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Heavy metal(loid) bioaccumulation in fish and its implications for human health

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Abstract
Heavy metal(loid)s (HM) pollution in aquatic environments is a serious issue due to the toxicity, persistence, bioaccumulation, and biomagnification of these pollutants. The main sources of HM contamination are industrial activities, mining, agricultural practices, and combustion of fossil fuels. Fish can accumulate HMs through a process called bioaccumulation. As larger predatory fish consume smaller fish, these HMs enter the main food chains and can become increasingly concentrated in their tissues and finally reach humans. Here, we provided a general and concise conclusion from current research findings on the toxicological effects on different body systems. Exposure to HMs can lead to a range of adverse health effects, including neurological damage, developmental disorders, kidney damage, cardiovascular problems, and cancers. Their long-term accumulation can result in chronic toxicity even at low levels of exposure. HMs exert cellular cytotoxicity by disrupting essential cellular processes and structures. They can interfere with enzyme function, disrupt cell membrane integrity, induce oxidative stress, and cause DNA damage, ultimately leading to cell death or dysfunction. Prevention and control of HMs involve implementing measures to reduce their release into the environment through regulations on industrial processes, waste management, and pollution control technologies. Additionally, monitoring and remediation efforts are crucial for identifying contaminated sites and implementing strategies such as soil and water remediation to reduce human exposure and mitigate the impact on ecosystems. To conclude, HM accumulation in fish poses serious risks to public health and the environment, necessitating urgent interdisciplinary efforts to mitigate their harmful effects and promote sustainable practices that reduce HM flow into biological systems.

Introduction
Heavy metal(loid)s (HMs) are generally defined as metals with relatively high densities, atomic weights, or atomic numbers. A density of more than 5 g/cm³ is sometimes quoted as the commonly used criterion (Pourret *et al.,* 2021). Indeed, a universally accepted, criterion-based definition for HMs does not exist, however, from a biomedical perspective, HMs can be defined as elements with high atomic mass or density (greater than 5 g/cm³) that exhibit toxic effects on biological organisms accumulate in ecosystems and pose environmental hazards due to their persistence and bioaccumulative potential (Ali and Khan, 2018). The criteria used and whether metalloids are included vary depending on the author and context. Therefore, it has been suggested that it is advisable to substitute the term "heavy metal(loid)s" with context-specific alternatives such as "metal", "metalloid", "trace metal elements", or "potentially toxic element". Some HMs are either essential nutrients (typically iron, cobalt, nickel, and zinc), or relatively harmless (such as ruthenium, silver, and indium), but can be toxic in larger amounts or certain forms. Other HMs, such as arsenic, cadmium, mercury, and lead, are highly poisonous (Balali-Mood *et al.,* 2021).
Essential heavy metals play crucial roles in various biological processes and are essential for human health. For instance, calcium and magnesium are integral for bone and teeth formation, enzyme activation, blood pressure regulation, and facilitating muscle contraction, nerve messaging, and blood clotting (Malik *et al.,* 2023). Chromium assists in maintaining normal blood sugar levels and helps cells extract energy from blood sugar (Tao, 2019; Monga *et al.,* 2022). Copper aids in fuel metabolism, red blood cell production, neurotransmitter regulation, and free radical elimination (Collins, 2021). Iron is vital for the formation of hemoglobin and myoglobin, enzyme activation, and the production of amino acids, collagen, neurotransmitters, and hormones (Jomova *et al.,* 2022).
Likewise, manganese is involved in bone formation and the metabolism of amino acids, cholesterol, and carbohydrates. Molybdenum activates several enzymes that detoxify the body and prevent harmful sulfite accumulation. Sodium and potassium both contribute to the balance of body fluids, nerve impulses, and muscle contraction. Lastly, zinc is involved in blood clotting, protein and DNA production, immune system support, wound healing, and cell division (Zoroddu *et al.,* 2019). While these metals are beneficial, they can be detrimental if present in excess amounts, thus, a balanced intake is essential for optimal health.

The emergence of HMs as a contemporary public health concern is attributable to escalating industrialization, urbanization, and human activities that release these elements into the environment. Intensive industrial processes, such as mining, manufacturing, and energy production, generate significant quantities of HMs, which, when released into air, water, and soil, contribute to environmental contamination (Li *et al.,* 2022). Urbanization further amplifies the problem, as the demand for construction materials and products containing HMs increases. On the other hand, agricultural practices, involving the use of fertilizers and pesticides, also introduce HMs into the soil and subsequently into the food chain (Alengebawy *et al.,* 2021). Inefficient waste disposal methods, including the improper handling of industrial, electronic, and household waste, contribute to metal pollution. Additionally, globalized trade and the combustion of fossil fuels contribute to the dispersion of HMs on a global scale. The cumulative effect of these factors poses a substantial risk to public health, as chronic exposure to HMs is associated with various adverse health outcomes, ranging from neurological disorders to cardiovascular diseases and cancer. Consequently, mitigating HMs pollution has become a critical focus in contemporary public health and environmental management strategies. This review aimed at addressing the bioaccumulation of HMs in fishes and their proved or expected health effects when reach humans.

Methods

This review provides a focused examination of the toxic mechanisms of HMs, specifically addressing the most prevalent ones: mercury, lead, cadmium, chromium, and arsenic. It draws general conclusions from current research findings on the toxicological effects on different body systems without delving into technical details due to the broad and multidisciplinary scope of the topic. The included studies were those documented in humans or other mammalian models, such as rabbits and mice. The literature for this review was sourced mainly from Google Scholar and PubMed. The search strategy targeted studies published between 2004 and 2024, with an emphasis on investigations involving human subjects and mammalian models. Research employing lower animal models or cell-based studies was excluded to maintain relevance to higher-order biological systems.

Sources of heavy metal(loid)s in fish

Certain HMs, including iron, manganese, copper, and zinc, naturally occur in aquatic environments due to geological processes and the Earth's composition. These elements originate from rocks, minerals, and soils and enter water bodies through natural weathering and erosion (Shah, 2021). Copper and zinc, essential trace elements, also occur naturally in the Earth's crust and can be present in water in small amounts. However, anthropogenic activities, such as industrial processes, urbanization, and agricultural practices, significantly contribute to elevated concentrations of these metals in aquatic ecosystems (Figure 1). Consequently, monitoring and managing HMs levels in aquatic environments are crucial for safeguarding both ecosystem integrity and human well-being.

Water contamination Contaminated water is a primary source of HMs exposure for aquatic life, including fish. Research indicates that heavy metals enter aquatic ecosystems through various anthropogenic activities such as industrial discharge, mining operations, agricultural runoff, and wastewater effluents (Aziz *et al*., 2023). HMs can enter water bodies through various sources such as industrial discharges, agricultural runoff, and municipal sewage (Zamora-Ledezma *et al.,* 2021). HMs often settle in the sediments at the bottom of water bodies due to their high density. Fish and other aquatic organisms can indeed be exposed to these HMs when they feed on organisms living in or near these sediments. This is a process known as benthic feeding. Benthic organisms, which live in and on the bottom sediments of water bodies, can accumulate HMs in their bodies (Panda *et al.,* 2023).

Industrial activities

Industrial effluents are the major source of HM contamination in aquatic ecosystems (Rahman *et al.,* 2014). Industries involved in mining, smelting, electroplating, and manufacturing of batteries, paints, pigments, and other chemical compounds often release HMs as part of their waste products. When

these effluents are discharged directly into water bodies without proper treatment, they can lead to significant contamination (Balali-Mood *et al.,* 2021; Poudel *et al.,* 2023). Fish living in these contaminated waters can accumulate HMs in several ways. One is through direct intake of contaminated water through their gills. Another is by consuming other organisms that have already accumulated these metals, a process known as biomagnification.

Agricultural activities

Agricultural practices can introduce HMs into the environment through certain pesticides and fertilizers, as well as through the disposal of animal waste (Alengebawy *et al.,* 2021). Mining can lead to HMs contamination when the process of extracting minerals from the earth disturbs naturally occurring deposits of HMs, causing them to be released into the environment. Urban runoff, which includes stormwater runoff from roads, rooftops, and other impervious surfaces, can carry HMs that have been deposited from the atmosphere or released from various human activities. When it rains, these HMs can be washed from the soil into nearby rivers and lakes (Zhang and Wang, 2020).

Atmospheric deposition

Industrial activities, incineration of waste, and even natural processes like volcanic eruptions can release HMs into the atmosphere (Shah, 2021; Li *et al.,* 2022). Once airborne, these metals can travel long distances before being deposited onto land or directly into water bodies. Fish and other aquatic organisms can absorb these metals directly from the water through their gills, or indirectly by consuming other organisms that have absorbed the metals (Müller *et al.,* 2020; Panda *et al.,* 2023).

Bioaccumulation in fish

The level of HM contamination in fish can vary widely depending on several factors, including the species of fish, its age and size, its diet, and the specific characteristics of its habitat, including the level of HM contamination in the water. Once in the water, HMs can be absorbed by fish through their gills, skin and by ingestion of contaminated water and food (Ahmad *et al.,* 2022). Over time, these metals can accumulate in the tissues of the fish, a process known as bioaccumulation. This is particularly concerning because when humans consume these fish, they can also be exposed to HMs, which can lead to health effects.

Fish tissues display varying patterns of bioaccumulation, and our understanding of these patterns depends on the assessment approach we take. The accumulation of metals in fish muscle is particularly noteworthy, as this tissue represents the main part consumed by humans. In contrast, the liver and gills are commonly accepted as reliable indicators for evaluating metal contamination in aquatic environments (Anandkumar *et al.*, 2019). However, the distribution of metals across different tissues can vary significantly, shaped by factors such as exposure pathways, trophic position, the physicochemical characteristics of the metals, and their concentrations in the surrounding water and diet (Ge *et al.,* 2020). This variability is the result of complex interactions among biological, chemical, and environmental processes. Each tissue has unique biochemical functions that affect its ability to accumulate heavy metals. For instance, muscle tissue differs from the liver and gills in metabolic activity, protein-binding capacity, and detoxification mechanisms (Anandkumar *et al*., 2019). Organs like the liver and kidneys act as primary detoxification centers, where metals can be sequestered or transformed, often leading to higher concentrations of these metals in these tissues compared to muscle tissue (Inayat *et al*., 2024; Şirin *et al*. 2024).

Even though mollusks tend to accumulate more cadmium than fishes, the metal can still find its way into humans through fish consumption (Tan *et al.,* 2019). It tends to accumulate in various organs of fish, such as bones, liver, kidneys, gills, muscles, and gonads, leading to structural and functional impairments in tissues (Vinanthi Rajalakshmi *et al.,* 2023). Its presence poses significant toxicity, being carcinogenic to both humans and animals, including fish, and detrimentally affecting fish growth, reproduction, and physiology (Emon *et al.,* 2023). It also acts as an endocrine disruptor in

freshwater fish populations, impacting reproductive and physiological functions (Amutha and Subramanian, 2013).

The organic form of a metal(loid) can be more toxic than its elemental form. For instance, methylmercury has greater biological toxicity than its inorganic forms. It represents the most toxic form of mercury, with fish being a significant contributor to its intake in both animal and human populations. Indeed, higher levels of mercury have been reported in predatory fish species such as swordfish and sharks (Sevillano-Morales *et al.,* 2015). Consequently, consuming fish may pose a risk of transferring methylmercury to humans. Toxicity studies of methylmercury chloride (CH_3HgCl) and methylmercury hydroxide (CH_3HgOH) on the cultured neuroblastoma cell line revealed greater toxicity for CH_3HgCl compared to CH_3HgOH, primarily due to the nuclear disruption caused by CH3HgCl (Patnaik and Padhy, 2018).

It is worth noting that cooking fish does not reduce its mercury content (Perelló *et al.,* 2008). Minamata disease originated from an event in the mid-1950s in Minamata Bay, Japan, where individuals experienced organic mercury exposure due to consuming contaminated fish (Hamada and Osarne, 2023). Prolonged exposure to mercury toxicity led to neurological impairment, characterized by symptoms including ataxia, muscle weakness, limb numbness, speech and swallowing impairments, and increased tendon reflexes in individuals exposed to significant amounts of methylmercury. Moreover, infants born to mothers who were exposed to mercury poisoning experienced profound developmental disabilities (Dos Santos *et al.,* 2018).

Cellular effects and mechanisms of toxicity

The specific mechanisms and cellular effects vary depending on the type of the metal, its chemical form, concentration, and the duration of exposure. Moreover, different tissues and cell types may respond differently to HM toxicity. Therefore, understanding these cellular mechanisms is crucial for developing strategies to mitigate the toxic effects of HMs and protect human health. It should be noted that the molecular mechanism of HM carcinogenicity is still ambiguous and complicated. Disruption of the biological functions of proteins regulating cell cycle, DNA maintenance, and apoptosis are expected to be the major mechanisms. For instance, cadmium was found to target transcription factors (Waisberg *et al.,* 2003; Kim *et al.,* 2015). There are common pathways through which many HMs exert their toxic effects on cells.

Oxidative stress Many HMs, including lead, cadmium, and mercury, induce oxidative stress within cells. They generate reactive oxygen species (ROS), which can damage cellular components such as proteins, lipids, and DNA. This oxidative damage contributes to cell dysfunction and death (Balali-Mood *et al*. 2021). HMs can generate ROS through several mechanisms. One common mechanism is through interaction with electron transport activities in the mitochondrial membranes (Shahid *et al.,* 2014).

Another mechanism is through the inactivation of enzymes and suppression of the antioxidant defense system. HMs can bind to certain enzymes and inhibit their activity, which can lead to an imbalance in the production and removal of ROS. Similarly, HMs can suppress the body's antioxidant defense system, which is responsible for neutralizing ROS. When this system is suppressed, ROS can accumulate and cause damage to cells (Balali-Mood *et al.,* 2021). Metals like copper, cadmium, zinc, iron, manganese, mercury, and aluminum can prompt ROS generation (Eskander and Saleh 2020). At the same time, the ROS-scavenging systems, comprising superoxide dismutase, catalase, ascorbate peroxide, peroxidase, and glutathione reductase, work to protect against the surplus ROS toxicity can also be damaged by HMs (Figure 2) (Eskander and Saleh 2020).

Interference with protein function

HMs can interfere with protein functions, including enzymes, through several mechanisms. They can bind to certain enzymes, inhibiting their activity, often involving the sulfhydryl groups of proteins (Kilpin and Dyson 2013). This binding can alter the structure and enzymatic activities of the proteins,

leading to toxic effects. HMs can also disrupt cellular events including growth, proliferation, differentiation, damage-repairing processes, and apoptosis (Ding *et al.,* 2022). Certain HMs have selective binding to specific macromolecules, such as the interaction of lead with aminolevulinic acid dehydratase and ferrochelatase (Sun *et al.,* 2022). Others including chromium, cadmium, and arsenic, cause genomic instability, potentially leading to carcinogenicity (Kilpin and Dyson 2013; Ding *et al.,* 2022).

Inflammation

HMs can indeed induce an inflammatory response due to their ability to generate ROS, which can lead to oxidative stress. Moreover, HMs like cadmium are known to be inhibitors for therapeutic immunotoxins, which can induce apoptosis or uncontrolled cell death (necrosis), leading to tissue damage and dysfunction (Sun *et al.,* 2023). Furthermore, it is believed that neuroinflammation plays a critical role in metal-induced neurotoxicity as well as the development of neurological disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Wei *et al.,* 2024).

System-based effects of heavy metal(loid) toxicity

Gastrointestinal tract

The gastrointestinal tract represents a significant target for the deleterious effects of HMs exposure. These toxic substances can exert their negative impact through various mechanisms, compromising the intricate balance and functionality of the gut ecosystem. One notable consequence is the disruption of the gut microbiota, a diverse community of microorganisms that play crucial roles in nutrient metabolism, immune regulation, and protection against pathogens (Balali-Mood *et al.,* 2021). HMs like cadmium, lead, and arsenic have been shown to alter the composition and diversity of gut microbes, leading to dysbiosis and impairment of the beneficial functions provided by the gut microbiome (Bist and Choudhary 2022). For instance, cadmium exposure has been linked to a reduction in the abundance of beneficial bacteria like Lactobacillus and Bifidobacterium, which are important for maintaining gut health and immune function (Bist and Choudhary 2022).

Furthermore, HMs can directly interfere with the absorption of essential nutrients in the gastrointestinal tract. Animal model studies showed that lead can compete with vital minerals like calcium for absorption, potentially leading to deficiencies that can affect various physiological processes (Osayande and Zou 2022). This competition occurs because Pb2+ has a higher affinity for binding to calcium-binding proteins and receptors compared to calcium itself, allowing lead to outcompete calcium and disrupt its absorption and utilization in the body. Calcium deficiency, in turn, can exacerbate lead absorption and retention, creating a vicious cycle.

HMs can also induce oxidative stress and inflammatory responses in the gut epithelial cells and intestinal mucosa (Balali-Mood *et al.,* 2021; Wei *et al.,* 2024). Metals like cadmium and arsenic can generate ROS and trigger inflammatory signaling pathways, leading to oxidative damage and inflammation in the gut. This can compromise the integrity of the intestinal barrier, increasing its permeability and potentially contributing to the development of gastrointestinal disorders like inflammatory bowel disease and leaky gut syndrome (Wei *et al.,* 2024).

Moreover, direct cytotoxicity, impaired gut repair mechanisms, and altered gut motility patterns are potential consequences of HM exposure, further exacerbating the negative impact on gastrointestinal health (Balali-Mood *et al.,* 2021). High concentrations of HMs, like mercury, can exert direct cytotoxic effects on the intestinal epithelial cells, leading to cell death and impaired gut function. Additionally, these toxic substances can interfere with the gut's natural repair mechanisms, such as cell proliferation and regeneration, hindering the recovery from intestinal damage.

Cardiovascular system

Chronic exposure to lead and cadmium has been linked to an increased risk of hypertension, stroke, coronary artery disease, and peripheral artery disease. Some HMs can promote blood clotting and increase the risk of thrombosis. This heightened coagulation response may contribute to the development of heart attacks and strokes. Studies have shown that higher blood levels of lead and

cadmium are associated with a 15-85% higher risk for stroke and heart disease (Yang *et al.,* 2020). HMs may contribute to increased vascular stiffness, which is associated with conditions like atherosclerosis and hypertension. Exposure to arsenic, cadmium, and titanium has shown a significant correlation with the presence of subclinical atherosclerosis. This association is predominantly influenced by arsenic and cadmium in the carotid region, cadmium and titanium in the femoral region, and titanium in the coronary territory (Grau-Perez *et al.,* 2022).

Vascular stiffness can strain the heart and elevate the risk of cardiovascular events. Exposure to lead, cadmium, and arsenic induces oxidative stress, impairs vascular endothelial function, causes chronic inflammation, disturbs lipid metabolism, affects myocardial function, and leads to abnormalities that contribute to cardiovascular risks (Chowdhury *et al.,* 2018; Yang *et al.,* 2020). Endothelial dysfunction is a critical early step in the development of cardiovascular diseases, as it can lead to reduced vasodilation, increased vascular permeability, and inflammation. Lastly, the interference of HMs with lipid metabolism can lead to abnormal levels of cholesterol and triglycerides (Wang *et al.,* 2023). Recent studies have revealed that HMs such as cadmium are associated with elevated levels of circulating total cholesterol, triglycerides, and low-density lipoprotein cholesterol (Kim *et al.,* 2018; Xu *et al.,* 2023). Furthermore, a cross-sectional study conducted by Zhang *et al.* (2022) has indicated that increased blood lead levels are correlated with a heightened risk of hyperlipidemia, suggesting a potential link stemming from oxidative stress induced by lead exposure.

Urinary system

HMs can exert toxic effects on the urinary system primarily affecting the kidneys and the bladder which increase the risk of malignant tumors in these organs (Khalaf *et al.,* 2023). Indeed, chronic kidney diseases have been linked to prolonged exposure to certain HMs (Orr and Bridges 2017). Cadmium, lead, mercury, and arsenic are established nephrotoxins and chronic exposure to elevated levels of these metals can lead to kidney dysfunction and compromise the organ's ability to filter and regulate fluids and electrolytes (Gao *et al.,* 2023). High levels of certain HMs, especially in cases of acute exposure or poisoning can lead to acute kidney injury. This condition is characterized by a sudden decrease in kidney function and can result in symptoms such as decreased urine output, fluid retention, and electrolyte imbalances. The renal tubules can also be impaired and their function in reabsorbing essential substances and excreting waste products could be hindered. This dysfunction can contribute to electrolyte imbalances and disrupt the body's overall fluid balance (Wang *et al.,* 2024).

Glomerular damage can result from some HMs toxicities, like lead and cadmium (Orr and Bridges 2017). This damage can lead to proteinuria (the presence of excess proteins in the urine) and impair the kidney's ability to filter blood properly. Some HMs can contribute to the development of renal fibrosis, a condition characterized by the excessive accumulation of scar tissue in the kidneys (Orr and Bridges 2017). Renal fibrosis can impair kidney function and contribute to the progression of kidney disease. Lastly, cadmium may increase the risk of urolithiasis (kidney stone formation) (Chen *et al.,* 2024). The presence of kidney stones can lead to pain, obstruction, and potential damage to the urinary tract.

Reproductive system

HMs can have toxic effects on the reproductive system, affecting both male and female reproductive organs. HMs may act as endocrine disruptors, interfering with the normal functioning of the endocrine system, which regulates reproductive hormones (Liu *et al.,* 2023). This disruption can lead to fertility issues and reproductive disorders. The specific effects depend on the type of metal, its concentration, and the duration of exposure. For instance, cadmium, lead, and mercury can accumulate in the testes and cause damage to the testicular tissue. This may lead to reduced sperm production (oligospermia) and impaired sperm quality. Additionally, exposure to HMs has also been associated with abnormalities in semen parameters, including sperm motility, morphology, and concentration (Calogero *et al.,* 2021).

Animal model studies have shown that lead and cadmium can accumulate in the ovaries and cause damage to ovarian tissue (Nampoothiri and Gupta 2006). This may result in disrupted ovarian function, leading to menstrual irregularities and fertility issues. Hormonal disruptions may contribute to difficulties in conceiving. Maternal exposure to HMs during pregnancy, such as lead and mercury, can pose risks to fetal development and may contribute to complications such as preterm birth, low birth weight, and developmental abnormalities. Cadmium exposure can lead to adverse effects on the female reproductive system and is considered a metalloestrogen that affects estrogen and progesterone receptors (Lin *et al.,* 2023). Specifically, cadmium exposure has been associated with adverse effects on the female reproductive system. Cadmium can accumulate in human endometrial tissue and is considered a metalloestrogen that can stimulate estrogen receptors and up-regulate progesterone receptors. This metal has been linked to oestrogen-dependent diseases such as breast cancer, endometrial cancer, endometriosis, and spontaneous abortions (Mukherjee *et al.,* 2022).

Nervous system

HMs can have significant toxic effects on the nervous system, impacting both the central nervous system and the peripheral nervous system. The neurotoxicity of HMs is well-documented, and exposure can lead to various neurological disorders including cognitive deficits, impaired memory, attention deficits, and alterations in mood and behavior. Long-term exposure to HMs may contribute to axonal degeneration, which involves the breakdown of nerve fibers. This can lead to a loss of sensation, muscle weakness, and other neurological symptoms. The toxic metal hypothesis suggests that damage to selective locus ceruleus neurons from these metals can lead to astrocyte dysfunction, transfer of metals to oligodendrocytes and neurons, and subsequent neuronal malfunction. Different combinations of toxic metals can result in varying clinical outcomes due to genetic variants and the age, frequency, and duration of exposure (Kothapalli, 2021).

Children exposed to lead and other HMs may experience developmental delays and learning disabilities. Even low-level exposure during critical periods of brain development can have lasting effects on cognitive function. Some HMs, including mercury and aluminum, have been implicated in the development or progression of neurodegenerative diseases such as Alzheimer's and Parkinson's disease. These metals may contribute to the accumulation of abnormal protein aggregates in the brain. HMs can interfere with the normal functioning of neurotransmitters. For instance, Lead inhibits heme synthesis, affecting energy metabolism and neurotransmitters like gamma-aminobutyric acid. Mercury, especially methylmercury, causes focal brain damage and is particularly harmful to the developing nervous system by destroying microtubules (Takahashi and Shimohata 2019).

Arsenic and lead chronic exposure can result in peripheral neuropathy characterized by damage to the peripheral nerves. Arsenic exposure can induce distal axonal sensory-motor peripheral neuropathy, potentially by inhibiting the conversion of pyruvate to acetyl coenzyme A and disrupting the Krebs cycle (Mochizuki *et al.,* 2019; Helso *et al.,* 2020). Symptoms may include numbness, paresthesia, muscle weakness, and pain in a stocking-glove distribution, with nerve conduction studies revealing sensory-motor axonal polyneuropathy. Both arsenic and lead neuropathies typically begin with sensory symptoms, followed by motor weakness if exposure continues (Valappil and Mammen, 2019).

Skin and other tissues

Different adverse effects on the skin and other tissues outside of the major organ systems have been linked to HMs exposure. The impact on skin and other tissues depends on factors such as the specific heavy metal involved, the route of exposure, concentration, and duration of exposure. Contact with certain HMs, including nickel, chromium, and cobalt, can lead to allergic contact dermatitis (Chamani *et al.,* 2023). This inflammatory skin condition is characterized by redness, itching, and skin rash upon exposure to the metal. Some HMs, such as arsenic and lead can cause changes in skin pigmentation which results in an increased risk of sunburn and other UV-related skin damage.

Some HMs, including lead and cadmium, may accumulate in bones and joints, contributing to joint pain and discomfort (Al-Ghafari *et al.,* 2019). This is particularly evident in cases of chronic exposure, such as lead poisoning. Exposure to certain HMs, such as lead and cadmium, can interfere with the production of red blood cells, leading to anemia (Peters *et al.,* 2021). This can result in fatigue, weakness, and other symptoms associated with low red blood cell count.

Control and prevention

HMs pollution in aquatic environments is a serious issue that requires comprehensive strategies to address. These pollutants, such as lead, cadmium, and mercury, are highly toxic, persistent, and can bioaccumulate and be biomagnified through the food chain, posing significant risks to both human and ecological health. The primary sources of HM contamination include industrial activities, mining operations, agricultural practices, and the combustion of fossil fuels. To effectively control and prevent the negative impacts of HMs in aquatic ecosystems, a multi-pronged approach is necessary. First, it is crucial to reduce the input of HMs into water bodies by implementing stricter regulations and enforcement on industrial waste disposal and mining practices, promoting sustainable agricultural methods that minimize the use of heavy metal-containing fertilizers and pesticides, and improving wastewater treatment to remove these pollutants before discharge. For instance, cadmium retention within waste landfills is significantly impeded by compacted municipal sewage sludge, primarily due to the precipitation and adsorption processes (Zhang *et al.,* 2016).

Passivation and stabilization represent prevalent methods aimed at restricting the continued diffusion and migration of HMs in the environment, proving to be effective and cost-efficient techniques. For example, hydroxyferric combined acid-base modified sepiolite was utilized to immobilize cadmium contaminated water and soil, demonstrating a notable passivation effect on biologically available cadmium within the soil (Xie *et al.,* 2020). Various techniques are employed to remove HMs, including chemical precipitation, filtration, oxidation, reduction, electrochemical treatment, reverse osmosis, and ion exchange. Unfortunately, these methods often have drawbacks such as high chemical reagent consumption, energy usage, substantial costs, and the risk of secondary pollution. Consequently, bioremediation stands out as a highly promising and eco-friendly approach for effectively treating HMs.

It is essential to routinely monitor the concentrations of HMs in water and fish to evaluate the degree of contamination and direct suitable control strategies. Establishing water quality standards and consumption advisories are essential to protect both aquatic ecosystems and public health (WHO 2022). These directives are designed to minimize exposure to HMs, encourage the growth of organisms that are endangered by intrinsic accumulation of pollutants, and regulate the fishing and consumption of heavily contaminated fish species. Through the implementation of a comprehensive approach that addresses the reduction of HMs emissions and the remediation of polluted environments, adverse effects of HMs pollution on aquatic ecosystems and human well-being can be efficiently alleviated.

Conclusions

HMs and their bioaccumulation in fish underscore the significant implications for public health and environmental sustainability. Through meticulous examination of the system-based negative effects on human and animal body systems, it becomes evident that HM contamination poses multifaceted challenges. From neurological impairments to cardiovascular complications and reproductive disorders, the detrimental impacts extend across various physiological systems, highlighting the urgency for precautions and effective mitigation strategies. Furthermore, the intricate interplay between environmental pollution and human health underscores the importance of interdisciplinary collaboration and evidence-based policymaking. Addressing HM pollution requires a multifaceted approach, encompassing rigorous monitoring, targeted remediation efforts, and the establishment of robust regulatory frameworks to safeguard both aquatic ecosystems and public well-being. Finally, it is imperative to prioritize proactive measures aimed at prevention and mitigation. By fostering

awareness, fostering sustainable practices, and promoting research-driven interventions, we can strive towards a future where the adverse effects of HMs on both environmental and human health are minimized, ensuring a healthier and more resilient society for generations to come.

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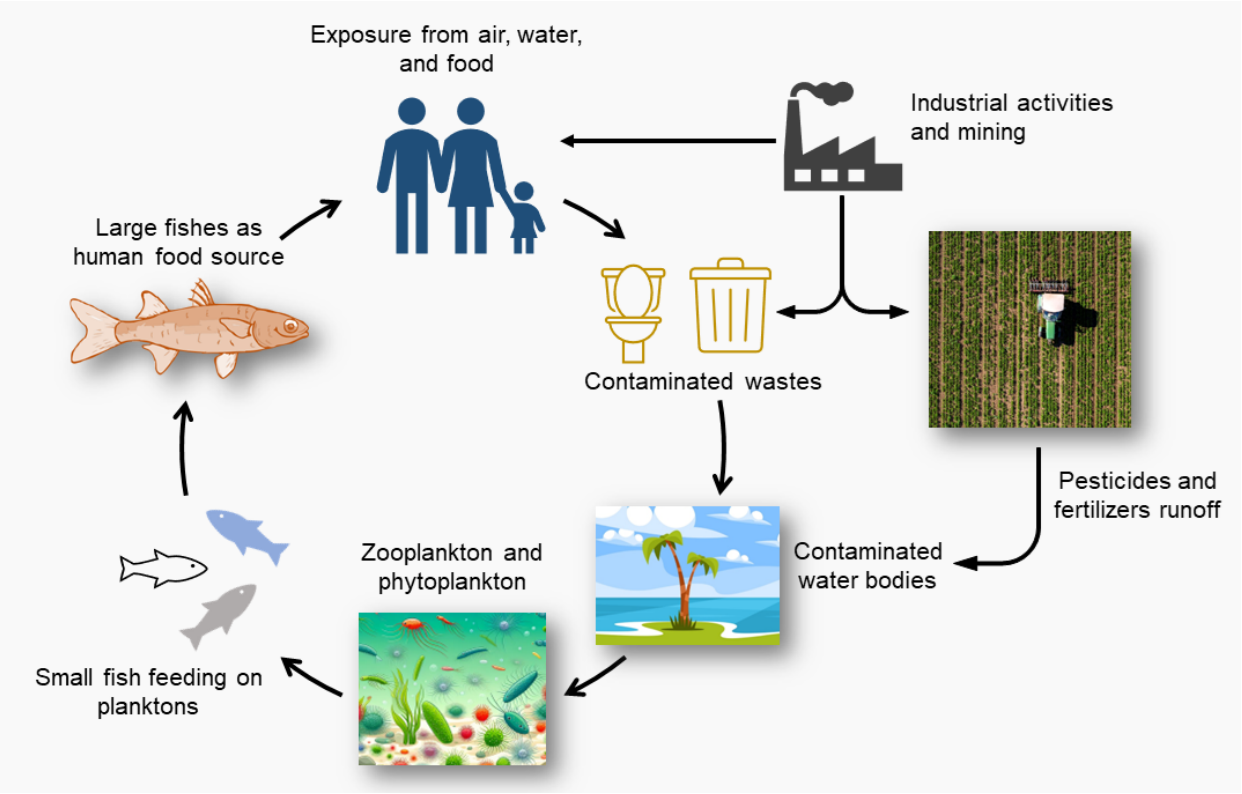

Figure 1. A schematic model of heavy metal(loid) bioaccumulation and circulation and their routes to reach humans.

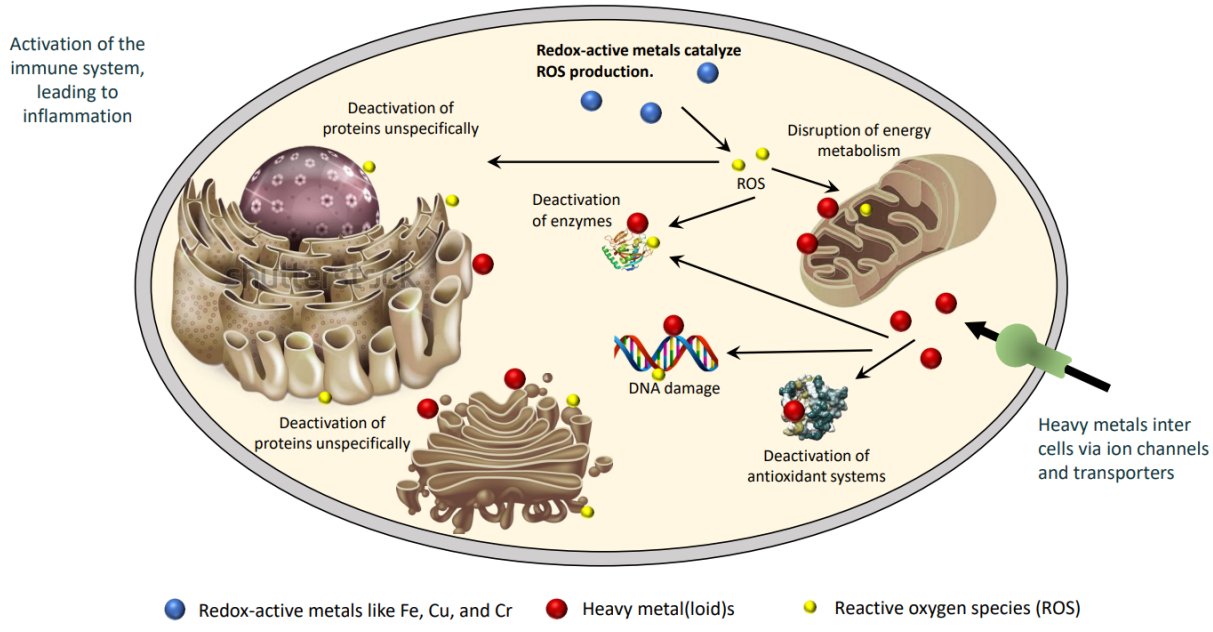

Figure 2. A simplified scheme of heavy metal(loid) cellular toxicity.