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REVIEW ARTICLE

A Global Mercury Contamination and its Potential Hazards: A Review

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ABSTRACT

Due to the ever increasing population, rapid industrialization and urbanization, the toxic effects of heavy metals has become a major concern in the globe. Mercury is one of the heavy metals that cause multiple adverse effects to the living systems. In 2017, the World Health Organization (WHO) included it on its list of 10 substances of concern. It is one of the best confounding metals in the environment. Unlike many metals, it is not biologically active. Because of natural processes like mining, erosion, and volcanism, it is a scarce element in the Earth's crust. Although all mercury compounds are hazardous to people and animals, the most toxic forms are the organic ones, particularly methyl and dimethyl mercury. Due to anthropogenic activities and natural processes mercury is released into the atmosphere and due to its long half-life period, the rate of environmental breakdown is low. It exists in the form of element (Hg^0) and divalent (Hg^2) forms, based on the degree of oxidation in the environment. Due to its devastating toxic effects on organisms, it is currently recognised as one of the strongest neurotoxins. Due to its strong negative impact on the immune system, it is linked to persistent candidiasis growths, anaemia, memory loss, tremors, depression, tiredness, insomnia, headaches. Mercury is known to cause five categories of pathophysiological disorders i.e., immune system disorders, collagen diseases, neurological illnesses, cardiovascular diseases, and infections. This review provides an overview of the sources of mercury, the cumulative effects of mercury on different ecosystems, and phytoremediation for environmental restoration. It gives detailed information about the dangers of mercury exposure and its environmental sources, to make awareness about the mercury usage in different means of day to day life.

Keywords: Mercury; Methylation; Minamata disease; Alzheimer's disease

1 INTRODUCTION

Environmental pollution has reached serious concern, manifesting itself in the form of climate change, acid rain and pollution of agricultural wetlands and forests. Heavy metals present in aquatic ecosystems, especially in rice fields, are of great concern due to their toxicity, abundance and persistence in the environment as well as their subsequent accumulation in aquatic biological systems [1]. In recent years, several monitoring studies have been conducted globally to estimate the extent of heavy metal pollution in aquatic ecosystems [2].

In nature, heavy metals make up a significant group of environmental contaminants [3]. One of the five main categories of harmful contaminants that are typically found in surface waters are heavy metals. hey are referred to be "Conservative pollutants" since they either do not break down at all or take so long to do so that they end up being hazardous [4]. Metals are widely released into the aquatic environment due to intensive mineral processing and mining operations carried out to satisfy the growing demands of the population. In addition to these initiatives, the situation is made worse by the growth of the chemical and heavy metal engineering sectors as well as growing vehicle pollution [5]. A minimum of 27 metals have been identified as harmful to both humans and the environment. Freshwater bodies are seriously threatened by industries due to the emancipation of heavy metals (Mn, Ni, Cr, Zn, As, Cd, Pb, Fe, and Cu) and their salts [6]. Because of this, the problem of environmental contamination brought on by hazardous metals has gained significant attention in the majority of today's huge cities.

Because aquatic organisms come into intimate and ongoing contact with soluble metals, the aquatic ecosystem is more vulnerable to the negative impacts of heavy metal

pollution [7]. Because of its well-known harmful effects, mercury has drawn the most attention among the metals of environmental concern [8]. Mercury has a complicated biogeochemical cycle and is a strong neurotoxicant [9]. It Hg is the third most dangerous heavy metal, according to the US Government Agency for Toxic Substances And Disease Registry [10]. It is regarded as a global pollutant due to its ubiquitous presence in the environment and higher potential for global transport [11, 12]. Heavy metals are readily absorbed by the organism and are carried by the blood to different organs [13]. When in circulation, these metals cause notable changes in the physiology and histology of the target organs in addition to their effects on blood components [14]. Certain metals have the potential to be detrimental to people if they get into the food chain since they may be poisonous or carcinogenic even at low concentrations. Metals remaining in contaminated sediments may accumulate in microorganisms which in turn enter into the food chain and eventually affect human wellbeing [15].

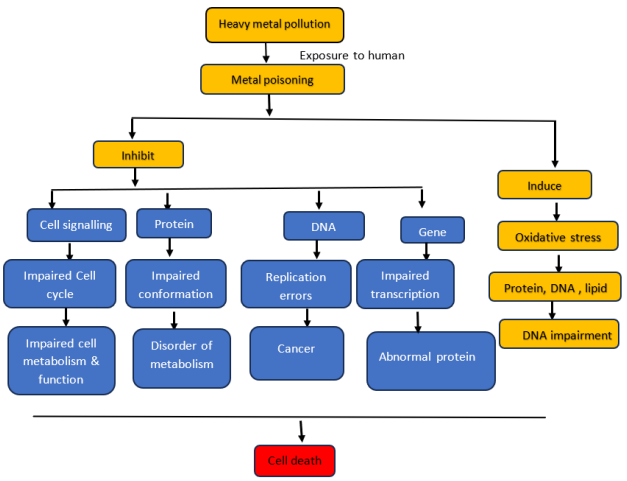

Figure 1: Mechanism of Heavy metal toxicity in organisms

The estimated annual anthropogenic mercury emissions worldwide are approximately 2000 mg (1 mg = 1 tonne = 106 g) [16], but the estimated annual emissions in India are approximately 240 mg. An estimated 538 mg of anthropogenic mercury emissions were produced in China in 2010 [17]. The nations with the biggest mercury emissions include the United States, China, India, Indonesia, Colombia, South Africa, Russia, and Ghana, according to UNEP's emissions inventory. 56% (1095 mg/year) of all human emissions into the atmosphere are accounted for by the combined emissions of these nations [18]. According to estimates, the total mass of mercury that has accumulated in soil is between 250 and 1,000 Gg (1 Gg = 109 g) [19].

Mercury is a highly toxic element present both in nature and as a contaminant introduced into the environment. Among heavy metals such as cadmium (Cd), lead (Pb), arsenic (As), chromium (Cr), mercury (Hg) are considered to be the most toxic because it accumulates and amplify to higher levels in the food chain. It is also considered as a very dangerous factor due to its cumulative and persistent nature in the environment [19]. This is the only element in the periodic table that has its own environmental convention, specifically the Minamata Convention, thus emphasizing the importance of the mercury pollution problem [20]. In aquatic environments, mercury is converted to a more toxic form, methyl mercury (MeHg) (CH_3HgX), where organisms are present in sediments. MeHg is easily absorbed by aquatic animals, and in aquatic food chains, it is subsequently accumulated by bioaccumulation and biomagnification [21]. The term "bioaccumulation" describes how a pollutant's concentration rises when it continues to be eaten by the same creature. Biomagnification, on the other hand, describes the rise in pollutant concentrations in various fish species at different trophic levels of the food chain [22].

Mercury is eliminated from water and soil by means of physical, chemical, and biological methods. The best method for eliminating mercury from soil and water that is also environmentally safe is called phytoremediation, or bioremediation. It is recognised that certain plant species, such as *Brassica juncea*, may be suitable candidates for removing mercury from soil [23]. This study's goal was to assess the state of the art regarding the primary sources of mercury as well as practical methods for mercury remediation (phytoremediation). This review explains the chemical characteristics of mercury as well as methods for evaluating it in various environmental contexts. We'll quickly go over the hazardous effects of mercury contamination poses to human health.

1.1 Chemical composition

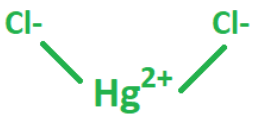

Figure 2: Chemical composition

Mercury has a high electron affinity [24] and is classified as a B-type metal cation, based on the cation's preference for complexing with ligands. The outermost electronic configuration of mercury is $5d^{10}6s^2$ and is therefore characterized by a "soft sphere" of highly polarized electrons in its outer shell [25]. The main properties of mercury and the average concentrations of mercury in some materials on Earth are summarized in Table 1 and Table 2, respectively.

Mercury can exist in two organic forms: methyl mercury (MeHg), dimethylmercury ($(CH_3)_2Hg$), ethyl mercury (C_2H_5Hg), and phenylmercury (C_6H_5Hg). Inorganic forms of mercury include mercury chloride ($HgCl_2$), mer-

Table 1: Physical properties of Mercury [24]

Parameter	Value
Atomic No	80
Atomic mass	200.59amu
Melting point	-38.87 C
Boiling point	357 C
Density	13.546g/cc
Ionic radii	1.16A
Electronegativity	1.9 (Paulling)
Heat of evaporation	61.3kJ/mol
Heat of fusion	2.295kJ/mol
Vapour pressure	0.0002Pa

Table 2: Average Concentrations of mercury in selected earth materials [26]

Material	Concentrations (mg/kg)
Bulk continental crust	0.04
Upper continental crust	0.05
Lower continental crust	0.014
Granite, granodiorite	0.03
Sandstone	0.03
Shale, Schist	0.01
Coal	0.18

cury sulphide (HgS), and mercury oxide (HgO) [27]. Mercury salts, another name for inorganic mercury compounds, are crystalline and amorphous substances. Methylmercury and phenylmercury are two organic derivatives of mercury that can be found in salt form as methyl mercury chloride and phenyl mercury acetate, respectively [27]. Mercury's ability to function biologically is dependent on how its many forms interconvert. For instance, inhaled Hg0 vapour is easily taken up by the lungs and mucosal membranes, where it is quickly converted to various forms through oxidation [28]. Because Hg's outermost orbital is electron-rich and does not readily share its valence electrons, Hg is found in a liquid state at normal temperature and atmospheric pressure. Hence, the bonding between Hg atoms is very weak and easily broken at normal temperature. The carbon-Hg link is chemically stable in organic Hg [27].

The solubility of vibrant composites of mercury varies in water. While Hg(0) is irreversible in water, Hg(I) chloride and HgS are less answerable, and Hg(II) chloride is easily answerable. Methylation of the inorganic form of mercury in water results in the construction of genuinely toxic MeHg in submerged systems. Fish include a type of bacteria called Pseudomonas that facilitates the methylation of mercury in water. MeHg enters the underwater ecosystem's food chain when it is created.

1.2 States of mercury in the environment

Mercury is naturally present in the environment in 3 forms

- **Elemental mercury or metal Hg(0)**

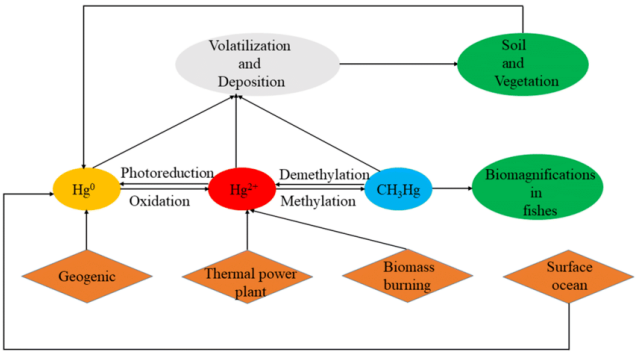

Figure 3: Mercury cycle in the environment [27]

It exists in liquid form with a vapor pressure of 0, 00185 mm at 25°C. This means elemental mercury is volatile. Temperature has a direct impact on how quickly mercury evaporates. Consequently, the amount of mercury in the air around us rises along with the temperature. The high lipid solubility of elemental mercury makes it easier for it to diffuse into the bloodstream through the alveoli and distribute into lipophilic bodily components, such as the central nervous system (CNS) and for it to cross the placenta. Elemental mercury attaches itself to several organs, proteins, and red blood cells in the bloodstream. Elemental mercury in erythrocytes can be converted to organic metabolites by catalase. Elemental mercury becomes ionised and gets stuck in the area where it can cause neurotoxicity if it crosses the blood-brain barrier. Adults have an approximate 60-day half-life for elemental mercury [28]. Additionally, microbes in the colon biologically convert elemental mercury into Hg^{+2} and CH_3Hg^{+1} [29].

- **Inorganic mercury (Hg^2)**

When mercury reacts with elements like sulphur, chlorine, or oxygen other than carbon, inorganic mercury is created. With the exception of mercury sulphide, often known as cinnabar, which is red and turns black when exposed to light, the majority of inorganic mercury composites are white maquillages or charges [30]. Because inorganic mercury mariners aren't lipid soluble, they can't easily get across the placental or brain barriers. Urine and faeces are the main ways that inorganic mercury mariners are eliminated. With a rapid-fire initial excretion phase and a slow-fire subsequent excretion phase, the excretion rate is biphasic and cure-dependent. It is estimated that the natural half-life is sixty days [31].

- **Organic mercury (Hg^{++}) (Mercuric)**

Organic mercury complex is formed when mercury reacts with carbon. The most common organic mercury compound in environment is methyl mercury. A persistent bioaccumulative toxin, methyl mercury has been connected

to a number of health issues in both humans and wildlife. The substance enters the body quickly through the digestive system, and methylmercury in particular is a strong neurotoxin. In both humans and animals, methyl mercury spreads throughout the body and readily passes through the placenta and blood-brain barriers. It appears that the creation of a methyl mercury cysteine complex mediates the transport of methyl mercury into tissues. This compound shares structural similarities with methionine and enters cells through a neutral amino acid carrier protein that is extensively distributed [32]. Reduced glutathione (GSH) and other sulfhydryl groups are highly affinized by methyl mercury. Several rat tissues have been found to contain a methylmercury GSH complex [33]. The Minamata tragedy marked the beginning of the recognition of methyl mercury's extremely harmful effects on the developing neurological system. There, it was noted that children born to mothers exhibiting minor symptoms of methyl mercury intoxication had severe neurological impairments that resembled cerebral palsy generally. Methyl mercury disrupts teratogenically the normal development of neurons in the foetus and may also have an impact on cell division, which is made possible by its ability to pass the placental barrier [10, 30]. Now, the question is: Where is mercury pollution coming from? How does mercury get into the land, water, and air to affect the public health? What effects does mercury have on reproduction and health? Which medications and mercury dosages are safe? What measures should be done to reduce the emission rate and counteract its toxic effects? We present data from the available literature in this article in an effort to address all of these questions.

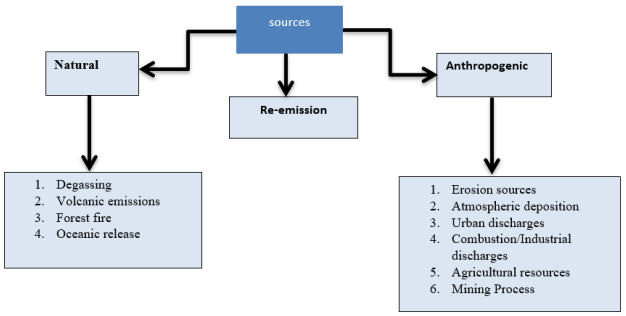

Figure 4: Sources of Mercury in the Environment.

2 TOXICITY

Mercury has no significant role in human biochemistry or physiology and is considered as the sixth most toxic substance on the earth [34]. It holds a place in the list of top ten chemicals of major public health concern and has been ranked third among the priority list of hazardous substances by The United States Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Mercury is also classified as one of the "thirty precarious dangerous pollutants" by the European Water Framework Directive (2000/60/EG) [35]. Due to its high toxicity to marine fauna, it is listed as a priority pollutant by the international agencies in charge of marine environmental protection [36]. Mercury is a deadly toxic heavy metal that could pose damage to the nervous system, cardiovascular system, kidneys and the immune system [37]. The organic forms of mercury induce neurotoxicity, due to its lipophilic character and ability to cross the blood–brain barrier, whereas the inorganic forms of the metal mainly cause renal toxicity [38]. Methyl mercury blocks the binding sites of enzymes and interferes with protein synthesis as well as thymidine incorporation into DNA [39, 40].

Acute-level exposure to mercury can lead to oxidative stress, cell cytotoxicity, and an increase in amyloid production, which can result in neurodegenerative illnesses including Alzheimer's and Parkinson's disease [41]. Even at minute concentrations, metals like mercury can be extremely harmful. For instance, mercury exposure can gradually degenerate *substantia nigra*, a small area of cells in the midbrain which causes a reduction in dopamine production which in turn leads to Parkinson's disease [42]. Acute doses of inorganic mercury induce cellular necrosis in the renal tube causing severe nephrotoxicity [43]. It may also lead to several renal disorders like dysuria, proteinuria, hematuria, oliguria and uremia. Exposure to inorganic mercuric salts also causes gastrointestinal problems like colitis, gingivitis, stomatitis and excessive salivation [44].

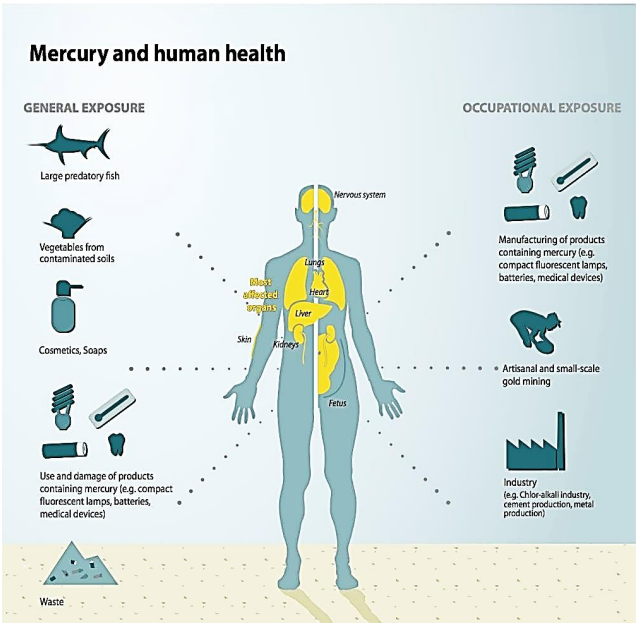

Figure 5: Mercury and Human health

2.1 Eutrophication

Eutrophication can alter water geochemistry by promoting the growth of autotrophic species, leading to an increase

in MeHg concentrations due to increased methylation [45]. Algal blooms and the presence of critical growth elements such as high nutrient content and solar exposure will cause eutrophication [46]. Eutrophication causes a decrease in pH, an increase in organic matter (OM) in the sediment, and anoxic/hypoxic conditions [47]. MeHg can also bioaccumulate in algae, and when they die, the metal will either be discharged into the water or biocondense along the food chain. Eutrophic conditions have been used to reduce the increase in MeHg levels by injecting oxygen nanobubbles into eutrophic water [48]. Thus, controlled MeHg uptake by algae can be employed as a MeHg mitigation strategy [49]. Figure 6A illustrates the relationship among wastewater flow, eutrophication, and MeHg levels. Methyl groups like oxytetracycline (OC) and tetracycline (TC) found in pharmaceutical wastewater, primarily from the manufacture of antibodies, increase the formation of MeHg [50]. MeHg production will increase as a result. This occurrence suggests that the primary mechanism of mercury methylation may not be biological methylation [51]. Figure 6B illustrates how antibiotics and mercury combine to produce MeHg in the sediments of the Earth's crust, lakes, and oceans. The first stage of aquatic bioaccumulation is the conversion of an inorganic substance into an organic one, i.e., methylated form (methylmercury). Both bacterial activity and enzymatic processes can be responsible for this process. Sulfate-reducing bacteria (SRB) are the primary producers of methylmercury (CH_3Hg) in anoxic water and sediment in aquatic habitats. Another potential location for mercury methylation has been suggested to be the methionine biosynthesis pathway. Scientists from Sweden and Japan found that fish were collecting methylmercury in 1969. Methylmercury is a highly toxic form of mercury that tends to accumulate in living tissues. This is especially problematic for living organisms because it can be absorbed into the body much faster than any other mercury compound Figure 6 B and Figure 7 illustrate how antibiotics and mercury can be used to produce MeHg. The production of MeHg from antibiotics and Hg is shown in Figure 6 B and Figure 7.

2.2 *Factors affecting methylation*

Mercury methylation in aquatic environments is influenced by dissolved organic carbon (DOC) and the pH of the water body. According to studies, higher levels of mercury in fish indicate higher net levels of methylation when the same fish are caught in the same region and there is a decrease in pH and/or COD content. Elevated levels of COD and acidity facilitate mercury's enhanced mobility in the environment, allowing it to more easily "Penetrate" into the food chain. When exposed to sunshine, particularly UV radiation, mercury and methylmercury have a general detoxifying effect. Methylmercury has the ability to be broken down by sunlight into Hg(2) or Hg(0), which can then escape from aquatic environments and re-enter the atmosphere as gases.

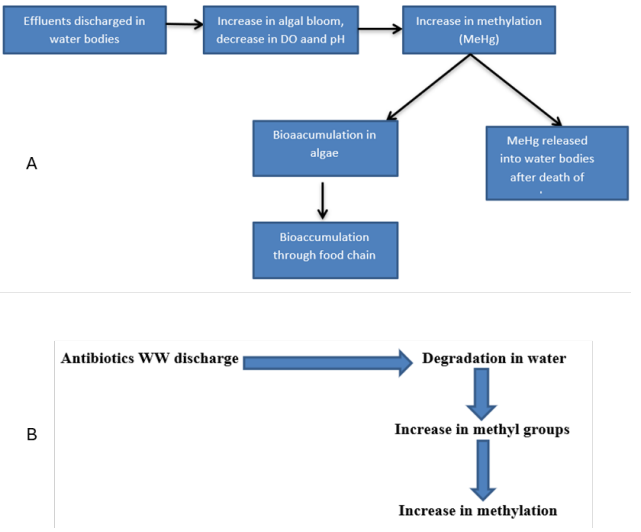

Figure 6: A : Effects of Eutrophication, B: Antibiotics and MeHg formation

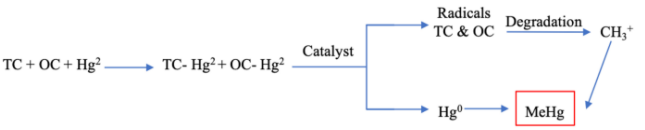

Figure 7: The assumed antibiotics degradation to form MeHg [51]

3 TOXICOKINETICS AND MECHANISMS OF MERCURY TOXICITY

The toxicity of all three kinds of mercury varies on the amount, type, application technique, and length of exposure [52]. Through general corrosion, inhibition of enzymes, and precipitation of proteins, mercury ions create poisons. Mercury forms bonds with phosphonic, carboxyl, amide, and amino groups in addition to sulfhydryl groups. This class of proteins includes enzymes and is linked to mercury. Most proteins that are linked to mercury become inactive [28]. It is thought that both organic and inorganic mercury behave toxic through similar processes. It has been demonstrated that there is a correlation between the relative toxicity of various forms of mercury (such as metallic mercury, monovalent mercury, divalent mercury, methylmercury, and phenylmercury compounds) and tissue concentrations. The discovery that mercury accumulates quickly in the kidneys lends credence to this notion, along with a few regions of the CNS [28]. Its contents include mercury, which is fat-soluble and readily translocates across cell membranes. Moreover, it has the ability to oxidise to mercury. Compared to mercury salts, which form monovalent mercury, these materials are more dangerous because mercury salts generate more complicated compounds. Therefore, they are absorbed more quickly after eating and produce more toxic substances [28]. The main mechanism of mercury biological

activity is due to the high binding affinity of divalent mercury ions to the thiol or sulfhydryl groups of proteins [53]. The function of mercury is difficult to ascertain since proteins with sulfhydryl groups are present in tissues and organs and because these groups frequently have significant effects on the structure or function of many proteins [54]. Potential consequences include the inactivation of certain structural proteins, enzymes, or transport systems [55, 56], as well as alterations in cell permeability brought about by the production of thiolates. The first include oxidative stress, broken microtubule formation, increased blood-brain barrier permeability, protein synthesis disruption, disruption of DNA replication and DNA polymerase activity, disruption of synaptic transmission, membrane disruption, and bodily damage. Reaction, disturbance of the homeostasis of calcium. These modifications may take place singly or in combination [54]. The lungs absorb less inorganic mercury compounds, most likely as a result of particles building up in the upper respiratory tract and being expelled through the mucous membrane. The ease with which the substance dissociates for absorption in the lumen and/or its solubility may influence the transit of inorganic mercury through the gut [54, 57, 58]. There is less inorganic divalent mercury that crosses the placenta and blood-brain barrier as a result of its lack of lipid solubility [59, 60]. Nonetheless, inorganic mercury is absorbed by the kidneys and liver [61].

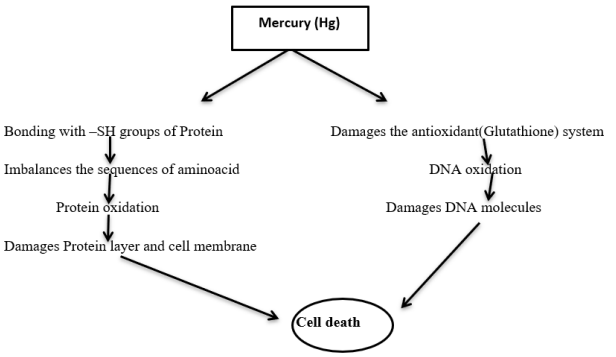

Figure 8: Mechanism of Hg toxicity in cell [62].

4 FATE OF MERCURY IN THE AQUATIC ECOSYSTEM

Mercury occurs in three different inter-convertible oxidation states in the aquatic environment Viz, Hg (0) (elemental), Hg (I) (mercurous) and Hg (II) (mercuric) [63]. The monovalent form is very rare due to its instability [64, 65]. Elemental mercury is volatile, sparingly soluble in water and has high vapour pressure and it is the dominant form of mercury in the atmosphere [66]. In the soil, sediment and water, the governing species is the inorganic mercury Hg(II) whereas methylmercury (MeHg) is the primary species found in biota [67, 68]. The residence time of elemental mercury is about 6 months to 1 year and it can intrude ecosystems that are very far from the point sources through long range atmospheric transport [69]. This elemental mercury undergoes oxidation which occurs mainly at the solid liquid interface in fog and cloud droplets [69]. Mercury, that is inorganic can easily change into its organic form in aquatic environments, in particular methyl mercury under favorable biogeochemical conditions [67]. The process of mercury methylation is greatly attributed to various physical, chemical and biological parameters, like temperature, pH, redox potential, dissolved organic carbon etc and is generally mediated by the sulphur reducing bacterias (SRB's) [70]. The different species of sulfate reducing bacteria includes *Clostridium butyricum, Desulfobulbus propionicus, Desulfovibrio desulfuricans, Desulfococcus multivorans, Desulfobacter sp., Desulfobacterium sp.* [71] and iron-reducing bacteria (FeRB) also contributes to the mercury methylation [70]. Most of the methylation reactions takes place in the upper layers of the bottom sediments because this part is known to be highly organic rich and thus microbial activity occurs at a faster rate [72].

5 DISTRIBUTION

Red blood cells carry methylmercury, of which a tiny amount is linked to plasma proteins [73]. The substance is widely distributed throughout the body due to its easy membrane penetration; nevertheless, larger concentrations (up to 10% of the total dose) accumulate in the central nervous system (CNS). Methylmercury is retained in its organic form in the central nervous system (CNS), but it is transformed and stored as inorganic mercury in other tissues, with the liver and kidneys often containing the largest concentrations. When compared to maternal blood, foetal blood contains higher quantities of methylmercury due to its easy placental passage [10]. When hair grows out of the follicle, methylmercury is integrated into the hair [14], where it is present in concentrations up to 250 times greater than in other tissues. According to information from a study by Dutczak et al [74], methylmercury is widely absorbed by the gall bladder and then cycles through the hepatic and biliary systems in macaque monkeys, guinea pigs, and hamsters. This process may be responsible for the extended biological half-life of methylmercury. The body can be exposed to methylmercury through several routes, and it can readily pass through membrane barriers such as the blood-brain barrier. This is because methylmercury-cysteine combination facilitates the movement of organic mercury into tissues. This specific amino acid has a high affinity for the methylmercuric cation due to the presence of sulfhydryl groups. Methylmercury has time to cross the membrane barriers since the metabolism of organic mercury moves slowly. As a result, as the methylmercury complexes cross the membrane barriers, they begin to metabolise into inorganic mercury. This leads to a significant build-up of

ionic mercury in various tissues, including the brain tissues. Because of this buildup in brain tissue, the half-lives of methylmercury in the blood and brain differ significantly. Human blood has a half-life of 49–164 days, while human brain half-lives could be much longer. Mercury has been observed to accumulate not only in the brain and other bodily tissues but also in the umbilical cords of foetuses.

6 TOXIC EFFECTS OF MERCURY

6.1 Endocrine toxicity

Through its capacity to decrease hormone-receptor binding or by inhibiting one or more essential enzymes or steps in hormone biosynthesis, as in the case of adrenal steroid biosynthesis and the inhibition of 21 alpha hydroxylase, mercury may affect endocrine function [75]. It appears that insulin, oestrogen, testosterone, and adrenaline are the hormones most impacted by mercury.

By blocking S-adenosyl-methionine, mercury can also prevent catecholamines from degrading, which can lead to an increase in adrenaline and hyperhidrosis, tachycardia, ptyalism (hypersalivation), and hypertension [76]. Exposure to mercury has been linked to decreased corticosterone plasma levels in the adrenal cortex [75]. Adrenocorticotropic hormone rises in response to decreased cortisol production, resulting in adrenal hyperplasia. Adisons disease may occur as a result of adrenal atrophy brought on by mercury-induced adrenal hyperplasia, which may ultimately cause the adrenals to become stressed [77]. Because of its impact on the pituitary gland, mercury is also known to induce high blood pressure and frequent urination [78].

One of the body's major endocrine glands is the thyroid. The thyroid regulates the body's rate of protein synthesis, energy expenditure, and hormone sensitivity. The thyroid exhibits a propensity to accumulate mercury. By occupying iodine-binding sites and blocking or changing hormone activity, mercury prevents the thyroid from producing hormones, which impairs regulation of body temperature, causes hypothyroidism, inflammation of the thyroid, and causes depression [77, 78]. The pancreas is likewise vulnerable to the harmful effects of mercury, just like the thyroid. Three sulfur-binding sites on insulin, the protein that controls blood glucose levels, are susceptible to binding by mercury, interfering with normal biological processes and resulting in dysregulation of blood glucose levels [79].

6.2 Neurotoxicity

Mercury can take two forms: organic and inorganic. Both are harmful. By blocking dihydroteridine reductase and interfering with the transport of phenylalanine, tyrosine, and tryptophan to neurons, mercury prevents the synthesis of neurotransmitters [80, 81]. Mercury's impacts on GSH levels have a knock-on effect on the levels of ATPases for Na^+, K^+, and Mg^{++}, all of which depend on sulfydrl molecules. Several mercurial chemicals block these enzymes, which are essential for the healthy operation of neurological and other tissues [82]. Neurotoxic edema occurs when these ATPases are inhibited [83]. It is also known that mercury inhibits norepinephrine, serotonin, and dopamine synaptic uptake [30]. There seems to be a higher affinity between Mercury and serotonin binding sites. Additionally, evoked acetylcholine release has been shown to rise in response to mercury, followed by an abrupt and total blockage [84].

Neurotransmitter release from presynaptic nerve terminals is impacted by extended exposure to methylmercury [85]. This is because it can change intracellular Ca^{+2} by increasing the permeability of the plasma membrane to Ca^{+2} and upsetting the control of Ca^{+2} from intracellular pools [86]. Both organic and inorganic forms of mercury are neurotoxins. In the brain, methylmercury builds up and is linked to lysosomes, nuclear envelopes, the Golgi complex, mitochondria, and endoplasmic reticulum. Methylmercury is mostly found in mitochondria and myelin sheaths of nerve fibres, where it causes demyelination [87]. Patients with methyl mercury intoxication show significant involvement of the cerebellar cortex on pathological examination; granule cells are more vulnerable than Purkinje cells. Glial cells are generally protected from direct injury, though reactive gliosis can happen. Mercury poisoning of neurons has been explained by a number of mechanisms. Neurotransmitter release from presynaptic nerve terminals is impacted by extended exposure to methylmercury [85]. This is because it has the capacity to modify intracellular Ca+2 by upsetting the regulation of intracellular pools and raising the plasma's permeability to calcium ions.

1. Protein repression
2. Disturbance in mitochondrial activity
3. Direct impact on a neuron's ion exchange
4. Neurotransmitter disruption
5. Destroying the neuron's structural basis

Particularly hazardous to developing newborns is methylmercury. This kind of mercury crosses the blood-brain barrier and the placenta, making it extremely hazardous. A developing foetus brain is where mercury concentrates since the metal is taken quickly and is not adequately removed. Mercury exposure can cause symptoms in newborns that resemble cerebral palsy, stiffness and other abnormalities of movement, seizures, aberrant reflexes, and eye issues. Neurons in the cerebellum and across the cerebral cortex have been lost in the brains of children who died from mercury poisoning. Mercury also appears to affect brain development by preventing nerve cells from finding their proper location in the brain. The adverse effects of mercury on GSH have secondary effects on Na^+, K^+ and Mg^{++} ATPase, all of which depend on sulfhydryl compounds.

Various mercury compounds block these enzymes, all of which are necessary for neurons and other tissues to function

normally [82]. Animals exposed to methylmercury recovered their levels of Na^+, K^+, and Mg^{++} ATPase when given GSH injections [88]. Inhibition of these ATPases causes neurotoxic swelling and astrocyte death when there are no nutrients to counterbalance this activity [89]. The primary cells in charge of maintaining the homeostatic balance of glutamate, Na/K, and pH at the synapses are called astrocytes. It is also known that mercury inhibits norepinephrine [90], serotonin [62], and dopamine [90]synaptic uptake. There seems to be a higher affinity between Mercury and serotonin binding sites. Additionally, evoked acetylcholine release has been shown to increase with Mercury, followed by an abrupt complete blockade [84]. Long-term exposure to methylmercury increases the expression of muscarinic cholinergic receptors on circulating lymphocytes, in the cerebellum, and in the hippocampal regions [85]. Neurotransmitter release from presynaptic nerve terminals is also impacted. This could be because of its capacity to change intracellular pools' Ca^{2+} concentration, as well as to raise the plasma membrane's Ca^{2+} permeability [86]. At this point, mercury builds up in the brain's motor function, harming neurons and brain cells, preventing the release of neurotransmitters, and having detrimental effects on the nervous system.

6.3 Nephrotoxicity

Research has demonstrated that over time, mercury builds up in the kidneys at ever-increasing quantities. Organic mercury is easily distributed throughout the body but tends to concentrate in the brain and kidneys [10]. Mercury is known to bind to microsomal and mitochondrial enzymes, leading to cell damage and death. Mercury in kidney cells is localized in lysosomes [62, 91]. Mercury is not destroyed during metabolism but is converted into different forms and oxidation states [10] and involves redox cycles. The main routes of excretion are urine and feces [10]. This may explain the kidney damage and failure associated with its toxicity [92]. Other studies have shown that mercury causes nephropathy, at the lowest effective dose, which is limited primarily to the S3 segment of the proximal tubule. With higher mercury doses, the lesions also shifted to include the S2 and S1 segments [43]. This kidney disease is thought to be due to the selective induction of apoptosis of proximal tubular cells [44]. Chronic oral exposure (2 years) of rats to inorganic mercury caused glomerulonephritis [41]. Methylmercury is excreted mainly in the feces as inorganic mercury [93]. This is a result of the biliary excretion of the compound and its subsequent conversion to an inorganic form by the intestinal flora. It is possible for some of the methylmercury released in the bile to be reabsorbed, resulting in an organic form of enterohepatic circulation. The biological half-life of methylmercury is roughly 70 days, with less than 1% of the body's methylmercury burden being eliminated each day [94]. With a terminal biological half-life of 76 days, a human volunteer expelled only about 6% of the ingested protein-bound radioactive methylmercury dosage over the course of 4 days [95]. Additionally, breast milk secretes methylmercury at a concentration of roughly 5% of that found in blood. Mercury's metabolism in its organic form leads to its elimination from the body through sweat, saliva, and breath [10]. In humans and experimental animals, the rate of mercury excretion is proportional to the concurrent body burden and may be explained by a one-compartment model with a biological half-life of 39 at 70 days (average about 50 days) for fish-eaters. Compared to non-lactating mothers, lactating women had much lower excretion durations for mercury. Mercury in hair has the same half-life as in blood, although there is more fluctuation (average 65 days; range 35 to 100 days).

6.4 Cellular and Nutritional Changes

Changes in platelets and red blood cells are examples of the cellular alterations that mercury can bring about. These cells have served as a stand-in indicator of mercury-induced brain tissue damage. Methylmercury can significantly solubilize microtubules in both platelets and erythrocytes when added to whole blood; this impact is more noticeable in erythrocytes than in platelets and is consistent with the known requirement for methylmercury sequestration in erythrocytes [96]. The brain has been shown to exhibit this impact on microtubules [56], which results in disruption of the cell cycle. Both neuronal and non-neuronal cells may undergo apoptosis as a result of this disturbance [97]. Because of its affinity for sulfhydryl and thiol groups, mercury exposure is linked to changes in macromolecular structure, changes in membrane permeability, and damage to DNA at the cellular level [56, 97]. Additionally, mercury has been shown to cause mitochondrial dysfunction and oxidative stress [98], which can change calcium homeostasis and promote lipid peroxidation [99]. Mercury reduces phagocytic activity and induces death in monocytes [96].

Additionally, methyl mercury may lead to a rise in lymphocyte apoptosis. This process involves the activation of death signalling pathways and the depletion of glutathione content, which puts the cell at risk for oxidative damage [100]. Mercury has been shown to lower DNA content and enhance the synthesis of collagenase-resistant proteins in synovial tissue [101]. These effects raise the likelihood of diminished joint development and decreased capacity to repair joint damage. In the body, selenium binds mercury and can actually mitigate the toxicity of methyl and mercuric chloride mercury [102]. Mercury attaches itself to GSH permanently, lowering its concentration [103]. The bile excretes the GSH-HG-GSH complex into the faeces. Mercury's inhibition of GSH reductase, which is responsible for recycling oxidised GSH and returning it to the pool of accessible antioxidants, [104] contributes to a portion of the irreversible loss of GSH. Furthermore, mercury inhibits GSH synthase, which results in the synthesis of less new GSH. It is clear that mercury creates an imbalance in the body's oxidative/antioxidative ratio since it encourages

the production of hydrogen peroxide, lipid peroxides, and hydroxyl radicals [104].

6.5 *Reproductive toxicity*

Studies show that mercury has negative effects o n the reproductive system [105], who administered mercuric chloride ($HgCl_2$) to rats and reported that mercury reduced reproductive performance. Inorganic mercury causes many different t ypes o f t issue d amage, i ncluding t esticular dysfunction. Published studies have reported that mercury can affect t esticular s permatogenesis a nd steroidogenesis in laboratory animals and men [106, 107], impairing fertility [108], reduces the quality of observations [105], causes testicular degeneration [105] and reproductive failure [108] The adrenal and gonadal glands can affect follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin, oestrogen, progesterone, and androgen during the week [108]. They c an a lso n egatively i mpact spermatogenesis [105], epididymal sperm count, and testicular weight. Mercury may promote pathological changes along the hypothalamic-pituitary. Additionally, there is proof that mercury and erectile dysfunction are related [108]. Methylmercury poisoning in rats affects t he s hape o f the epididymal tissue, motility, count, and energy consumption of the sperm. As shown by a considerable decrease in the average number of nest sites or by their absence in females living with treated males, all of these factors contribute to the decline in fertility medical care [106].

6.6 *Cardiotoxic effects*

Mercury, both organic and ionic, builds up in the heart and is linked to hypertension and irregular cardiac rhythms, including ventricular tachycardia and tachycardia [109]. It is not evident from the vascular effects o f m ercury [107] whether the toxicity is due to direct cardiotoxicity or indirect toxicity from effects o n t he n eurons t hat g overn heart function.

6.7 *Immunotoxicity*

Mercury decreases the ability of monocytes to phagocyte and enhances the apoptosis of lymphocytes and monocytes. It has been demonstrated that workers exposed to mercury vapour produce less IL-1 and NF alpha [110]. According to certain studies, mercury compounds can both reduce cellular immunological responses, which increases infections [111], a common sign of immunotoxicity [112], and activate the immune system, resulting in autoimmunity. Increased levels of ACH and corticosterone show that modifications i n t he hypothalamic-pituitary-adrenal axis take place concurrently with immunological changes [112]. Raising corticosterone levels could worsen already-existing immunosuppression. Mercury can lead to antibiotic-resistant bacteria in addition to aberrant responses in the humoral and cellular immune systems. The gut bacteria of primates in a study developed resistance to penicilin, streptomycin, kanamycin, chloramphenicol, and tetracycline within 5 weeks of the primates having amalgam tooth fillings [113].

6.8 *Impacts on ocular organs*

Some persons have developed gray-yellow-brown eye discolouration as a result of long-term occupational mercury exposure. It is not believed that this mist impairs vision. Some individuals have also reported having keratopathy, or a grey stripe on their cornea.

6.9 *Carcinogenicity*

According to NASA (2000), MeHg is a Class C human carcinogen that is considered "probable". MeHg enhanced the frequency of kidney tumours in animal experiments, but only in male rats that already had tumours. In female mice, no increase was seen. Since this process was only noticed at nephrotoxic MeHg concentrations, the tumorigenic effect is believed to be "secondary" to cellular deterioration and repair. Thus, it was determined that "chronic exposure to subtoxic doses of MeHg does not appear to enhance tumour formation in the absence of a tumor-initiating agent" [109].

7 METHYL MERCURY TOXICITY AND ASSOCIATED DISEASES

7.1 *Minamata disease*

Minamata illness, also known as Chisso-Minamata disease, is a neurological condition brought on by extreme mercury toxicity. Ataxia, numbness in the hands and feet, generalised muscle weakness, field vision narrowing, hearing loss, and speech abnormalities are some of the symptoms. In severe situations, weeks after symptoms appear, a person may die, become paralysed, or enter a coma. The condition can also impact foetuses in the womb in a congenital form. In 1956, the disease known as Minamata was initially identified in the Japanese prefecture of Kumamoto City. Minamata disease was first discovered in Minamata city in Kumamoto Prefecture, Japan, in 1956. It was brought on by the 1932–1968 methylmercury leak into industrial effluent from the chemical facility owned by Chisso Corporation. When fish are feeding in the Gulf of Minamata and Shiranui Sea, this extremely poisonous toxin bioaccumulated in the fish and shellfish, resulting in mercury poisoning for the local population. Governments and corporations did little to stop the pollution while humans, dogs, cats, and pigs continued to die for almost 30 years. Cats who suffer from such strong animal effects have been referred to as having "jumping cat fever" [114] or "dancing cat fever" [114].

7.2 *Alzheimer's Disease*

Methylmercury is a neurotoxin that is created by a number of industrial activities and is a major source of contamination in our oceans. Methylmercury is a fat-soluble chemical that enters the food chain and builds up in fish meat that is sold in our stores. Larger and longer-lived fish are now known to carry significant health concerns, particularly for youngsters and pregnant women, who are recommended to limit or

Figure 9: Patients affected by Minamata disease

even avoid consuming certain species like fresh tuna and marlin. A build-up of mercury in the body is associated with several disorders, including Alzheimer's disease, where it is believed that mercury contributes to the death of nerve cells. These disorders can have significant, long-term impacts on the neurological system. Lipoproteins, which include low-density lipoprotein (LDL) and high-density lipoprotein (HDL), are lipid and protein combinations that carry fats through the bloodstream. This function is frequently linked to cholesterol and, consequently, to cardiovascular health. On the other hand, one in seven individuals carries a gene that triggers the production of apoE4, a unique lipoprotein that is believed to be crucial in the onset of Alzheimer's disease. An individual's typical chance of acquiring Alzheimer's disease is three times higher if they inherit the apoE4 gene from one parent, and ten times higher if they inherit the gene from both parents [94].

Numerous theories exist explaining why individuals carrying the apoE4 gene have a higher risk of developing Alzheimer's disease compared to those carrying the apoE3 and apoE2 genes. One such theory focuses on the function of these lipoproteins in transferring mercury throughout the body since the accumulation of mercury in the brain has been associated with the advancement of Alzheimer's disease. An amino acid chain makes up the structure of lipoproteins. The amino acid cysteine contains sulphur, which belongs to a class of compounds known as "mer-captans", whose Latin name means "captures mercury". This makes cysteine particularly significant. Two cysteine amino acids found in apoE2, the protective version of apoE, are especially useful in clearing the body of mercury. On the other hand, apoE3 is the least efficient at eliminating excess mercury from the body because it only has one cysteine and lacks apoE4 [115]. Fish oil appears to have a protective effect against the death of neurons, which delays the onset of dementia. However, consuming large amounts of fish oil may counteract any therapeutic benefits unless it is thoroughly filtered to ensure that all heavy metals are eliminated. Neurodegeneration and inflammation are the main pathogenic mechanisms; these two processes lead to oxidative stress, which hastens the damage to neurons. For unclear reasons, hyperphosphorylation of the tau protein results from neurodegeneration. Microtubules, which make up the cytoskeleton of neurons and are necessary for proper metabolism and neuronal function, are subsequently degraded as a result of this. A minimum of 14 sulfhydryl groups make up tubulin, and when tubulin binds to mercury with great affinity, tubulin function is lost and neurofibrillary tangles are formed. Given that human nerve cells are nonregenerating, any obstruction of the neural tube is extremely dangerous. Damage is caused by neuronal degeneration in the entorhinal cortex, the early hippocampus, and the cholinergic projection system of the basolateral prefrontal brain [116, 117]. In severe emotional phases, the neuronal loss exceeds 90% and is greatest in the nucleus basalis of Meynert (NBM) [116, 118]. Although there is not much damage to the cerebral cortex, memory ability is severely decreased due to a concurrent drop in brain cholinergic activity, which normally dictates the functional condition of the cerebral cortex [117].

Parkinson's illness with methylmercury apoptosis, or programmed cell death, is known to have a significant role in neurodegenerative illnesses including Parkinson's and Alzheimer's. The production of tumour necrosis factor alpha (TNF), reactive oxygen species (ROS), oxidative stress, decreased glutathione levels, and liver enzyme impacts are some of the mechanisms that contribute to the death of neurons and immune cells. inhibits the production of beta-amyloid [119], cytochrome p50, protein kinase C (pKC), lipid peroxidation, excessive free cysteine levels, excessive glutamate toxicity, excessive dopamine poisoning, DNA fragmentation [118, 119], increased toxicity of calcium currents, and mitochondrial membrane dysfunction. Parkinson's disease has been linked in large part to dysfunction of the mitochondrial membrane. Apoptosis, or the death of neurons and immune cells, is one of the many immune cell responses that TNF (tumour necrosis factor-alpha) regulates in animals. Parkinson's disease, Alzheimer's disease, and other inflammatory and reproductive neurological disorders are linked to this process.

Sphingolipids and other cell signalling systems are a component of the regulatory mechanisms that govern TNFa-mediated apoptosis. An amino acid called glutathione is a regular biological process that regulates apoptosis. Neurons are damaged when glutathione levels in the brain are low, reactive oxygen species rise, toxic exposures like mercury disturb the central nervous system and cell signalling pathways, and neuronal apoptosis occurs. The most prevalent amino acid in the body, glutamate functions as an excitatory neurotransmitter in the central nervous system (CNS) and induces the input of calcium. In addition to their role in maintaining the environment surrounding nerve cells, astrocytes, a kind of cell found in the brain and central nervous system, also play a role in neutralising excess glutamate by converting it to glutamic acid. Neurotoxicity and edema will result from glutamate and calcium if astrocytes are unable to promptly neutralise excess glutamate. Mercury thus reduces the activity of

astrocytes in the brain and central nervous system, which causes an increase in neurotoxicity connected to glutamate and calcium, which is what causes most of the symptoms of fibromyalgia chemical interactions. Parkinson's disease is mostly brought on by this as well [119].

8 PHYTOREMEDIATION

Removing the exposure source is the most crucial step in treating mercury poisoning. Plants have been used for millennia to cure a wide range of conditions, from heart illness to laryngitis. A technique called phytoremediation employs plants to take pollutants out of polluted environments. The process of using live green plants directly to break down, contain, or make different types of environmental pollutants such as heavy metals or persistent organic compounds harmless is known as phytoremediation [120]. By utilising genetically modified plants and the mercury-resistant bacterial genes merA and merB, phytoremediation of methylmercury can be accomplished. Mercury reductase, which is produced by the mer A gene, converts the extremely toxic ionic mercury (Hg(2)) into the less toxic and more volatile elemental mercury (Hg(2)). An organic mercury enzyme that transforms methylmercury into Hg(2) is encoded by the mer B gene. Tobacco or Arabidopsis (mustard) have had these genes, either separately or in combination, cloned [120].

Studies have shown that *Cyrtomium macrophyllum* leaf tissues are highly resistant to mercury stress due to increased superoxide dismutase activity and mercury stress-induced accumulation of glutathione and proline. Possible reason to tolerate high concentrations mercury in soil [121] was detected at high levels. Another group developed mercury-eating Arabidopsis by inserting into its genome a synthetic merApe9 gene, which is an adaptation of a bacterial gene encoding the production of mercury reductase [122]. These results indicate that genetically modified plants have the ability to reduce and detoxify mercury [123]. Phytoremediation of Hg Among the various technologies that can remediate Hg contaminated sites, phytoremediation is a green alternative for effective remediation technology [120]. Through a translocation process that moves pollutants from soil to plant tissue, this method is utilised to eliminate or significantly lower the amounts of toxins in soil [124]. Generally speaking, plants like Indian mustard (*Brassica juncea*) and Jatropha curcas are employed in phytoremediation of mercury in soil [31]. On the other hand, elevated levels of mercury in soil have an impact on biomass, hinder plant development, and have long-term consequences for soil fertility [124]. Nutrient intake is decreased and photosynthetic activity is decreased. The cytotoxic effects of mercury (Hg) diminish photosynthetic activity and impede the plant system's ability to absorb nutrients and minerals [12]. Restoring regions impacted by mining also involves the application of phytoremediation techniques. Applying this technology in the field also requires an understanding of the behaviour and properties of mercury in plant systems [125]. Plants can be utilised to detect pollution levels and the long-term consequences of mercury toxicity in environmental media, according to a study by Cassina et al. (2012) [126]. The study also discovered that elevated soil mercury levels are associated with a greater risk of mercury buildup in the plant's aerial sections. A further investigation by Sun et al. (2016) [12] on the remediation of mercury contamination revealed that beard grass (*Polupogon monspelieensis*) only gathered a small quantity of mercury in its shoots less than 65 mg/kg during the period when mercury accumulation in roots is higher. Indian mustard plants (*Brassica juncea*) grown in recently enriched soils were shown to have small mercury accumulations in their shoots. The study also showed that mustard plants display a number of stress signs, including chlorosis and water content loss during growth. When Sun et al. (1996) [12] investigated *Pteris vittata*, the Chinese fern, they discovered that the plant had more mercury accumulation than P. monspeliensis and *B. juncea* (1469 mg Hg/kg in shoots in recently enriched soil). and less signs of stress manifest. Two plant species, *B.juncea* and *Helianthus annuus*, were employed by Hussein et al., 2007 [127] for the efficient removal of mercury. It was shown that *B.juncea* absorbed mercury more effectively, whereas sunflower showed a better response in terms of plant biomass production.

Research also demonstrates that the application of thio ligands and plant hormones (cytokinin) improves plants' capacity to clean up pollutants. In order to investigate the process of phytoremediation of mercury through the uptake of various forms of Hg into the roots and shoots of tobacco plants that have undergone genetic modification with bacterial genes merA and merB through the chloroplast genome, Henriques and colleagues (2015) [128] studied transgenic tobacco plants.

9 SAFE DOSAGE LIMITS

Two parts mercury per billion parts of drinking water (2 ppb) is the maximum that the US EPA has established. The highest amount of methylmercury that can be found in seafood is one part per million (1 ppm) as determined by the US Food and Drug Administration (FDA). A maximum of 1 mg of mercury can be found in the air at any workplace, according to the Occupational Safety and Health Administration. At the moment, mercury vapour values above 0.01 mg/m3 are regarded as hazardous [129]. Health officials, scientists, and physicians are trying to identify strategies to minimise mercury emissions and so reduce atmospheric mercury pollution to some extent, taking into account the safety limitations in certain measure.

10 CONCLUSION

Mercury has no beneficial effects on organisms and is therefore considered a "major threat" because it is very harmful. Atmospheric mercury pollution continues to be one of the

most important environmental problems in the modern world. Current research aims to highlight the harmful effects of mercury on the environment and organisms. Therefore, by making people aware of the health effects of mercury and the sources of its entry into the environment, many strategies can be adopted to minimize mercury use and exposure. The following general conclusions can be drawn from this review article • Global risk from anthropogenic atmospheric Hg emissions is a major issue regardless of its remediation measures and guidelines because of resilance and accumulation ability of Hg. • The gaseous elemental mercury (GEM) has long lifetime in atmosphere, which has risks of spreading the pollution to different regions causing a global issue.• All three forms of mercury discussed in this review paper can cause adverse health effects in organisms, particularly the organic form of mercury (methylmercury) has the highest level of toxicity • Neurotoxicity is the most sensitive indicator of methyl mercury which is evident from the deadly diseases namely Minamata disease, Alzheimer's disease and Parkinson's disease. • Water is the major sink for atmospheric Hg, but the main issue is the accumulation of Hg as MeHg in marine species. Fish is the main food product that has high Hg concentration because of its bioaccumulation and biomagnification. • It is seen that rapid economic and population growth can play an important role in the mitigation process by following the regulations and guidelines of the Minamata Convention and using a variety of remediation techniques plant-based, use minimal Hg-containing products, and follow proper waste disposal techniques.

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