MERCURY-INDUCED HEAVY METAL TOXICOSIS: A REVIEW

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INTRODUCTION

Most heavy metals in the environment can cause conditions collectively referred to as heavy metal toxicosis or poisoning. Such conditions are influenced by the quantity involved, pathophysiology and even radioactivity of the heavy metal (1–3). Cases of heavy metal poisoning in humans have been documented since antiquity (4), becoming more relevant over the last century due to global industrialisation, greatening the risk of occupational and environmental exposure. This concerns pesticide use, industrial runoff or effluent, spills, and leakages, amongst others. Bioaccumulation can subsequently occur once toxic heavy metals contaminate the environment, which negatively impacts different organisms, including humans. In recent times, protocols to phase out all heavy metal use and improve occupational and environmental health and safety have started implementation (5,6). Consequently, notable decreases in heavy metal emissions are now being observed in some geographic regions (Figure 1).

From the heavy metals that exist, arsenic, cadmium, lead, mercury, and thallium are consistently mentioned in literature for their toxic effects (2,7–10). Physiologically important heavy metals, otherwise known as trace minerals, are also known to cause human poisoning (8,9). The term 'heavy metal toxicosis' encompasses the signs and symptomatology observed in most cases of poisoning by heavy metals, however, unique pathophysiological mechanisms between different aetiological heavy metals make a heavy metal toxicosis caused by one heavy metal different from another (Table 1). For the purpose of this review, the discussion will only tackle heavy metal toxicosis induced by mercury (Figure 2).

Heavy metal toxicosis has a worldwide incidence and this is especially true for mercury, with all humans considered to have some degree of exposure to this heavy metal throughout their lifetime. Due to its ubiquity, high potency, and eco-biological effects, mercury has been ranked as one of the top ten chemicals that are of major concern to public health by the World Health Organisation (11). This is reflected in the findings of a 2020 report which gathered exposure and poisoning case data from fifty-five regional poison centres that served the entire population of the United States and its territorial extent for the year of 2019. A total of 2,337 single exposures to mercury, in any chemical form, had been documented, with most cases being unintentional (89.4%), in adults aged 20 or over (69.1%), and with mercury thermometers being the commonest exposing source (44.1%) (12). A smaller scale study done in Beijing, China also reported similar demographic findings (13). Countries which have a large or significant proportion of workforce in the mining or chemical plant industry have higher rates of mercury-induced toxicosis, these include mainly Asian countries such as Bangladesh, China, and India, and African countries such as Burkina Faso, South Africa, Tanzania, and Zimbabwe (10,11,14–18). Other countries like Iraq and Japan have increased prevalence of mercury-related disease due to previous industrial incidents (10,11,18). Higher incidence of mercury

poisoning is also observed in countries where there is less strict regulation of the occupational sector and consumer market, such as Egypt and Somalia (19,20). Conditions related to chronic mercury exposure are more common in countries with large fishing populations and high fish consumption, such as Brazil, Canada, China, Colombia, and Greenland (11).

The toxic effects of heavy metals like mercury are attributed to their physicochemical similarity to trace minerals required by the human body, enabling them to undergo redox reactions and form coordination complexes, displacing physiologically important metals from their ligands. This also allows binding to other cellular components where metals are not normally found, such as nucleic acids, structural proteins, and enzymes, interrupting normal function. Coordinate bonding is also of pharmacodynamic importance, particularly in chelation therapy, which is currently the main treatment modality for mercury-induced heavy metal toxicosis (mercury poisoning).

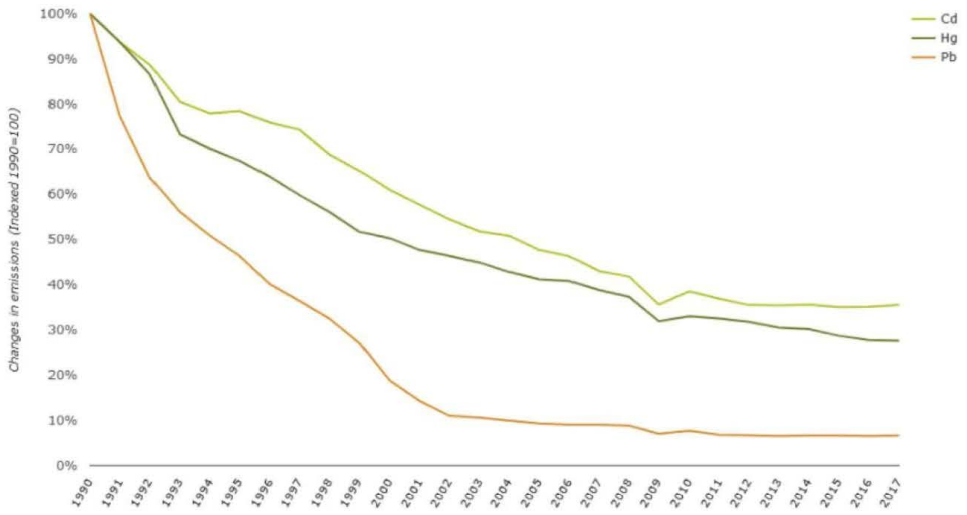

Figure 1: Trends in heavy metal emissions across the 33 EEA member countries. (Taken from European Environment Agency, 2019)

		Organ systems and their associated signs, symptoms, and pathology in heavy metal toxicosis									
		Respiratory	Digestive	Cardio-vascular	Renal	Repro-ductive	Endocrine	Nervous	Musculo-skeletal	Integu-mentary	Haemato-poietic	Systemic
Toxic heavy metal	Arsenic	Chronic lower respiratory disease	Vomiting, haematemesis, diarrhoea, abdominal pain	Arrhythmia, hypertension, stroke	Haematuria		Diabetes	Nausea, encephalopathy, neuropathic pain, confusion, fatigue, convulsion, nyctalopia	Muscle cramps	Hypo-pigmentation, hyper-pigmentation, hyperkeratosis, alopecia		Multiorgan effects, cancer
	Cadmium	Pneumonitis, tracheo-bronchitis, alveolitis, lung cancer, pulmonary oedema, cough			Kidney failure	Testicular degeneration, prostate cancer		Dizziness, fatigue, anosmia	Osteomalacia, osteoporosis, muscle pain		Anaemia	Fever, chills
	Lead		Vomiting, abdominal pain, diarrhoea, constipation		Kidney failure, acquired Fanconi syndrome	Erectile dysfunction		Encephalopathy, encephalitis, nausea, nerve palsy, amnesia, insomnia, delirium, cognitive deficit, tremor, hallucination, convulsion, dysarthria, paraesthesia, depression, fatigue, incoordination, toxic psychosis	Muscle pain	Lividity	Anaemia	Weakness, loss of appetite, weight loss, malaise
	Mercury	Cough, dyspnoea, asthma, bronchitis, adult respiratory distress syndrome	Diarrhoea, vomiting, stomatitis, hypersalivation, appendicitis, gingivitis, xerostomia, mouth ulceration, tooth loss, abdominal pain, constipation, colitis	Tachycardia, hypertension	Nephrotic syndrome, glomerulo-nephritis			Nausea, neurasthenia, parageusia, tremor, peripheral neuropathy, formication, diaphoresis, paraesthesia, delayed reflex, hyperexcitability, erethism, memory loss, Minamata disease, vision loss, hearing loss, incoordination, dysarthria	Acrodynia, myalgia	Acrodynia, desquamation, dermatitis, subcutaneous granuloma, hyper-pigmentation, vesiculating or scaly rash, nail discolouration		Fever, pain, weakness, chills, loss of appetite
	Thallium		Glossitis, hepatitis, abdominal pain, vomiting, constipation, diarrhoea	Hypertension				Peripheral neuropathy, optic neuropathy, tremor, ataxia, formication, paraesthesia, dysaesthesia, insomnia, neuropsychiatric disorders, nausea	Myalgia	Alopecia, xeroderma		Weakness

Table 1: The symptomatic and pathological variation exhibited in different heavy metal toxicoses as induced by some of the most toxic heavy metals currently known. (Adapted from Henningsson et al., 1993; Wössmann et al., 1999; Patrick, 2002; Ibrahim et al., 2006; Siu et al., 2009; Park and Zheng, 2012; Maret and Moulis, 2013; Afal and Wiener, 2014; Jaishankar et al., 2014; Senthilkumaran et al., 2017; Bjeloševič et al., 2018; CDC, 2018; Ganguly et al., 2018; Azeh Engwa et al., 2019; WHO, 2019; Kemnic and Coleman, 2021; Rajkumar and Gupta, 2021)

MERCURY IN THE ENVIRONMENT

The quantity of mercury within the natural environment has been elevated by anthropogenic pollution (35), bioaccumulating in prone aquatic ecosystems that include predatory fish such as shark, tilefish, swordfish, king mackerel and tuna, freshwater fish such as pike, bass, muskellunge and walleye, and shellfish (Figure 3) (36–38), which are the main natural source for humans to acquire mercury poisoning (11,18,39). This has led to recommendations being made for children and pregnant or breastfeeding women to avoid the consumption of such fish to reduce the risk of impaired neurodevelopment of the child or foetal brain (11,18). Occupational roles within the mining, hydroelectric, chemical, and agricultural industries (36,40), and consumer products and appliances, such as glass thermometers, barometers, certain fluorescent lamps, dental amalgams, button cells, old television sets, laboratory preparations, certain vaccines, topical products, and traditional medication or practices also pose risk for mercury poisoning (7,41,42). A gradual phase out process (Figure 1) has reduced the incidence of mercury poisoning, however lack of strict regulation in some areas has allowed for some mercury-containing products to remain commercially available, and considerable risk is still present (43).

Figure 2: A glass ampoule containing pure elemental mercury. Being liquid at room temperature enables mercury to seep through any potential cracks that may form in such apparatus if mishandled, increasing the likelihood of an exposure incident.

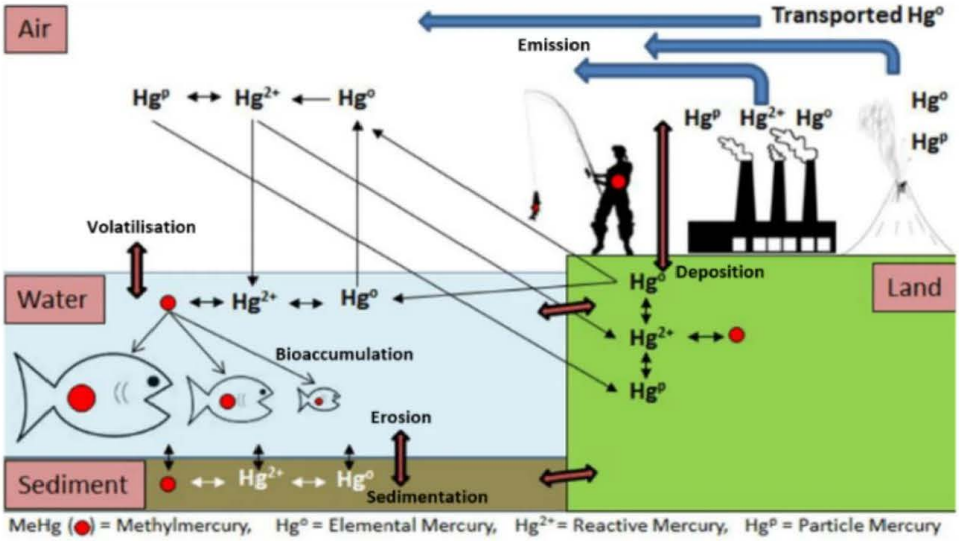

Figure 3: The mercury cycle, depicting the physical and chemical transformations of mercury in different environmental reservoirs, and its bioaccumulative properties. (Taken from NHDES, 2019)

PHYSICOCHEMICAL INFLUENCE ON MERCURY POISONING

Like other metals, part of the chemical nature of mercury is the ability to form organic and inorganic compounds. Physicochemical differences between the pure metal, its organic compounds, and its inorganic compounds, can significantly influence the toxicology of mercury, from the exposing source to the symptoms manifested (Table 2). This may complicate diagnosis and thus highlights the need to collect a detailed history and correlate this with the clinical presentation and subsequent investigatory findings.

In the natural environment, organic and inorganic forms (compounds) of mercury are mostly found, acting as different, interlinked mercury reservoirs influenced by both natural and artificial processes, comprising the mercury cycle (Figure 3) (36–38). Mercury in pure metallic form is very rarely found in the natural environment, and large quantities of it are instead artificially formed (37). The physicochemical properties of the encountered form dictate the place of absorption and bloodstream entry, hence, many potential aetiologies attributable to mercury poisoning (26). Being a volatile liquid metal at room temperature (Figure 2), pure elemental mercury emits colourless, odourless vapours, making inhalation the most likely route of exposure. This also makes it possible for mercury to be aspirated via syringe, being implicated in cases of self-harm, where a mercury bolus would have been intravenously administered. In such cases, the bolus itself does not cause systemic toxicity, instead it acts as an embolus, causing physical blockage of blood vessels at the injection site and in more vulnerable areas such as the lungs (44). Elemental mercury is only able to cause systemic poisoning by inhalation due to the thinness and dense vascularisation of the pulmonary mucosa, thus any inhaled vapours are easily absorbed into the circulation (44).

The toxicodynamics of organomercury compounds gained relevance in environmental toxicology much more recently, particularly with methylmercury due to its significant bioaccumulative properties within food chains, enabling predatory species to accumulate large amounts of the compound, which are then consumed by humans (45). Therefore, organomercury exposure typically happens by ingestion (46). Poisoning by inorganic mercury is comparatively rarer since potential sources of exposure are quite limited, but usually occurs either by ingestion or contact because of its continued use in topical products in certain regions (26). Organomercury compounds are the most capable of traversing the bodily mucosae due to their lipophilic nature that allows them to dissolve in oily sebaceous skin secretions and traverse cell membranes, enabling significant transdermal, pulmonary, and gastrointestinal absorption (44). Certain compounds, such as dimethylmercury, have also demonstrated the ability to permeate through latex gloves (2,47). Larger organomercury compounds are less toxic to humans as their larger carbohydrate chains reduce the ability of the molecule to cross cellular membranes (44). If ingested, the mercury atoms of organomercury compounds may be liberated from their molecules as divalent cations (Hg^{2+}) by the acidic environment in the stomach or by intestinal bacteria (2). Such cations are identical to those liberated from toxic mercuric salts. Inorganic mercuric salts exhibit efficient gastrointestinal absorption, owing to the ability of Hg^{2+} ions to utilise non-specific metal transporters within the gastrointestinal mucosa for their uptake (48).

In the bloodstream, atoms of mercury and organomercury compounds can cross continuous capillaries, including those of the blood-brain barrier and placenta, due to a greater lipid solubility. This may either occur by simple diffusion or via a transporter (46). The mercuric cation is water soluble and can only pass through more porous fenestrated or sinusoidal capillaries (49). Intracellularly, it is the inorganic and organic forms of mercury that mainly cause pathology in relation to sulfhydryl binding (Figure 4). Elemental mercury instead may bind other moieties, including phosphoryl, carboxyl, and amide side groups (50).

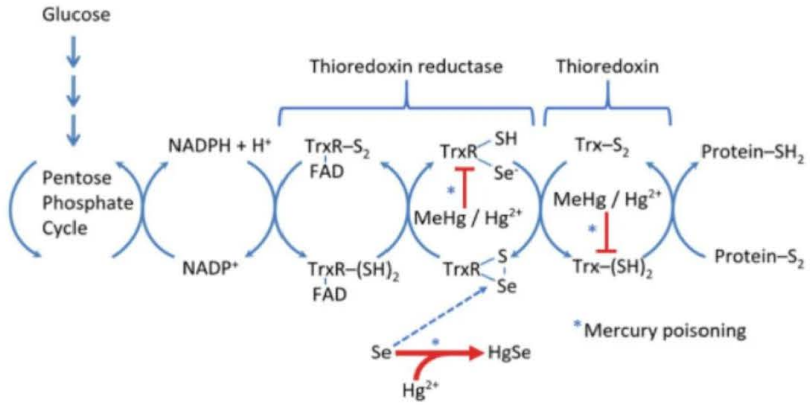

Figure 4: Schematic representation of the biomolecular basis of mercury poisoning as caused by organic and inorganic mercury. Note: NADP+: nicotinamide adenine dinucleotide phosphate; FAD: flavin adenine dinucleotide; Hg2+: mercury (II); Se: selenium; MeHg: methylmercury; HgSe: mercury selenide. (Adapted from Holmgren and Lu, 2010)

		Elemental mercury (Hg^0)		**Inorganic mercury (e.g.: Hg^{2+})**		**Organic mercury (e.g.: MeHg)**	
Route of exposure		Inhalation, ingestion, contact, injection		Ingestion, contact, injection		Ingestion, contact	
Place of absorption		Pulmonary, *intestinal* [a], *transdermal*		Intestinal, transdermal, *pulmonary*		Intestinal, pulmonary, transdermal	
Toxicity		Acute	Chronic	Acute	Chronic	Acute	Chronic
Affected organ systems and significantly associated symptoms	Nervous	Paraesthesia, weakness, tremor chills, delayed reflex, hyperexcitability, erethism [b], memory loss	Acrodynia [c], erethism [f], headache, tremor [f], incoordination		Acrodynia, erethism	Paraesthesia, peripheral vision loss, hearing loss, ataxia, incoordination, tremor, dysarthria	Minamata disease, congenital Minamata disease [d]
	Renal	Acute renal failure	Chronic renal disease [e]	Acute renal failure	Membranous glomerulonephritis, chronic renal disease	May manifest as a result of chemical conversion to other forms within the body	
	Gastrointestinal	GI upset, appendicitis	Gingivitis [f], stomatitis, xerostomia, mouth ulceration, hypersalivation, tooth loss, GI upset, abdominal pain, constipation, reduced appetite	Oral pain, gingival irritation, stomatitis, chest pain, abdominal pain, nausea, vomiting, GI haemorrhage, colitis, sloughing or necrotising of GI mucosa, diarrhoea			
	Respiratory	Cough, dyspnoea, asthma, bronchitis, adult respiratory distress syndrome, lung damage, hypoxia					
	Integumentary	Dermatitis, subcutaneous granuloma	Acrodynia	Grey-brown hyperpigmentation, swelling, dermatitis, vesiculating or scaling rash, nail discolouration	Acrodynia		
	Musculoskeletal		Acrodynia, myalgia, proximal weakness		Acrodynia		

Table 2: Pathophysiological variability of different forms, sources, and exposures of mercury results in different symptomatic manifestations that may complicate diagnosis, also applicable to other heavy metal toxicoses. Sites written in italics indicate a less likely mode of absorption. (Adapted from Haddad and Stenberg, 1963; Bradberry et al., 1996; McKinney, 1999; Boyd et al., 2000; Ibrahim et al., 2006; Chan, 2011; Park and Zheng, 2012; Jaishankar et al., 2014; Kim et al., 2015)

ROUTES OF EXPOSURE

Exposure routes depend on the source and form of mercury involved, generally including inhalation, ingestion, contact, and rarely intravenous injection in self-harm or murder cases (2,24,26,48,58). Organic mercury is the most frequently involved form, being almost ubiquitous in the natural environment and highly bioaccumulative (Figure 3) (45,46). Thus, toxic amounts could easily be ingested, as demonstrated by previous incidents concerning the consumption of food and drink with excessive levels of methylmercury (59,60). Inorganic salts of mercury are less accessible to the public, however, sales of certain topical products such as skin lightening creams and ointments, cosmetic soaps, eye make-up, mascara, and cleaning products containing these salts mean that contact exposure is still a relevant means of acquiring mercury poisoning (26).

PATHOPHYSIOLOGY

The chemical form influences how much and where mercury can enter and leave the circulation (Table 2). Once taken up by tissues, intracellular mercury may be converted into the inorganic ion, Hg^{2+}, through oxidation or demethylation (24). The pathophysiology of mercury poisoning usually involves this mercuric cation, or else an organomercury compound should this be implicated in the exposure (Figure 4). Both forms bind sulfhydryl groups of intracellular thiol molecules such as cysteine, thioredoxin, glutathione, albumin and S-adenosylmethionine, impairing function (24). With regards to thioredoxin (Figure 4) and glutathione, their respective antioxidant-generating redox reactions, present in all living cells of the human body, become blocked (61,62). Inorganic mercury additionally sequesters cellular selenium, forming mercury selenide and inhibiting thioredoxin reductase selenoenzyme biosynthesis (Figure 4). This decreases antioxidant recycling, rendering the cell unable to reduce reactive oxygen species and control oxidative damage (51,63,64). Consequently, cellular components such as mitochondria, lipids, microtubules, ribosomes, endoplasmic reticula, and genes become oxidatively altered or damaged, and homeostatic processes involving membrane potential, proteins and calcium become disrupted (24). Tissue load and rate of oxygen consumption determine the extent of the damaging effects, therefore tissues such as brain tissue are more vulnerable (65). In the brain these processes lead to neurotoxic build-up of serotonin, glutamate, and aspartate due to a degraded microtubular structure (24). Inhibition of S-adenosylmethionine, a catecholamine-O-methyltransferase cofactor, further deteriorates neural physiology, causing catecholamine accumulation, hence leading to adrenergic symptoms that are likened to a phaeochromocytoma (22,23,30). Other manifestations of mercury poisoning include renal impairment, autoimmunity, and skin irritation (24,26), however these mostly occur when certain forms of mercury are involved.

SIGNS AND SYMPTOMS

As mentioned earlier, mercury may chemically convert from one form to another in both extracellular and intracellular compartments, linking different pathophysiological processes together, and in turn, signs and symptoms may be mixed (Table 2) (2,24). Poisoning by organomercury is typically associated with neurological symptoms collectively known as Minamata disease (66,67). Inorganic mercury poisoning may also cause neurological symptoms, however it is more likely to cause renal damage than other forms of mercury poisoning (24,26,68). Additionally, there is now also evidence to support that inorganic mercury poisoning results in decreased hepatic and bone marrow function since these tissues possess capillary sinusoids (69,70). Organic and inorganic mercury also cause autoimmunity as part of the poisoning, whereby antibody production has been observed for myelin basic protein and glial fibrillary acidic protein in the brain, and the glomerular basement membrane of renal nephrons (71,72). These can be good indicators in the clinical presentation and investigatory findings (66,67). Elemental and inorganic mercury are more likely to cause an acute form of mercury poisoning that is more site-specific rather than systemic, as it is more difficult to reach pathology-inducing levels in the blood from their most common exposure routes. For instance, the application of topical products containing inorganic mercury can cause mild cutaneous symptoms such as irritation, suggested to be due to mercuric salt accumulation in sweat glands, sebaceous glands, and hair follicles (56). These acute exposures are also thought to have long-term implications, including a predisposition to Alzheimer's disease and Young's syndrome (26,73).

DIAGNOSIS AND MANAGEMENT

Symptom-based diagnosis of mercury poisoning is not recommended due to its variability and non-specificity (Table 2) (7). Diagnostic efforts should be focused on physical findings, appropriate history of when and how the exposure came to be, determination of the exposing agent, and identification of raised mercury body levels. Blood mercury biomarker indices may only be considered in combination with other clinical findings and if the exposure is either recent, chronic, or involves organic forms of mercury, as only these conditions have clinically significant blood mercury levels (74). The stability of mercury is greater in urine and hair; hence biomarker indices of such samples would be more indicative of possible poisoning. Furthermore, an association between urine mercury levels, memory, and language aptitude is also deemed to be diagnostically significant (75). Autoantibody levels of anti-glomerular basement membrane antibodies are suggested to be specific to mercury poisoning as well (75).

The management procedure for mercury poisoning is similar to other heavy metal toxicoses. The patient should first be isolated from the intoxicating source to prevent further inhalation or ingestion of, or physical contact with mercury, and subsequently decontaminated by removing contaminated clothing and washing, with possible lavage (24,39,75–79). This may be followed by further investigation to determine the extent of bodily dispersal and assess the state of exposed mucocutaneous tissue.

Chelation therapy is the primary treatment modality for mercury poisoning (Table 3) (9). Chelating agents are ions or molecules that possess atoms or side groups which can coordinate bond with a metal atom or ion by donating a pair of electrons, therefore acting as a ligand (9). Essentially, such agents exploit the ability of a metal ion, such as the mercuric ion, Hg2+, to bind to electron donor molecules within the body, such as sulfhydryl side groups, by possessing these side groups themselves (Figure 5). These actions stabilise the charged metal ion in a preferably inert and non-toxic complex with the chelating agent, favouring bodily excretion mainly via the renal and biliary systems (9,80). Various chelating agents are now available for administration, possessing different electron donor groups, with combination therapy also being common (Table 3) (9,79).

In severe mercury poisoning, patient stabilisation under vital organ monitoring is required. This may involve artificial ventilation, plasmapheresis, haemodialysis, haemoperfusion, intravenous therapy and possible mineral and antioxidant supplementation to mobilise the metal (9,34,75–79,81,82). Intervention may however not always be required, for example, since pure elemental mercury exhibits poor gastrointestinal absorption, it can be left to pass naturally from the body along with faeces under careful monitoring in cases where this has been ingested (54).

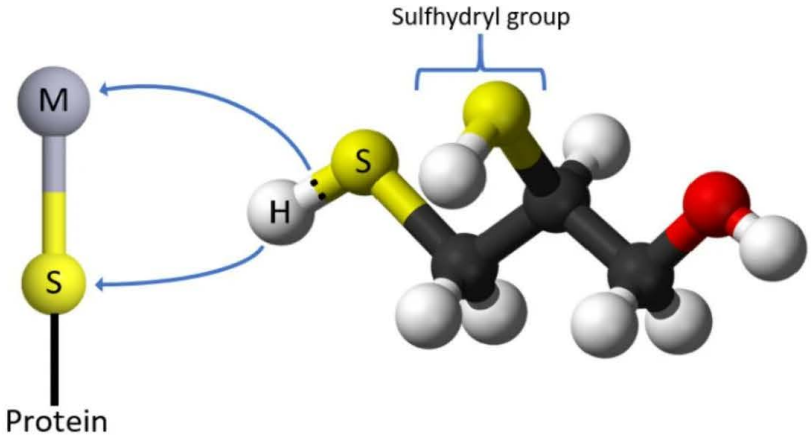

Figure 5: Simplified ball-and-stick model representing the mechanism of action of chelating agents. A molecule of dimercaprol is depicted where one of its sulfhydryl groups (labelled, -SH) is donating an electron pair (• •) to a metal atom (M) bound to a protein via a side group containing sulfur (S). This restores the original protein side group and isolates the metal atom from the protein. (Adapted from Wikimedia Commons)

		Metal												
		Cr [a]	Mn	Fe	Co [a]	Cu	Zn	Ag [a]	Cd	Sn [a]	Au	Hg	Tl	Pb	Bi
Chelating agent	Dimercaprol								✓ [b]		✓	✓		✓	✓
	Unithiol								✓			✓			✓
	Sodium calcium edetate		✓	✓		✓	✓		✓					✓	
	Siderophores			✓											
	Penicillamine					✓ [b]						✓		✓	
	Succimer								✓			✓		✓	
	Succimer analogues								✓			✓		✓	
	Prussian blue												✓		

Table 3: The viability of chelation therapy for treating mercury poisoning in comparison to various other metal toxicoses. Note: Cr: Chromium; Mn: Manganese; Fe: Iron; Co: Cobalt; Cu: Copper; Zn: Zinc; Ag: Gold; Cd: Cadmium; Sn: Tin; Au: Gold; Hg: Mercury; Tl: Thallium; Pb: Lead; Bi: Bismuth. (Adapted from Aaseth et al., 2016; Rafati Rahimzadeh et al., 2017; Kim et al., 2019)

CONCLUSION

In this review, the physicochemical influences, pathophysiology, clinical presentation, diagnosis, and management of mercury-induced heavy metal toxicosis have been outlined and discussed. Emphasis is to be made on how mercury poisoning can easily be prevented and its incidence reduced with proper regulation, enforcement and education when it comes to consumerism, occupational safety, and environmental health. Failure to do so will lead to significantly worse outcomes for both humans and the environment due to the reactive nature of mercury, and therefore merits a global cooperative effort.

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