Chapter 5
Effects of Mercury: Neurological and Cellular Perspective

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5.1 Introduction

Earth's crust harbours a plethora of potentially toxic elements known to be harmful for cellular life. Natural and anthropogenic factors expose these dangerous elements to atmosphere and land–water system. In many cases, it enters the body through respiratory and food chain route causing severe threat to health and life of humans and other organisms. These metallic elements are Hg, As, Pb, Cd, Cr, Fe, Mn, Ni and Cu. With the advancement in modern technologies, the proportion of toxic metals and their compounds in drinking water and food items exceeded the maximum permissible limit. This paper reviews the prehistoric usage of mercury and related toxicity in human beings. The health effect of different important heavy metals is described below.

Chinese were the pioneer users of mercury who mined it in 1100 BC to get red substance (mercury sulphide) called Chinese red, vermilion, or cinnabar. Phoenicians (people around Mediterranean Sea) too used this material in 415 BC. It was named 'Quick Silver' by Aristotle in 400 BC in Greece. The naming of the planets by the Mesopotamians was based on the names of metals, and Mercury is still the name of the planet nearest to the sun. Mercury and its derivatives have been utilised for more than three thousand years as dental amalgam, antiparasitic, antipruritic, diuretic, antiseptic, antisyphilitic and alternative medicines. Mercury was used to treat syphilis from 1550 to 1940 until penicillin was discovered by Fleming (Ozuah 2000). One of the specialised branches of *Ayurveda 'rasashaastra'* is the science of mercury (Savrikar and Ravishankar 2011). Mercury sulphide commonly called as Cinnabar has been extensively used by Chinese and Indian medical practices for

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N. Kumar (ed.), *Mercury Toxicity*, Environmental Science and Engineering,
https://doi.org/10.1007/978-981-99-7719-2_5

the treatment of pneumonia, syphilis, insomnia, high fever, nervous disorder, tongue paralysis and deafness (Kamath et al. 2012). Since the toxic effect of mercury has been explored and its usage is minimised, still a lot of traditional medicine contains significant amount of mercury. Research carried out in the US about the availability of traditional medicine containing mercury showed that one-fifth of both US- and India-made Ayurvedic medications sold online had mercury, lead and arsenic levels (Saper et al. 2008).

Mercury is the natural element available is Earth's crust, air and water. Natural phenomenon of volcanic eruptions, weathering of rocks and forest fire exposes mercury to the environment and constitutes the geogenic sources of mercury. Burning of coal is the largest contemporary source of anthropogenic mercury released in air and terrestrial surfaces. Of these 71% are straightway released in air, remain there for a week to a year, transported to several kilometres away by wind to finally settle down on land surfaces and/or water (Sprovieri et al. 2010; Streets et al. 2018). ASGM (Artisanal and small-Scale Gold Mining) utilises mercury amalgamation during gold extraction from its ore. This process too releases a significant amount of mercury in environment. Mercury is mixed with the ore of gold and amalgamation is formed. Mercury is evaporated to get the residual gold. This is the simple and cost-effective process to get the precious gold and maintain the livelihood in the country of Uganda in African continent (Keane et al. 2023). Domestic release of mercury is through fluorescent lamp, thermometer breakage, and some types of batteries. Presently 9000 tonnes of mercury are released in air, land and water annually (UNEP 2013a). Mercury is extracted commercially from cinnabar, a mineral which has 86% concentration of mercury.

Mercury is bioaccumulated (higher concentration in aquatic plants and animals as compared to water) and biomagnified in higher food chain (Fig. 5.1). Gastrointestinal absorption of metallic mercury is low, but once it enters the human body it is oxidised to mercuric salts such as mercuric chloride. Mammalian kidney is the main site for mercuric compound decomposition. Mercury poisoning is related to neuro toxin, which results in distortion of gait and motor co-ordination (Clarkson and Magos 2006). Reproductive anomalies in mammals and other vertebrates are also related with mercuric poisoning.

Minamata Convention on Mercury was held in Kumamato, Japan in 2013 to discuss and regulate the use of toxic mercury. Minamata bay in Japan had a tragic fate (neurological disorder) in 1950s when its residents were unintentionally poisoned by eating mercury (methyl mercury) contaminated fish. A factory in Minamata discharged its industrial effluent to sea containing methyl mercury, a byproduct in the manufacture of acetaldehyde. In 1965 another case was detected in Niigata, Japan in Agano River basin. During 1971–72 in Iraq, bread contaminated with methyl mercury was reported and the reason was fungicide used in wheat seed (Millar 2022). The main aim of the Convention is to protect the public health as well as the environment from anthropogenic emissions and releases of mercury and its compounds (UNEP 2013a). Article 7 (A separate article) is dedicated to Artisanal and Small-Scale Gold Mining (ASGM) in Minamata Convention to work on it, as this process is among

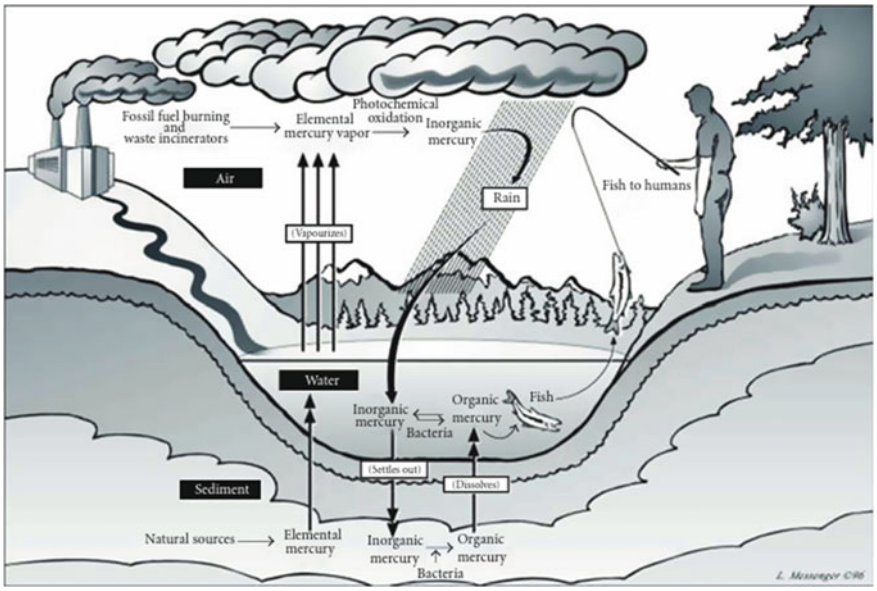

Fig. 5.1 Mercury biogeochemical cycle

the largest emitters of mercury in atmosphere. India ratified Minamata convention in 2018.

One of the main sources of mercury emissions into the environment is combustion of coal. India is the world's second-largest producer and user of coal. In India, coal-fired power plants (CFPPs) are the main source of mercury emissions, accounting for more than half of all atmospheric emissions (Burger Chakraborty et al. 2013). Coal is available in abundance in India and growing energy demands require more power plants to be set up. Minamata Convention Article 8 recognises Coal-fired power plants (CFPP) as one of the greatest sources of mercury emissions. India has currently 2,04,080 MW (2022) of installed coal-fired power plants (Government of India, Ministry of Power). Additional 62,200 MW of power plants (coal-fired) are under construction. The average level of mercury in Indian coal is 0.14 g/t, with a range of 0.003 to 0.34 g/t. With estimated emissions of 144.7 tonnes of Hg per year, India is the second-largest mercury emitter in the world. Other sectors which are mercury emitters can be summarized in Table 5.1 (UNEP 2013b).

South Indian Hill city of Kodaikanal (Tamil Nadu) witnessed a severe mercury poisoning for its worker in a thermometer manufacturing plant and an undisclosed amount of money was paid to them to calm down the dispute. The 591 workers campaigned for 15 long years for compensation from Hindustan Unilever Limited. It brought attention worldwide and finally it was settled in 2016. The compensation was paid to the workers but the damage it has already done to environment will have long-term impacts on the region. The amount of mercury found in soil was 25 mg/kg that is 250 times higher than International permitted limits (Agnihotri 2016).

Table 5.1 Amount of mercury released in India through various processes

Sector	Tonnes of Hg/year
1. Coal burning	89.4
2. Non-ferrous metal production	22.5
3. Cement production	13.4
4. Ferrous metal production	1.9
5. Chlor-alkali production	0.94
6. E-waste	13.6

Source UNEP (2022)

Kodai lake is situated in the north of thermometer factory. In the Kodai sediment, there was 276–350 mg/kg HgT and around 6% methyl mercury. Lesser methylation was found in sediments from Berijam and Kukkal, with HgT levels of 189–226 mg/kg and 85–91 mg/kg, respectively. Fish from Kodai Lake have HgT levels between 120 and 290 mg/kg. The findings indicated that mercury emissions from the thermometer manufacturing factory were responsible for the mercury pollution in the lake (Karunasagar et al. 2006).

In India, alarming rate of mercury is observed in water, industrial effluents, and fishes. India has an industrial effluent discharge range of 0.058 to 0.268 mg/l that contains mercury. This exceeds the mandated Indian and WHO norms of 0.001 mg/l (for drinking water) and 0.01 mg/l by a significant margin (for industrial effluents). This has led to severe contamination of fishes in the respective areas. Fish stock at Kolkata, Mumbai, Karwar (Karnataka) and North Koel River (Jharkhand) have shown high levels of mercury (Table 5.2).

High level of mercury is detected in soil and ground water in water basin of Eastern India, which have chlor-alkali plants. They are the largest consumer of mercury in India. This sector produces chlorine and sodium hydroxide. An estimated approx. 9 tonnes of toxins were released in air during 1997–2000 (Banerjee, n.d.). The rice plant analysed in the region did not show significant concentration of mercury, but the plants like cabbage and Amaranthus showed high mercury level viz. 8.91 mg/kg. Some of the aquatic plants with high bio concentration of mercury included *Marsilea* spp., *Jussiea repens, Spirodela polyrhiza, Paspalum scrobiculatam, Monochoria hastata, Pistia stratiotes, Hygrophila schulli, Eichhornia crassipes* and *Bacopa monniera. Chloris barbata, Cynodon dactylon, Cyperus rotundu*, and *Croton bonplandianum*, among wild terrestrial plants, were seen flourishing on

Table 5.2 Region of India showing water species mercury contamination

Region	Species	Observed total (mg) of Hg/kg dry weight
1. Maharashtra	Fish Crabs	0.03–0.82 1.42–4.94
2. Karwar (Karnataka)	Oyster	0.18–0.54
3. North Koel (Jharkhand)	Fish	300–350

highly polluted soil that contained mercury concentrations as high as 557 mg/kg (Lenka et al. 1992).

Most of the studies related to mercury toxicity in India showed that the mercury levels in blood, urine and breast milk of residents of integrated steel plants or those who lived nearby had rates of up to 30 times higher than those from distant areas (Pervez et al. 2010; Sahu et al. 2014a; Sharma and Pervez 2005). Vulnerable populations are often the marginal sections of the society (women and children) consisting primarily of waste segregators, rag pickers and factory workers' families or living close to the factories (Mondal et al. 2016). As high as 1 ppm of mercury in fairness cream and other cosmetic items have been detected in India (1 ppm = 103 μg/kg; regulatory limit) which is cause of concern for cosmetic industry (Pramanik et al. 2021). Chronic exposure due to mercury contamination has serious negative consequences on health and living organisms as its impact is extremely vulnerable to the entire ecosystem. The usage of fossil fuels must be reduced and one must rely more on renewable sources of energy to minimise the impact of serious impacts of mercury (Das et al. 2023).

High levels of mercury concentration in water and humans have been reported in Singrauli town (Sonbhadra district) of Uttar Pradesh in India. The district lodges thermal power plants and coal mines. Analysis of the drinking water samples showed high mercury concentration within a range of 3 to 26 μg/L (3–26 times the allowable limit) in 20% sample water. The mercury in soil samples had 0.5–10.1 mg/kg concentration. The average concentrations of mercury in human hair, blood and nails were found to be 7.4 mg/kg, 34 μg/L and 0.8 mg/kg respectively. The average mercury concentration in the blood of these persons were 45 and 28 μg/L in the case of men and women respectively which is far greater than the US Environmental Protection Agency's safe standard of 5.8 g/L (USEPA) (Sahu et al. 2014b). Obra and Anpara localities showed higher concentration of arsenic and mercury (Ahamad et al. 2021). In a study conducted at Kanpur the particulate mercury (HgP) observed in PM_{10} was approximately 100 to 4340 pg m^{-3}, with mean concentration 776 ± 846 pg m^{-3} during the sampling period. Concentration of mercury in air was examined by some of the researchers in Kanpur, UP, India. During the winter, significant Mercury Particulate (HgP) concentrations were found, with the maximum concentration observed in March (4340 pg m^{-3} on 4th march) and lowest during summer (100 pg m^{-3} on 14th June, in the year 2007) (Guo et al. 2020). $PM_{2.5}$ and PM_{10} are the major air pollutants in city and along with dust it carries toxic heavy metals too.

In 2020, maximum permitted limits of 1.0 mg/kg for total mercury and 0.25 mg/kg MeHg in milk and honey (and other foods) were published by the Food Safety and Standards Authority of India (FSSAI). For the separation and detection of Hg species in food samples, an Agilent 1260 HPLC coupled to the 7850 ICP-MS offers an efficient and affordable approach (Jain et al. 2021). India is the largest producer of milk (22% of global production) followed by the US, China, Pakistan and Brazil. India ranked 7th in the world for honey production in the year 2019 (FAO, UN). The use of untreated sewage and industrial effluents for irrigational purposes led to danger of toxic metal contamination. High toxicity of agricultural land contaminates the food crops and grasses which is later consumed by the cattle. In this regard, a

robust mechanism of mercury detection in food items will pave a way for greater safety in food products.

Idol immersion is an important point source of water body pollution. Idols are constructed from a range of non-biodegradable and biodegradable materials including wood, paper, hay, clay, plaster of Paris, fabric, bamboo, adhesive material, thermocol, paints and others. They are also embellished with various pigments and colours (Joshi et al. 2017). The paints used for colouring idols contain toxic metals like lead and mercury. Few specific studies have been done on water quality after idol immersion with reference to mercury level in the water. River Budhabalanga, Balasore, Odisha, India showed increase in mercury level after 10 days of idol immersion (0.067 mg/L) while the prescribed limit is 0.001 mg/L of mercury as per BIS and ICMR standards (Das et al. 2012). Namami Ganga is the flagship programme of Government of India to clean Ganga and develop riverfronts along its cities. River front has been developed at Patna and several measures have been taken to clean Ganga. Sewage Treatment Plants (STPs) are made to treat the sewage of the city. Manual cleaning of riverbank is done frequently. Measures have been taken to create a separate idol immersion pool in Patna at Barharwa Ghat on river Ganga (Das et al. 2020).

Domestic sewage is an important source of toxic metal contamination of rivers. Sludge generated from STP (sewage treatment plants) contains the toxic material. Sewage sludge contains high amount of organic matter along with toxic heavy elements. Since sewage sludge is an important source of mercury and other toxic materials, its handling requires utmost care. Usage of contaminated sludge as manure is equally dangerous because it will again enter the food chain. Water discharged from sewage treatment plants need to be monitored for presence of heavy metals before using it for irrigation purpose. Flue gases escaping from incinerators also contain toxic metals harmful for human health.

We observe that the toxic element once released in ecosystem continues to cycle from land–water-air to living cells damaging one form or another. So, the ultimate solution is to minimise its occurrence at the point source and rely more on renewable sources of energy rather than fossil fuels.

5.2 Impact of Mercury on Floral Community

The Minamata Convention on Mercury (2013) aims to reduce anthropogenic mercury (Hg) risks to humans and the environment worldwide (Outridge et al. 2018). Researchers found that Hg has potential toxic impacts on plants even at very low concentration (Li et al. 2017). Numerous studies revealed that the vegetations cultivated near mercury sources may contain high concentration of Hg. Coal-fired power plants account for releasing maximum mercury to the environment. In a study, some samples of vegetables and grains collected within 10 km distance from power plants had exceeded the allowable upper limit of Hg content when compared with samples purchased from grocery stores away from power plants. In addition, it was also

observed that if the fly ashes were rinsed off from leaf surfaces of plants, the mercury content was found to be decreased significantly (Li et al. 2017).

In the ecosystem, the atmospheric mercury uptake by vegetation accounts for 60–90%. Among vascular plants, the highest mercury concentration is found in the leaves in comparison to any other plant tissues. In woody biomass, it has been observed that the atmospheric Hg was first taken up by leaves, which is then translocated within plants, contributing unquantified source of Hg deposition. Hg taken up by roots accounts for minor transfer of mercury content in tissues above ground representing recycling of Hg within soil, whereas the Hg transportation from foliage to roots increases environmental Hg uptake and its deposition. The Hg deposition by non-vascular plants such as mosses and lichens exceed that of vascular plants and hence usually considered when quantifying environmental mercury deposition (Zhou et al. 2021). Due to presence of barrier to Hg transportation from roots of plants to foliage part, the Hg uptake from soil accounts for less absorption through roots. Thus, only modest increase of Hg from plant root is accountable even in areas of high Hg soil concentration (Patra and Sharma 2000).

Hg is considered as a toxic element as it has no beneficial impacts on animals and plants. So, it is regarded as 'main threat' and acts as a pollutant of the air, water and soil (Asati et al. 2016). It accounts for growth retardation in plants, decreases photosynthetic pigment and total biomass (Jameer Ahammad et al. 2018) and put many negative impacts on them (Natasha et al. 2020).

A study of mercury treatment among four species of plants producing non-edible oil demonstrated a considerable reduction in the leaf tissues leading to decline of the leaf thickness in majority of species. The anatomical structure of plant leaves had also shown the sign of Hg stress as revealed by decrease in leaf thickness, lower epidermis, upper epidermis, spongy tissues and palisade tissues. At the same time, decrease in chlorophyll content were observed in all four species with remarkable increase of MDA content of leaves (Hamim et al. 2019).

Mercury contamination in the soil has several negative impacts on plants viz. reduction in growth and metabolism of plants (Asati et al. 2016; Patra and Sharma 2000), transpiration rate, photosynthesis, chlorophyll synthesis (Marrugo-Negrete et al. 2016; Teixeira et al. 2018a, b) and water uptake. Besides, increased lipid peroxidation was also reported due to increased contamination of mercury in the soil (Cho and Park 2000). The impact of a number of stress-indicating antioxidant enzymes such as peroxidase (POD), superoxide dismutase (SOD) and ascorbate peroxides (APX) has been shown to be curtailed at higher mercury concentration (Zhou et al. 2021; Manikandan et al. 2015; Magarelli and Fostier 2005; Israr et al. 2006).

Hg-exposed plants exhibited significant reduction of dry and fresh biomass. The decrease in biomass, morphological symptoms and shoot growth rate were observed as the result of mercury's toxic impact on uptake of minerals and plant metabolism (Jameer Ahammad et al. 2018). According to a number of studies, heavy metal serves as stressor in plants, causing physiological constraints that lowers plant vigour and restrict plant growth (Schützendübel et al. 2001).

Heavy metals generally affect the living organism at cellular level by damaging and blocking important biomolecules such as enzymes and polynucleotides, denaturing or inactivating proteins, by displacement of metal ions from molecules (e.g., Mg from chlorophyll) ultimately disrupting the cell membrane or organelles (Patra et al. 2004). Hg concentration induces phytotoxicity by changing the permeability of cell membrane, affinity to react with phosphate group, having high affinity to react with sulfhydryl (SH) group, and by disturbing functions of critical and non-protected proteins (Patra et al. 2004; Patra and Sharma 2000).

Mercury concentration induces injury in seeds as well as reduces its viability. Hg disturbs the sulfhydryl group, disrupting its stability and affecting germination of seeds and development of embryo (specially –SH ligands rich tissues). In Zea mays, mercuric chloride has also been seen to inhibit the seedlings' gravimetric response and diminish primary root elongation (Patra et al. 2004).

Microalgae are primary producers and may serve as a prominent entry site for the metal into the marine food web. They are among the phytoplankton that serve as foundation of the food web in marine environments (Faucheur et al. 2014). These microorganisms can be used as bioindicators of pollution due to their vulnerability, as they can bioaccumulate trace metals and phytoremediation strategies can be developed to reduce contamination in aquatic habitats (Renuka et al. 2015). Mercury shows great affinity for cysteine residues in proteins and binds via the thiol functional group. Upon mercury exposure, essential processes in plant cells and algae are disrupted due to inhibition or activation of various enzymes (Nesci et al. 2016).

The deleterious impacts of genetic materials have been observed due to mercury toxicity. Numerous DNA reactive sites are exposed due to nature of easily deformable outer electron shell of mercury. Patra et al. (2004) concluded effect of mercury depends on the time of exposure and concentration in plants leading to marked effects in S-phase that induces damages resulting in severe clastogenicity.

5.3 Impact of Mercury in Faunal Community

Mercury can bioaccumulate in animal tissues. The organic form of mercury viz. MeHg (Methylmercury) exists more in living organisms than any other form because it has tendency to get absorbed quickly while getting excreted at slower rate. Animals at the top of the food chain may have larger concentrations of mercury than those at the bottom, indicating that its concentrations increase as one moves up the food chain. This is also known as trophic bio-magnification (Chen et al. 2018; Rice et al. 2014; Ruus et al. 2017).

MeHg is regarded as bioindicator of mercury levels due to the direct relationship between aquatic biota and the environment (Condini et al. 2017). Methylmercury (MeHg) is thought to be the most hazardous form and is subjected to extensive research (Rice et al. 2014; Ruus et al. 2017). Researchers stated that MeHg can cross the blood–brain barrier and accumulate in the CNS (central nervous system) of humans and fish (Aschner et al. 2000), which damages the brain neurologically

(Berntssen et al. 2003). Additionally, MeHg is known to have harmful impact on the kidneys, CNS, cardiovascular, immunological and gastrointestinal systems (Holmes et al. 2009). MeHg is regarded as a highly neurotoxic substance that predominantly affects glial cells and causes oxidative stress and neuroinflammation. Additionally, this seems to have negative impact on the reproduction, kgenome and different physiological systems in both animals and humans (Rice et al. 2014).

The toxic impacts of mercury also affect the microorganisms present in the Hg-concentrated soil (Ha et al. 2017; Ruus et al. 2017). In a research, it was found that among soil microorganisms, bacterial communities are more affected by Hg toxicity, when compared to fungal communities. Even with the least bioavailable Hg in the soil, the abundance of the mercuric reductase gene revealed a decreased ability of bacteria to detoxify mercury. In soils having high concentration of mercury, researchers discovered a wide variety of Hg-responsive species, however they were not restricted to any one soil type or taxonomic group (Frossard et al. 2017).

Small organisms can be found at the base of the food chain, which extends to larger predatory fish like sharks, tilefish, king mackerel and swordfish as well as marine mammals (Ullrich et al. 2001). Methylmercury concentrations in large predatory fish and marine mammals can be up to 100,000 times greater than those in the surrounding aquatic environment. People who frequently consume seafood are therefore more likely to be exposed to concentrations of mercury, which has been correlated to damage to the neurological, immunological and cardiovascular systems as well as the brain, lungs and kidneys (Dabeka et al. 2004).

The rise in the price of gold on the global market as well as other socioeconomic factors are driving the expansion of artisanal small-scale gold mining (ASGM), which is responsible for significant mercury (Hg) emissions into the air and rivers in the Global South. Hg has the potential to endanger both animal and human populations by hastening the degradation of neotropical freshwater environments. Researchers investigated the possible reason of Hg contamination in fishes living in regions with high biodiversity values and growing ASGM-dependent human populations living in Peru's Madre de Dios. ASGM activity was hypothesised to be the major reason for Hg contamination upon investigation of local water quality, environmental Hg exposure and by studying trophic levels of fishes. It was observed that the level of mercury contamination is positively related with ASGM activity. The amount of mercury accumulation was found more in higher trophic level with less amount of dissolved oxygen (DO). Additionally, it was reported that top carnivorous animals and people of neotropical region depending on freshwater ecosystem are facing ASGM-dependent mercury toxicity (Barocas et al. 2023).

5.4 Impact of Mercury Toxicity in Humans

Humans have utilised animals and their products as a source of nutrition for ages. Fishes have been universally used as rich source of protein with low fat content along with minerals and vitamins. Cattles are also good source of nutrition providing dairy

products and meat as well. Though some aquatic or terresterial animals may get exposed to mercury and serves as source of mercury for human since the metal has tendency to bioaccumulate in the living tissues. Accumulation of mercury doesn't have negative impact only on environment rather it harms animals and populations consuming these animals and their products. Mercury can't be removed by cooking process so it is a matter of great concern that meat and dairy products might bioaccumulate dangerous heavy metals like mercury as these products have significant role in human nutrition. Consumption of these sources of mercury viz. contaminated milk and meat enters humans leading to many health consequences in pregnant women, developing embryos and infants. Mercury induces malformation in embryo so it is also called embryocidal and teratogenic agent. Additionally, due to its mutagenic and carcinogenic nature people exposed to it may develop risk of cancer, deafness and blindness and permanent neurological anomalies (Noto 2021).

Mercury has ability to induce pathophysiological changes in the hypothalamus–pituitary–adrenal and gonadal axis that might have an impact on reproductive function by ways of changing hormonal levels of androgens, progesterone, inhibin, oestrogen, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the blood (Davis et al. 2001; Schrag and Dixon 1985). Both men and women experience infertility as a result of elevated mercury levels (Dickman et al. 1998). Mercury adversely effects on testicular weight, epididymal sperm count and spermatogenesis in males (Boujbiha et al. 2009). Additionally, evidence suggests that mercury has potential to induce erectile dysfunction (Schrag and Dixon 1985).

Studies have proven that mercury prevents the anterior pituitary in females from releasing FSH and LH, which can influence the level of oestrogen and progesterone causing painful or irregular menstruation, ovarian dysfunction, tilted uterus and premature menopause (Chen et al. 2006). Mercury is strongly associated with menstruation disorders including short, lengthy or irregular cycles, abnormal bleeding and painful periods (Davis et al. 2001).

Mercury is linked with foetal toxicity, which can be observed in spontaneous abortions, miscarriages, low birth weights and stillbirths in addition to severe reproductive problems. Mercury is known to pass through the placenta, where it may interfere with embryonic brain growth, leading to psychomotor retardation and cerebral palsy in later stages of development (Castoldi et al. 2001; Myers and Davidson 1998). Mercury exposure during pregnancy has been related with numerous birth abnormalities in neonates including defects in neural tube, abnormal craniofacial feature, delayed growth and others (Yoshida 2002).

Humans have also been subjected to embryo-pathogenic effects due to methylmercury. MeHg is a substance that quickly crosses the placenta and harms the developing foetus's brain. Foetal autopsies revealed a broad hypoplasia of the cerebellum, a reduction in the amount of nerve cells in the cerebral cortex, a significant loss in total weight of brain, improper migration of nerve cells and an abnormal arrangement of the brain's centres and layers (Choi et al. 1978; Mottet et al. 1985).

Peripheral motor neurons, autonomic ganglia, ganglia, brain and spinal cord are thought to bind mercury strongly immediately after its entrance to the body tissues.

Although the neurological system is the main organ where mercury is stored, symptoms could still develop in a variety of other organ systems due to mercury's temporary and persistent systemic dispersion. Furthermore, researchers suggest that a person's genetic heritage may differ in mercury toxico-kinetics (Gundacker et al. 2010). It is universally acknowledged that occupational chronic exposure to high mercury vapour concentrations can lead to high mercury level accumulation in the brain (Falnoga et al. 2000) and other tissues as the inorganic mercury deposited in brain following exposure of mercury vapour has long half-life. In addition to the brain (Guzzi et al. 2006), metallic mercury gets accumulated in the muscles (Björkman et al. 2007), adrenals (Berlin and Ullberg 1963), liver (Danscher et al. 1990), kidneys (Guzzi et al. 2006; Kumari 2021), thyroid (Björkman et al. 2007), myocardium (Frustaci et al. 1999), skin (von Burg 1995), breast (Crespo-López et al. 2009), sweat gland, pancreas, enterocytes, lungs, salivary glands, testes and prostate (Berlin and Ullberg 1963) and may be linked with dysfunction of these organs. Additionally, mercury shows strong affinity towards sulfhydryl groups that affect T cell activity and binding sites present on the surface of T cells (Hultman and Pollard 2022). Breast milk contains mercury, which rapidly accumulates in the placenta and embryonic organs (Vimy et al. 1990).

Cardiomyopathy has also been associated with abnormal deposition of mercury in the heart. Researchers showed that the average level of mercury deposited in the cardiac tissue of people who died of idiopathic dilated cardiomyopathy was 22,000 times more in their cardiac tissues than those people who died of other types of heart diseases (Haffner et al. 1991). Angina or chest pain can also be brought on by mercury poisoning, especially in people under the age of 45 (Frustaci et al. 1999). The cardio-protective effect of paraoxonase 1 may be inhibited by MeHg, according to in vitro investigations (Drescher et al. 2014). There is strong evidence connecting mercury to haemolytic and aplastic anaemia, since mercury and iron may compete with each other for binding with haemoglobin, which interrupts synthesis of haemoglobin. Additional evidences have revealed that mercury may contribute for the development of leukaemia, Hodgkin's disease, mononucleosis and other diseases in addition to anaemia (Pyszel et al. 2005).

The pituitary, thyroid, adrenal glands and pancreas may be disrupted by low exposure levels of mercury, which can have an impact on the endocrine systems of both people and animals (Minoia et al. 2009). Mercury is assumed to affect endocrine function by inhibiting one or more essential steps or enzymes in biosynthesis of hormones, as is the case with synthesis of adrenal steroid and suppression of 21-hydroxylase. Mercury is also thought to impair hormone-receptor binding (Iavicoli et al. 2009). By inactivating *S*-adenosyl-methionine, mercury can also prevent the breakdown of catecholamines, leading to a build-up of adrenaline, ptyalism (hyper salivation), hyperhidrosis, hypertension and tachycardia (Clifton 2007).

The diagnosis of autism is characterised by difficulties in social interaction, language and communication, a need for consistency and regularity, sensory anomalies and aberrant movements (Solt and Bornstein 2010). Some researchers have suggested that cases of autism may be associated with mercury poisoning because mercury can produce immunological, neurological, sensory, motor and behavioural

dysfunctions, that are comparable with features characterising or linked with autism (Bhardwaj et al. 2009). MeHg in the diet has a significant effect on the overall mercury level in the brain in a population that consumes fish. Therefore, distinction between mercury species is required to assess how exposure to dental amalgam and fish consumption impacts the level of mercury concentrations in the brain (Björkman et al. 2007).

The thyroid gland regulates the metabolism, protein synthesis and hormone sensitivity. The thyroid exhibits a tendency to accumulate mercury, similar to the pituitary. By occupying iodine-binding sites, mercury inhibits or modifies the function of hormones, impairing body temperature regulation and causing depression, hypothyroidism and thyroid inflammation (Wada et al. 2009).

The negative consequences of mercury are extremely harmful for the pancreas. Mercury may combine with the three sulphur-binding sites of insulin thereby interfering with normal biological processes and disrupting the regulation of blood glucose levels (Chen et al. 2006). Teenagers and other vulnerable groups seem to be greatly influenced by low levels of pituitary function induced by mercury toxicity which are ultimately linked to depression and suicidal thoughts in them. Mercury poses direct impact on neurohypophysis leading to frequent urination and elevated blood (McGregor and Mason 1991).

5.5 Mercury-Induced Cytotoxicity

Because of its affinity for sulfhydryl and thiol groups, mercury exposure causes changes in macromolecular structure at the cellular level in addition to causing DNA damage (Wang and Jia 2005). Additionally, it has been demonstrated that mercury causes mitochondrial dysfunction and oxidative stress (Lund et al. 1993), which might enhance lipid peroxidation and affect calcium homeostasis (Peraza et al. 1998). Mercury has the ability to act as a catalyst for Fenton-type reactions, which is known to raise levels of reactive oxygen species (ROS) (Peraza et al. 1998). Four basic processes that can be attributed to mercury-mediated genotoxicity are—oxidative stress and free radical generation, effect on DNA repair pathways, impact on microtubules and its direct association with DNA molecules (Crespo-López et al. 2009).

Although the exact process that leads to put harmful impact of mercury on the cardiovascular system is not known yet, it is thought to induce an increase in oxidative stress. Free radical generation is increased by mercury exposure, possibly as a result of mercury's involvement in the Fenton reaction along with declining activity of antioxidant enzymes like glutathione peroxidase (Genchi et al. 2017). Reactive oxygen species (ROS) are produced as a result of mercury toxicity and these ROS are capable of destroying crucial metabolic pathways, which ultimately results in cell death (Barón-Sola et al. 2021; Ajitha et al. 2021). MeHg has been shown to stimulate reactive oxygen species (ROS), including hydroxyl radical, superoxide radical, oxygen singlet, hydrogen peroxide, peroxyl radical, nitric oxide and alkyl

radical, which can damage the cells. The doses necessary to cause these responses vary according to the concentration of MeHg available in the environment (Ercal et al. 2001).

The production of ROS is a natural phenomenon against any stress. The preservation of a healthy thiol state is primarily indicated by the GSH/GSSG ratio, which is essential for shielding cells from oxidative damage. The key enzymes involved in reducing glutathione disulphide (oxidised glutathione; GSSG) and detoxifying peroxides are glutathione peroxidase (GPx) and glutathione reductase (GR), respectively (Dringen 2000). Even in the absence of considerable changes in GSH levels or the GSH/GSSG ratio, MeHg can result in oxidative stress due to its direct interaction with nucleophilic protein groups (Farina et al. 2010). Another notable in vivo investigation revealed that prenatal MeHg exposure prevented the antioxidant GSH system from developing normally in the first few weeks following birth (Stringari et al. 2008).

The negative charge produced by the respiratory chain of the mitochondrial matrix (Go and Jones 2013) allows the inorganic Hg^{2+} to penetrate mitochondria and disorganise oxidative phosphorylation (OXPHOS) (Dröse et al. 2014). Mercury gets localised in protein content of mitochondria (Mieiro et al. 2015), because of its higher affinity to -SH group of cysteine residue of protein (Mailloux et al. 2015; van Iwaarden et al. 1992), leading to alteration in protein structure.

Mercury was found to be intracellularly linked to membrane organelles viz. mitochondria, Golgi complex, nuclear envelopes, endoplasmic reticulum and lysosomes, according to a biochemical and electron-microscopic histochemical study with trace levels of mercury within the nucleus (Chang 1977). Mitochondrial malfunction coupled with decreased ATP was reported. It was capable to induce oxidative stress with rise in lipid peroxidation and reduction in glutathione. Thrombosis, dyslipidemia, loss of endothelial function, mitochondrial anomalies, dysfunction of vascular smooth muscle were observed as negative indication on vascular system against toxic impacts of mercury. Mercury has potency to generate negative impact on omega-3 fatty acid and immune response in fishes. Mercury-induced therapeutic consequences include considerable atherosclerosis, proteinuria condition having renal anomalies, CVA, MI, CHD and hypertension. Studies provide strong and logical correlation between biochemical, pathological and functional medicines (Houston 2005).

The cytotoxic impact of mercury can be best studied using histo-pathological biomarkers, since these changes provide a quick way to identify the influence of irritants in the various cells, tissues and organs (Bernet et al. 1999). In vivo study of the toxic impacts of mercuric chloride on kidney and liver of a fresh water air-breathing fish *Clarias batrachus* have shown prominent anomalies in the histological architecture of liver and kidney in piscine model (Kumari 2021). Various histopathological anomalies encountered in renal corpuscles were shrinkage and constriction of glomerular tufts, appearance of hyalinised, necrotic and avascular glomeruli, and their fusion, inflammation of podocytes and widening of urinary space as well. Besides, increased incidence of necrotic tubule with hyalinized and degenerated renal epithelial cells, infiltration of oedematous fluid, lymphocytes, plasma cells and debris of cytoplasmic organelles in the lumen of proximal and distal convoluted tubule,

collecting tubule, massive fibrosis of arcuate artery and arcuate vein, congestion of inter-tubular space with fibrous tissues, neoplastic plasma cells, other inflammatory cells, etc. (hydronephrotic kidney) were reported. The electron micrographs of renal tissues of mercury-treated fish showed discontinuity in nuclear membrane, thick deposition of heterochromatin at periphery of inner lamella, increased incidence of apoptotic vesicle, reduction in the number of cytoplasmic organelles, congregation and fusion of degenerating mitochondria with dissolved cristae, loosened and inflamed cisternae of RER, clumping of lumen of DCT, PCT and more specifically CT with bulk of inflammatory cells, pus, fibrous clots, fusiform vesicles, appearance of autophagic and apoptotic vesicles, etc. (Kumari 2021).

Light photomicrographs of treated liver showed constriction in central vein due to infiltration of eosinophilic inclusions, plasma cells, hemorrhagic clots and edematous fluid and deposition of fibrous tissues around it. Besides appearance of swollen and hydropic hepatocytes with bridging necrosis, congested sinusoids filled with bile, perivenular fibrosis and plugging of portal vein by hemorrhagic clots and eosinophilic inclusions, hepatocellular necrosis, neoplasia, hepatoblastoma and chronic venous congestion were prominently marked (Kumari 2021). The worldwide pollutant mercury has a significant negative impact on many facets of human health. It has hazardous impact on many physiological systems in humans such as urinary system, immunological system, cardiovascular system, skin, endocrine system and respiratory system (Chen anf Driscoll 2018).

5.6 Mercury-Induced Neurotoxicity

It was revealed that mercury rapidly penetrates and damages the blood–brain barrier, causing the system to become dysfunctional. It was discovered that the granule cells in the cerebellum and sensory neurons in the spinal ganglia were especially susceptible to mercury poisoning in experimental mice. According to ultrastructural investigations, coagulative type of degeneration was primarily seen in organic mercury poisoning while vacuole type of degeneration of the neurons was primarily linked to inorganic mercury intoxication (Chang 1977).

Methylmercury (MeHg) is deadly poisonous substance to CNS (central nervous system). Prenatal phase of life is assumed to be most vulnerable time (Davidson et al. 2000). MeHg prevents essential brain growth processes such as neuronal cell division and its migration (Sager et al. 1984). The earliest examples of prenatal poisoning were documented during the methylmercury outbreaks in Japan, describing abnormal features in the brain of foetus. The cytoarchitecture of the human prenatal brain was disrupted, and it appeared to be more vulnerable to methylmercury than the adult brain. Blindness, ataxia and mental retardation were all signs of prenatal exposure, while moderate exposure was linked to motor skill impairment, high exposure caused severe mental retardation and mortality (Davidson et al. 2000; Myers et al. 2003).

Biochemical and cytochemical tests revealed that mercury-intoxicated mice had much lower neuronal RNA and protein production. Reduction in protein production was thought to cause cell death in these neurons. In chronic mercuric dichloride intoxication, RNA levels of neurons were restored. This study may indicate that these animals are more resistant to the damaging effects of mercury. Mercury-poisoned animals also had enzymatic system disruptions in the glycolytic pathway. Mercury poisoning was discovered to be especially dangerous to granule cells in the cerebellum and sensory neurons of spinal ganglia. Ultrastructural studies revealed that inorganic mercury poisoning was related with vacuolar neurodegeneration, whereas organic mercury poisoning was associated with coagulative neurodegeneration. Nerve fibre degeneration was also found (Chang 1977).

In an experiment, prolonged low doses of inorganic mercury exposure in adult rats resulted in deposition of mercury in the brain parenchyma coupled with oxidative stress and damage of cell via cytotoxicity leading to cell death, which impairs motor function (Fig. 5.2). The motor cortex exhibited cytotoxicity and apoptosis as a result of chronic $HgCl_2$ exposure, demonstrating that inorganic mercury has lethal impact on central nervous system. Although other brain regions, such as basal ganglia and cerebellum, may also be involved in the detrimental impact of exposure, the motor cortex may be particularly important in the motor deficits brought on by inorganic mercury. On inorganic mercury exposure, astrocyte and neuronal cellular densities in the motor cortex were decreased. Additionally, research findings showed that abnormalities in behaviour were connected to both cellular and molecular damage (Teixeira et al. 2018a, b). Another toxicological investigation had already shown that the decline in both astrocyte and neuronal numbers is typically linked to the functional damage observed in behavioural testing (Flores-Montoya et al. 2015; Maodaa et al. 2016).

Rice et al. (2014a), have considered MeHg as a highly neurotoxic chemical that mainly damages glial cells, induces oxidative stress and triggers neuroinflammation. Gender is a crucial aspect to consider when investigating MeHg-exposed animals and analysing motor defects. An unexpected observation from mice exposed to methyl mercury-containing drinking water as revealed that female mice were found to be more resistant to MeHg-induced motor disability than male mice. In line with this finding, two weeks of ad libitum exposure to MeHg in drinking water resulted in a severe motor dysfunction in male adult Swiss mice but not in females (Malagutti et al. 2009). Malagutti et al. (2009), also added that sex steroids have neuroprotective properties because 17-estradiol co-administration prevented male mice from the neurotoxic effects induced by oral exposure of methyl mercury. Large myelinated fibres were found to me more vulnerable in comparison to small neuronal cells (Chang 1977).

A study was done on 80 community members with median age of 57 years native to Grassy Narrows First Nation, Ontario, Canada, in which 55% of members were women. The water of their territorial region had mercury contamination by means of industrial discharge. These people experienced long-term exposure to methyl mercury due to consumption of contaminated fishes. In this study, the mercury-exposed visual characteristics were documented between 1970 to 1997 in which all

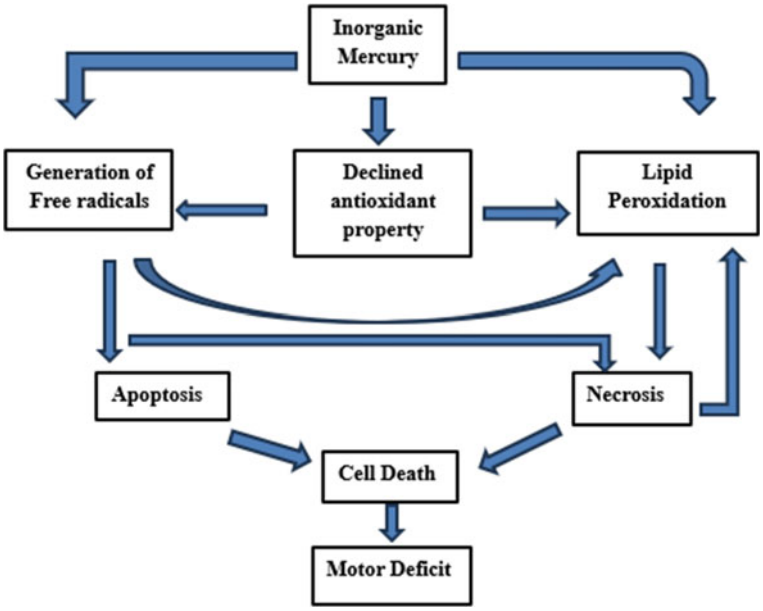

Fig. 5.2 Model of oxidative stress brought on by inorganic mercury deposits

the community members had their eyes and vision tested for optical coherence tomography (OCT), automated visual field, sensitivity to colour and contrast and visual acuity. As a result, it was observed that community members with chronic exposure to mercury had lost contrast sensitivity, impaired colour vision and significant loss of visual fields (Tousignant et al. 2023).

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