The Effects of Mercury Exposure on Neurological and Cognitive Dysfunction in Human: A Review

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Abstract Mercury (Hg) is a naturally occurring noxious and volatile heavy metal found in the environment in the various forms. In the environment mercury is released via natural (weathering of rocks, volcanic eruptions) and anthropogenic activities (mining, coal fired power stations, waste incineration and industrial processes. Mercury occurs in inorganic and organic form; inorganic form consists of metallic or elemental mercury (Hg) whereas organic form covers Hg bound compounds like methyl, ethyl and phenyl mercury. By the assistance of certain microorganisms mercury can be transformed into its toxic form, namely methylmercury (MeHg). Methylmercury can act as a neurotoxin and bioaccumulates in the tissues of aquatic plants and animals and can affect the health of individuals who eat these animals and fishes. High exposure to mercury engenders complications like changes in the central nervous, digestive and immune system besides this, it also have toxic effects on liver, lungs and kidneys. Neurological and cognitive and motor dysfunction may be noticed after ingestion, inhalation or by any kind of exposure to mercury compounds. Patients with high mercury exposure show symptoms like nausea, irritability, tremors, headache, hypertension, hallucinations and even death in certain cases. Resourceful approach should be taken to evaluate the risk of occupational exposure and also to consuming fish with regard to human and animal health. Current chapter will discuss all the problem findings and recent advances of mercury poisoning and their effect on neurological functions.

Keywords Mercury-toxicity · Cognitive dysfunction · Neurological disorders · Methylmercury

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1 Introduction

Mercury is a pernicious heavy metal found naturally in the environment. It is a silvery odorless metal, slowly tarnishing in moist air. It is the only metal that is liquid at normal temperatures. Mercury is naturally introduced into the environment by volcanic fumes, forest fires, weathering of rocks and through soils. Anthropogenic activities primarily; mining, combustion (burning of fossil fuels), waste incineration, coal burning power plants and industrial processes contributes to unnatural introduction of mercury. Mercury is found in its organic and inorganic form: inorganic form which includes metallic or elemental mercury which can later transform into mercury vapor (Hg); and organic form, which includes mercury bound compounds (methyl, ethyl, phenyl, or similar groups) [1]. Loads of mercury is mostly emerged from combustion of coal which can be dispersed in the air to long before being settled on the land surface [2]. All types of mercury have been acknowledged as toxic, as it has no biological benefit from it [3].

The possible threats related to health are associated with mercury vulnerability have led to the adoption of alternative substances and practices in many industries. Regarding the use of mercury as an antiseptic and medical preservative, the medical field has moved away from its use due to the availability of safer alternatives. Antiseptics are now primarily based on compounds such as alcohol, iodine, hydrogen peroxide, and chlorhexidine, which are effective without the same risks posed by mercury. As for dental amalgam, it is a mixture of metals, including silver, tin, copper, and mercury. Dental amalgam has been used for filling cavities for many years due to its durability and cost-effectiveness. However, concerns have been raised about the potential release of mercury vapor from dental amalgam fillings. The amount of vapor released can vary depending on factors such as chewing, teeth grinding, and exposure to high temperatures from hot food or drinks. Mercury vapor is highly volatile and lipid soluble, which means it can cross biological barriers such as the blood–brain barrier and lipid cell membranes. Once in the body, mercury can be accumulated in its inorganic forms within cells. However, the overall health risks associated with dental amalgam fillings and mercury vapor exposure are a subject of ongoing scientific debate. Mercury might potentially have noxious repercussions on the central nervous system, digestive system and immune system also. According to WHO, mercury is considered to be one of the top ten chemicals that possess considerable health problems. It can also affect the lungs, kidneys, skin and eyes. Food that usually contains mercury includes fish [4].

Mercury absorption depends on the type of mercury. As the route of absorption of metallic or elemental mercury (Hg^0) is mostly by lungs (80%) via inhalation, although lesser is absorbed by the gastrointestinal tract. Hg^0 is absorbed in the lungs and converted into Hg^{2+} in red blood cells [5]. After setting foot into the circulation it is promptly dispersed to the tissues, but accumulates profusely in the kidneys. Elemental mercury can be in the body for a long term (from weeks to months). Because of its lipophilic physicochemical property it can easily cross the membrane barriers.

2 Chemical Properties and Availability

Mercury has a comparatively high vapor pressure. Mercury has two cationic states; Hg^{2+} (mercuric) and Hg^{1+} (mercurous) while elemental mercury (Hg) has no charge. Hg^{2+} can be associated with inorganic molecules (mercuric chloride, cinnabar mineral, oxygen and hydroxyl ions) and organic molecules (carbon based) like dimethylmercury, which is way more harmful than inorganic forms. However Hg^{2+} with inorganic molecules is more stable. Mercuric cation is also found in carbon based compounds. Mercury existing in nature as an element that is non-biodegradable, meaning it cannot be broken down or decomposed by living organisms. However, it can undergo various transformations and transport processes in the environment.

Mercury (Hg) can exist in many physical and chemical forms in the environment, having different transport and deposition properties and effects on ecosystems. Apart from natural and direct, anthropogenic environmental changes like oxygen depletion, acidification and draining of water-drenched areas may mobilize metals apart from availability to organisms. Mercury generally exists in three forms namely elemental or metallic mercury (H^0), inorganic mercury (Hg^{2+}) and organic mercury (MeHg or methyl mercury). Mercury (Hg) is an element that exhibits unique chemical properties. It can form various compounds and amalgams with different elements like salts of mercury: Mercury can form salts with oxygen (O), sulfur (S), and chlorine (Cl); For example, mercuric sulfide (HgS), mercuric oxide (HgO) and mercuric chloride ($HgCl_2$).vapor and liquid form is the inorganic form of mercury. When monoatomic gas is released from volatile liquid Hg, it is called Hg vapors. Hg vapors play predominant role in global cycling of heavy metals because of its existence as mercurous (1+) or mercuric (2+)cation [6].

Inorganic mercury runs in a cycle between air, land and water. The salts of inorganic mercury can attach to air particles which are later deposited on land via rain or snow or it can returns to the atmosphere in the form of gas with the particles and redeposits elsewhere. During all this process inorganic mercury undergoes a series of physical and chemical transformations. These transformations are facilitated by certain microorganisms and converting it into an organic form of mercury such as methylmercury; which is highly toxic. Commonly methylmercury exposure happens to fish consuming populations, since fish have high concentration of methyl mercury in their tissues. Overexposure and consumption of methyl mercury containing products can lead to severe problems which may include: lack of movement coordination Loss of peripheral vision; “Pins and needles” feelings, mostly in the feet, hands and the mouth; hearing, speech, walking disability; and/or Muscle frailty [7].

3 Toxigenicity and Mechanism

Mercury enters the body through vapors. It can affect nervous system, enzyme system and causing cognitive dysfunction. Mercury toxicity in humans depends and differs with the degree of exposure, dose and form of mercury. Vapor inhalation can cause severe pneumonitis and can be fatal in extreme cases. After inhalation of mercury vapors primarily it aims the brain. Mercurous and mercuric salts predominantly can cause impairment of the gut lining and kidney; while methylmercury is broadly distributed all over the body. Methyl mercury can bioaccumulate and biomagnify through the aquatic food web [8].

Methylmercury can induce cell damage through various mechanisms; Disruption of Calcium Homeostasis: Methylmercury can interfere with calcium signaling and disrupt the balance of calcium ions within cells. Calcium ions play pivotal roles in various cellular processes, including signal transduction, enzyme activation, and neurotransmitter release. By disrupting calcium homeostasis, methylmercury can impair these cellular functions, leading to cellular dysfunction and damage Induction of Oxidative Stress: Methylmercury can induce oxidative stress within cells. Oxidative stress occur when there is a variance between the production of reactive oxygen species (ROS) and the cell's potential to detoxify them or restore the resulting damage. Methylmercury can either directly generate ROS or interfere with the cell's antioxidant defenses, such as glutathione, which help neutralize ROS. The accumulation of ROS can cause damage to cellular components, including lipids, proteins, and DNA, accelerating cell dysfunction and death. Interactions with Sulfhydryl Groups: Methylmercury has a high affinity for sulfhydryl (–SH) groups, which are present in many cellular proteins and enzymes. It can form strong covalent bonds with sulfhydryl groups, disrupting the structure and function of important proteins and enzymes. This interaction can lead to the inhibition of enzymatic activities, impair cellular processes, and disrupt the overall functioning of cells. These mechanisms collectively contribute to the toxicity of methylmercury and its potential to begin cellular damage, particularly in the central nervous system, where methylmercury tends to accumulate and exert its most severe effects [9].

Once mercury gets inside the body, it undergoes the processes of absorption, distribution, metabolism, and excretion (ADME). Mercury can be absorbed through the respiratory system when mercury vapors are inhaled or through the gastrointestinal tract when ingested. It can also be absorbed through the skin, although to a lesser extent. Once absorbed, mercury can circulate through the bloodstream, where it can reach various organs and tissues. It has a particular affinity for the central nervous system, including the brain, where it can accumulate over time. Mercury can undergo metabolic transformations in the body. The main form of mercury encountered in the environment is elemental mercury (Hg^0), which can be converted into inorganic mercury (Hg^{2+}) by certain bacteria or through oxidative processes. Inorganic mercury can further undergo metabolic conversions in the body, such as being transformed into methylmercury (MeHg) by certain microorganisms, particularly in aquatic environments. The excretion of mercury from the body occurs mainly through urine and

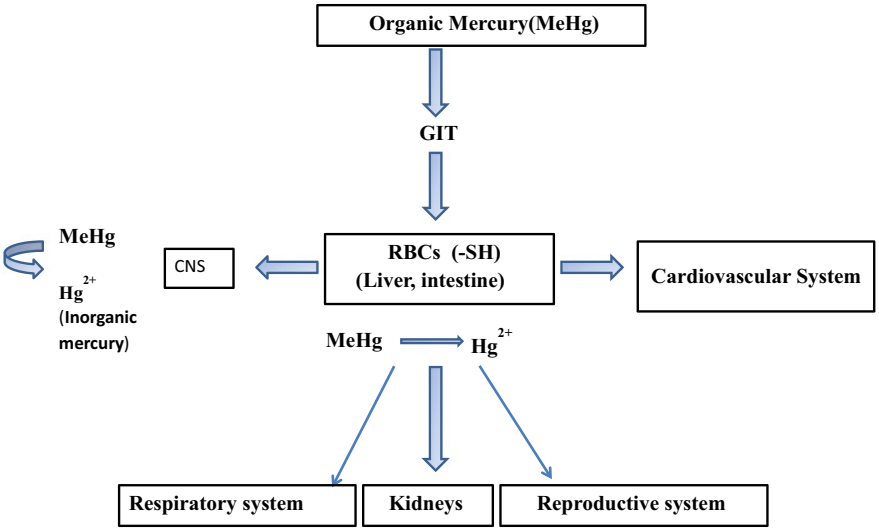

Fig. 1 Schematic representation of mercury distribution after entering the body [11]

feces. Inorganic mercury and methylmercury can be eliminated through these routes, although methylmercury has a prolonged half-life in the body in comparison to inorganic mercury [10]. A Schematic representation of mercury distribution after entering the body is illustrated in Fig. 1.

The toxicity of mercury arises from its capability to attach to sulfhydryl groups in enzymes and proteins, leading to the disruption of their normal function. This can result in extensive neurological symptoms and conditions, including neurobehavioral changes, cognitive impairment, motor dysfunction, and sensory disturbances. Methylmercury, in particular, is noted to have an intense affinity for the central nervous system and can promptly cross the blood–brain barrier, leading to its accumulation in brain tissues [12].

It should be noted that the toxicokinetics of mercury may differ depending on its chemical form. For example, elemental mercury vapor is primarily associated with neurological effects, while methylmercury, commonly found in contaminated seafood, is known for its neurotoxicity. Other forms of mercury, such as inorganic mercury compounds, can also contribute to toxic effects but may affect different organ systems. Overall, the toxic effects of mercury are multifaceted, and its ADME processes play a crucial role in determining its toxicokinetics and potential harm to the body, particularly in relation to the development of neuropathological conditions [10].

To support cellular defense against damage from free radicals, it is necessary to maintain the optimal intracellular concentrations of glutathione (GSH). Glial cell namely astrocytes, in the central nervous system, play a vital role in providing GSH precursors, particularly cystine, to neurons. Astrocytes take up cystine from the extracellular space through various transport mechanisms, namely; System XAG which

plays a significant role in cystine uptake and is regulated by various factors, including oxidative stress, second is the system XC^- responsible for the exchange of extracellular cystine with intracellular glutamate [13] it is highly expressed in astrocytes and plays a critical role in supplying cystine to neurons and third is the gamma-glutamyltranspeptidase (GGT). GGT is an enzyme that takes part in the metabolism of glutathione. It catalyzes the breakdown of extracellular GSH into its constituent amino acids. This breakdown releases cysteine, which can be further processed by astrocytes to regenerate GSH. Research was carried out to investigate the effect of methylmercury (MeHg) on cystine transport in both astrocytes and neurons. It has been observed that MeHg exposure can impair cystine uptake by astrocytes, leading to reduced availability of cysteine for GSH synthesis. This disruption in cystine transport can compromise the cellular defense mechanisms against oxidative stress and contribute to MeHg-induced neurotoxicity. Understanding the effects of MeHg on cystine transport in astrocytes and neurons is crucial for comprehending the impact of mercury toxicity on cellular antioxidant defenses and neuronal health [14].

The toxicokinetics of mercury accompanies one- or two-compartment model, depending on the route of exposure, dose, and whether it is a single or repeat exposure which results in accumulation of merury in the body. In the case of single exposures, mercury can be described using a one-compartment model, which assumes that the distribution and elimination of mercury occur in a single homogeneous compartment within the body. However, with repeat or continuous exposure to any form of mercury, the body's handling of the metal becomes more complex. In such cases, a two-compartment model is often used to describe the toxicokinetics of mercury. This model considers the body as having two compartments: a central compartment (e.g., blood) and a peripheral compartment (e.g., tissues) [15]. Studies have demonstrated that continuous exposure to mercury can lead to the accumulation of the metal in the body over time. Mercury can be distributed throughout various tissues, including the brain, and may persist in these tissues even after exposure has ceased. This accumulation of mercury in the brain can have long-term effects on neurological function. During the initial few days after mercury exposure, metal levels in the blood are closely related to the overall retention of mercury in the body. However, after this initial period, the amount of mercury in the blood declines more rapidly compared to the whole-body load. This indicates that mercury is being redistributed from the blood to other tissues, including organs such as the brain. It is important to note that the toxicokinetics of mercury may differ with specific form of mercury (e.g., elemental, inorganic, or organic) and the route of exposure (e.g., inhalation, ingestion, or dermal contact) [16]. Among all the mercury species methylmercury is the highly toxic form. It is highly volatile and can pass through the biological membranes. After getting access into the brain, mercury is oxidized by the hydrogen peroxidase–catalase pathway and is easily converted into inorganic divalent mercury. Primarily absorbed metallic mercury is eliminated in the urine, about 10% and feces, some passes in the milk (5% and in small quantity exhaled out. Gaseous form of mercury when reaches brain it is transformed into oxidized form.

Inorganic mercury absorption via GI tract is 10–40% also distributed to different organs and majorly accumulates in the kidneys. A study on female Sprague–Dawley

rats showed the distribution of mercury across the different parts of the body when dosed with a single dose of mercuric chloride (7.4 or 9.2 mg Hg/kg, p.o.). 12.6 and 18.9 ppm mercury was detected in the kidneys with traces in the liver, brain and serum in addition [17]. Although these compound do not cross the membrane barriers easily.

However the absorption of organic mercury (e.g. methylmercury) via GI tract is about 95% which later distributed to other organs from the circulation. Alike metallic mercury methyl mercury is concentrated majorly in the brain and fetus. Also, it has the ability to transform it into inorganic divalent cation in the brain region (tissues) and can stay there for a long term. However in comparison with metallic mercury the conversion is less [18]. Organic mercury is excreted in the form of feces for several months, although some of it is excreted via urine and milk also.

4 Mercury Toxicity

4.1 Humans

Various studies indicated that even exposure to low dosage of inorganic mercury can cause neurological and cognitive dysfunctions. The hippocampus in brain is peculiarly at risk to the harmful effects of mercury; hippocampus has a role in learning, spatial navigation and memory encoding. Neurological damage, inflammation and oxidative stress are the possible outcomes when inorganic mercury accumulates in the hippocampus region [19]. In skin-lightening creams inorganic mercury is used because it inhibits melanin formation and also acts as a bactericide and fungicide [20]. The nervous system is vulnerable to metallic mercury. Elevated levels metallic mercury exposure can cause brain, lungs and kidney impairment and can also acutely affect the growing fetus. Post exposure symptoms may include: nausea, vomiting, coughing, diarrhea, elevated hear rate or blood pressure, skin allergies and eye irritation. Mentioned symptoms occur when exposed to higher levels however, prolonged exposure to lower levels would cause indefinite repercussions which includes coordination problems, irritability, trouble sleeping, tremors, memory problems and complications in vision and hearing. All these symptoms from a continued exposure to low levels of mercury are improvable, once the exposure is ceased and the mercury has been removed from the body [21]. Acrodynia, also known as pink disease or Swift's disease, is a condition primarily affecting children with high levels of mercury vapor exposure. The symptoms of acrodynia include reddening and tenderness of the palms of the hands and soles of the feet, followed by peeling of the skin in these areas. Children with acrodynia may also exhibit worsen irritability, mood swings, struggling sleeping, and muscle or joint pains. In some cases, exposure levels that cause acrodynia can lead to coughing or chest pain [22].

Generally acrodynia is associated with urine mercury concentrations of 100 μg (or higher) of mercury per liter of although it's worth noting that not all cases may meet

this specific threshold. When pregnant women are exposed to mercury, the mercury can cross the placenta and reach the developing fetus. Additionally, nursing infants can be exposed to mercury through breast milk. Hence after suspicion to exposure to high levels of mercury, it is recommended to seek medical attention for proper evaluation, diagnosis, and appropriate management [23].

4.2 Animals

Persistent contact with little dosage of mercury chloride ($HgCl_2$) has been shown to have detrimental effects on hippocampus in animal models, resulting in hippocampal dysfunction. The hippocampus is a brain region critical for learning and memory processes. Impairments in spatial learning and memory, as well as alterations in synaptic plasticity, have been observed in animal studies following chronic exposure to low doses of inorganic mercury. Altogether inorganic mercury such as $HgCl_2$ may cause cognitive loss. Although more investigation is required to fully acknowledge the basic mechanisms behind and also to find out safe levels of exposure [24]. Another study by [25] exhibited how mercury significantly affected the growth of mice when administered with different concentration of mercury (0−160 mg/l $HgCl_2$). Drop in weight gain was observed along with some pathological changes in cecum tissues. Moreover, malondialdehyde (MDA) content is increased by the exposure of mercury and also significantly decreases superoxide dismutase (SOD) activity and glutathione peroxidase level which eventually increases the oxidative stress in mice. It also affects the gut microbiota of the mice. Several past studies validate that the breakdown of all forms of mercury is analogous for humans and animals. The absorption and breakdown of mercury occurs in the tissues and red blood cells via redox reaction that occurs in intestinal microflora. The elimination half-life refers to the time it takes for half of the mercury concentration in the blood to be removed from the body and it supposedly varies with species, sex, dosage, etc. like the elimination half-life in the blood of monkeys receiving inorganic and organic mercury was found to be 26 days. Another study showed that highest concentration of total mercury was observed in mesenterial lymph nodes supervened by liver and kidneys of sled dogs fed on methylmercury-loaded meat and from predatory marine animals. It also exhibits that the lymphatic system may take part majorly in carrying mercury to aimed organs. demethylation occurs in all organs, excluding the skeletal muscles. Demethylation of methylmercury was considered to be slighter in the brain in comparison to other organs [16]. A study by [26] on mice illustrated the acute stages when subcutaneously treated with methylmercury. Methylmercury was elicited to induce cerebellar toxicity. Also after being exposed to Hg^{2+} a decrease in renal and hepatic nonprotein sulfhydryl (NPSH) content was observed. Cellular oxidative stress can be elicited by Lipid peroxidation, which act as a marker and has been observed after Hg^{2+} exposure. Hg^{2+} facilitates the formation of H_2O_2 in the mitochondria. Studies have illustrated that in this overall process selenium plays a crucial role in transporting mercury. This concept was accepted by observing that when rats were

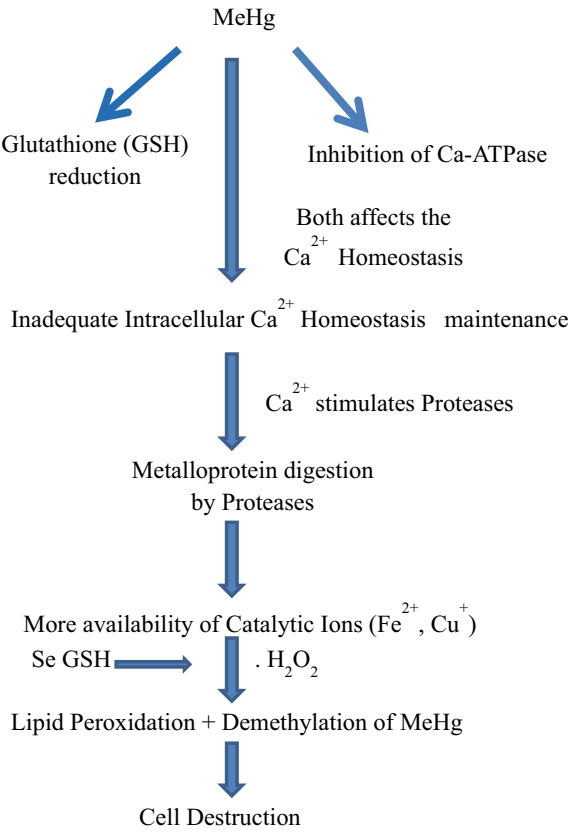

Fig. 2 Reactions of Methylmercury

administered with selenium, five days later it was detected as Se-cysteine. Hence presumed that methylmercury is chemically trapped as methylmercury-SH-cysteine or as methylmercury-SeH-cysteine complexes (Fig. 2) [27].

5 Mercury Toxicity in Humans

For individuals who have not been exposed to significant amounts of mercury, the typical concentration is about 2 ppm for hair. However, hair mercury levels can vary with the factors such as age, gender, diet, and geographic location. The normal reference range for mercury in blood is commonly reported in range of 1–10 μg/dL. For urine the reference range is around 2–20 μg/L. However, it's worth noting that these reference ranges are approximate and as with other biological samples,

reference ranges may differ depending on the laboratory and the analytical procedure used. Environmental contamination and exposure to mercury can have significant health consequences. Mercury is a neurotoxin. Various routes are accountable for mercury exposure including inhalation of mercury vapors, ingestion of contaminated food and water, and dermal contact with mercury-containing products. Vaccines and anti-RhoD-immunoglobulins thimerosal is used as a preservative. The central nervous system is particularly vulnerable to the toxic effects of mercury. High levels of mercury exposure are linked with a range of neurological symptoms and health effects. The specific symptoms you mentioned, such as behavioral changes, irritability, fatigue, tremors, headaches, hearing and cognitive impairment, dysarthria (difficulty speaking), incoordination, hallucinations, and even death, have been observed in individuals with acute or high-level mercury poisoning. In addition to these acute effects, chronic low-level exposure to mercury has also been linked to neurological and developmental problems, especially in children and developing fetus. It's important to note that the health consequences of mercury exposure can vary depending on factors such as the dose, extent of exposure, age, overall health, and individual susceptibility. Mercury (Hg) is a significant concern for human health. The symptoms from mercury toxicity can manifest as irritability, fatigue, behavioral changes, convulsions, headaches, hearing and cognitive ailment, dysarthria, hallucinations, incoordination and even death. Additionally, mercury exposure has been associated with cardiovascular problems, particularly hypertension, in both humans and animals (Table 1). Studies have found that mercury exposure has significant role in oxidative stress and apoptosis. Besides, motor and cognitive destruction and neural loss have been confirmed in several studies carried out on animal models [28]. While mercury has been historically used in various applications such as antiseptics, medical preservatives, and fungicides, its use in these areas has significantly decreased in recent years due to concerns about its toxicity.

In the 1950s organic mercury was discarded into Minamata Bay which later became the cause of minamata bay epidemic. Around 20,000 people were poisoned by consuming fish from this contaminated water body. Neurological problems along with other symptoms like difficulty in coordination, abnormal reflexes, seizures and speech problems were seen in 7% of the children born to mothers who consumed adulterated fish. In adults tremors, nausea, weakness, loss of hearing, depression, loss

Table 1 Mercury toxicity and its effects

	Neurological	Motor	Renal	Cardiovascular
Adult	Memory loss, Dementia, Tremors, Incoordination, Hallucination	Retard fine motor function, Tiredness, Reduced muscular strength	Increased Plasma, Creatinine levels	Alter normal cardiovascular homeostasis
Children	Lesser memory and Attention Score, cerebral palsy	Movement abnormality, late walking	Increased Plasma, Creatinine levels	Alter normal cardiovascular homeostasis

of appetite and problematic vision was observed. In total 46 people died because of mercury exposure [29]. Another accident took place in Iraq, 1972, where approximately 459 people lost their lives and 6,500 people fell ill after consuming wheat bread containing mercury-based fungicide. Marine food is the major constituent of the diet to the people of Faroe Islands (North Atlantic). A study in 1984 evaluated how children born to mothers who ate mercury contaminated whale meat were affected. Investigators observed that children born to mothers with a 10–20 ppm mercury concentration had lesser memory, language and attention capability in comparison to the children born to mothers with lower mercury levels [30].

6 Effect of Mercury on Neurological Functions

Various mechanisms has been put forward to understand how mercury affects nervous system and kills neurons which includes protein inhibition, mitochondrial disruption, affecting ion exchange in a neuron, obliteration of structural framework of neurons and neurotransmitters and affecting cognitive functions. Generally neurons are targeted and killed by methyl mercury in the specific region of the nervous system counting Cerebellum, Visual cortex and Dorsal root ganglia [9]. In the main, developing babies are more vulnerable to methylmercury, as it is the highly toxic mercury type and can make way across the membranes and blood barriers in the body. After crossing the placental barrier mercury get accumulated in fetus's brain. methylmercury (MeHg) is one of the most toxic compound of mercury that has been considerably investigated for its detrimental consequences on the nervous system. MeHg is known to bioaccumulate in the food chain, particularly in fish and seafood, making it a significant concern for human exposure [31]. The neurological alterations engendered by methemoglobin toxicity have been well-demonstrated in both human population and experimental animals. After crossing the blood–brain barrier MeHg accumulate in the brain, where it brings out its noxious effects. The exact mechanism by which MeHg causes neurotoxicity is not completely known, but it is presumed that oxidative stress plays a crucial role. Oxidative stress occur when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of the body's antioxidant defense systems to neutralize them. ROS, such as free radicals and peroxides, are highly reactive molecules that can cause damage to cellular structures, including lipids, proteins, and DNA. They can start a chain reaction of oxidative damage, leading to cellular dysfunction and death. MeHg exposure has shown raised ROS production in the brain. It can directly generate ROS through redox cycling or by inhibiting the activity of antioxidant enzymes that help neutralize ROS. The increased ROS production disturbs the antioxidant defense mechanisms, leading to oxidative stress [32]. Oxidative stress has been involved in the pathogenesis of various neurodegenerative diseases including Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. In these diseases, there is evidence of increased oxidative damage and impaired antioxidant defense systems in affected brain regions. However, the exact mechanisms by which oxidative stress contributes

to the development and progression of these diseases are still under investigation [33]. It is noteworthy that while oxidative stress is believed to be involved in the neurotoxicity of MeHg and the pathogenesis of neurodegenerative diseases, it is likely that multiple mechanisms contribute to the overall toxicity. Other mechanisms that have been proposed include disruption of calcium homeostasis, mitochondrial dysfunction, and interference with neurotransmitter systems [34].

Additionally, more research is required to thoroughly explain the complex mechanisms of MeHg-induced neurotoxicity and its relationship to neurodegenerative diseases. Understanding these mechanisms could provide valuable insights for developing strategies to prevent or mitigate the harmful effects of MeHg exposure and potentially shed light on the underlying processes of neuro-degeneration in general [35]. Methylmercury is mainly risky to growing babies. Because of quick metal absorption, mercury is accumulated inside the brain of the growing fetus and is not excreted proficiently. Children exposed to mercury may be born with symptoms parallel to cerebral palsy, spasticity and different movement abnormalities, convulsions, visual problems and atypical reflexes. The brains of children died due to mercury poisoning exhibit neuron loss within the cerebellum and all around the cerebral cortex. Mercury also seems to affect brain growth by means of stopping neurons from locating their suitable region within the brain [36]. Many of the effects and complications are mentioned in the Table 2. The prime mechanisms taking part in MeHg neurotoxicity currently being studied includes intracellular calcium homeostasis impairment [37], oxidative stress and the alteration of glutamate homeostasis.

Synaptic transmission, a neurobiological process can be disturbed by mercury doing neuronal damage via hyperactivation of the receptors of NMDA (N-methyl-D-aspartate). In rat cortical neurons overactivation of postsynaptic NMDA receptors was elicited, after exposure to inorganic mercuric chloride ($HgCl_2$). $HgCl_2$ alters the membrane excitability and neuronal cytoskeletal proteins disassembly and increases the amount of intracellular Ca^{++} that enters through NMDA receptors [43].

Table 2 Characterization of mercury (Hg) and its effects

Form of mercury	Organ/Body part involved	Acute/Chronic effects	References
Elemental Hg	Peripheral Nervous system, lungs, skin	Amyotrophic Lateral Sclerosis (ALS) Erethism, Hyperirritability, Lungs-Chemical Pneumonitis Skin-erythmatous and Pruritic Skin Rash, Acrodynia, Dermatitis	[38] [39] [40]
Inorganic Hg	Gastrointestinal tract	Tachycardia, Hypertension, Necrosis of Intestinal Mucosa, Ulceration of Mouth, Tongue and Lips	[40]
Organic Hg	Brain	Cerebellar Ataxia, Dysarthria, and Constriction of the Visual Fields, Hypoplasia of Bone Marrow, and Atrophy of Lymph Nodes	[41] [42]

Methylmercury toxicity can truely exhibit various neurological signs, which can vary depending on the amount and duration of exposure. Some of these signs may include: paresthesia (abnormal sensations or a "pins and needles" sensation in the skin), ataxia (lack of muscle coordination); leading to unsteady movements and difficulties with balance, tremors (involuntary rhythmic movements); hearing impairment is a common neurological symptom associated with methylmercury toxicity and Sensory disturbances; methylmercury can disturb sensory functions, leading to problems in vision, taste, and smell. Methylmercury has a confusing trait that there can be a notable delay between exposure and the appearance of symptoms. This latency period in humans can range from a few weeks to several months; with some cases reporting symptoms may not appear for as long as 150 days after exposure. This delayed onset can make it challenging to identify the source of exposure and link it to the symptoms. However symptoms and their onset can vary among individuals due to characteristics such as the amount of exposure, individual susceptibility, and other factors that may influence the metabolism and elimination of methylmercury from the body. Most of the fish species to a certain extent contains methylmercury or its compounds and is present in higher levels in predatory marine fish like swordfish and shark, with relatable levels in other predatory fish such as large tuna. A joint US EPA/FDA issued recommendatory that pregnant women and nursing mothers should kept away from consuming high-mercury fish [44].

Although, the molecular mechanism behind the toxicity of methylmercury is still unclear. With the help of synchrotron X-ray absorption spectroscopy (XAS) [45] studied more about the forms of mercury that can be present in the human brain tissue. In the research subjects/individuals were poisoned with high levels of methylmercury, subsequently individuals exhibited increased cortical selenium along with nanoparticles of mercuric selenide, inorganic mecury and methylmercury bound to organic sulfur. This concentration of mercuric selenide and methylmercury cysteineate was much lesser in the individuals consuming high fish diet intheir lifetime. It was also noticed that selenium levels were not disturbed by the exposure of mercury. These outcomes explicate a lead to detoxification pathway in the central nervous system and helps in further biological monitoring.

Mercury compounds, including methylmercury (MeHg), have been found to inhibit the Na^+–K^+–ATPase (adenosine triphosphatase activated by Na^+ and K^+) in various tissues. Na^+–K^+–ATPase is an enzyme responsible for maintaining the electrochemical gradient of sodium and potassium ions across the cell membrane, which is essential for proper cellular function. Studies have shown that mercury compounds, including MeHg, can inhibit both the active cation flux (movement of ions) and the Na^+–K^+–ATPase activity itself [46]. The inhibition of Na^+–K^+–ATPase by mercury compounds occurs with a time delay after exposure, and it is not affected by non-penetrating mercurials, suggesting that the critical site of inhibition is within the cell membrane. Although, the inhibitory effect on Na^+–K^+–ATPase is not solely to mercury. Other metals such as lead, zinc, aluminum, copper, iron, and cobalt are also known to hinder on Na^+–K^+–ATPase. These metals can interfere with the normal functioning of the enzyme and disrupt the ion transport processes in cells. It should be noted that the effects of mercury and other metals on Na^+–K^+–ATPase can

have significant implications for cellular and organ function. Disturbance in Na^+–K^+–ATPase activity can affect various physiological processes, including nerve cell signaling, muscle contraction, and fluid balance [47]. According to [48, 49] estimated methyl mercury neurotoxicity thresholds range from 50 to 200 mg/L of blood [48, 49].

7 Effect on Cognitive Functions

Cognitive function includes varied mental processes and abilities that allow individuals to interact with and understand the world around them such as perception, memory, learning, problem solving, attention, decision making, language abilities etc. Cognitive dysfunction refers to a broad range of impairments in cognitive functions and processes. Mercury toxicity can affect these cognitive functions in several ways: Neurotoxicity: Mercury has a neurotoxic effect, meaning it can damage nerve cells in the brain. This can lead to cognitive impairments, including difficulties with memory formation and retrieval, decreased attention span, and reduced processing speed. Inhibition of neurotransmitters: Mercury can disrupt the normal functioning of neurotransmitters, acting as chemical messengers and are involved in transmitting signals between nerve cells. This interference can disrupt communication between brain cells and contribute to cognitive dysfunction. Oxidative stress: Mercury can induce oxidative stress in the brain, which occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. Oxidative stress can damage brain cells and contribute to cognitive impairments. Inflammation: Mercury exposure can trigger an inflammatory response in the brain. Chronic inflammation has been linked to cognitive decline and neurodegenerative disorders. It is noteworthy to mention that the severity of cognitive dysfunction related to mercury exposure can vary depending on factors such as the dose and duration of exposure, individual susceptibility and the specific form of mercury (e.g., elemental, inorganic, or organic). Methylmercury (CH_3Hg^+) is an electrophilic toxicant that exhibits a strong affinity for thiol and selenol groups. There are various critical targets of CH_3Hg^+ like thiol-containing proteins, which include various enzymes and transporters taking part in neurotransmitter transport, metabolism, and signaling, as well as antioxidant selenoenzymes like glutathione peroxidases and thioredoxin reductases [50]. When CH_3Hg^+ binds to these thiol and selenol containing proteins, it disrupts their normal function and impairs their ability to carry out essential physiological processes. This disruption can significantly affect developing synapses in the brain and may lead to the behavioral and cognitive impairment, as these processes have a crucial role in normal brain cell physiology. The deregulation of neurotransmitter-related proteins can interfere with the proper transmission and regulation of signals between neurons, affecting various neurological processes. Additionally, the targeting of antioxidant selenoenzymes can lead to increased oxidative stress and cell damage [51]. Studying the AOP associated with CH_3Hg^+ neurotoxicity can indeed provide valuable insights for the growth of in silico Physiological Based

Kinetic (PBK) models. PBK models are computational tools that simulate the distribution, metabolism, and elimination of chemicals in the body based on physiological and biochemical principles. By identifying the key events and biological pathways involved in CH_3Hg^+ neurotoxicity, researchers can develop a mechanistic understanding of how methylmercury affects the nervous system. This information can then be incorporated into PBK models to predict the concentration of methylmercury in different tissues and organs over time. PBK models can help in assessing the exposure levels at which negative impact occur, predicting the toxicokinetics of methylmercury in different populations, and informing risk assessments. They can also aid in evaluating the effectiveness of different mitigation strategies and interventions to reduce exposure and minimize neurotoxic effects. Overall, studying the AOP associated with CH_3Hg^+ neurotoxicity can serve as a foundation for developing in silico PBK models, which in turn can enhance our understanding of the toxicokinetics and potential health effects of methylmercury exposure. These models have the potential to support risk assessment and inform decision-making regarding exposure mitigation strategies [52]. A case study by [53] a patient who ingested liquid Hg^0 as a suicidal attempt by consuming 6 oz (oz) of Hg^0 with wine. After performing several cognitive (WTAR-estimated premorbid psychometric intelligence was low average to average; processing speed, cognitive flexibility, and response inhibition was poor) and mental status examination (Mild upper-extremity action tremor was evident; in terms of in rate, latency, rhythm, and articulation speech was unremarkable; volume was increased and was disoriented). Patient was observed with behavioral distress as a sign of bipolar disorder with irritable mood and pressured speech. Another case study by [54] elicit 91 years old subject who exhibited cognitive waning as Alzheimer's disease. Patient had remarkably high levels of mercury by the consumption of fish containing high mercury content. He also had dental amalgams which were decades old. Urine test demonstrated increased levels of mercury in the red blood cells. The two forms of mercury: methylmercury (from fish consumption) and inorganic mercury (from dental amalgams) were highly elevated. Further suggesting that mercury may play a role as a cofactor in the growth of Alzheimer's disease. Eddins et al. [55] analyzed the effect of mercury exposure treatment affecting cognitive function in neonate for 12 weeks. Study showed that decrease or deletion of metallothioneins (MT) shoot up the susceptibility to mercury-induced developmental neurocognitive impairment. Metallothionein effects on monoamine transmitters and this may be associated with the cognitive effect. Furthermore, it was observed that MT1/MT2-null mice showed notably cognitive impairment after mercury exposure. Exposure to mercury vapor MT1/MT2-null mice show both short term and long-term defects in locomotion in the open field maze [56]. Katamanova et al. [57] collected data from the workers who have been exposed to mercury exposure during their long work period, was based on the physiological and psycologial analysis along with the chronic intoxication of mercury. Patients with light or mild cognitive disorders exhibits lower extent of cognitive induced abilities, bad long-term memory and integrative thinking, patients with average cognitive disorders are usually identified by contract visual, long-term memory, loss of concentration, poor optic and spatial

gnosis while marked cognitive disorders patients deals with fall in long-term, short-term, quaint memory, lacking intelligence, optic and spatial gnosis and associative thinking. Another work by [58] showed how prenatal mercury vapor exposure can affect the cognitive responses of mice, for which two strains (MT-null and wild type) of pregnant mice were repeatedly exposed to elemental mercury vapor at 0.50 and 0.56 mg/m^3 for 6 h/day until the 18th day of gestation. A notable decrease in locomotor activities was expressed by male MT-null mice in contrast learning disabilities and response action was found retarded in females. Results exhibited that susceptibility in MT-null mice were more susceptible to the behavioral neurotoxicity of prenatal mercury exposure in comparison to wild-type mice.

8 Conclusion

Mercury is a neurotoxin which can cross the blood brain barrier and give rise to complications. Once inside the body, mercury can be accumulated in its inorganic forms. Mercury can deeply affect human health and can have impact on central nervous system leading to cognitive dysfunction and other neurological defects. Toxicokinetics of mercury is different for its different chemical form. The prime mechanisms taking part in MeHg neurotoxicity currently being studied includes intracellular calcium homeostasis impairment oxidative stress and the alteration of glutamate homeostasis. Globally there is ample documentation of mercury and its derivatives having major negative effects on many life forms including terrestrial and aquatic. Action should be taken to limit the threats to human health and the environment posed by mercury leaks. Even at modest doses, several of the neurobehavioral tests showed enough sensitivity to distinguish between groups with varied Hg body burdens. Neurobehavioral effects with a significant dose–effect relationship, mostly associated with long-term exposure to low levels of organic mercury People working with prolong mercury exposure lead to chronic intoxication of mercury.

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References

1. Bernhoft RA (2012) Mercury toxicity and treatment: a review of the literature. J Environ Public Health
2. Budnik LT, Casteleyn L (2019) Mercury pollution in modern times and its socio-medical consequences. Sci Total Environ 654:720–734
3. Hylander LD, Goodsite ME (2006) Environmental costs of mercury pollution. Sci Total Environ 368(1):352–370

4. Berlin M, Zalups RK, Fowler BA (2015) Mercury. Academic, In Handbook on the toxicology of metals, pp 1013–1075
5. Halbach, S. and Clarkson, T.W., 1978. Enzymatic oxidation of mercury vapor by erythrocytes. *Biochimica et Biophysica Acta (BBA)-Enzymology*, *523*(2), 522–531.
6. Boening DW (2000) Ecological effects, transport, and fate of mercury: a general review. Chemosphere 40(12):1335–1351
7. Martin S, Griswold W (2009) Human health effects of heavy metals. Environ Sci Technol Briefs Citiz 15:1–6
8. Lescord GL, Johnston T, Branfireun BA, Gunn JM (2019) Mercury bioaccumulation in relation to changing physicochemical and ecological factors across a large and undisturbed boreal watershed. Can J Fish Aquat Sci 76(12):2165–2175
9. Ceccatelli S, Daré E, Moors M (2010) Methylmercury-induced neurotoxicity and apoptosis. Chem Biol Interact 188(2):301–308
10. Rice KM, Walker EM Jr, Wu M, Gillette C, Blough ER (2014) Environmental mercury and its toxic effects. J Prev Med Public Health 47(2):74
11. Fernandes Azevedo B, Barros Furieri L, Peçanha FM, Wiggers GA, Frizera Vassallo P, Ronacher Simões M, Fiorim J, Rossi de Batista P, Fioresi M, Rossoni L, Stefanon I (2012) Toxic effects of mercury on the cardiovascular and central nervous systems. J Biomed Biotechnol
12. Ajsuvakova OP, Tinkov AA, Aschner M, Rocha JB, Michalke B, Skalnaya MG, Skalny AV, Butnariu M, Dadar M, Sarac I, Aaseth J (2020) Sulfhydryl groups as targets of mercury toxicity. Coord Chem Rev 417:213343
13. Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I, Methner A, Pergande M, Smith SB (2013) The cystine/glutamate antiporter system xc−in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 18(5):522–555
14. Allen JW, Shanker G, Tan KH, Aschner M (2002) The consequences of methylmercury exposure on interactive functions between astrocytes and neurons. Neurotoxicology 23(6):755–759
15. Farris FF, Kaushal A, Strom JG (2008) Inorganic mercury pharmacokinetics in man: a two-compartment model. Toxicol Environ Chem 90(3):519–533
16. Gupta RC (ed) (2012) Veterinary toxicology: basic and clinical principles. Academic
17. Lecavalier PR, Chu I, Villeneuve D, Valli VE (1994) Combined effects of mercury and hexachlorobenzene in the rat. J Environ Sci Health B 29(5):951–961
18. Risher JF, De Rosa CT, Jones DE, Murray HE (1999) Updated toxicological profile for mercury. Toxicol Ind Health 15(5):480–516
19. Dutta SS (2019) Hippocampus functions. News-Medical.net. Updated August 20
20. Gilbert SG (2014) Mercury tragedies: incidents and effects
21. Risher J (1999). Toxicological profile for mercury
22. Dathan JG, Harvey CC (1965) Pink disease—ten years after (the epilogue). BMJ 1(5443):1181
23. Meadows-Oliver M (2012) Environmental toxicants: lead and mercury. J Pediatr Health Care 26(3):213–215
24. Aragão WAB, Teixeira FB, Fagundes NCF, Fernandes RM, Fernandes LMP, da Silva MCF, Amado LL, Sagica FES, Oliveira EHC, Crespo-Lopez ME, Maia CSF (2018) Hippocampal dysfunction provoked by mercury chloride exposure: evaluation of cognitive impairment, oxidative stress, tissue injury and nature of cell death. Oxidative Med Cell Longev
25. Zhao Y, Zhou C, Guo X, Hu G, Li G, Zhuang Y, Cao H, Li L, Xing C, Zhang C, Yang F (2021) Exposed to mercury-induced oxidative stress, changes of intestinal microflora, and association between them in mice. Biol Trace Elem Res 199:1900–1907
26. Stringari J, Meotti FC, Souza DO, Santos AR, Farina M (2006) Postnatal methylmercury exposure induces hyperlocomotor activity and cerebellar oxidative stress in mice: dependence on the neurodevelopmental period. Neurochem Res 31:563–569
27. Hansen JC, Danscher G (1997) Organic mercury—an environmental threat to the health of exposed societies? Rev Environ Health 12(2):107–116

28. Cariccio VL, Samà A, Bramanti P, Mazzon E (2019) Mercury involvement in neuronal damage and in neurodegenerative diseases. Biol Trace Elem Res 187:341–356
29. Harada M (1995) Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. Crit Rev Toxicol 25(1):1–24
30. Greenwood MR (1985_. Methylmercury poisoning in Iraq. An epidemiological study of the 1971—1972 outbreak. J Appl Toxicol 5(3):148–159
31. Grandjean P, White RF, Weihe P, Jørgensen PJ (2003) Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood. Ambul Pediatr 3(1):18–23
32. Sasaki S, Negishi T, Tsuzuki T, Yukawa K (2023) Methylmercury-induced reactive oxygen species-dependent and independent dysregulation of MAP kinase-related signaling pathway in cultured normal rat cerebellar astrocytes. Toxicology 487:153463
33. Singh A, Kukreti R, Saso L, Kukreti S (2019) Oxidative stress: a key modulator in neurodegenerative diseases. Molecules 24(8):1583
34. Jellinger KA (2010) Basic mechanisms of neurodegeneration: a critical update. J Cell Mol Med 14(3):457–487
35. Bridges CC, Zalups RK (2010) Transport of inorganic mercury and methylmercury in target tissues and organs. J Toxicol Environ Health, Part B 13(5):385–410; Roulet M, Lucotte M, Canuel R, Rheault I, Tran S, Gog YDF, Farella N, Do Vale RS, Passos CS, Da Silva EDJ, Mergler D (1998) Distribution and partition of total mercury in waters of the Tapajós River Basin, Brazilian Amazon. Sci Total Environ 213(1–3):203–211
36. Myers GJ, Davidson PW (1998) Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. Environ Health Perspect 106(suppl 3):841–847
37. Sirois JE, Atchison WD (2000) Methylmercury affects multiple subtypes of calcium channels in rat cerebellar granule cells. Toxicol Appl Pharmacol 167:1–11
38. Vroom FQ, Greer M (1972) Mercury vapour intoxication. Brain 95(2):305–318
39. Weiss B (2014) Psychological indices of toxicity. Encycl Toxicol 558–567
40. Park JD, Zheng W (2012) Human exposure and health effects of inorganic and elemental mercury. J Prev Med Public Health 45(6):344
41. Eto K (1997) Pathology of minamata disease. Toxicol Pathol 25:614–623
42. Takeuchi T (1968) Pathology of Minamata disease. In: Kutsuma K (ed) Minamata disease. Kumamoto Shuhan Publishing Co., Kumamoto, Japan, pp 141–256
43. Xu F, Farkas S, Kortbeek S, Zhang FX, Chen L, Zamponi GW, Syed NI (2012) Mercury-induced toxicity of rat cortical neurons is mediated through N-methyl-D-Aspartate receptors. Mol Brain 5:1–14
44. Taueg C, Sanfilippo DJ, Rowens B, Szejda J, Hesse JL (1992) Acute and chronic poisoning from residential exposures to elemental mercury-michigan, 1989–1990. J Toxicol Clin Toxicol 30(1):63–67
45. Korbas M, O'Donoghue JL, Watson GE, Pickering IJ, Singh SP, Myers GJ, Clarkson TW, George GN (2010) The chemical nature of mercury in human brain following poisoning or environmental exposure. ACS Chem Neurosci 1(12):810–818
46. Kade IJ (2012) Mercury toxicity on sodium pump and organoseleniums intervention: a paradox. J Biomed Biotechnol
47. Aschner M, Aschner JL (1990) Mercury neurotoxicity: mechanisms of blood-brain barrier transport. Neurosci Biobehav Rev 14(2):169–176
48. National Research Council (2000) Toxicological effects of methylmercury. National Academy Press, Washington, DC
49. World Health Organization (1976) Environmental health criteria. 1. Mercury. Environmental health criteria. 1. Mercury
50. Madabeni A, Nogara PA, Bortoli M, Rocha JB, Orian L (2021) Effect of methylmercury binding on the peroxide-reducing potential of cysteine and selenocysteine. Inorg Chem 60(7):4646–4656
51. Punt A (2018) Toxicokinetics in risk evaluations. Chem Res Toxicol 31(5):285–286
52. Sturla SJ, Boobis AR, FitzGerald RE, Hoeng J, Kavlock RJ, Schirmer K, Whelan M, Wilks MF, Peitsch MC (2014) Systems toxicology: from basic research to risk assessment. Chem Res Toxicol 27(3):314–329

53. Cercy SP, Wankmuller MM (2008) Cognitive dysfunction associated with elemental mercury ingestion and inhalation: a case study. Appl Neuropsychol 15(1):79–91
54. Foley MM, Seidel I, Sevier J, Wendt J, Kogan M (2020) One man's swordfish story: The link between Alzheimer's disease and mercury exposure. Complement Ther Med 52:102499
55. Eddins D, Petro A, Pollard N, Freedman JH, Levin ED (2008) Mercury-induced cognitive impairment in metallothionein-1/2 null mice. Neurotoxicol Teratol 30(2):88–95
56. Yoshida M, Watanabe C, Horie K, Satoh M, Sawada M, Shimada A (2005) Neurobehavioral changes in metallothionein-null mice prenatally exposed to mercury vapor. Toxicol Lett 155:361–368
57. Katamanova EV, Shevchenko OI, Lakhman OL, Denisova IA (2014) Cognitive disorders in patients with chronic mercury intoxication. Med Tr Prom Ekol 4:7–12
58. Yoshida M, Watanabe C, Horie K, Satoh M, Sawada M, Shimada A (2005) Neurobehavioral changes in metallothionein-null mice prenatally exposed to mercury vapor. Toxicol Lett 155(3):361–368