

Review Article

Toxic Effects of Mercury on the Cardiovascular and Central Nervous Systems

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Environmental contamination has exposed humans to various metal agents, including mercury. This exposure is more common than expected, and the health consequences of such exposure remain unclear. For many years, mercury was used in a wide variety of human activities, and now, exposure to this metal from both natural and artificial sources is significantly increasing. Many studies show that high exposure to mercury induces changes in the central nervous system, potentially resulting in irritability, fatigue, behavioral changes, tremors, headaches, hearing and cognitive loss, dysarthria, incoordination, hallucinations, and death. In the cardiovascular system, mercury induces hypertension in humans and animals that has wide-ranging consequences, including alterations in endothelial function. The results described in this paper indicate that mercury exposure, even at low doses, affects endothelial and cardiovascular function. As a result, the reference values defining the limits for the absence of danger should be reduced.

1. History

More than 2500 A.C., the prehistoric man used the cinabrio (mercury sulfide), due to its red-gold color, to draw on cave walls and perform face painting. Subsequently, mercury has been used in the amalgamation (direct burning of metallic mercury on the gravel, promoting the separation of gold), in photography and as an antiseptic in the treatment of syphilis [1, 2].

Exposure to mercury brought harmful effects to health of humans, but changes resulting from human exposure to

mercury only called the attention of the scientific society after the accidents in Japan and Iraq [3]. In Japan, a serious accident occurred resulting from the deposition of industrial waste with large quantities of mercury in the Minamata Bay. Mercury was then ingested by human through fish intake, thus triggering signs and symptoms such as ataxia, speech impairment, visual field constriction, sensory disturbance, deafness, blindness, tremors, involuntary movements, mental retardation, coma, and death. Infants whose mothers were infected developed mental retardation, peripheral neuropathy, cerebral palsy, and blindness. These changes became

known as Minamata disease or Russell-Hunter syndrome [4, 5]. In Iraq, mercury poisoning occurred in 1971 when wheat grains were treated with fungicides containing organic mercury. This poisoning killed over 500 people who ate bread made with contaminated wheat [6, 7].

2. Mercury Characteristics

Mercury is characterized as a highly malleable liquid at normal temperature and pressure [8]. Its name is derived from the Latin word *hydrargyrum*, meaning metal that resembles liquid silver [8]. Mercury is classified into three main groups: elemental mercury, inorganic mercury, and organic mercury. Mercury exists in several forms: inorganic mercury, among which there have been the metallic mercury and mercury vapor (Hg^0) and mercurous mercury (Hg^+) or mercuric mercury (Hg^{++}) salts; organic mercury, also called organometallic, which results from a covalent bond between mercury and a carbon atom of an organic functional group such as a methyl, ethyl, or phenyl group. The biological behavior, pharmacokinetics, and clinical significance of the various forms of mercury vary according to its chemical structure [3].

2.1. Inorganic Mercury Compounds

2.1.1. Elemental Mercury or Metallic Mercury Compounds. In its liquid form, the elemental mercury (Hg^0) is poorly absorbed and presents little health risk. However, in the vapor form, metallic mercury is readily absorbed through the lungs and can produce body damage [9–11]. Because of its soluble characteristics, elemental mercury is highly diffusible and is able to pass through cell membranes as well as the blood-brain and placental barriers to reach target organs. Once in the bloodstream, mercury undergoes catalase and peroxidase-mediated oxidation in red blood cells and tissues and is transformed into inorganic mercuric mercury (Hg^{++}) and mercurous mercury (Hg^+), a process that limits its absorption [9, 12]. Inorganic mercury has low lipophilicity and thus has a limited ability to cross cell membranes [9].

Elemental mercury is used in thermometers and sphygmomanometers because of its uniform volumetric expansion, high surface tension, and lack of vitreous adherence to surfaces. Low electrical resistance and high thermal conductivity allow metallic mercury to be used in electrical and electronic materials. Because of its high oxidation power, metallic mercury is used in electrochemical operations in the chlorine and soda industries. Metallic mercury is also used in metallurgy, mining, and dentistry because of the easy amalgam formation with other metals. In addition, gold extraction with archaic and dangerous methods predispose miners to mercury poisoning. The burning of metallic mercury on the gravel promotes the separation of gold, a process called amalgamation, which causes emission of large amounts of mercury vapor that is inhaled immediately by the miner, since they do not use appropriate personal protective equipment [13, 14].

Occupational exposure to mercury vapor and the release of mercury from or during removal of amalgam dental fillings increase its blood and plasma concentration [15, 16]. After exposure, blood concentrations attain 18 nmol/L [15], and after exposure to dental and removal of amalgam fillings plasma concentrations attain 5 nmol/L [17]. Occupational exposure also affects central nervous system [15] and amalgam tooth fillings impair sheep kidney function [18]. However, toxicological consequences are still a matter of debate [3, 19–23].

2.1.2. Mercurous Mercury and Mercuric Mercury Compounds. The mercurous mercury in the form of mercurous chloride (Hg_2Cl_2) is little absorbed in the body. It is believed that in the body the form of metallic mercury is changed to elemental mercury and mercuric mercury [24].

Mercuric mercury compounds, such as mercury salts, result from the combination of mercury with chlorine, sulfur, or oxygen. Mercuric mercury can be found in different states when combined with other chemical elements, including mercuric chloride (HgCl_2), which is highly toxic and corrosive; mercury sulfide (HgS), which is often used as a pigment in paints due to its red color; mercury fulminate ($\text{Hg}(\text{CNO})_2$), which is used as an explosive detonator [8, 25]. Among the mercuric mercury compounds, mercuric chloride (HgCl_2) calls the attention. It was used as a preservative for development of photographic film and has been ingested accidentally or as a suicide measure [26]. As elemental mercury, the mercuric mercury in the blood stream binds to sulfhydryl groups on erythrocytes, glutathione, or metallothionein or is transported suspended in plasma [27]. Mercuric mercury accumulates in placenta, fetal tissues, and amniotic fluid, but it does not cross the blood-brain barrier efficiently [28]. Evidence exists showing the transport of mercuric mercury via one or more amino acid transporters [29]. Evidence also shows that the accumulation in the brain occurs through its binding to cysteine [24].

In the cardiovascular system, acute inorganic mercury exposition *in vivo* promotes reduction of myocardial force development [30] and inhibited myosin ATPase activity [31]. Chronic exposure increases vascular resistance and induces hypertension [32–34]. Numerous studies have also revealed that mercury generates oxygen free radicals mainly by activation of NAPHoxidase [35, 36].

2.2. Organic Mercury. Organic mercury compounds, also called organometallic, result from a covalent bond between mercury and the carbon [8] atom of an organic functional group such as a methyl, ethyl, or phenyl group. Methylmercury (CH_3Hg^+) is by far the most common form of organic Hg to which humans and animals are exposed. CH_3Hg^+ in the environment is predominantly formed by methylation of inorganic mercuric ions by microorganisms present in soil and water [37–39]. The expression methylmercury monomethylmercurial is used to denote compounds that contain the cation methylmercury (CH_3Hg^+). Some of these compounds were used as pesticides and had medical applications as antiseptics and diuretics.

The organomercury antiseptics still used are Merthiolate, Bacteran, and Thimerosal [40].

Thimerosal is an organomercurial compound that since 1930 has been widely used as a preservative in biological material such as vaccines and serums used to prevent microbiological growth [41]. Thimerosal is metabolized in the human body and degraded into ethylmercury and thio-allylate. The chemical difference between these compounds is an important determinant of their toxicity [42, 43].

3. Forms of Mercury Exposure

Mercury is now considered an environmental pollutant of high risk to public health because of its high toxicity and mobility in ecosystems [11, 44]. Exposure to mercury can occur from both natural and artificial sources. Human activities that can result in mercury exposure include the burning of fossil fuels, chlor-alkali industries, mining, the burning of waste, and the use of coal and petroleum [10, 40, 45].

More natural sources of mercury include volcanic activity, earthquakes, erosion, and the volatilization of mercury present in the marine environment and vegetation [10, 46–48]. Mercury emitted both naturally or as a result of human activity is primarily found as inorganic metal vapor (Hg^0) [49]. Among the natural sources of mercury, the largest emissions are from the degassing of the earth's crust. More than five tons of mercury is estimated to be released into the sea every year as a result of erosion and geochemical cycles [50].

Mercury contaminates the environment through a cycle involving the initial emission, the subsequent atmospheric circulation of the vapor form, and the eventual return of mercury to the land and water via precipitation (Figure 3) [46]. The emission of mercury is an important part of this cycle of contamination and can occur through natural processes or as a result of human activities, as mentioned above [48].

Mercury present in seas and rivers after methylation can contaminate fish [51, 52]. The consumption of fish contaminated with mercury is a major source of mercury exposure in the Amazon basin. Studies show that the concentration of mercury in the muscles of fish that are widely consumed in the Amazon region are greater than the limit set by WHO (World Health Organization) as safe for human consumption (0.5 g/kg) [4, 10].

4. Transport and Elimination of Mercury

Inhaled elemental mercury vapor, for example, is readily absorbed through mucous membranes and the lung and is rapidly oxidized but not as quickly as to prevent the deposition of considerable amount in the brain [54]. Methylmercury is easily absorbed through the gut, and it is deposited in most tissue but does not cross the blood-brain barrier as efficiently as elemental mercury. However, to enter the brain, it is progressively demethylated to elemental mercury (Figure 2) [24]. Mercury salts, in contrast, tend to be insoluble, relatively stable, and hardly absorbed.

Then, toxicity for man varies depending on the form of mercury, dose, and rate of exposure. The target organ for inhaled mercury vapor is primarily the brain [24]. Mercurous and mercury salts especially damage the lining of the intestine and kidneys [5], and as methyl mercury, it is widely distributed throughout the body (Figure 1) [24]. Toxicity varies with dosage; a large acute exposure to elemental mercury vapor induces severe pneumonia, which in extreme cases can be fatal [24]. Low level of chronic exposure to elemental or other forms of mercury induces more subtle symptoms and clinical findings [3].

Oxidized mercury binds strongly to SH groups; this reaction can inactivate enzymes, lead to tissue damage and interfere with various metabolic processes [55–57]. Ingested methylmercury is almost completely absorbed and transported into the bloodstream [10]. Methylmercury enters cells mainly by forming a complex with L-cysteine and homocysteine and is eliminated in conjunction with glutathione [58]. After absorption, it is distributed primarily to the central nervous system and kidneys. Methylmercury elimination usually occurs in the urine and feces [59].

5. Doses of Mercury and Safety Legislation

The chemical form of mercury in the air affects its time of permanence and its dispersion in the atmosphere. The elemental mercury form can persist for more than four years in the air, while its compounds are deposited in a short time at locations near their origin. In the northern hemisphere, their average concentration in the atmosphere is estimated at 2 ng/m^3 and in the southern hemisphere is less than 1 ng/m^3 . In urban areas, there is a great variability of these concentrations being found up to 67 ng/m^3 with a mean of 11 ng/m^3 in Japan [53]. FUNASA (Fundação Nacional de Saúde) standards of mercury in the air consider a mean of 1 ng/m^3 in the period of one year [60].

In 2004, the Joint FAO (Food and Agriculture Organization of the United National)/WHO Expert Committee on Food Additives (JECFA) established that the safe concentration of methylmercury intake, without the appearance of neurological disorders, is 1.6 mg/kg of body weight. However, in 2006, JECFA stated that this concentration is not safe for intrauterine exposure, because fetuses are more sensitive to the onset of neurological disorders after exposure to methylmercury [61].

Currently, the general population is exposed to mercury by the following main sources: the consumption of contaminated fish, the use and manipulation of dental amalgam, thimerosal contained in vaccines, workers in industries of chlorine, caustic soda, miners, and workers in industries of fluorescent lamps [62, 63]. Each of these sources of exposure contains specific toxicological characteristics [64].

In Brazil, the rules for vaccination of the Ministry of Health, published in June 2001, shows that thimerosal is used in many vaccines. These vaccines prevent flu (influenza vaccine), rabies (rabies vaccine), infection with meningococcus serogroup b, and hepatitis B [65].

The US Environmental Protection Agency's recommended a reference blood concentration of mercury to be

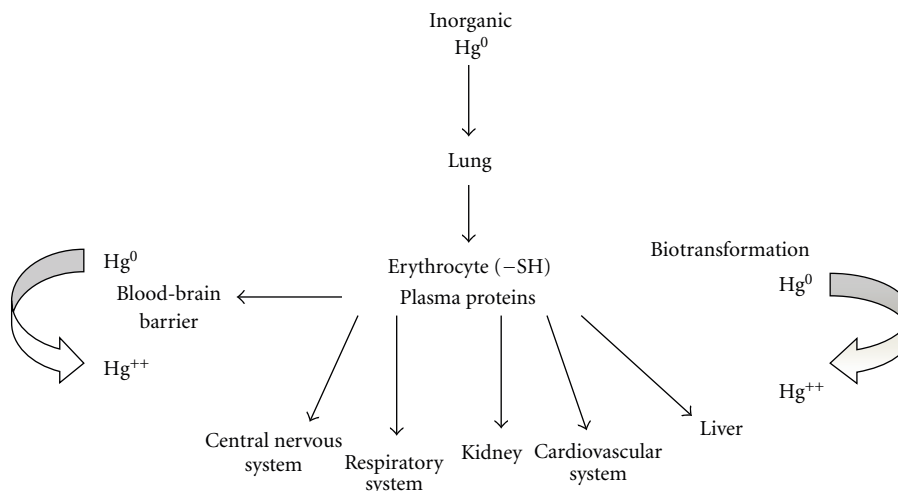


FIGURE 1: Scheme showing the entry of elemental mercury in organisms and their distribution in different organs.

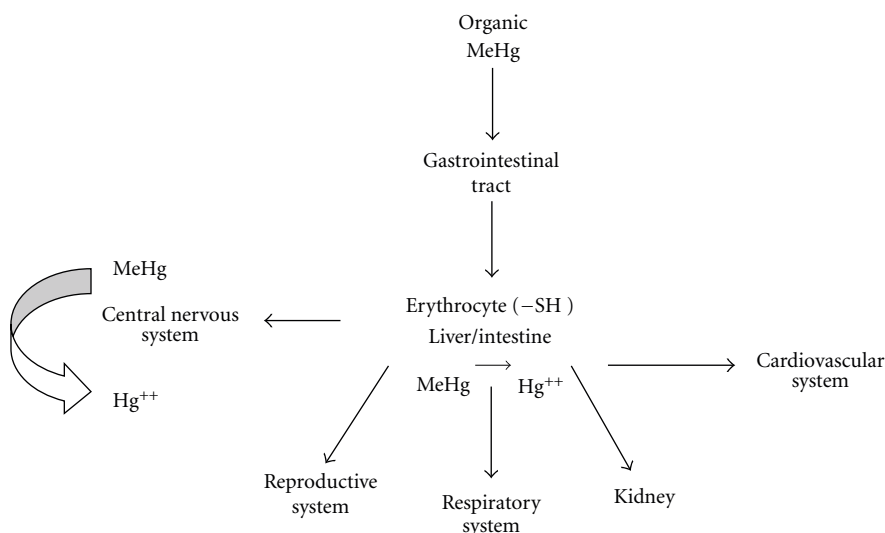


FIGURE 2: Scheme showing the entry of organic mercury in organisms and their distribution in different organs.

5.8 ng/mL; concentrations below this level are considered to be safe [66, 67]. Some studies have reported that the blood mercury concentration in the control population is approximately 1 ng/mL. On the other hand, levels of 7–10 ng/mL have been reported in workers exposed to mercury or in residents of Guizhou (China), an area that is known to suffer mercury contamination [68, 69]. In a recent biomonitoring study in New York City, the blood mercury concentration was found to be 2.73 ng/mL, and levels reached 5.65 ng/mL in adults that consumed fish regularly [70].

WHO [10] states that an allowable concentration of mercury in human hair is less than $6 \mu\text{g/g}$. In the Amazon basin, where fish is the main source of dietary protein, mercury concentrations in hair reached up to $150 \mu\text{g/g}$. Furthermore, only two of 40 cities studied have average mercury concentrations below the recommended amount [10, 71]. In individuals who have amalgam, the daily release of mercury amalgam is approximately 4–5 $\mu\text{g/day}$, and a

positive correlation exists between the blood concentration of mercury and the number of amalgams. It is estimated that each dental amalgam releases 3–17 μg mercury vapor per day and that the blood concentration of mercury after removal of the restoration can reach 5 nmol/L [72–74]. However, even at concentrations below recommended levels, there is strong evidence that exposure to ethyl mercury, the major component of thimerosal, is associated with the onset of neurological and heart disorders in children [75].

In the following sections, we will describe results obtained from animals with chronic and acute exposure to mercury. Some of these studies were performed with mercury exposure protocols that led to blood concentrations slightly above the reference values. Nevertheless, these concentrations could be easily found in exposed populations and may even be considered low when compared with concentrations in humans who consume large amounts of fish or who live in areas contaminated with mercury.

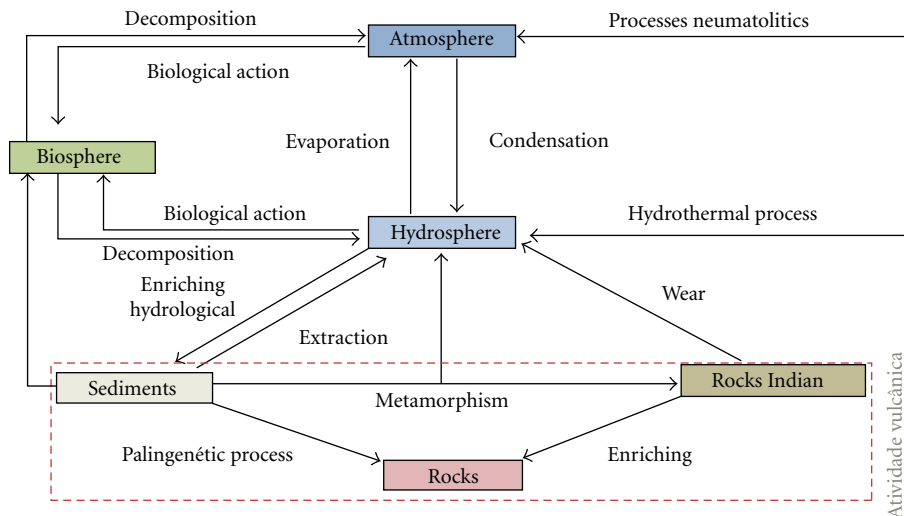


FIGURE 3: Cycle of mercury in the environment. Modified from Azevedo and Chasin 2003 [53]. Scheme demonstrating constant flow of mercury compounds in the hydrosphere, lithosphere, atmosphere, and biosphere.

6. Effect of Mercury on the Central Nervous System (CNS)

Among the compounds of mercury, the methylmercury is primarily responsible for the neurological alterations present in humans and experimental animals. It is believed that the mechanisms are related to the toxic increase in reactive oxygen species (ROS). Oxidative stress is associated with the etiology of neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease [54, 55], but these mechanisms have yet to be fully recognized.

Reinforcing the hypothesis that the majority of injuries caused by methylmercury (MeHg) in the central nervous system are related to its ability to increase reactive oxygen species, Zhang et al. (2009) [20] reported that after pre-treatment of bovine cells with pyrroloquinoline quinone (PQQ), an antioxidant, the cytotoxicity induced by MeHg is significantly attenuated. PQQ reduces the percentage of apoptotic cells, decreased significantly ROS production, suppressed lipid peroxidation, and increased antioxidant enzyme activity in cells exposed to MeHg. Furthermore, the protective effects elicited by an antioxidant (ebselen) strengthen the idea that seleno-organic compounds represent promising approaches to neutralize MeHg-induced neurotoxicity [19].

Studies also demonstrate that mercury has the ability to reduce the number of neuron and cytoarchitecture in individuals with prenatal exposure to mercury [76, 77]. In animal models, some of these symptoms are reproduced. Low-dose prenatal exposure to methylmercury during 10 gestational days impairs motor and mnemonic function in adult mice [23]. This hypothesis is supported by studies that describe methylmercury inhibition of cell division and migration both "in vivo" and "in vitro" [76–78].

In addition, because of its high affinity for sulfhydryl groups in tubulin, methylmercury inhibits the organization of microtubules that are important in CNS development [79–81]. The binding to SH groups also interferes with the intracellular signaling of multiple receptors (e.g., muscarinic, nicotinic, and dopaminergic) and promotes the blockade of Ca^{++} channels in neurons [82, 83]. In addition, inorganic mercury has the ability to increase the permeability of chloride channels of GABA A receptors in the dorsal root ganglion, which is associated with neuronal hyperpolarization [84].

Corroborating these findings, the study conducted by Maia et al., (2010) [21] demonstrates that the poisoning by methylmercury changes the nitrergic activities of adult mice, and the predominance of alterations may be related to different locations. Besides increasing the nitrergic activity methylmercury and mercuric chloride also have the ability to increase the release of neurotransmitters such as acetylcholine, dopamine, norepinephrine, and serotonin. Similar findings have also been reported to be a mechanism implicated in the effects of methylmercury and $HgCl_2$ on the central nervous system function [85–89].

Halbach et al. [90] studied a correlation in Iraqi children between the level of maternal exposure to methylmercury during pregnancy and psychomotor retardation. Sandborgh-Englund et al. [91] corroborated this finding in children from the Faroe Islands; they found that children exposed to mercury in the prenatal period had defects in attention, memory, language, and motor function. In addition, exposure to methylmercury in pregnant women or early childhood leads to changes in the CNS development of the fetus or child, respectively [50, 92, 93]. Thereupon, changes caused by mercury poisoning result in significant clinical deficit in motor skills, coordination, and general activity rate of cognitive and psychological disorders [23].

7. Effect of Mercury on the Cardiovascular System

For decades, the toxic effects of mercury were associated mainly with the central nervous system; however, inorganic mercury also produces profound cardiotoxicity [94–99]. Halbach and collaborators [100] showed that mercury concentrations in hair reached up to 150 $\mu\text{g/g}$ in populations living in the Amazon basin. Furthermore, nearly all of the inhabitants of 40 cities studied have blood concentrations above the reference values. In this population, it has been demonstrated that exposure to mercury by frequent consumption of fish has a strong positive correlation with increased arterial blood pressure [101]. Other studies also correlate mercury exposure with increased risk of hypertension, myocardial infarction, coronary dysfunction, and atherosclerosis [102–105]. Data presented by Yoshizawa et al. [106] showed that mercury exposure was associated with the progression of atherosclerosis and an increased risk of developing cardiovascular disease. Houston [107] followed patients for approximately 13.9 years and found an association between the concentration of mercury in the hair and the risk of developing cardiovascular events or dying from cardiovascular disease and other causes.

Mercury levels are predictors of the levels of oxidized low-density lipoprotein (LDL) [106]. Oxidized LDL particles are frequently found in atherosclerotic lesions and are associated with the development of atherosclerotic disease [107, 108] and acute coronary insufficiency [109]. Another mechanism by which mercury exerts toxic effects on the cardiovascular system is through the inactivation of the “paraonase” [110], an enzyme that slows the LDL oxidation process and that has an important antiatherosclerotic action [101].

The mechanism by which mercury produces toxic effects on the cardiovascular system is not fully elucidated, but this mechanism is believed to involve an increase in oxidative stress. Exposure to mercury increases the production of free radicals, potentially because of the role of mercury in the Fenton reaction [111–113] and a reduction in the activity of antioxidant enzymes, such as glutathione peroxidase. The MeHg reaction with the glutathione peroxidase occurs via thiol (–SH) and/or selenol (–SeH) groups from endogenous molecules [114]. Even though there are 4 of glutathione molecules containing selenine in their active sites, only the cytoplasmic glutathione peroxidase 1 (GPx 1) changes hydrogen peroxide to water [115, 116].

The reduction in glutathione peroxidase with selenium-dependent activity is the result of the decreased bioavailability of selenium, a molecule that is required for enzymatic activity [117–119]. The high affinity of mercury to the thiol group can lead to decreased glutathione peroxidase selenium-dependent activity. Other antioxidant enzymes which participate against reactive oxygen species due to mercury intoxication are catalase and superoxide dismutase. The increment of ROS and reduction of the antioxidant activity increase the risk of developing cardiovascular disease [118, 120, 121].

Sherwani et al. (2011) [122] showed that MeHg has the capacity to induce phospholipase D (PLD) activation through oxidative stress and thiol-redox alterations. They investigated the mechanism of the MeHg-induced PLD activation through the upstream regulation by phospholipase A₂ (PLA₂) and lipid oxygenases such as cyclooxygenase (COX) and lipoxygenase (LOX) in the bovine pulmonary artery endothelial cells. Their results showed that MeHg significantly activates both PLA₂ and PLD. MeHg also induces the formation of COX- and LOX-catalyzed eicosanoids in endothelial cells.

Cardiovascular changes resulting from mercury poisoning are also described in animal models. However, the mechanism involved in the effects of mercury on the cardiovascular system is not fully understood but seems to be dependent on both the dose and time of exposure. Raymond and Ralston [123] studied the hemodynamic effects of an intravenous injection of HgCl₂ (5 mg/kg) in rats and observed that mercury produced cardiac diastolic failure and pulmonary hypertension. Moreover, Naganuma et al. [124] reported that acute exposure to HgCl₂ (680 ng/kg) increased blood pressure, heart rate, and vascular reactivity to phenylephrine in rats; this increased reactivity seems to depend on an increased generation of free radicals. Perfused hearts from animals exposed acutely to HgCl₂ showed a reduction in left ventricular systolic pressure, heart rate, and atrioventricular conduction delay [125, 126].

Our group has found that chronic exposure to low doses of mercury (1st dose 4.6 $\mu\text{g/kg}$ followed by 0.07 $\mu\text{g/kg/day}$ for 30 days, im) attained a blood mercury concentration of approximately 8 ng/mL, a concentration similar to the levels found in exposed humans. This exposure produced a negative inotropic effect in perfused hearts, although increasing myosin ATPase activity. *In vivo*, arterial or ventricular pressures did not change [127]. The reduction in contractility was explained by alterations in calcium-handling mechanisms; protein expression of SERCA, Na⁺ K⁺ ATPase (NKA), and sodium/calcium exchanger (NCX) was diminished; phospholamban (PLB) expression was increased; the response to β -adrenergic stimulation was reduced following mercury exposure [128, 129].

The chronic exposure to low concentrations of mercury was also able to induce endothelial dysfunction in resistance and conductance vessels, most likely because of the decreased nitric oxide (NO) bioavailability due to the increased superoxide anion (O₂^{•-}) production from NADPH oxidase [36, 130, 131]. This study was evidenced by the following effects of mercury treatment observed in aorta, coronary, and mesenteric arteries: (1) the endothelium-dependent vasodilator response induced by acetylcholine (ACh) was decreased [36, 130]; (2) vasoconstrictor responses to phenylephrine or serotonin were increased, and NO endothelial modulation of these responses was decreased [36, 130, 131]; (3) vascular superoxide anion production, the expression of SOD-2, NOX-1, and NOX-4 (two main isoforms of NADPH oxidase), plasmatic malondialdehyde levels, and plasmatic antioxidant status were all increased [36, 130]; (4) both the superoxide anion scavenger SOD and the NADPH oxidase inhibitor apocynin restored

the NO endothelial modulation of vasoconstrictor responses and the impaired ACh-induced vasodilatation in vessels from the mercury-treated rats [36, 130]. We also observed that mercury treatment increased the participation of COX-2-derived vasoconstrictor prostanoids in vasoconstrictor responses [132]. Other researchers have also observed a selective loss of NO-mediated vasodilatation with no effect on the EDHF-mediated component of relaxation, implying that chronic mercury exposure selectively impairs the NO pathway as a consequence of oxidative stress, while EDHF is able to maintain endothelium-dependent relaxation at a reduced level [133]. On the other hand, using this low dose of mercury, Blanco-Rivero et al. [134] observed an increase in vasoconstriction responses to electrical field stimulation mediated by alterations of adrenergic and nitrgergic function in rat mesenteric arteries. HgCl₂ reduced neuronal NO bioavailability, most likely as a result of reduced nNOS (neuronal nitric oxide synthase) activity and increased O₂⁻ production as well as increased noradrenaline release and vasoconstrictor response. It is important to emphasize, regarding chronic low-dose exposure to mercury for 30 days, that although rats grow normally and have no changes in arterial blood pressure, endothelial function is already blunted affecting vascular reactivity [36, 131].

Taken together, these data show that chronic low doses of mercury have an important and deleterious effect on vascular function by reducing NO bioavailability. The degree of severity of mercury exposure is comparable to traditional cardiovascular risk factors, such as hypertension diabetes or hypercholesterolemia. Therefore, mercury could be considered an important risk factor for cardiovascular disease that could play a role in the development of cardiovascular events. The association between mercury exposure and an increased risk of developing cardiovascular and neurological diseases is apparent. Thus, continuous exposure to mercury can be dangerous, and current reference values, once considered to be without risk, should be reevaluated and reduced.

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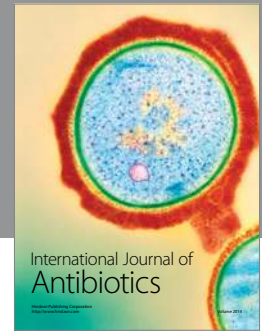
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