are exposed to high levels of mercury vapor; accidents could also occur when elemental mercury is accidentally vaporized in a confined and/or high temperature environment in industry or at home [7,29]. In a case of a family poisoned by mercury vapor from home gold ore processing in a poorly ventilated kitchen resulted in 2 children dying and the parents suffering from severe respiratory distress [7]. Acute exposure to mercury vapor by inhalation can produce central nervous system toxicity such as tremors, paresthesia, memory loss, hyperexcitability, erethism, and delayed reflex, which are commonly reversible [18].

Chronic

With chronic exposure to mercury vapor, the notable target organs of toxic effects are the central nervous system and the kidneys. The major clinical features of chronic mercury poisoning from mercury vapor inhalation have been identified in occupational histories as a triad of tremors, psychological disturbances or erethism, and gingivitis [1,5]. Tremor is considered to be the early neurological sign of poisoning by elemental mercury, which presents intentional tremor or resting tremor, or both. Erethism is a form of toxic organic psychosis characterized by excessive timidity, diffidence, increasing shyness,

morbid irritability, mental hyperactivity, and outbursts of temper, along with memory impairment, difficulty in concentration, depression, and somnolence. Gingivitis, stomatitis, and excessive salivation are also associated with high occupational exposure. Proteinuria is the most common sign of the kidney effects due to tubular damage, and nephrotic syndrome can occur in severe cases. In addition, peripheral nerve abnormality can present but is not common. However, workers exposed to mercury vapor may have abnormalities in sensory and peripheral nerve conduction [1]. Elemental mercury vapor may affect the human immune system and can result in a decreased resistance to infection, cancers, or immune dysregulation that can induce the development of allergy or autoimmunity [30].

Mercuric ions have a high affinity to the sulfhydryl groups of proteins in the cells, leading to non-specific inhibition of enzyme systems and cellular damage. While this is considered to be a principal mechanism of mercury toxicity, oxidative stress and the autoimmune response also contribute to the mechanism in mercury toxicities [5,19]. Overexpression of metallothionein following mercury exposure probably plays a role as a protective mechanism in the body [18].

Recently, the possible role of inorganic mercury in Alzheimer's disease has been suggested [31]. In an extensive literature review, experimental data from *in vivo* and *in vitro* studies strongly suggested an influence of inorganic mercury on the nervous system with mercury-induced pathological changes seen in Alzheimer's disease. Nonetheless, epidemiological studies suggest a much weaker relationship between mercury exposure and the pathoetiology of Alzheimer's disease. Thus, a clear association between inorganic mercury and Alzheimer's disease has not yet been established. Nor is there sufficient evidence to support the relations between early exposure to mercury and the late onset of Alzheimer's disease. The brain is high oxygen consuming organ and demands a high level of antioxidants as compared to other organs. Selenium and sulfur groups play a role in maintaining such homeostasis of oxidation and reduction in the brain [32]. Therefore, the long-term retention of inorganic mercury in the brain due to its strong affinity for selenium and selenoproteins, and potential oxidative stress, may play a role in inducing or promoting neurodegenerative diseases. Further studies are needed to elucidate the relationship between mercury exposure and neurodegenerative diseases, especially in the aged.

ISSUES ON HEALTH EFFECTS OF INORGANIC AND ELEMENTAL MERCURY

In this review article, we discussed two issues those are arguing about the effects of inorganic and elemental mercury compounds on human health also interested in public health.

Mercury in Skin Lightening Products

Inorganic mercury creams and ointments have been used as antiseptics. However, recently, cosmetic soaps and creams including inorganic mercury compounds have been produced in several countries. Those products have usually contained mercury and mercury salts such as ammoniated mercury, mercury iodide, mercurous chloride, mercurous oxide, and mercuric chloride. Young women use skin lightening products and cosmetics for their skin lightening and anti-freckle effects; they are used commonly in some African and Asian populations, and dark-skinned populations in Europe and North America [33]. About 40% of Korean women are reported to use skin lighteners [33]. Also, other cosmetics, such as eye makeup, cleaning products, and mascara, contain mercury as an ingredient. Inorganic mercury is absorbed through the skin by the transport of mercury across the epidermis and also via sweat glands, sebaceous glands, and hair follicles [19]. Mercury salts inhibit melanin formation by competing with copper in tyrosinase [34], resulting in skin lightening. The health effects of inorganic mercury compounds are mentioned in the section on toxicity in this review.

Mercury poisoning after the use of skin-lightening products has been reported from several countries including Africa, Europe, US, Mexico, Australia, and China. For example, a 34-year-old Chinese woman developed nephritic syndrome with minimal change after using a skin lightening cream, and her blood and urine mercury levels returned to normal with resolution of proteinuria after chelation therapy with D-penicillamine [35]. In Mexico, a 30-year-old women developed malar rash, erythema on the palms and soles, hypersalivation, intention tremor, emotional lability, weakness, and insomnia with a high mercury level in urine and blood after using a cosmetic cream for 5 years [36]. In the US (Arizona, California, New Mexico, and Texas), 317 women who used a cream (Crema de Belleza-Manning), self-reported a high prevalence of symptoms associated with mercury poisoning, inducing fatigue (67%), nervousness and/or irritability (63%), severe headaches (61%), insomnia (51%), memory loss (44%), loss of strength in the legs (44%),

tingling or burning sensations (39%), tremors or shaking of the hands (38%), depression (31%), and a metallic taste in the mouth (20%) with a high level of mercury in the urine [37]. Accordingly, it is necessary to prevent additional mercury exposure by strict prohibition of mercury use in cosmetic products, thorough assessment of mercury contamination in imported products, and public education on the adverse health effects of mercury-containing cosmetic products.

Mercury in Dental Amalgam

For more than 150 years, the amalgam in dental filling, consisting of about 50% metallic mercury, has been used. Mercury is either released as mercury vapor or inorganic ions from the amalgam filling by abrasion of the amalgam surface. Adults are exposed to mercury at approximately 2 to 5 $\mu\text{g}/\text{d}$ from dental amalgam fillings, which is 25% to 50% of the total mercury absorbed daily in an adult [38]. Mercury vapor in the oral cavity may be inhaled into the lungs and absorbed through the respiratory system. Metal ions may pass into the oral fluid and be ingested in the gastrointestinal tract. Mercury vapor or inorganic mercury is distributed by the blood to most of the organs in the body. However, the major target organs are the central nervous system and the kidney for mercury vapor and the kidney for inorganic mercury. The adverse health effects of metallic mercury vapor and inorganic mercury have already been discussed in this review.

The adverse health effects due to additional mercury exposure from dental amalgam remains a subject of debate among researchers. No differences in the number of amalgam fillings and in mercury levels of blood and urine were observed between self-complaints of somatic symptoms related to mercury exposure and less complaints in females with amalgam filling [39,40]. From those studies, Bailer et al. [39] and Zimmer et al. [40] suggested that mercury released from amalgam fillings was not associated with complaints reported by amalgam-sensitive subjects. Bellinger et al. [41] also reported that the association was not found between mercury exposure from dental amalgam and psychological health effects in children.

However, it is generally accepted that dental amalgam restoration may play the role of a major source of elemental mercury in the general population [2]. Several studies report that mercury levels of urine and blood are associated with amalgam exposure by dental filling in the general population and by occupational practice in dental practitioners [42-44]. The positive association between dental amalgam filling and urine mercur-

ry level was reported in elementary school children [45], and the level of urinary mercury was higher in dental hygienists than in the general population in Korea [46]. From autopsy studies, mercury levels in tissue samples including the brain were correlated with the total number of surfaces of amalgam restorations [2]. Kingman et al. [42] estimated that each 10 amalgam surfaces increased mercury level by 1 $\mu\text{g}/\text{L}$ in urine in an association study on mercury levels in urine and blood and amalgam exposure. Also, amalgam-related symptoms improved after amalgam filling removal [47], and the reduced mercury levels in blood and urine were observed following dental amalgam filling removal [48]. These findings support the causality between mercury exposure from dental amalgam filling and adverse health effects.

Though significant health effects of mercury from dental amalgam have not been observed in the human population in Korea, 2 cases of mercury dermatitis on the peri-oral cavity and neck were reported after amalgam dental restoration [49]. There is still debate over whether the mercury absorbed from dental amalgam filling is associated with symptoms or signs of adverse health effects. However, a World Health Organization expert group concluded that dental amalgam is a principal source of mercury vapor in the general population [3]. Thus, mercury exposure from dental amalgam is essentially a public concern.

EXPOSURE ASSESSMENT AND MANAGEMENT

The blood mercury level is useful when measured soon after a short-term and high-level exposure, but the level decreases within days of exposure. The blood mercury does not correspond to the total body burden of mercury. Estimation of mercury concentration in the urine is the best biomarker of long-term exposure to elemental and inorganic mercury, and also as an indicator of body burden. Urinary mercury is derived directly from mercury deposited in the kidney tissue, which serves as the main deposit site during chronic mercury exposure [5,50]. Mercury analysis of hair may be useful for assessing chronic exposure because of the abundant sulfhydryl groups in hair. However, hair mercury is not recommended for biological monitoring of elemental and inorganic mercury exposure given the strong likelihood of external contamination and relatively small proportion of accumulation relative to organic mercury.

The top priority in management of mercury poisoning is to stop exposure to mercury immediately and to lower mercury concentrations in critical organs or injured sites. Mercury excretion can be increased by using chelating agents, such as dimercaprol (or British anti-lewisite), penicillamine and 2,3-dimercapto-1-propanesulfonic acid.

In summary, even though overt mercury poisoning is rare today, the risk to human health remains a major public concern due to the wide distribution and continuous contamination of mercury in the environment from natural and anthropogenic sources. The health effects of exposure to mercury in individuals remain not entirely clear at present. It is strongly recommended that the use of mercury products in industry and medicine should be eliminated as completely as possible as a preventive measure in public health.

ACKNOWLEDGEMENTS

This research was supported by a grant (10162KFDA994) from the Korea Food and Drug Administration in 2010-2011.

CONFLICT OF INTEREST

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

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