Aquatic Sciences (2024) 86:107
https://doi.org/10.1007/s00027-024-01121-7

Aquatic Sciences

REVIEW

Heavy metal contamination in fish: sources, mechanisms and consequences

Gagandeep Singh[1] · Sharali Sharma[1]

Received: 3 October 2023 / Accepted: 30 August 2024

Abstract
This comprehensive review provides a thorough exploration of a mounting environmental issue: heavy metal contamination in aquatic ecosystems and its far-reaching impacts on fish populations and human health. Starting with the generalized sources of different heavy metals that lead to their entry into the aquatic environment, this review then considers each of the major heavy metals (copper, cadmium, chromium, arsenic, nickel, lead, zinc, and mercury) and ventures deep into the intricate mechanisms governing the uptake, bioaccumulation, and toxicity of heavy metals in fish, shedding light on the profound consequences these processes have for fish health and behavior. A critical aspect emphasized in this article is the activation of antioxidant defense mechanisms and involvement of metallothionein in fish as an adaptive response aimed at mitigating the pervasive oxidative stress triggered by heavy metal exposure. Of utmost concern is the trophic transfer of heavy metals from contaminated fish to humans through consumption, which poses a direct threat to human health regarding various physiological functions. The article underscores the urgency of addressing this issue comprehensively. Given the concerning discoveries at hand, this review fervently supports the enactment of rigorous regulations, the embracing of sustainable management techniques, and the stringent enforcement of pollution containment strategies.

Keywords Bioaccumulation · Contamination · Heavy metals · Toxicology · Metallothionein

Introduction

Environmental degradation, driven by industrial expansion, fuel consumption, and resource depletion, is an increasingly urgent issue. Among the pollutants infiltrating ecosystems from both natural and anthropogenic sources, heavy metals pose significant ecological threats due to their toxicity and tendency to accumulate in the food chain (Sing et al. 2023; Briffa et al. 2020). These metals, including copper, cadmium, chromium, arsenic, nickel, lead, zinc, and mercury, enter the environment primarily through industrial activities, waste disposal, and agricultural practices (Gheorghe et al. 2017; Briffa et al. 2020). The persistence of heavy metals in the environment leads to harmful effects on living organisms, such as growth inhibition and chlorosis, and disrupts soil microbiota, impacting soil fertility (Garai et al. 2021; Shi et al. 2023). Aquatic organisms, particularly fish, are highly susceptible to heavy metal contamination through direct exposure to polluted water and sediment (Sarker et al. 2023). Bioaccumulation of these metals in fish can lead to serious health issues, including impaired reproductive capacity, reduced survival rates, and increased risks of cancer, birth defects, and genetic mutations (Malik and Maurya 2014; Kiran and Sharma 2022). Fish, as primary components of aquatic food chains, are particularly vulnerable to heavy metal toxicity, which affects their nervous systems and overall interactions with the environment (Youssef and Tayel 2004; Luo et al. 2014). Human populations that consume fish are consequently at risk of heavy metal exposure, which can lead to biomagnification—where the concentration of toxic substances increases at each trophic level of the food chain—posing significant health risks (Has-Schon et al. 2006; Rahman et al. 2012). This narrative review aims to provide a comprehensive overview of the bioaccumulation and toxic effects of specific heavy metals on fish health, emphasizing the mechanisms of uptake, bioaccumulation, and toxicity. It will also address the activation of antioxidant defense mechanisms in fish as an adaptive response to heavy

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✉ Sharali Sharma
sharmashanali@gmail.com

[1] Department of Biosciences, University Institute of Biotechnology, Chandigarh University, Gharuan, Mohali, Punjab, India

metal exposure. Furthermore, the review will discuss the implications of heavy metal contamination for human health, particularly through the consumption of contaminated fish, and proposes measures to mitigate these impacts on the ecosystem. By summarizing key points related to heavy metal contamination in aquatic environments, this review seeks to highlight the urgent need for effective regulations and sustainable management practices.

Sources of heavy metal contamination

Heavy metals can contaminate water through natural and anthropogenic activities (Kabata-Pendias and Pendias 1984; Salgarello et al. 2013). Natural activities, such as weathering of rocks, volcanic eruptions, fires, and natural weathering processes, contribute to the presence of heavy metals in water (Figure 1) (Priti and Paul 2016). These natural sources also include wet and dry deposition of atmospheric salts, water-rock interaction, and water interaction with the soil. On the other hand, anthropogenic sources, including urbanization and industrialization, are major contributors to water contamination (Priti and Paul 2016). Urbanization leads to the pollution of water due to solid waste and untreated liquid waste, including plastic waste such as plastic bags (Gumpu et al. 2015). Agricultural activities also contribute to water pollution through the use of fertilizers, pesticides, and erosion of soil (Vanisree et al. 2022). Industrial sources play a significant role in heavy metal contamination, posing a threat to aquatic ecosystems and accumulating in living organisms (Ismanto et al. 2023). Industrial effluents, leakages, and dumping are major contributors to water contamination (Sankhla et al. 2022). Domestic sewage, both from households and industrial activities, contains toxins, solid waste, and bacteria, significantly polluting water resources (Ismanto et al. 2023). Mining activities introduce heavy metals into water systems through leaching and acid mine drainage, mobilizing these metals (Sankhla et al. 2016).

The bioavailability of heavy metals is a critical aspect in understanding their impact on the environment and living organisms. Bioavailability refers to the extent to which a substance can be absorbed and utilized by an organism. Chemical factors play a crucial role in determining the bioavailability of heavy metals. The chemical forms of heavy metals in the environment, such as their oxidation states, complexation with other substances, and binding to soil particles, significantly influence their ability to be absorbed by organisms. For instance, the bioavailability of heavy metals like cadmium and lead is often higher in acidic environments because of their increased solubility and mobility under

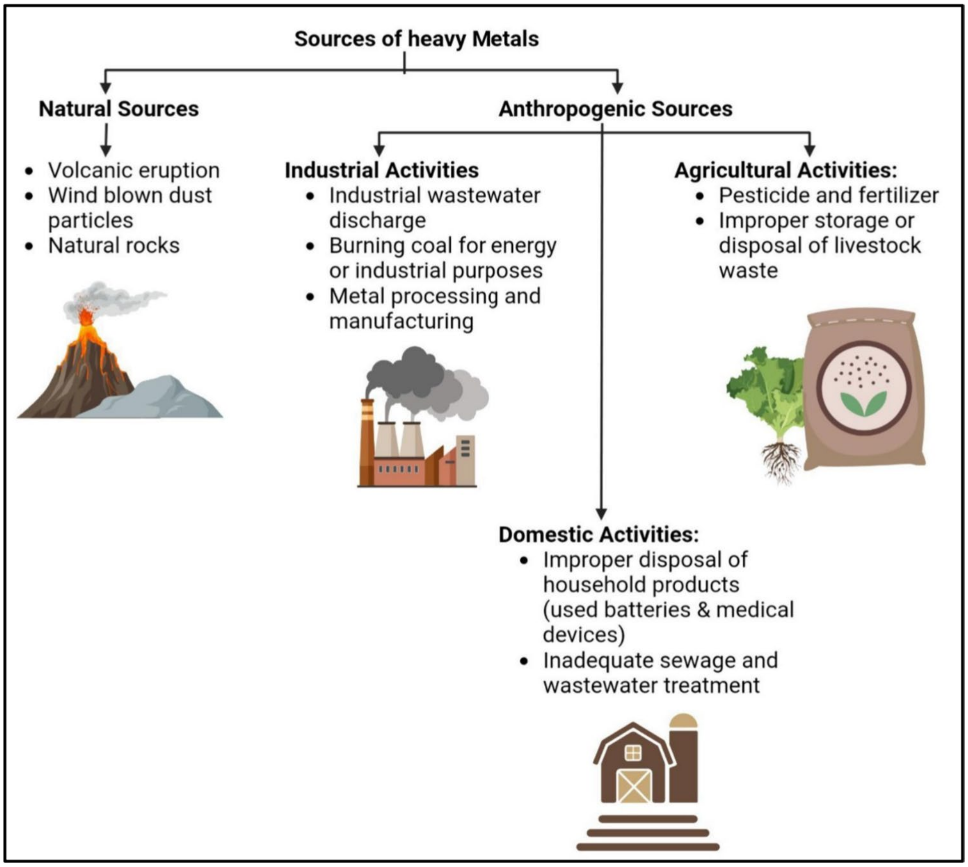

Fig. 1 Sources of heavy metal pollution in water bodies: a visual representation illustrating the different sources of heavy metal pollution in water bodies, highlighting the natural sources (rock and mineral weathering), industrial activities (industrial wastewater discharge, coal combustion, metal processing and manufacturing), agricultural activities (pesticide and fertilizer use, livestock waste), and domestic activities (improper disposal of household products, inadequate sewage and wastewater treatment).

these conditions (Kai-jun et al. 2014; Wang et al. 2020; Zheng et al. 2022). Soil pH is another key factor affecting the bioavailability of heavy metals. Studies have shown that acidic soils can lead to increased bioavailability of heavy metals like cadmium, chromium, and lead, which can then be taken up by plants and potentially enter the food chain (Kai-jun et al. 2014; Wang et al. 2020). On the other hand, alkaline soils can reduce the bioavailability of these metals by forming insoluble compounds that are less accessible to organisms (Wang et al. 2020; Zheng et al. 2022). Organic matter content in soil also plays a significant role in determining the bioavailability of heavy metals. Organic matter can bind to heavy metals, reducing their bioavailability by making them less soluble and less accessible to organisms (Kai-jun et al. 2014; Wang et al. 2020; Zheng et al. 2022). Additionally, the presence of microorganisms in soil can influence the bioavailability of heavy metals by altering their chemical forms and solubility (Wang et al. 2020; Zheng et al. 2022). The bioavailability of heavy metals can also be influenced by the presence of other substances in the environment. For example, dissolved organic matter (DOM) can enhance the bioavailability of heavy metals by increasing their solubility and mobility (Li and Gong 2021). Similarly, the presence of certain plant species can affect the bioavailability of heavy metals by altering the chemical forms and solubility of these metals in the soil (Yanqin 2008; Boisselet 2012). The sources and bioavailability of specific heavy metals will be discussed in detail when examining their individual effects under respective headings. Heavy metals present in soil and water can enter organisms through the food chain, impacting human health when contaminated vegetables and marine organisms are consumed (Truby 2003).

Different heavy metals and their accumulation in fishes

An assortment of heavy metals, namely copper, cadmium, chromium, arsenic, nickel, lead, zinc, and mercury, exhibit bioaccumulation tendencies within fish species. These metals infiltrate aquatic ecosystems through a combination of natural processes and human-induced activities, thereby introducing potential hazards to both aquatic organisms (Table 1) and human consumers. Subsequent sections will meticulously examine the specific sources, bioaccumulation patterns, and scientific investigations concerning the impacts of these heavy metals on fish health.

Chromium (Cr)

Chromium is a prevalent trace element found in both seawater and the earth's crust, existing in various oxidation states such as Cr^{2+}, Cr^{3+}, and Cr^{6+} (Bakshi and Panigrahi 2018; Garai et al. 2021). Among these states, Cr^{3+} and Cr^{6+} are the most stable (Vincent et al. 1995; Velma et al. 2009). While Cr^{3+} is less hazardous because of its non-corrosive nature, limited membrane permeability, and low biomagnification potential in the food chain, Cr^{6+} poses greater risks due to its strong oxidative capabilities and ability to breach cell membranes (Ram et al. 2019). Human activities from sources like petroleum refining, metal processing, leather tanneries, alloy production, textile production, and wood preservation contribute to chromium toxicity in aquatic ecosystems (Panov et al. 2003; Huang et al. 2004). Chromium toxicity towards aquatic organisms is contingent upon a multitude of biotic factors, including their age, developmental stage, and species type. Additionally, abiotic factors such as temperature, pH, and water alkalinity play a crucial role in determining its impact. Fish that were first exposed to chromium had a variety of behavioral abnormalities, including erratic swimming, mucus secretion, a change in body color, and lack of appetite, among others (Nisha et al. 2016). *Cyprinus carpio* was chronically exposed to chromium at a concentration of about 2–200 mol/l, and this exposure caused cytotoxicity as well as a reduction in phagocyte- and mitogen-induced lymphocyte activation (Steinhagen et al. 2004). When exposed to chromium, *Tilapia sparrmanii* had slower blood clotting times, which led to internal bleeding and an elevation in pH (Van Pittius et al. 1992). Chromium buildup in *Labeo rohita*, an Indian large carp, reduces the amount of total protein and lipids in the muscle, liver, and gills (Vutukuru 2003). *Colisa fasciatus*, a freshwater teleost, showed decreased hepatic glycogen upon exposure to chromium (Nath and Kumar 1987). Cr^{6+} poisoning in *Salmo gairdneri* (rainbow trout) caused respiratory and osmoregulatory failure at pH 6.5 and 7.8 (Van Der Putte et al. 2009). When Chinook salmon were exposed to chromium over an extended period of time, it resulted in physiological anomalies, microscopic lesions, DNA damage, and decreased growth and survival rates (Table 1) (Farag et al. 2006). In *Salmo gairdneri* (rainbow trout), Cr exposure at a dose of 2 mg/l had an impact on fish development and embryo hatching (Van der Putte et al. 1982).

Different fish tissues exhibit variable chromium bioaccumulation. Chromium is accumulated most heavily in the liver, gills, and kidney and at extremely low levels in muscle tissue (Garai et al. 2021). Numerous studies have reported the bioaccumulation of chromium in different organs of various fish species, leading to physiological disturbances and organ-system failures (Islam et al. 2020; Jamil Emon et al. 2023). Additionally, Cr toxicity alters the lipid, protein, and glycogen content in fish gills, muscle, and liver. It induces hepatic stress, affects important organs like the liver and kidney, and disrupts the endocrine system of certain freshwater fish species (Jamil Emon et al. 2023). The impact of

Table 1 Comparative analysis of heavy metals and their impact on fish species

Heavy metal	Impacts on fish	Fish species	Hazardness	References
Chromium (Cr)	Behavioral abnormalities, cytotoxicity, reduced phagocyte activation	*Cyprinus carpio*, *Tilapia sparrmanii, Labeo rohita, Colisa fasciatus, Salmo gairdneri,* Chinook salmon	Cr^{3+} is less hazardous because of low biomagnification, Cr^{6+} is more hazardous because of oxidative potential	(Van der Putte et al. 1982; Nath and Kumar 1987; Van Pittius et al. 1992; Vutukuru 2003; Steinhagen et al. 2004; Farag et al. 2006; Van Der Putte et al. 2009; Nisha et al. 2016)
Cadmium (Cd)	DNA damage, hepatocyte necrosis, reduced glycogen reserves	*Cyprinus carpio*, *Tilapia nilotica, Anguilla rostrata, Leuciscus idus, Hypophthalmichthys molitrix*	Non-essential metal, high toxicity to fish, impacts growth and immune system	(Verbost et al. 1987; Gill and Epple 1993; Vetillard and Bailhache 2005; Cicik and Engin 2005; Cavas et al. 2005; Jia et al. 2011; Omer et al. 2012; Das and Mukherjee 2013; Witeska et al. 2014; Garriz et al. 2019)
Copper (Cu)	Impaired behavior, reproductive issues, decreased cardiac function	*Clarias batrachus, Oreochromis niloticus, Cyprinus carpio, Mytilus edulis, Channa punctatus*	Essential micronutrient, becomes hazardous at higher concentrations	(Radi and Matkovics 1988; Cyriac et al. 1989; Gainey and Kenyon 1990; Varanka et al. 2001; Johnson et al. 2007; Monteiro et al. 2009; McIntyre et al. 2008; Eyckmans et al. 2011; Yacoub and Gad 2012; Kong et al. 2013; Bawuro et al. 2018)
Lead (Pb)	Necrosis, altered behavior, impaired reproductive system	*Clarias batrachus, Clarias gariepinus, Gymnotus carapo, Tinca tinca, Acipenser sinensis*	Highly hazardous heavy metal, human-induced sources contribute to contamination	(Katti and Sathyanesan 1983; Shah 2005; Olojo et al. 2005; Cretì et al. 2010; Hou et al. 2011; Afshan et al. 2014; Tanekhy 2015; Biswas and Ghosh 2016; Lee et al. 2019)
Nickel (Ni)	Respiratory disorders, histological alterations	*Oreochromis niloticus, Hypophthalmichthys molitrix, Channa punctatus, Cyprinus carpio, Tilapia nilotica*	Abundant trace element, essential at low concentrations, hazardous at high levels	(Sreedevi et al. 1992; Ghazaly 1992; Athikesavan et al. 2006; Abou-Hadeed et al. 2008; Al-Ghanim 2011; Palermo et al. 2015; Atli 2018)
Arsenic (As)	Epithelial lifting, oxidative stress, developmental arrest	*Nile tilapia, Oreochromis mossambicus, Channa punctatus, Gymnotus carapo, Oryzias latipes*	Discharged from human activities, harmful even at low levels	(Kothary and Candido 1982; Shukla and Pandey 1984; Tripathi et al. 2003; Ishaque et al. 2004; Ghosh et al. 2006; Wang et al. 2004b; Ahmed et al. 2013; Dangleben et al. 2013; Hossain 2014)
Mercury (Hg)	Neurotoxicity, impaired reproduction, bioaccumulation in tissues	*Clarias batrachus, Channa punctatus, Oreochromis niloticus, zebrafish, Gymnotus carapo*	Highly hazardous heavy metal, significant rise in contamination due to industrialization	(Giblin and Massaro 1975; Evans et al. 1993; Mona et al. 2011; Vergilio et al. 2013; Begam and Sengupta 2015; Zhang et al. 2016; Bradley et al. 2017)
Zinc (Zn)	Gill tissue damage, reduced swimming speed, hypocalcemia	*Tilapia nilotica, Zebrafish embryos, Phoxinus phoxinus,* Killifish, *Channa punctatus*	Crucial micronutrient, essential for various metabolic processes	(Bengtsson 1974; Spry et al. 1988; Murugan et al. 2008; Ayotunde et al. 2011; Loro et al. 2012; Salvaggio et al. 2016)

Cr on the blood profile of *Pangasianodon hypophthalmus* was investigated, revealing notable alterations in cellular and nuclear characteristics (Islam et al. 2020; Suchana et al. 2021). High levels of Cr in fish diets were found to decrease growth and feed utilization. Chronic Cr exposure negatively impacted fish reproduction, lowering spawning success, deforming testis, decreasing sperm motility, and hampering oocyte formation (Jamil Emon et al. 2023).

Cadmium (Cd)

Cadmium, a trace element averaging between 0.1 to 0.5 ppm in the earth's crust, often associates with copper, lead, and zinc ores. In surface and groundwater, its concentration ranges from 1 to 5 mg/l, while in ocean water, it varies between 5 and 110 mg/l (Garai et al. 2021). Existing solely in compound forms like cadmium oxide, cadmium chloride, and cadmium sulfide, cadmium lacks a native elemental state (Garai et al. 2021). Both natural processes and human activities contribute to cadmium's introduction into aquatic ecosystems. Geological sources, including mantle and crust materials, release cadmium through rock weathering and volcanic activity. Concurrently, industrial applications (e.g., plastic stabilizers, batteries, pigments, and electroporating industries) and fossil fuel combustion are anthropogenic origins of cadmium contamination in water bodies (Muntau and Baudo 1992; Perera et al. 2015). Within aquatic ecosystems, cadmium compounds, in soluble or sedimentary states, are assimilated by flora and fauna, eventually entering fish bodies through the food web (Perera et al. 2015). Fish directly absorb the free cadmium ions which are dissolved in water through their skin, gills, and digestive systems (Li et al. 2009). Because it is a non-essential metal, cadmium is extremely hazardous to fish. It increases the generation of ROS (reactive oxygen species) and inhibits the electron transport chain in mitochondria (Wang et al. 2004a). *Cyprinus carpio* experienced DNA damage as a result of low-level cadmium exposure (Jia et al. 2011). Cd^{+2} was discovered to limit trans-epithelial influx of calcium in rainbow trout gills (Verbost et al. 1987). Fish exposed to subchronic levels of cadmium chloride developed micronucleated as well as binucleated cells in their gills, blood, and liver (Cavas et al. 2005; Omer et al. 2012).

Histopathological changes were observed in Tilapia (*Oreochromis niloticus*), including fatty vacuolation in the liver, hepatocyte necrosis, submucosal blood vessel congestion in the gut, and glomerular shrinkage and necrosis in tissues of the kidney (Gill and Epple 1993). Cadmium exposure in fish resulted in a distinct haematological response. *Anguilla rostrata* (American eel fish) exposed for 8 weeks to 150 g/l cadmium develop anemia as a result of decreased hemoglobin and erythrocyte counts. After cadmium exposure, a significant rise in leukocyte and big lymphocyte counts was also noted (Cicik and Engin 2005). When *Cyprinus carpio* was exposed to sublethal concentrations of cadmium, there was a significant reduction in the glycogen reserves in the liver and muscles, accompanied by a notable increase in blood glucose levels (Cicik and Engin 2005). Inhibiting vitellogenesis and being an endocrine disruptor, cadmium has been found in *Oncorhynchus mykiss* (rainbow trout) (Vetillard and Bailhache 2005). Sexual development and gonad functions of *Cyprinus carpio* were both impacted by cadmium chloride exposure (Das and Mukherjee 2013). The sluggish rate of elimination of cadmium makes it a severe environmental hazard. Exposure of *Leuciscus idus* larvae to cadmium has been shown to result in morphological abnormalities and reduced survival rates during the embryonic stage, primarily attributed to mortality among newly hatched larvae (Witeska et al. 2014).

Bioaccumulation studies have indicated that cadmium tends to exhibit the lowest levels of accumulation in the epidermis, while the liver, kidney, and gills exhibit the highest levels (Witeska et al. 2014). Among these organs, the gill has been identified as the primary site for rapid cadmium detoxification. Moreover, Cd interferes with iron metabolism, resulting in anemia and disruptions in hematological indices. Cd induces inhibition of antioxidant enzymes, resulting in the initiation of lipid peroxidation processes in animal organisms. Additionally, Cd negatively impacts fish's reproductive performance, causing alterations in sperm morphology, fibrosis in the testis, and reduced sperm motility and viability, all contributing to compromised reproductive functions (Garriz et al. 2019; Jamil Emon et al. 2023). Considering its pronounced bioaccumulation kinetics, cadmium emerges as one of the most prominently recognized and perilous heavy metals, with detrimental effects on aquatic organisms.

Copper (Cu)

The freshwater ecosystem experiences copper contamination primarily because of the excessive application of algaecides, fungicides, and insecticides in agricultural settings, with subsequent waste disposal into water bodies. Additional sources of copper toxicity encompass mining, sewage sludge, plastics, metal refining, electroplating industries, and atmospheric deposition (Mendil et al. 2010; Panagos et al. 2018). Copper, functioning as an essential micronutrient and trace element, plays a pivotal role in the growth and metabolic processes of various organisms. It serves as a critical constituent of metabolic enzymes and glycoproteins in fish and other animals, contributing to neurological function and hemoglobin synthesis (Sorensen 1948; Nordberg et al. 2007). Nevertheless, higher concentrations of copper have deleterious impacts on living organisms (Richard Bull 2000). Notably, freshwater fish exhibit susceptibility to copper at levels ranging from 10 to 20 ppb (Carol Ann Woody and Louise 2012).

Copper toxicity to aquatic life depends on a number of variables, including pH, anions, water hardness, and DOC (dissolved organic carbon). Fish primarily acquire copper through either their diet or exposure to the surrounding environment (Dang et al. 2009). Freshwater fish exposed to copper in the water developed an oxidative stress response (Eyckmans et al. 2011). Fish with chronic copper toxicity have poor development, shorter life spans, lowered immunological responses, and reproduction issues (Table 1) (Yacoub and Gad 2012). Apoptosis was induced by copper poisoning in the gills of *Oreochromis niloticus* (teleost fish) (Monteiro et al. 2009). The liver tissue of *Cyprinus carpio* underwent biochemical and morphological alterations after exposure to copper sulfate (Varanka et al. 2001). Upon subchronic exposure to copper sulfate, fish gill epithelial cells, blood erythrocytes, and liver cells developed micronuclei and binuclei.

Complex fish behaviors that are crucial for survival, like social interaction, predator avoidance, and reproductive behavior, were hampered by copper. Heart rate and cardiac function are decreased in *Mytilus edulis* with copper intoxication (Gainey and Kenyon 1990). *Oreochromis mossambicus* subjected to copper treatment exhibited increased red blood cell (RBC) count, hemoglobin content, and hematocrit value (Cyriac et al. 1989). Copper has been shown to disrupt the functioning of olfactory neurons and exert neurotoxic effects on fish (Mcintyre et al. 2008). In zebrafish larvae, exposure to copper resulted in heightened sensitivity compared to embryonic or adult stages, leading to impaired lateral line function (Johnson et al. 2007). Similarly, goldfish (*Carassius auratus*) larvae exposed to copper demonstrated a significant incidence of physical malformations and mortality (Kong et al. 2013). Notably, fish gills and body tissues contain lower copper levels compared to the liver, which exhibits the highest concentration (Bawuro et al. 2018). The bioaccumulation of this trace element has been observed to impact lipid peroxidation, oxidative metabolism, and protein content in carp tissues (Radi and Matkovics 1988). Apart from this, elevated copper levels in fish diets were observed to result in a reduction in fish appetite, leading to adverse effects on feed utilization and growth. Additionally, Cu toxicity was found to induce deformities in reproductive organs and significantly decrease the fecundity, fertilization, and hatching rate, as well as the gonadosomatic index (GSI), in multiple fish species (Vajargah et al. 2020; Jamil Emon et al. 2023).

Lead (Pb)

Regarded as a highly hazardous heavy metal, lead (Pb) occurs naturally in the forms of PbS, $PbCO_3$, and $PbSO_4$. Human activities, including the utilization of lead-arsenate insecticides, lead-based pigments, and the combustion of fossil fuels such as coal, oil, and gasoline, contribute significantly to the overall increase of environmental lead levels (Vajargah et al. 2020). The aquatic ecosystem experiences direct detrimental effects from lead contamination originating from multiple sources, including industrial effluents, stormwater runoff from roads, agricultural areas, lead-containing dust, and municipal sewage (Sepe et al. 2003). Salinity, pH, hardness, and other factors all affect how soluble lead is in water. In soft or even acidic water, lead dissolves most readily. Lead poisoning in fish can occur at concentrations of 10–100 mg/l (Taee et al. 2020). Fish exhibit altered behavior, impotence, and slowed growth when exposed to sublethal levels of lead (Afshan et al. 2014). After continuous exposure to a low quantity of lead nitrate, Katti found that the brain, liver, and gonads of *Clarias batrachus* had changes in lipid as well as cholesterol content (Katti and Sathyanesan 1983).

Clarias gariepinus (African catfish) exposed to lead showed histological deformation of the gill and liver tissue. *Mastacembelus pancalus* (freshwater teleost) exposed to lead displayed histological changes in the ovarian tissue (Biswas and Ghosh 2016). Fish exposed to lead also showed signs of parenchymal cell necrosis, hepatic cord and connective tissue fibrosis, and collapse of blood vessels, along with decreased growth and body weight (Olojo et al. 2005). Reduced hematocrit value, red blood cell count, and hemoglobin content were seen in *Oreochromis niloticus* (Nile tilapia) after lead exposure (Tanekhy 2015). Lead toxicity causes synaptic impairment and neurotransmitter dysfunction in fish, which leads to oxidative stress (Lee et al. 2019). Lethal and sublethal lead exposure in *Tinca tinca* (tench) led to changes in immunological characteristics (Shah 2005). The liver, kidney, spleen, and gills are the primary sites of lead bioaccumulation in fishes (Creti et al. 2010). *Acipenser sinensis*, a species of Chinese sturgeon, experienced morphological changes and decreased free movement as a result of lead bioaccumulation (Hou et al. 2011).

Studies exploring the properties of nano-scale lead dioxide ($nPbO_2$) have yielded valuable insights into its potential neurobehavioral nanotoxicity, indicating a propensity for $nPbO_2$ to induce neurobehavioral impairments with ramifications at both the genetic and organismal levels (Kung and Chen 2023; Ribas et al. 2023). Furthermore, in-depth investigations examining the combined effects of lead and titanium dioxide nanoparticles (TiO_2 NPs) reveal intriguing patterns: at lower concentrations, TiO_2 NPs appear to intensify the Pb-induced reduction in cell viability, while higher concentrations independently restore cell viability, even in the presence of LPS stimulation (Ribas et al. 2023). This accumulating body of evidence underscores the critical importance of comprehending the toxic impact of lead and metal oxide nanoparticles on aquatic organisms to effectively mitigate their environmental consequences and safeguard precious aquatic ecosystems (Kung and Chen 2023; Ribas et al. 2023).

Nickel (Ni)

Nickel, a plentiful trace element, exhibits wide environmental distribution and typically coexists with oxygen or sulfur. Its occurrence stems from both natural phenomena and anthropogenic interventions, leading to the dispersal of nickel into the surroundings. Mining operations and the subsequent transformation of nickel into compounds or alloys constitute prominent sources of environmental nickel release. Furthermore, emissions of nickel arise from waste incineration processes, alongside oil- and coal-fueled power plants. Despite its role as an essential element for various organisms at minimal concentrations, elevated nickel concentrations can give rise to potential hazards. The toxicity of nickel to fishes is influenced by various physiochemical characteristics of water, including pH, temperature, hardness, ionic strength, and dissolved organic carbon (DOC) (Binet et al. 2018). Nile tilapia (*Oreochromis niloticus*) exposed to nickel chloride demonstrated noticeable behavioral changes such as irregular swimming patterns, increased opercular movement, respiratory disorders, and skin lesions. Hematological parameters of the Nile tilapia subjected to nickel exposure exhibited alterations, including an increase in red blood cell (RBC) count and a reduction in hemoglobin (Hb) and white blood cell (WBC) counts (Table 1) (Abou-Hadeed et al. 2008). In addition to Nile tilapia, the freshwater species *Hypophthalmichthys molitrix* has also shown adverse effects when exposed to nickel. Histopathological examinations revealed abnormalities in various tissues, including the liver, gills, kidney, and intestine (Abou-Hadeed et al. 2008). The liver tissue showed fusion of the gill lamellae, blood vessel degeneration, necrosis of the hepatocytes, enlargement, pyknotic nuclei, vacuolation, and lesions. On exposure to nickel, tubular cells in the kidney tissue also showed signs of hyperplasia and degeneration (Athikesavan et al. 2006). Decreased ATPase activity in the brain was seen in *Oreochromic niloticus*, a freshwater fish exposed to nickel chronically and acutely (Atli 2018). The liver's antioxidant defense mechanism was impacted by nickel exposure in the *Prochilodus lineatus*, which also caused DNA damage to the fish's gills and blood cells (Palermo et al. 2015). The common carp, *Cyprinus carpio*, experienced stress after being exposed to a heavy concentration of nickel for a brief period of time. *Cyprinus carpio* was also observed to exhibit behavioral alterations and altered hematological characteristics at sublethal nickel exposure levels (Al-Ghanim 2011). *Cyprinus carpio*, a freshwater fish, revealed some negative effects of nickel toxicity on its protein metabolism.

Following exposure to a fatal dosage of nickel, the detected abnormalities were reduction in soluble, structural, and total proteins, elevation in free amino acids as well as protease activity, and an increased amount of ammonia in the kidney and gills (Sreedevi et al. 1992). Prior to death, fish with nickel poisoning displayed behavioral abnormalities such as surfacing and rapid mouth and operculum movement. Nickel builds up in fish blood, muscles, kidney, and liver, with kidney showing the largest accumulation (Ghazaly 1992). *Tilapia nilotica*'s liver and muscle showed a general decline in glycogen levels as a result of bioaccumulation. High levels of nickel bioaccumulation in *T. nilotica* resulted in lymphopenia and leukopenia as well as increased packed cell volume, blood cell count, and Hb content. Nickel oxide nanoparticles have been found to exhibit eco-toxicity and pose harmful effects on aquatic organisms, leading to notable bioaccumulation in liver, intestine, gill, and kidney tissues. The depuration rates of these nanoparticles varied across different tissues and nickel compounds. Furthermore, fish exposed to nickel oxide nanoparticles displayed histopathological anomalies, suggesting potential adverse consequences. These significant findings emphasize the urgency of implementing robust regulations to mitigate and prevent additional environmental contamination resulting from the presence of nickel oxide nanoparticles (Kharkan et al. 2023).

Arsenic (As)

Arsenic, an omnipresent chemical element, is discharged into the aquatic ecosystem through diverse human-induced origins such as industrial manufacturing, smelting operations, and power generation. Furthermore, the application of arsenic-based insecticides, herbicides, and fungicides in agricultural fields contributes significantly to the contamination of aquatic ecosystems. Fish residing in these environments are exposed to arsenic through ingestion of contaminated food as well as direct contact with arsenic-contaminated water via their gills and integument. Arsenic exists in various chemical forms, including elemental, trivalent, and pentavalent arsenic. Among these forms, the trivalent arsenic compounds, known as arsenites, are particularly hazardous because of their high absorption rate in fish tissues (Garai et al. 2021).

The toxicity of arsenic is influenced by several abiotic factors present in water bodies, such as temperature, pH, salinity, organic matter content, phosphate concentration, suspended particles, and the presence of other toxins (Min et al. 2014). Prolonged exposure to low levels of arsenic lead to its bioaccumulation in the tissues of liver and kidney in freshwater fish (Kumari et al. 2017). For example, *Oreochromis mossambicus*, a freshwater fish species possessing gills and a liver, exhibited histological alterations following arsenic exposure. These alterations included epithelial lifting and edema, epithelial hyperplasia, desquamation, lamellar fusion, and necrosis in the gills. The liver histology revealed hepatocyte shrinkage, macrophage infiltration, vascularization, sinusoid enlargement, nuclear hypertrophy, vascular degeneration, and localized necrosis (Ahmed et al. 2013). Similarly, the freshwater teleost *Channa punctata* exhibited various histological changes in the heart tissue, including necrosis (Hossain 2014). Some fish species are more sensitive to certain heavy metals than others. For example, *Catla catla* is more sensitive to arsenic with a 96h LC50 of 20.41 mg/l, while *Clarias gariepenus* is more tolerant with a 96 h LC50 of 89 mg/l (Shahjahan et al. 2022; Lavanya et al. 2011).

Acute exposure to sodium arsenite caused alterations in the common Indian catfish *Clarias batrachus*, such as changes in hemopoiesis, erythrocyte membrane rupture, decreased iron absorption by erythrocytes, and hemolysis (Tripathi et al. 2003). Arsenic exposure also affected the total leukocyte count over time in the catfish *Clarias batrachus*, leading to decreased organo-somatic indices in the spleen and kidney. Furthermore, arsenic influenced T- and B-cell activity and interfered with the catfish's ability to phagocytose microorganisms (Ghosh et al. 2006). In the Japanese medaka (*Oryzias latipes*) embryo, sublethal levels of arsenic resulted in developmental arrest (Ishaque et al. 2004). Rainbow trout (*Salmo gairdnerii*) exposed to arsenic exhibited the production of stress response proteins (Kothary and Candido 1982). Arsenic poisoning in zebra fish embryos significantly reduced the expression of genes involved in innate immune responses, which are essential for defense against bacterial and viral infections (Dangleben et al. 2013). In a study by Wang et al., two fish cell lines (TO-2 cells from Tilapia ovary and JF cells from *Therapon jarbua* fin) were exposed to sodium arsenite. The researchers observed apoptosis in JF cells, likely induced by disruption of the cell cycle and the development of oxidative stress in TO-2 cells (Wang et al. 2004b). Long-term exposure to arsenic oxide in freshwater fish *Colisa fasciatus* resulted in decreased ovarian functions as well as a decline in second- and third-stage oocyte development (Shukla and Pandey 1984). Bioaccumulation of arsenic in fish has significant impacts on various physiological systems, including reproduction, growth, gene expression, ion control, histopathology, and immune system function (Garai et al. 2021).

Fish exposed to arsenic exhibit a diverse array of behavioral changes, indicating potential neurotoxic effects and sensory system irritability induced by the toxic element. These alterations include erratic movement, fast opercula movement, jumping out of the test medium, lateral swimming, and loss of balance. Alongside behavioral shifts, arsenic poses a significant threat to various major organs and organ systems within fish, including the skin, gastrointestinal tract, brain, muscles, gonads, kidneys, and liver. Prolonged arsenic exposure causes histopathological changes and impaired functionality in fish organs. Skin exposed to sodium arsenate suffers considerable damage, affecting mucous cells. Arsenic toxicity in gills leads to respiratory discomfort and cell abnormalities, hindering oxygen consumption. The brain's sensitivity to arsenic results in altered tissue components and behavioral indicators. Muscles experience degeneration and atrophy. Arsenic disrupts fish reproduction, affecting ovaries and spermatogenesis. Biochemically, it alters carbohydrate, protein, and lipid markers. Additionally, it disrupts the antioxidant system and alters enzyme activities within fish tissues. Hematological changes are also observed in fish following arsenic exposure, including declines in hemoglobin, packed cell volume, leukocyte numbers, and red blood cells, rendering the fish immunocompromised and susceptible to infections. Moreover, arsenic exposure can induce cytotoxicity in fish cells, leading to apoptosis, micronuclei formation, DNA-protein crosslinking, and mutations, with potential implications on gene expression and transcription factor activities (Malik et al. 2023).

Mercury (Hg)

Mercury, a highly hazardous heavy metal in the environment, has experienced a significant rise in contamination due to extensive industrialization in the twentieth century (Shukla and Pandey 1984). Recognizing its detrimental nature, the United States Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) have ranked mercury as the third most harmful environmental substance, preceded by lead and arsenic (Garai et al. 2021). Although natural sources like forest fires and volcanic eruptions contribute to mercury emissions, human activities such as mining, burning of fossil fuels, and the use of fungicides, electronic devices, batteries, and paint substantially contribute to mercury pollution (Pack et al. 2014). Mercury exists in various forms, including ionic compounds that can combine with other elements such as sulfide, chloride, organic acids, and organic compounds, particularly methylmercury, which is considered the most chemically hazardous form and constitutes a significant portion of mercury found in fish (Boening 2000). Microorganisms, such as anaerobic sulfate-reducing bacteria, iron reducers, and methanogens, play a crucial role in the methylation of inorganic mercury (Morel et al. 1998) (Amlund et al. 2007). Rising water temperatures associated with climate change have been found to stimulate the process of mercury methylation.

Fish can be exposed to mercury through their gills, skin, and alimentary canal. The acute lethal concentrations of inorganic mercury for salmonids range between 0.3 and 1.0 mg/l, while for cyprinids, it falls between 0.2 and 4 mg/l. Regarding frequently occurring organic mercury compounds, the acute lethal values for salmonids range from 0.025 to 0.125 mg/l; for cyprinids, they range from 0.20 to 0.70 mg/l. The upper limit of tolerable concentration for the inorganic mercury in salmonid species is determined to be 0.001 mg/l, while for cyprinid species, it is established at 0.002 mg/l (Svobodova et al. 1993). Even at sublethal concentrations, mercury exhibits high toxicity to fish, inducing biochemical, structural, and physiological changes in the fish nervous system. Methylmercury (CH_3Hg) is widely recognized as the most neurotoxic compound due to its lipophilic properties, enabling it to efficiently traverse the blood-brain barrier and accumulate within the nervous system of fish. Mercury can alter the configuration of purines, pyrimidines, and nucleic acids which can impact the physical properties and structural integrity of the plasma membrane (Baatrup 1991).

Long-term exposure to mercurial compounds can cause damage and necrosis in the kidney tubules of *Clarias batrachus* (Kirubagaran and Joy 1988). African catfish (*Clarias gariepinus*) exposed to mercury oxide toxicity showed significant increases in serum levels of cortisol, alanine aminotransferase, aspartate aminotransferase, cholesterol, urea, alkaline phosphatase, and creatinine, while hemoglobin and hematocrit values were significantly decreased (Mona et al. 2011). Freshwater fish *Channa punctatus* displayed oxidative damage and upregulation of proinflammatory cytokines after exposure to 0.3 mg/l of $HgCl_2$ for 7 days (Begam and Sengupta 2015). Exposure to inorganic mercury in zebra fish resulted in oxidative stress and histological changes in their gonads. Furthermore, mercury exposure disrupted gene transcription in the hypothalamic-pituitary-gonadal (HPG) axis, leading to alterations in sex hormone levels in adult zebra fish (Zhang et al. 2016). Mercury poisoning was observed to have a pronounced impact on the male reproductive system of *Gymnotus carapo*, a species of tropical fish. Exposure to $HgCl_2$ resulted in disorganized seminiferous tubules, congested blood vessels, increased interstitial tissues, and decreased germ cell and sperm count (Vergilio et al. 2013). Mercury has a strong affinity for proteins, leading to its accumulation in fish muscle, where over 90% of total mercury is found (Bradley et al. 2017). Due to the slow elimination rate of methyl mercury from fish, elevated levels of mercury can also be detected in the blood, in addition to the muscle tissue (Giblin and Massaro 1975). The liver can serve as a site for mercury storage, detoxification, or redistribution within the fish's body (Evans et al. 1993).

Gymnotous carapo, a tropical fish, is highly susceptible to mercury's toxic effects on its male reproductive system. Mercury accumulates primarily in the fish's muscle tissue, with the liver playing a crucial detoxification role. These fish serve as vital bio-indicators, assessing aquatic ecosystem health and physiological changes. Mercury toxicity affects hepatic and renal tissues, causing various abnormalities. Analyzing blood parameters reveals fish health and metabolic anomalies due to mercury exposure, inducing oxidative stress and reactive oxygen species. The Ganga River and nearby wetlands are at risk of mercury contamination, posing threats to aquatic species and biodiversity (Das et al. 2023).

Zinc (Zn)

Contamination of the environment with zinc is on the rise because of various human activities, including industrial operations, mining, coal and trash burning, and steel production (Han et al. 2023) (Wuana and Okieimen 2011). Zinc, a prevalent trace element and crucial micronutrient for every living organism, assumes a crucial function in various metabolic processes. These functions encompass protein and nucleic acid synthesis, immune response, cell division, energy metabolism, and growth. Furthermore, zinc serves as a cofactor for a multitude of enzymes that participate in critical processes such as metabolism, neuronal function, digestion, and other essential physiological functions (MacDonald 2000) (Chatterjee et al. 2019). Zinc deficiency can lead to various physiological disorders, including impaired reproductive rates, cardiovascular diseases, and cancer. However, excessive zinc can also be harmful (Azaman et al. 2015). Moreover, the toxicity of zinc varies among species and depends on the embryonic stage of the fish. The toxicity of zinc to aquatic organisms is influenced by various environmental factors, such as water hardness, temperature, and concentration of dissolved oxygen. Acute toxic concentrations of zinc can cause damage to the gill tissue, leading to fish mortality, while chronic toxic concentrations induce stress-related mortality (Skidmore 1964).

Fish take up zinc through their gills and digestive system. The divalent cationic form of zinc is the primary mechanism of its toxicity, as it interferes with calcium ion absorption in the tissues, causing hypocalcemia and eventually resulting in fish mortality (McRae et al. 2016). *Tilapia nilotica* exposed to zinc sulfate exhibited reduced swimming speed and loss of body balance, along with frequent necrosis and vacuolation in the liver hepatocytes (Ayotunde et al. 2011). Zebra fish embryos that were exposed to different doses of $ZnCl_2$ displayed delayed hatching ability, growth defects, and skeletal deformities attributed to impaired calcification (Salvaggio et al. 2016). *Phoxinus phoxinus* fish exposed to zinc demonstrated altered movement patterns and behaviors. The fish showed a tendency to form denser shoals near the bottom, displayed decreased activity levels, and were more prone to being startled (Bengtsson 1974). Killifish (*Fundulus heteroclitus*) treated with zinc showed increased hepatic lipid peroxidation, a biomarker of oxidative stress, and decreased liver catalase activity (CAT) (Loro et al. 2012).

Accumulation of zinc in fish takes place through both their gills and digestive system, although the extent to which water serves as a source of zinc is not yet comprehensively understood (Spry et al. 1988). Murugan et al. (2008) analyzed zinc deposits in *Channa punctatus* tissues and found that they were highest in the liver, followed by the kidney, intestine, gills, and muscles.

In their recent study, Xia et al. (2023) delved into the intricacies of Zn toxicity in fish cells using cutting-edge bioimaging techniques. The research unveiled fascinating observations, demonstrating that the effects of Zn toxicity and bioaccumulation were contingent on both the dosage and exposure time. Notably, cytotoxicity manifested when Zn concentrations reached the range of 200–250 µM after a mere 3 h, with a critical cellular Zn:P quota threshold of approximately 0.7. Remarkably, the pivotal role of lysosomes in regulating Zn homeostasis during brief exposures was highlighted, but intriguingly, beyond a specific threshold concentration (> 200 µM) and extended exposure time (> 3 hours), the delicate balance of homeostasis was disrupted. This, in turn, led to a noteworthy spillover of Zn into the cytoplasm and other cellular organelles, indicating the severity of the Zn impact. Adding to the significance of these discoveries, the researchers established that the content of Zn within mitochondria proved to be a dependable predictor of Zn-induced toxicity in fish cells. Such valuable findings offer crucial insights into the intricate cellular responses triggered by Zn exposure and its potential ramifications on the delicate balance of aquatic ecosystems (Xia et al. 2023).

Heavy metals and fish metabolism

Fish metabolism is highly susceptible to the detrimental effects of heavy metal toxicity, particularly due to the onset of oxidative stress. As seen in the previous sections of this review, although most of the heavy metals are essential for basic biological functions, excess or insufficient quantities can disrupt metabolic processes and cause serious disorders. Heavy metals that are essential for numerous physiological processes are those with proven biological activities (Abadi et al. 2015). However, a different class of heavy metals has no biological function and, at larger quantities, causes tissue toxicity. Oxidative stress arises from an imbalance between the generation of reactive oxygen species (ROS) and the fish's antioxidant defenses. Certain substances, such as transitional metal ions, insecticides, and petroleum pollution, trigger the production of ROS, which leads to cellular damage and disrupts normal physiological functions. In polluted regions, fish exhibit significant changes compared to those in pristine environments, indicating the presence of oxidative damage.

Mechanisms of metal-induced oxidative stress in fish

The extensive investigation into metal-induced oxidative stress in fish has provided valuable insights into the potential hazards associated with elevated metal concentrations. Copper, an essential element for cellular metabolism, can turn harmful when present in excess, leading to oxidative damage through redox cycling. Consequently, highly reactive hydroxyl radicals and other species wreak havoc on fish tissues. To counteract copper-induced oxidative stress, fish have developed protective mechanisms such as metallothioneins (MTs) and ceruloplasmin. Chromium exists in hexavalent and trivalent forms, the latter acting as a detoxification mechanism in biological systems. However, chronic exposure to hexavalent chromium can exacerbate oxidative stress by causing lipid peroxidation and DNA damage in fish. Iron, vital for various biological processes, can catalyze the generation of reactive oxygen species (ROS) through the Fenton reaction, resulting in oxidative damage to fish proteins, lipids, and DNA (Valko et al. 2005).

Metallothioneins (MTs) play a crucial role in protecting fish from the detrimental effects of heavy metal contamination in aquatic environments. MTs are low-molecular-weight, cysteine-rich proteins that can bind and sequester a variety of heavy metals, including cadmium, lead, zinc, mercury, and copper (Wang et al. 2016). The primary function of MTs in fish is to maintain homeostasis of essential metals like zinc and copper while also providing protection against the toxicity of non-essential heavy metals (Wang et al. 2016). When fish are exposed to elevated levels of heavy metals in their environment, MTs are rapidly induced and upregulated to bind and detoxify these harmful substances (M'kandawire et al. 2017; Bakiu et al. 2022). The metal-binding capacity of MTs is facilitated by the high cysteine content, which allows the formation of metal-thiolate clusters that can accommodate up to seven divalent metal ions per MT molecule (Wang et al. 2016). This metal-sequestering ability of MTs helps to prevent the accumulation of toxic heavy metals in sensitive tissues and organs, thereby mitigating the oxidative stress, DNA damage, and other deleterious effects that these pollutants can have on fish physiology, growth, and reproduction (Wang et al. 2014; Emon et al. 2023). The expression of MT genes is tightly regulated by metal-responsive transcription factors, which activate MT synthesis in response to increased intracellular metal concentrations (Kumar et al. 2017). By serving as a dynamic metal buffer and detoxification system, MTs are considered valuable biomarkers of heavy metal pollution in aquatic ecosystems, as their expression levels in fish tissues, particularly the liver, can provide a direct indication of the degree of metal contamination (M'kandawire et al. 2017). Rainbow trout (*Salmo gairdneri*) shows higher MT induction in the liver compared to the gills during sublethal copper exposure (de Boeck et al. 2003). A study on the African catfish (*Clarias gariepinus*) found that MT expression levels were highest at the most polluted site, indicating its potential as a biomarker of heavy metal pollution (M'kandawire et al. 2017). The structure and metal-binding properties of MT can also differ between fish species, with variations in the number and arrangement of cysteine residues that facilitate metal sequestration. For example, the MT from the African catfish (*C. gariepinus*) was found to bind up to seven divalent metal ions per molecule, similar to other fish MTs (M'kandawire et al. 2017).

Methylmercury (MeHg) poses a significant threat to fish by inducing oxidative stress. MeHg depletes the crucial antioxidant glutathione (GSH) and disrupts the fish's antioxidant system. To combat mercury-induced harm, fish employ metallothioneins as protective agents. Cadmium, while not directly producing ROS, negatively affects GSH and cell thiol status, leading to oxidative damage in fish. Exposure to cadmium triggers metallothionein production and increases lipid peroxidation as part of the fish's defensive response. Lead interacts with cell membranes, causing oxidative damage through various mechanisms in fish and prompting an increase in metallothionein production as a protective measure (Sharma et al. 2020). Arsenic-induced oxidative damage in fish occurs through ROS and reactive nitrogen species, with GSH playing a crucial role in combatting arsenic poisoning (Sharma et al. 2020). Fish demonstrate an adaptive response by elevating GSH levels to cope with arsenic-induced oxidative stress. Understanding these mechanisms is crucial for mitigating the adverse effects of metal exposure on fish populations and maintaining the health of aquatic ecosystems as a whole.

Antioxidant defenses in fish

Fish have a variety of antioxidant defenses to protect themselves from the harmful effects of reactive oxygen species (ROS) when they are under oxidative stress. These defenses include a range of antioxidant enzymes, including superoxide dismutase (SOD), which effectively converts superoxide radicals into less harmful hydrogen peroxide. Catalase (CAT) assumes a vital role by further neutralizing hydrogen peroxide, converting it into harmless water and oxygen. Not to be overlooked, glutathione peroxidase (GPx) emerges as another crucial enzyme, diligently reducing hydrogen peroxide and lipid peroxides with the aid of glutathione (GSH) as a co-factor. Alongside the arsenal of enzymatic defenses, fish also rely on non-enzymatic antioxidants, exemplified by glutathione (GSH) and oxidized glutathione disulfide (GSSG), to provide supplementary protection against oxidative damage (Fig. 2). These intricate and sophisticated antioxidant mechanisms effectively enable fish to cope with oxidative stress and uphold the integrity of their cellular functions, even in the face of challenging environmental conditions (Monteiro et al. 2010).

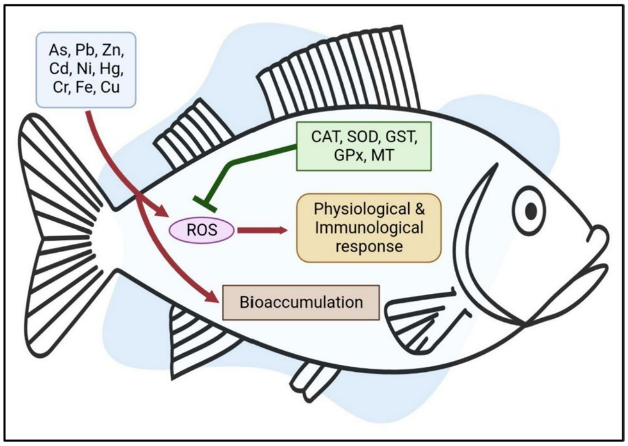

Fig. 2 Heavy metal-induced oxidative stress, detoxification and bioaccumulation in fish: heavy metals generate reactive oxygen species (ROS), leading to oxidative stress. Fish employ antioxidant defense mechanisms, including catalase (CAT), glutathione S-transferase (GST), superoxide dismutase (SOD), glutathione peroxidase (GPx), and metallothionein (MT), to counteract ROS and scavenge metals. High metal ion concentration can cause severe toxicity and trigger physiological and immunological responses. Bioaccumulation of metals occurs in fish tissues, posing long-term risks to fish and aquatic ecosystems.

Fish also depend on various proteins, such as ferritin, ceruloplasmin, and metallothioneins, to handle and detoxify hazardous metals. Among these proteins, metallothioneins play a crucial role in the detoxification process as they can bind with metals like zinc, cobalt, lead, mercury, silver, and cadmium. Notably, different fish species may have different isoforms of metallothioneins, which aid in their ability to adapt to metal exposure effectively. Consequently, metallothioneins serve as important biomarkers in identifying responses to toxic substances within aquatic environments (Aziza et al. 2016; El-Hak et al. 2022).

Complexity of metal-induced oxidative stress in fish

Metal-induced oxidative stress in fish is a highly intricate and multifaceted process, subject to the influence of numerous factors. The interplay of metal type, duration of exposure, and the particular fish species assumes paramount significance in shaping the ultimate outcomes. Central to this scenario is the production of reactive oxygen species (ROS), an inevitable byproduct of oxidative metabolism. When the delicate balance between ROS production and the capacity of antioxidant defenses to counteract them is disrupted, oxidative stress ensues. Within fish, a formidable array of antioxidant defenses acts as vigilant guardians against the detrimental effects of ROS. Among these defenses, pivotal roles are played by various enzymes, including SOD, CAT, GPx, and GST. Each enzyme serves a vital function in mitigating the harmful effects induced by ROS, bolstering the overall resilience of fish tissues in the face of metal-induced oxidative stress. Moreover, the mechanisms governing metal detoxification assume equal importance in determining the extent of oxidative damage. Over time, fish have evolved specific pathways dedicated to sequestering, metabolizing, and excreting metals, thereby minimizing their toxic impact. Notably, metallothioneins, essential proteins, are instrumental in binding to metals and facilitating their detoxification, effectively shielding fish from the adverse consequences of metal exposure (Sharma et al. 2020; Kumar et al. 2022; Raeeszadeh et al. 2022; Lee et al. 2023).

In aquatic environments, the buildup of heavy metals not only impacts fish populations but also increases the possibility of trophic transfer to higher trophic levels in the food chain or web. As a result, the translocation of these elements from aquatic to terrestrial ecosystems has deleterious repercussions on human health, accelerating the onset of conditions including cancer and neurological diseases.

Impacts of accumulation of heavy metals on human health

Heavy metals are essential for various physiological processes in humans but become hazardous when their concentrations surpass safe limits. Fish, as an integral part of aquatic ecosystems, can accumulate high levels of heavy metals because of environmental pollution. Consequently, the consumption of contaminated fish poses a significant risk to human health (Figure 3). Table 2 provides the prescribed regulatory limits for certain harmful heavy metals regarding human exposure.

Cadmium is a highly dangerous heavy metal classified as a human carcinogen (Congeevaram et al. 2007). Acute ingestion of Cd can result in severe gastrointestinal effects, while prolonged exposure to Cd can lead to kidney damage, lung cancer, and disruption of secondary metabolism (Charkiewicz et al. 2023; Congeevaram et al. 2007). Women are particularly susceptible to Cd accumulation, which can cause Itai-itai disease, glomerular and tubular dysfunction, bone fractures, and gastrointestinal irritation (Cervantes 1991; Kao et al. 2008). Cd also affects immune cells and contributes to cardiovascular abnormalities, respiratory distress syndrome, diabetes, and reproductive dysfunctions (Mishra and Tripathi 2009; Choo et al. 2006). Remediation strategies include chelation therapy and dietary interventions to reduce Cd absorption and accumulation.

Nickel induces detrimental effects on human health, primarily affecting the lungs and kidneys (Pandi et al. 2009). Inhalation of nickel oxide can lead to lung cancer, chronic bronchitis, and impaired lung function (Begum et al. 2022; Pandi et al. 2009). Nickel accumulation promotes chromosomal damage, inhibits natural killer (NK) cell activity, and causes symptoms such as dermatitis, diarrhea, and chest tightness (Florea and Busselberg 2006) (Schaumloffel 2012). Severe cases of nickel exposure can result in adult respiratory distress syndrome (ARDS) (Buxton et al. 2019).

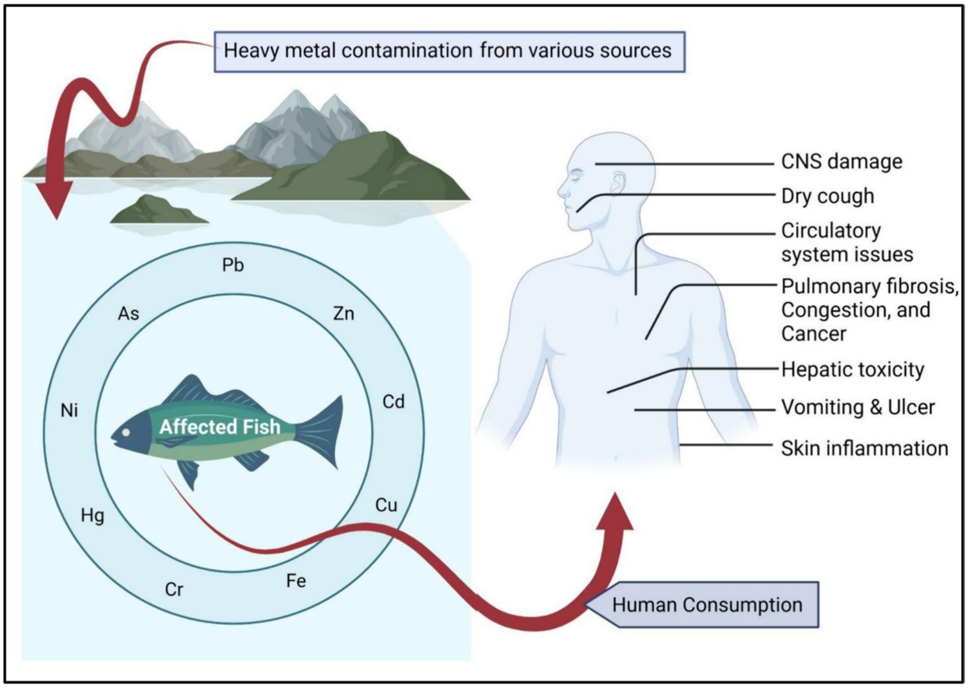

Fig. 3 Impacts of heavy metal contamination in water bodies on human health: an illustrative depiction showcasing the cycle of heavy metal contamination in water bodies, focusing on the accumulation of various heavy metals (such as Pb, Zn, Cd, As, Ni, Hg, Cr, Fe, Cu) in water, leading to the contamination of fish. The image highlights the subsequent consumption of these contaminated fish by humans and the resulting health problems. The associated health issues include CNS damage causing mental retardation, dry cough, pulmonary fibrosis, congestion, and lung cancer, vomiting and ulcers, circulatory system issues, diarrhea and gastrointestinal discomfort, hepatic toxicity, and skin inflammation.

Table 2 Heavy metal contamination in water: concentration levels, toxicity, and adverse effects on human health

Heavy metal	Maximum concentration level in water μg l^{-1}	Toxicity		Adverse effect on health	References
		Tolerable daily intake (mg/per day)	Lethal dose mg kg^{-1} body weight		
Lead (Pb)	10	0.025–0.052	94–158	Mental retardation, kidney damage, nervous system damage, and cancer	(Jones et al. 1979; Fu and Wang 2011; Guerra et al. 2012; Pratush et al. 2018; Carolin et al. 2017; WHO 2017; Vareda et al. 2019; Wani et al. 2020)
Cadmium (Cd)	3	0.018–0.052	4.4–6.2	Lung cancer, hepatic toxicity, and diseases affecting the respiratory system, liver, kidney, and reproductive organs.	(Jones et al. 1979; Fu and Wang 2011; Guerra et al. 2012; Carolin et al. 2017; Vareda et al. 2019; WHO 2017; Zamora-Ledezma et al. 2021)
Mercury (Hg)	6	0.03	5.1–10.0	Brain, kidney, respiratory, and reproductive system damage	(Jones et al. 1979; Fu and Wang 2011; Suhada et al. 2016; Vareda et al. 2019; WHO 2017; Zamora-Ledezma et al. 2021)
Zinc (Zn)	–	15–20	16.1–25.3	Pain, fever, skin inflammation, vomiting, and anemia	(Jones et al. 1979; Fu and Wang 2011; Pratush et al. 2018; Carolin et al. 2017; Vareda et al. 2019; WHO 2017)
Nickel (Ni)	70	0.089–0.231	–	Chest pain, dry cough, nausea, breathing problems, diarrhea, skin eruption, gastrointestinal ache, pulmonary fibrosis, and renal edema	(Jones et al. 1979; Fu and Wang 2011; Guerra et al. 2012; Pratush et al. 2018; Suhada et al. 2016; Carolin et al. 2017; WHO 2017; Vareda et al. 2019)
Chromium (Cr)	50	0.013–0.099	–	Pulmonary congestion, liver and kidney damage, skin inflammation, vomiting, and ulceration.	(Jones et al. 1979; Fu and Wang 2011; Guerra et al. 2012; Pratush et al. 2018; Carolin et al. 2017; WHO 2017; Vareda et al. 2019)
Copper (Cu)	2000	10	4.0–7.2	Hair loss, kidney damage, anemia, and headaches	(Jones et al. 1979; Fu and Wang 2011; Pratush et al. 2018; Carolin et al. 2017; Vareda et al. 2019; WHO 2017; Zamora-Ledezma et al. 2021)
Arsenic (As)	10	0.03	41	Circulatory system issues, skin damage, and an increased risk of developing cancer.	(Jones et al. 1979; Azimi et al. 2017; Srivastava et al. 2017; Ullah et al. 2017; Vareda et al. 2019; WHO 2017; Zamora-Ledezma et al. 2021)

Although the molecular mechanisms of nickel-induced toxicity are not yet fully understood, it is believed that mitochondrial dysfunction and oxidative stress play a primary and crucial role in the metal's toxic effects (Genchi et al. 2020). Remediation strategies include engineering controls, personal protective equipment, and dietary interventions to reduce Ni exposure and accumulation.

Arsenic, a highly toxic heavy metal, is a known carcinogen (Vahidnia et al. 2007). Exposure to low to moderate levels of inorganic arsenic is associated with diabetes, hepatic and renal failure, and neurological disorders (Vahidnia et al. 2007). Arsenic poisoning affects the brain, peripheral nerves, and cardiovascular system (Mundey et al. 2013). Common symptoms of arsenic poisoning include skin diseases, neurological problems, cellular hypertrophy, chronic bronchitis, and gastrointestinal disturbances (Sheikh and Khalili 2008). Chronic low-level As exposure (around the WHO guideline of 10 µg/l) is associated with increased cancer risk (Sanyal et al. 2020). Remediation approaches include water treatment, dietary interventions, and bioremediation.

Mercury is considered the most hazardous non-essential metal for humans (Park and Zheng 2012). Mercury exists in various forms, including methylmercury (MeHg) and elemental (metallic) mercury, each with different toxicity profiles. MeHg is a powerful neurotoxin that can cause sensory disturbances, lack of coordination, and impairment of speech, hearing, and walking. Elemental mercury exposure can lead to tremors, emotional changes, insomnia, and neuromuscular effects. EPA has issued fish consumption advisories to limit MeHg exposure (US Environmental Protection Agency 2015). Exposure to mercury, particularly through fish consumption, leads to cognitive, motor, and sensory disturbances (Park and Zheng 2012). Prolonged exposure to high levels of mercury causes brain impairment, pulmonary edema, pneumonia, and lung conditions (Rice et al. 2014). Even low-level exposure results in depression, skin rashes, tremors, and memory loss (Rice et al. 2014). Mercury interferes with thyroid hormone activity, affects glucose regulation, and contributes to male and female infertility (Mathew et al. 2011) (Wadhwa et al. 2012).

Lead is a hazardous heavy metal that disrupts various biological processes and affects neurodevelopment in infants (Assi et al. 2016). Lead exposure increases reactive oxygen species (ROS) production and leads to oxidative stress, protein, membrane, and lipid damage (Assi et al. 2016). High lead levels are associated with hypertension, cardiovascular disease, kidney damage, and anemia (Vij and Dhundasi 2009). Lead exposure impacts both male and female reproductive systems, causing infertility, chromosomal damage, and hormonal alterations (Martin and Grisworld 2009). Charkiewicz and Backstrand (2020) discovered that lead (Pb) poses significant dangers when it is absorbed and accumulates in the body's major organs. This accumulation can lead to a variety of symptoms, which differ based on individual factors, duration of exposure, and dosage. In adults, lead exposure can result in elevated blood pressure, slower nerve conduction, mood swings, fatigue, drowsiness, fertility issues, reduced libido, headaches, impaired concentration, constipation, and, in severe cases, encephalopathy or even death.

Regional variations, mitigation, and global regulations

Heavy metal contamination is a significant concern in various regions worldwide and shows regional variations. For instance, in Asia, the use of pesticides and fertilizers in agriculture has led to high levels of cadmium and arsenic in soil and water, posing a risk to human health and the environment (Ngai et al. 2021; Jan et al. 2022; Teschke 2022). In Europe, the use of lead in paint and gasoline has resulted in significant contamination of soil and water, particularly in urban areas (Steinnes 2013; Lubal 2024). In Africa, the lack of proper waste management and industrial activities has led to high levels of heavy metal contamination in soil and water, affecting both human health and the environment (Okeke et al. 2024; Wang et al. 2024). To address the issue of heavy metal contamination, international efforts have been made through regulations, agreements, and consideration of broader environmental consequences. The United Nations has played a crucial role in addressing the issue through various initiatives, such as the Minamata Convention on Mercury, which aims to reduce global mercury emissions and releases (Kessler 2013; Rekha 2023). The Stockholm Convention on Persistent Organic Pollutants (POPs) has also been instrumental in addressing the issue of heavy metal contamination by banning the production and use of POPs, which are known to accumulate in the environment and pose significant health risks (Wang et al. 2022). Several international agreements and regulations have been put in place to address the issue of heavy metal contamination. For instance, the European Union's Water Framework Directive sets limits for the concentration of heavy metals in water, while the United States' Clean Water Act regulates the discharge of pollutants into waterways (Roy et al. 2024). The International Maritime Organization's (IMO) MARPOL Convention regulates the discharge of pollutants from ships, including heavy metals (Sepúlveda et al. 2020). Regional agreements like those under the United Nations Environmental Program (UNEP) also focus on preventing coastal and open ocean areas from marine pollution (Yousuf 2021). The EPA has set a maximum contaminant level (MCL) for Cd in drinking water of 0.005 mg/l (Faroon et al. 2012). The World Health Organization (WHO) has established a maximum allowable limit of 10 µg/l for arsenic in drinking water, along with other metals (Table 2). However, many countries have reported arsenic levels exceeding this limit, especially in Asia (Aziz et al. 2023). To be effective, such targets and regulations on heavy metal pollution need to be supported by monitoring and enforcement mechanisms. Governments and regulatory agencies should review or establish health-based targets for heavy metal contamination in consultation with local authorities and stakeholders.

Currently, bioremediation is the most effective and environmentally friendly technique for environmental restoration. It is also cost-effective. Bacterial strains like *Oceanobacillus profundus* and *Lactobacillus acidophilus* ATCC4356 can reduce lead by 97% and 73.9%, respectively. Similarly, some algae and fungal species have demonstrated lead removal efficiencies of 74% (Spirulina), 97.1% (Chlorella kessleri), 95.5% (*Penicillium janthinillum*), and 86% (*Aspergillus flavus*). The biodegradation of lead by various microbes represents the most efficient and sustainable approach (Kumar and Singh 2023). Similar measures are available for other metals as well. Preventive actions to manage heavy metal contamination include best practices for siting and planning new water sources, preventing and reducing catchment pollution, and consistent maintenance of water systems. Corrective actions like treating contaminated water should be implemented once heavy metal pollution has been identified (Wren Tracy et al. 2020).

Conclusion

This thorough analysis clarifies the important effects that heavy metal toxicity in fish can have on human health. Our study sheds light on the numerous industrial and agricultural practises as well as other environmental heavy metal contamination sources. We now understand how different fish species acquire heavy metals and which organs and tissues they favour. The harmful effects of heavy metal accumulation on fish physiology, such as increased oxidative stress, changes in tissue structure, and weakened immune function, have also been thoroughly investigated. In this review, we specifically highlight the potential health concerns associated with consuming fish contaminated by heavy metals, focusing on the specific health impacts of each metal. Of particular concern are the effects of nickel on the lungs and kidneys, arsenic's ability to cause cancer, mercury's impact on neurological and reproductive health, and the effects of lead on neurodevelopment. To protect both aquatic ecosystems and human health, it is crucial to implement strict regulations and effective pollution management techniques. This includes establishing monitoring programs and developing plans to mitigate heavy metal exposure. It is equally important to raise public awareness and provide education about the dangers of consuming contaminated fish, empowering individuals to make informed decisions regarding seafood consumption. Continued research in this field is essential for a comprehensive understanding of the long-term effects of heavy metal accumulation and for the development of successful mitigation strategies. By taking proactive measures, we can prevent the negative consequences of heavy metal contamination for both aquatic ecosystems and human health.

Acknowledgements Authors thank the Department of Biosciences-UIBT, Chandigarh University, Gharuan, Mohali-Punjab, India, for providing the required facilities during the study.

Author contributions G.S. wrote the main manuscript, prepared figures 1-3 and tables 1-2, and S.S. supervised at each step and approved the manuscript.

Data availability Data are contained within the article.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The manuscript is a review article and totally based on the literature. Therefore, no ethical or animal approval is required.

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