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MERCURY – POLLUTION AND TOXICITY

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Mercury is a well-known environmental pollutant. Although in the past it was used in therapeutics, nowadays there is a lot of concern regarding its toxic action. Regardless of the form in which it is found, elemental, inorganic or organic, mercury has only harmful effects on living organisms. As it was demonstrated by Japanese and Iraqi tragedies, which happened in the second half of the last century, a lack of control over pollution can cause real ecological and humanitarian disasters.

Keywords: environmental pollution, elemental mercury, methylmercury, Minamata disease.

MERCURY IN THE ENVIRONMENT

From the toxicological point of view, mercury compounds can be classified in three categories: elemental mercury, inorganic mercury and organic mercury. Inorganic compounds of mercury comprise its salts, where the oxidation number of the metal could be +1 (Hg_2Cl_2, for example) or +2 ($Hg(CN)_2$, $HgCl_2$ etc.). In the organomercuric compounds, the metal is bonded to a carbon atom from an organic radical, as methyl, ethyl etc.

In the earth's crust, mercury exists mainly as sulfide or in the elemental state, its concentration being 50 ppm. The pollution sources with this element are natural and anthropogenic as well. In the first category are included volcanic activity, erosion of mineral deposits or emissions from the surface waters. The main anthropogenic sources are artisanal and small-scale gold mining, coal burning, non-ferrous metal production, cement production, waste disposal.

The atmosphere is the main vehicle by which mercury is transported and redistributed even in the Arctic and Antarctic areas. There are various models that estimate mercury emissions in the atmosphere. In accordance to them, the amount of mercury released in the air is between 4000 and 9230 t/year[1], or even 11800 t/year[2]. Sources of mercury atmospheric pollution can be primary, of natural or anthropogenic origin, and secondary, which involve the re-emission into the atmosphere of mercury previously deposited on the earth's surface. In the atmosphere around 30% of the mercury is from anthropogenic sources, 10% from the natural ones, 60% being reemitted from the surface waters and the soil[3]. According to UNEP, in 2010 the emissions from anthropogenic sources were calculated at 1960 t, while in 2015 they were estimated at 2200 tones[4,5]. The increase is explained by the improvement of the collection of information regarding pollution as well as by the growing of the industrial activity in East Asia. Another study mentions that between 2010 and 2015 global mercury emissions increased from 2188 tons to 2390 tones, with an annual rate equal to 1.8%[6]. During this period, emissions decreased in North America by 13.2% (USA 10%, Canada 3.2%) and OECD Europe – 5.8%, but they increased in Central America – 5.4%, East Asia – 4.6% and Eastern Africa – 4%. Almost half of the global emissions are produced in the East Asian region, with 1012 tons of mercury released in the air in 2015[6]. In USA the anthropogenic emissions were 51.8 tons in 2014, while in 1989 they were 162 tones taking into account only their two main sources[7]. On a global level, the main sources that contribute to anthropogenic mercury pollution are the following: artisanal and small-scale gold mining – 37.7%, coal burning – 21.4%, non-ferrous metal production – around 15% cement production – around 11% and waste disposal – 7%[5]. In 2008, the pollution from primary and secondary natural sources was estimated at 5207 tons. Percentage wise, these sources contribute to the pollution as follows: oceans – 52%, tundra, grassland and forests – 16%, biomass burning – 13%, deserts, metalliferous and non-vegetated zones – 10%[8]. Globally, the atmos-

pheric concentration of mercury is estimated at 1.5–1.7 ng/m^3 in the Northern Hemisphere and 1.1–1.3 ng/m^3 in the Southern Hemisphere[9].

Atmospheric compounds of mercury can be classified in three categories: elemental gaseous form (Hg^0), bivalent mercury compounds in gaseous form (reactive gaseous mercury) and particulate mercury, namely Hg(II) compounds absorbed by particulate matter. The main form is the elementary one (over 95%) which has a low reactivity and a poor solubility in water (59 µg/L at 25^0C)[10]. This is the reason for the long residence time of mercury in the atmosphere which is six to eighteen months or even two years and allows it to be airborne at long distances from the emission source[1, 11]. Solubility of Hg(II) compounds is appreciably higher than that of Hg(0) (73 g/L for $HgCl_2$, 53 mg/L for HgO etc.) which makes their lifetime in the air to be much shorter (some days). Therefore, the oxidation of Hg(0) to Hg(II) is a crucial process for the effective removal of atmospheric mercury. It can take place both in the gas phase and in the liquid phase, the oxidation rate in the liquid phase being higher than in the gas phase. As oxidants were considered O_3, HO, NO_2, Cl, Br, ClO, BrO. The main reactions taken into account in the gas phase are those with ozone and hydroxyl radicals:

$$Hg + O_3 = HgO + O_2$$

$$Hg + HO = HgOH$$

$$HgOH + O_2 = HgO + HO_2$$

$$HgOH = Hg + HO$$

The first reaction has a rate constant equal to 3×10^{20} cm^3 molec^{-1} s^{-1}, which means a 1.4 year mercury lifetime[10]. It was appreciated that these chemical processes account for 80%, respectively 76%, of the oxidized mercury in the atmosphere[12]. However, the formation of HgO is considered uncertain in the first reaction and HgOH is an unstable compound that regenerates elemental mercury through decomposition[13]. Also, these reactions do not explain the fast oxidation of Hg(0) and high levels of Hg(II) in air during the polar springtime. It was suggested that this could be due to halogen atoms, chlorine and bromine, especially to bromine. While the concentration of chlorine atoms is too low to be considered effective in mercury oxidation, the concentration of bromine atoms is enough to eliminate Hg(0) in a few days[14]. The HgBr product formed initially has a 10 seconds lifetime at 298 K, but it is stabilized by subsequent reactions which give stable oxidation compounds:

$$Hg + Br = HgBr$$

$$HgBr + X = HgBrX$$

where X = ClO, BrO, NO_2, HO, HO_2[12, 15].

Mercury returns to the earth through dry depositions, as Hg(0) and Hg(II), or wet depositions, as Hg(II). In 2009, the wet depositions at four locations in the northeastern USA ranged from 6.4 to 13.4 µg/m^2 [16]. There is a seasonal variation of the elemental mercury depositions, as it was measured in a wetland meadow from Virginia, USA. In the spring they amounted to the highest level, 4.8 ng/m^2/h, followed by the winter depositions – 4.1 ng/m^2/h, while in the summer they were 2.5 ng/m^2/h, and in the autumn 0.3 ng/m^2/h[17]. In 2015, the mercury depositions to land and freshwaters were estimated at 3600 t, while those to the oceans amounted to 3800 t[5]. Reaching the surface of the earth, mercury from dry deposition can be absorbed in the leaves or it can remain on their surface or on the surface of the soil. Hg(II) from this second category can undergo photoreduction generating Hg(0), which, in turn, can go back to the atmosphere. The amount of dry depositions is estimated at 2470 t/year, while that of wet depositions at 790 t/year. By comparison, in the preindustrial era, the respective amounts were 775 t/year and 230 t/year[18].

In the soil, mercury exists in three forms: mineral – derived from mercury rocks, adsorbed on the surface of soil particles, where Hg(II) is attracted by negative charged particles, and in the composition of the organic matter. The mercury content of the soil increases dramatically as a result of pollution. In China for example, the background soil mercury level is 37 µg/kg. But in six places located at a maximum distance of 10 km from two coal-fired plants its concentration varies between 124.58 ± 6.14 µg/kg and 383.23 ± 32.59 µg/kg[19]. According to LUCAS Topsoil survey accomplished by analyzing over 23,000 samples from European Union countries, except Croatia, the topsoil mercury mean concentration is 0.04 mg/kg, with a range of 0–1.59 mg/kg[20]. The highest values were founded in some gold and mercury mining areas, located in Eastern Slovakia, Lazio province in Italy, North-West England and the Maramureș County in Romania. However, in some mining areas the mercury level in soil was found to be higher. In Central Spain, Almading district, where mining has

been going on for 2000 years, mercury is encountered in the form of cinnabar and bound to organic matter, its concentration being near 9 mg/kg[21]. In Romania, in four districts of the city of Baia Mare, the capital of the Maramureș County, the Hg concentration exceeds 1 mg/kg in a quarter of analyzed soil samples, while its mean level is 0.7 mg/kg[22].

In water sources, mercury exists both in the dissolved phase and suspended form. In uncontaminated rivers the concentration of the element is between 1–7 ng/L, while the mean level in sea water is estimated at 30 ng/L[23]. Stream water near the Almaden mine contains the pollutant at a level as high as 13 mg/L, whereas MeHg concentration is up to 30 ng/L. At the same time, the analysis of the corresponding sediments revealed mercury levels as high as 2.3 mg/g, from which 82 ng/g is methylmercury[24]. In surface oceans, at less than 100 m depth, the pool of mercury is about 54 Mmol, from which 75–95% is Hg(II) in complexed forms, 5–25% exists as elemental dissolved Hg(0) and 1–5% is methylmercury (MeHg). In deep ocean, the percent of organic mercury compounds increases, 5–25% being dimethylmercury (Me_2Hg), while 1–10% is MeHg[25]. In salty waters, dissolved Hg(II) is mainly in the form of chlorides and mixed halides, $HgCl_2$, $HgCl_3^-$, $HgCl_4^{2-}$, $HgCl_2Br^-$, while in fresh waters hydroxides predominate $Hg(OH)_2$, $HgOH^+$, $Hg(OH)_3^-$. In the deep areas, where oxygen content is low, it exists mainly as sulfuric species[25].

In water sources, inorganic mercury can be converted in organomercuric compounds by abiotic and especially biotic processes. An example of abiotic reaction is that between Hg(II) and methyltin(IV) species, these representing up to 90% of organotin compounds in water sources. They are utilized as catalysts, fungicides, insecticides etc., and their concentration can reach 1200 ng Sn/L – monomethyltin in seawater. The reaction between trimethyltin and Hg(II) is the following[26]:

$$Me_3Sn(IV) + Hg(II) \rightarrow Me_2Sn(IV) + MeHg(II)$$

Biotic methylation is accomplished by microorganisms carrying a specific gene cluster, *hgcAB*, especially by sulphate – reducing bacteria (SRB). Because all of them are anaerobes, it was supposed that mercury methylation take place only in anoxic conditions (sediments). Recently, however, it was demonstrated that this process can develop in other microenvironments, like periphyton or settling particles from oxic water columns[27]. The methylation mechanism is similar to that by which methyl cobalamin, an active form of vitamin B_{12}, generates CH_3Hg^+ in reaction with Hg(II). This reaction is shown in the following Figure 1[10].

Methylmercury, a powerful neurotoxic agent, is the main organomercuric compound found in living organisms. It accumulates in aquatic ones, the bioaccumulation factors for the primary and secondary carnivores being between 7×10^5 and 3×10^6 [10]. This compound was the main culprit for Minamata and Niigata tragedies, where, because of it, thousands of poisoning cases were registered[28].

MERCURY IN FOOD

Mercury has appreciable phytoavailability, its concentration in terrestrial plants being directly proportional to that in the soil. The toxic can enter the plants by being absorbed by their roots, or through the stomata, when it is deposited on their leaves. There are plants that concentrate more mercury than others but regardless of this it accumulates more in the roots than in the shoots or leaves. An example is Indian mustard (*Brassica juncea*), which was recorded to have 264–325 mg Hg/kg in the shoots and 1775–2089 mg Hg/kg in the roots, when it was grown on a contaminated soil having a mercury content of 1000 mg/kg[23]. An acidic pH of the soil increases the uptake of mercury by plants, while a pH higher than 7.5 decreases it. The content of soil organic matter is also a parameter by which mercury uptaking depends. For vegetables, at a quantity less than 20 g organic matter/kg soil, tuber plants have the highest absorption capacity, while eggplant has the lowest. At more than 30 g organic matter/kg soil, mercury uptake is almost the same[29]. Mercury content in some plants grown in contaminated sites is presented in the following table[19, 23, 30].

It is important to mention that for lettuce leaves (China) the mercury concentration decreases with 19–63% as a result of rinsing with water. The Food Safety Standard in China is 10 µg /kg for fresh weight vegetables and 20 µg /kg for grains. In EU, according to the Regulation (EC) no. 396/2005, amended at 16 January 2018 – Commission Regulation (EU) 2018/73, the maximum residue levels for mercury in cereals, fruits and vegetables, fresh or frozen, was established at 0.01–0.02 mg/kg[31].

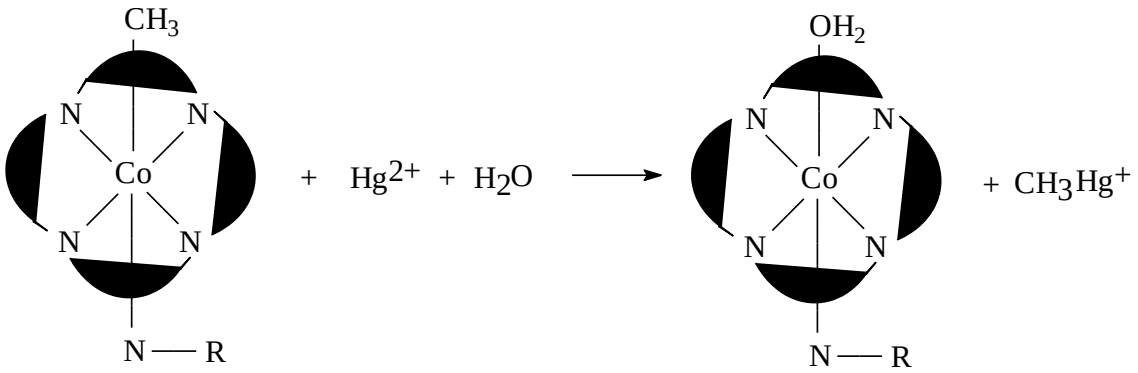

Figure 1. Schematic reaction between methyl cobalamin and Hg(II).

Table 1

Mercury concentration (mg/kg) of edible plants from some contaminated areas

Pollution source	Country	Plant, part	Range/maximum
Coal-fired power plant	China	Lettuce, leaves	7.23 – 39.04
		Tomato, fruit	9.79 – 71.80
		Eggplant, fruit	3.25 – 42.37
		Cucumber, fruit	2.18 – 38.45
		Rice, grains	24.99 – 62.95
		Maize, grains	0.55 – 21.02
Chloralkali, chemical industry	Egypt	Radish, roots	0.03 – 0.29
	Finland	Edible mushroom	1.10 – 4.70
	Switzerland	Spinach, leaves	0.11 – 0.59
Mining area, metal processing industry	Mexico	Maize, grains	0.9
	China	Maize, grains	0.41
	Yugoslavia	Edible mushroom	37.6
		Carrot, roots	0.5 – 0.8

As it was already shown, methylmercury is easily bioaccumulated by fish and seafood, over 95% of the mercury in their body being in the organic form. The highest level of the toxic is in fish muscles, the degree of risk for health being as follows: < 0.10 mg/kg – no risk; 0.10–0.30 mg/kg – low risk; 0.30–0.50 mg/kg – moderate risk; 0.50–2.00 mg/kg – high risk; > 2.00 mg/kg – severe risk. A study carried out in Baltic Sea, North Atlantic and Greater North Sea, revealed that in Baltic Sea, with the exception of European perch, none of the 11 fish species studied could be included in the high and sever risk categories. In contrast to this, 40% of the fish from North Atlantic and Greater North Sea fell in the high risk category[32]. In Brazilian Amazon, near mining zones, the mercury concentration in Caras and Trairas fish is in the range 2.21–6.11 mg/kg. In several types of fish from USA, the mercury level is presented in the following Table[33]:

Table 2

Mercury content (mg/kg) of fish sold in USA and the degree of safety for public consumption

Species	Mercury level	Safety
Herring	0.044	safe
Mackerel, Atlantic	0.050	safe
Catfish	0.049 ± 0.084	safe
Salmon, wild (Alaska)	0.014 ± 0.041	safe
Sardines, Pacific (US)	0.016 ± 0.007	safe
Trout, rainbow (farmed, freshwater)	0.072 ± 0.143	safe
Atlantic cod	0.095 ± 0.080	unsafe
Carp	0.140	unsafe
King mackerel	0.730	unsafe
Shark	0.988 ± 0.631	unsafe

In accordance with the EU regulation no. 1881 adopted in 2006 and last amended on April 12, 2022, the maximum admitted level for mercury in fishery products and in the muscle meat of fish is 0.5 mg/kg. For some species, including shark, pike, snake mackerel, swordfish and tuna, the level was set at 1 mg/kg, while for other species, like carp, Atlantic cod, Atlantic herring, mackerel, salmon and trout it was established at 0.3 mg/kg[34].

MERCURY IN THE BODY – TOXICOKINETICS

The main way for the elemental mercury to enter the body is the respiratory one. Around 80% of it is absorbed by pulmonary alveoli, while only a small percentage of the ingested mercury passes through the intestinal mucosa and 1% penetrates the skin[35]. A controversial source of intoxication is represented by the mercury outgassed from dental amalgam fillings, which contributes to a daily retention of the toxic estimated at 3–17 μg[36]. However, other data showed that in some patients with at least nine amalgam restorations the average daily amount of inhaled mercury was only 1.7 μg, although brushing and the habit of chewing gum increase this value[37]. The removal of amalgam fillings causes a drop in plasma and red cells of the inorganic mercury concentration, after 60 days being at 27% compared to the previous level[38]. Another source of human exposure at elemental mercury is its presence in the atmosphere, estimated to be 2 ng/m^3 in rural areas and 10 ng/m^3 in urban ones. The daily amount of toxic absorbed in the bloodstream from this source is about 32 ng in rural zones and 160 ng in urban zones[39].

In erythrocytes, Hg(0) is oxidized at Hg(II), partly under the action of catalase, the mechanism of reaction being the following[40]:

$$Cat – Fe – OH + H_2O_2 \rightarrow Cat – Fe – OOH + H_2O$$

$$Cat – Fe – OOH + H_2O_2 \rightarrow Cat – Fe – OH + + H_2O + O_2$$

$$Cat – Fe – OOH + Hg \rightarrow Cat – Fe – OH + HgO$$

where Cat is the abbreviation for catalase, the enzyme which acts in organism in the process of hydrogen peroxide decomposition.

Due to its liposolubility, elemental mercury can cross cell membranes by simple diffusion, including the blood brain barrier and the placenta. Also, mercury vapor can follow an unusual way of transportation to the brain, via the nerve cells of the olfactory system[41]. Through repeated exposure, mercury is stored in the kidneys and brain (especially in the gray matter). In the cerebral cortex higher concentrations were found in the occipital and parietal areas. Also, it accumulates in the cerebellar nuclei as well as in some nuclei of the brain stem. In an experiment conducted on squirrel monkeys, mercury was identified in their cerebellum three years after the exposure ceased[36, 42]. Its biological half time varies depending on the tissue. It was estimated that for 80% of mercury this value is around 60 days, except the brain, where halving its concentration could last several years[36]. In tissues, like in erythrocytes, Hg(0) is oxidized at Hg(II) and in this form it is excreted mainly through the urine and feces. After a short-term exposure about one-third of the absorbed Hg(0) is exhaled, but after longer periods of time only small quantities of elemental mercury are eliminated through respiratory way[39].

Inorganic mercury compounds, mercurous and mercuric salts, are absorbed mainly via gastro-intestinal tract in a percentage varying between 7 and 15%, depending on their water solubility[41]. For $HgCl_2$ a 2% absorption degree was reported, but its corrosive action may enhance the absorption by affecting the permeability of the digestive tract[36]. Hg_2Cl_2, having a water solubility of 2 mg/L is poorly absorbed, and this is mainly due to its oxidation to Hg(II). Bivalent mercury has a high affinity for sulfur, therefore in the body it binds to cysteine (Cys) thiol groups of proteins or of non-protein molecules like glutathione (GSH). In blood, Hg(II) is distributed almost equally between plasma and erythrocytes. In plasma it circulates mainly bound to – SH groups of albumin. In erythrocytes the thiols groups can be classified in three categories: belonging to cysteine fragments of hemoglobin (Hb), which represent about 85% of the total, GSH – 10% and membrane cell – less than 5%[43]. Mercury binding to hemoglobin affects the monomer Hb interactions necessary for the oxygenation and deoxygenation processes and probably, leads to the autooxidation of Fe(II) to Fe(III), i.e. to the conversion of hemoglobin in methemoglobin[44].

Usually, mercuric mercury does not cross the membrane cells of the targeted tissues as a complex with proteins like albumin. Consequently, it dissociates from it and binds to the non-protein thiols, forming compounds similar in shape and size with some endogenous molecules. In this way, "tricking" the transporters of amino acids and peptides, Hg(II) crosses cell membranes[45]. For

example, it is taken up in the proximal tubule of the nephrons as a Cys conjugate, Cys-S-Hg-S-Cys. This has a very similar structure with cystine, the dimer of cysteine containing a disulfide bond (Cys-S-S-Cys), and consequently, the mercuric complex enters the kidney cells by means of cystine transporters[46]. Unlike this mechanism, Hg(II) is taken up in hepatocytes as a complex with albumin or ferritin, by endocytosis. Normally, mercuric mercury should not penetrate the placenta and accumulates in the fetus. However, experiments on mice have shown that after injections with different doses of $HgCl_2$, the toxic accumulates in the placenta and in the fetal organs in a dose-dependent manner[47]. Also, Hg(II) does not cross readily the blood brain barrier, and it is believed that it results in the brain by the oxidation of elemental mercury. But, as in the case of the placenta, it cannot be ruled out the possibility of penetrating this barrier as a thiol-conjugate, due to their structural similarity with amino acids[36].

Mercuric mercury accumulates primarily in the kidney and in the liver. In mice, two weeks after administration of a single oral dose of $HgCl_2$ (1 mg Hg/kg body), 40–50% of the toxic was found in the kidneys, 10 – 20% in the liver and around 1% in the brain [48]. Other organs in which Hg(II) accumulates are the intestinal tract, the spleen and the epithelium of the skin. It is eliminated from the body in a three – phase process, as results from an experiment conducted on mice, which received $HgCl_2$ in drinking water (5 mg/L) during 84 days. The first phase (1–2.5 days) corresponds to the elimination of Hg(II) unabsorbed from the digestive tract, the second (11.5–12 days) to the elimination from easily accessible deposits and the third (44 – 83 days) to the clearance of aged deposits[49]. Mainly, it is excreted through urine and feces. In small quantities Hg(II) leaves the body through saliva, sweating or by being exhaled as a consequence of its reduction to Hg(0)[36].

The main way of organomercuric compounds to enter the body is oral, especially through contaminated fish and seafood intake. Between 80 and 90% of organic mercury in the human body is from aquatic organisms consumption and 75–90% of it is methylmercury (MeHg)[50]. In the food it is bound to proteins, but in the stomach, under the action of hydrochloric acid, it separates. In the duodenum, methylmercury interacts with cysteine forming cysteinyl – methyl mercury, a complex having structural resemblance with methionine. This allows it to cross the intestinal wall in percent close to 100%, being absorbed 17 to 35 times faster than inorganic mercury[50].

In the blood, methylmercury accumulates in erythrocytes (> 90%), forming bonds with the thiol groups of the cysteine fragments in the beta-chain of globin. Its concentration here is 20 times higher than in the plasma[51]. The uptake of the toxic by the red blood cells is facilitated by the complexes it forms with cysteine and glutathione (GSH). GSH is an antioxidant molecule, a tripeptide which contains cysteine (Cys), glycine (Gli) and glutamic acid (Glu) fragments, methylmercury being linked to the Cys – SH group (CH_3Hg – S – CysGlyGlu). These S-conjugates of the toxic, being substrates for organic anion transporters (OAT), allow its accumulation in the red blood cells[52]. Methylmercury is distributed in the whole body in around 30 hrs. It is able to cross the placenta and the blood brain barrier, due to its Cys conjugate, which is transported by a neutral amino acid carrier in the brain capillary endothelial cells[45]. After distribution, blood to brain ratio of the toxic is about (5 – 7):1, the same ratio being recorded between fetal brain and maternal blood[51]. Also, it accumulates in the scalp hair, making it a useful marker for the intoxication with this compound. However, the pattern of methylmercury distribution resembles that of inorganic mercury, its concentration being higher in the kidney and in the liver.

In the body, methylmercury undergoes a demethylation process. In a case of mass poisoning that occurred in Iraq in 1972, around 6000 people were intoxicated with organomercuric compounds, primarily with methylmercury. The cause was the consumption of bread produced from cereal seeds treated with such compounds. After 2 – 3 months of high doses of toxic ingestion, inorganic mercury represented 7% of the total mercury in the victims' blood, 22% in plasma and 39% in milk[53]. Also, the autopsy performed in three cases revealed a 16–40% inorganic mercury in the liver[54]. In an experimental study having monkeys as subjects, daily doses of MeHg (50 μg Hg/kg body) were administered for 6, 12 or 18 months. The results indicated that inorganic mercury in the blood was 7% from the total mercury. Accumulation in brain was biphasic, with a percent of inorganic mercury of 9% at 6 – 12 months, 18% at 18 months and 74% at 6 months after finishing the experiment. The biological half-time for total mercury in the blood was 26 days and for MeHg in the brain, following termination of the exposure, was 35 days. The same value for inorganic mercury was very long, in the order of years[55].

The mechanism of demethylation seems to take place through reactive oxygen species, primarily superoxide anion ($O_2^{\cdot -}$)[56]. A study conducted on mice showed that the byproduct of demethylation is formaldehyde, which results in a dose-dependent manner from methylmercury. Moreover, the amount of formaldehyde is 500 times higher than that of inorganic mercury itself, which suggests that inorganic mercury enhanced the CH_2O production. Manganese superoxide dismutase diminishes the amount of formaldehyde, while $O_2^{\cdot -}$ increases it, confirming that superoxide anion is involved in the reaction mechanism[57]. Another possibility of demethylation involves the reaction of RS – MeHg (R = GSH, Cys) conjugates with selenoaminocids, taking into account that the MeHg – selenol complexes are more stable[58, 59]:

$$RS - MeHg + RSeH \leftrightarrow RSH + RSe - MeHg$$

where RSe – MeHg is selenocysteine – MeHg or, if R = CH_3, bis(methylmercuric)selenide, $(MeHg)_2Se$. The latter compound has a reduced stability at physiological temperature and decomposes:

$$(MeHg)_2Se \rightarrow Me_2Hg + HgSe$$

On its turn, Me_2Hg regenerates MeHg, and CH_4 results as a byproduct:

$$Me_2Hg + H^+ \rightarrow MeHg^+ + CH_4$$

Beyond the uncertainties related to this mechanism, granules of HgSe were detected in the kidneys and liver of sea birds and marine mammals[58].

The biological half-time for MeHg is between 45 and 70 days[51]. Its excretion takes place through biliary secretion and urine, most of the toxic leaving the body through feces (about 90%)[36]. Reaching the intestine, a large part of MeHg is reabsorbed and, via enterohepatic circulation, returns to the liver. The export of the toxic from hepatocytes into the biliary canaliculi is made in the form of GSH complex, through the same carrier of glutathione itself[60]. Once in the bile, MeHg – GSH complex is catabolized by γ-glutamiltransferase and cysteinyl-glycinase enzymes, resulting MeHg – Cys conjugate. In this form, it can be reabsorbed by the biliary ducts line cells or by the enterocytes in the intestine[61]. Also, some of the mercury in the bile is in inorganic form. Besides, being exported through the bile in the intestine, MeHg comes into contact with the microflora here, being subjected to demethylation and converted into the inorganic form. This process facilitates the elimination of the toxic from the body because the absorption degree of inorganic mercury is much lower than that of the organomercuric compounds[62].

MERCURY IN THE BODY – TOXICODYNAMICS

The symptoms of the mercury poisoning depend on the nature of the toxic substance and the form of exposure to its action. Central nervous system and kidneys are the main targets for the elemental mercury and mercury compounds. The inorganic mercury is more nephrotoxic than mercury in the organic form, while the main target of the organomercuric compounds is the central nervous system. Acute poisoning usually occurs by inhaling mercury vapors or ingesting mercury salts, while chronic intoxication is the result of exposure to the action of organomercuric compounds. The symptoms associated with the two types of poisoning, as they result mainly from intoxication of human subjects, are briefly described in the table below[48, 63].

Table 3

Symptoms of mercury poisoning in different systems of the body

Target system	Acute intoxication	Chronic intoxication
Central nervous system	Irritability, tremors, lethargy, confusion, decreased reflexes and nerve conduction	Headache, tremor, insomnia, depression, ataxia, dysarthria, unsteady gate, paresthesias
Renal	Hematuria, proteinuria, anuria, collapse	Albuminuria, polydipsia, polyuria
Pulmonary	Cough, shortness of breath, bronchiolitis, bronchitis, edema, emphysema, interstitial and alveolar fibrosis, respiratory failure	–
Gastrointestinal tract	Nausea, abdominal pain, vomiting, bloody diarrhea, intestinal mucosa necrosis	Constipation, diarrhea

For the cardiovascular system, the epidemiological studies are inconclusive, no correlation being proven between hypertension or cardiovascular diseases and exposure to mercury [48]. However, an analysis made in the case of 14 studies totaling 34000 subjects, carried out in 17 countries, showed a certain correlation between mercury exposure and the occurrence of cardiovascular diseases. The values of the relative risk parameter were as follows: 1.21 for ischemic heart disease (IHD), 1.68 for cardiovascular disease mortality (CVD) and 1.50 for mortality due to other heart diseases[64].

The same situation of uncertainty is encountered in the case of the liver system, although a certain increase in the serum level of gamma-glutamyl-transferase (GGT) was found in the case of 508 adults exposed to mercury[65]. At the same time, in the case of 560 elderly people, a relationship between the blood mercury concentration and that of the serum level of all liver enzymes – aspartate aminotransferase (AST), alanine aminotransferase (ALT) and GGT was found[66].

The toxic action of mercury is explained by its affinity for the thiol groups of enzymes and proteins. Also, it can replace some metal ions of the prosthetic groups of these molecules, affecting their normal functioning. At the same time, MeHg induces developmental neurotoxicity by altering DNA methylation. The methylation occurs mostly on cytosine followed by guanidine residues of DNA (CpG), at the fifth carbon atom of the cytosine pyrimidine ring (5 – methylcytosine). The effect of this reaction is the suppression of certain gene expression, as was found in the case of *NR3C1* or *MED31* genes, which encode the synthesis of glucocorticoid receptor, respectively of a transcriptional regulator essential for fetal development[67–69].

In Minamata disease, through the autopsy of over 200 bodies, the main lesions were identified in the cerebral cortex. In acute cases, swollen and shrinked neurons were observed, as well as neuronal loss and ischemic changes. Other histopathological modifications were edema in the perivascular space, perivascular demyelination and cortical atrophy[70]. In the chronic onset cases, the symptoms were milder. The neuronal loss does not exceed 30%, the cerebral lesions are localized in both types of intoxication, but are not so obvious in the chronic ones[71]. Depending on the extent of the lesions, Minamata disease was classified in six stages[70]: a decrease in the number of neurons by less than 30% (1); a 30–50% loss of neurons (2); a neuronal loss above 50% (3); a progress toward a spongy state (4); microscopic spongy state (5); macroscopic spongy state (6). The lesions were located in certain areas, as calcarine region – anterior ends of the calcarine fissures, precentral and postcentral gyri, temporal transverse gyrus. A CT scanning performed on 12 patients with Minamata disease, aged to 28 to 74 years, revealed that cortical atrophy was more obvious in the occipital lobe, being characterized by an enlargement of the calcarine and parieto-occipital sulci[72].

Cerebellar lesions mainly affect the vermis as well as the granular cells in the inner layer of the cortex. As in the case of the cerebrum, a six degree cerebellar lesions could be detected[70]: apical scar formation due to the disappearance of granule cells located under the layer of Purkinje cells (1); 30–50% loss of granular cells (2); loss of granular cells more than 50% (3); complete loss of granule cells without affecting the Purkinje ones (4); disappearance of both Purkinje and granule cells (5); microspongy appearance of the granular cells layer (6).

These changes are correlated with the symptoms observed in mercury poisoning. The defining symptom of Minamata disease is the bilateral concentric constriction of the visual field caused by lesions in the calcarine area, which had a prevalence of 29.3% among residents in Minamata[73]. Injury of the primary auditory area of the temporal transverse gyrus explains the hearing problems encountered by around 29% of the Minamata inhabitants. Cerebellar lesions are the cause of the most encountered symptoms of poisoning with organomercuric compounds: ataxia, with a prevalence of over 95% among Iraqi intoxicated persons, and dysarthria, with a high prevalence, too[74]. Other common symptoms were numbness and paresthesias, but also much more serious problems, like cognitive impairment and psychiatric features – restless, mental confusion, dementia.

The most dramatic effects of the methylmercury intoxication occur in prenatal life. The toxic crosses the placenta probably as an S-conjugate with cysteine and through the neutral amino acid carrier system L it gains access to the placenta. In Minamata disease no obvious abnormalities were observed at birth and in the first six months of the life. But, after this period, the symptoms started to appear: convulsions, failure of the eyes to follow, instability of the neck. The prevalence of the symptoms was as follows[75]: intelligence disturbance, cerebellar symptoms, disturbance of body growth, deformity of limbs, dysarthria and primitive reflex –

100%; hyperkinesia and hypersalivation – 95%; strabismus – 77%; pyramidal symptom – 75%.

CONCLUSIONS

Mercury and its compounds are strong toxics whose harmful action was unknown for hundreds of years. More than that, during the time, they were used in therapeutics, to treat syphilis, cholera, pleurisy and chronic diseases of the nervous system. Today it is known that far from having any beneficial effects, these compounds have an eminently injurious action. Humanity had to experience the Minamata and Iraqi tragedies, with thousands of victims, to realize this. In order to limit mercury pollution and to prevent such events, in 2013, at Minamata, "Minamata Convention on Mercury" was adopted and ratified by 140 states to date. Caught in the vortex of industrial civilization, it remains to be seen to what extent the humanity will take concrete and safe steps to ensure the health of the Earth.

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