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Neurotoxicity and hepatotoxicity induced by heavy metals in freshwater fish

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Abstract

Over recent years, aquaculture has been advancing significantly faster than other animal husbandry sectors. However, fish intake may endanger human health due to contamination with heavy metals. The levels of heavy metals are continuously increasing in freshwaters due to multiple anthropogenic activities. They bioaccumulate and affect different organs of freshwater fish. The review aims to provide data on the hepatotoxic and neurotoxic impacts of cadmium, lead, mercury, aluminum, arsenic, and chromium in freshwater fish. Neurotoxicity is mainly induced through the generation of severe oxidative stress in cells leading to abnormal neurotransmitter secretions, increased expression of apoptotic and detoxifying genes, neuroinflammation and mutations in the epigenome resulting in disrupted social and flight behavior, boosted auditory thresholds, impairing foraging ability, abnormal swimming patterns, hyperactivity, breathing problems and ultimately low mortality rate. Similarly, heavy metal-induced oxidative stress also serves as a key factor for the dysfunction of the liver. It causes lipoperoxidation, the uncontrolled activity of kinases and nuclear receptors, mitochondrial dysfunction, abnormal endocrine secretions, and activation of the intrinsic apoptotic pathway, developing necrotic regions in the liver. Ultimately, establishing histopathological lesions resulting in liver damage. For estimating environmental risk and developing pollution control strategies, the knowledge of the mechanisms of heavy metals is important.

1. Introduction

Over recent years, aquaculture has been advancing significantly faster than other animal husbandry sectors (Kalita et al. 2023; Nwafili and Chibanya 2023; Basir et al. 2024; Tenaya et al. 2024). Interestingly, about 17% of animal protein and over 6% of total protein consumed by humans is sourced from aquaculture (Boyd et al. 2022; Montesqrit et al. 2024). Vitamin B and omega-3 fatty acids are present in rich quantities in fish with lower saturated fats (Jabeen et al. 2024; Karadaş 2024). Unfortunately, fish consumption may threaten the health of humans due to a variety of contaminants, such as heavy metals. Heavy metals are classified into two groups, essential heavy metals and non-essential heavy metals (Arinola et al. 2025). Essential heavy metals are needed at optimum levels for all the body's vital functions, such as copper, zinc, nickel, iron, manganese, selenium, chromium, and cobalt. Otherwise, minimal amounts result in deficiencies, and excessive levels cause toxicity (Jagaba et al. 2024). Non-essential heavy metals, such as lead, aluminum, mercury, cadmium, etc., also known as xenobiotics, have no biological significance. However, excessive levels of these metals have toxic effects on the tissues of humans and animals (Ngu et al. 2022). They are naturally existing constituents of the crust of the earth and are recognized as the micronutrients of the hydric ecosystems with restricted tolerable concentrations, which have been elevating due to multiple anthropogenic activities including ever-increasing urbanization, and agricultural practices such as overuse of herbicides, fertilizers, fungicides, and industrialization (Bashir et al. 2020; Sonone et al. 2020; Pandey and Tiwari 2021; Rasheed and Du 2023; Mukanga et al. 2024; Santoso et al. 2024). These factors elevate the susceptibility of fish and humans as well as other invertebrates and vertebrates to natural hazards, including neurological disorders such as cognitive function impairment, tremors and Parkinson's and Alzheimer's diseases, hepatic and kidney disorders, cancer, reproductive problems including miscarriages, infertility and stillbirths, cardiovascular disorders and other health issues (Kolarova and Napiórkowski 2021; Monchanin et al. 2021; Mitra et al. 2022; Soliman et al. 2022). Heavy metals bioaccumulate in the fish from the heavily contaminated aquatic environment. In comparison to marine fish, freshwater fish have become more vulnerable to the toxicity of heavy metals. Because freshwater fish live by losing salt and gaining water, on the other hand, marine fish live by gaining salt and losing water. Freshwater fish have

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higher concentrations of salts in their body as compared to their surroundings, which causes the continuous entering of water into the body through osmosis; on the other hand, marine fish have lower concentrations of salt in their body as compared to their surroundings, which causes the continuous losing of water through the body (Boyd et al. 2025; Kaur et al. 2025). Heavy metals enter the fish body through ingestion, gills, and skin (Najibzadeh 2025; Suleman et al. 2025). The bioaccumulation of metals in different parts of the fish is determined by the environment, water solubility, eating patterns, and fish physiology, such as health, age, size, fertility status, species, absorption rate, and different ecological niches (Sharma et al. 2024; Zaghloul et al. 2024). This study aims to provide information regarding the heavy metals-induced hepatotoxicity and neurotoxicity in freshwater fish.

2. General mechanisms of neurotoxicity in fish

The mechanisms of neurotoxicity include disruption of the activity of neurotransmitters, such as acetylcholinesterase, and hence impairment of neural signaling pathways (Medda et al. 2020). Heavy metal intoxications upregulate oxygen radical species production, leading to neuronal apoptosis through increased lipid peroxidation and mitochondrial dysfunction (Liu et al. 2023). Moreover, they allow penetration of more toxins due to the disintegration of the blood-brain barrier resulting in neuroinflammation and glial cell stimulation (Wang et al. 2021a). Consequently, this leads to neural atrophy and cognitive dysfunctions. Defects in the development and growth of the nervous system, which could be induced by environmental or hereditary elements, are generally referred to as neurodevelopmental disorders (NDDs) (Yilmaz et al. 2024). Regardless of whether external morphology remains unchanged, behavior is a sensitive indicator of changes in interior physiology (de Lagrán et al. 2024). In fish, behavior changes are frequently caused by impaired neurodevelopment and abnormal release of neurotransmitters, which are associated with exposure to heavy metals (Green and Planchart 2018; Althobaiti 2024; Murumulla et al. 2024). The World Health Organization reported lead, mercury, and cadmium as dangerous elements (WHO 2020). Additionally, aluminum, arsenic, and chromium are also reported to induce severe neurotoxicity in freshwater fish through different mechanisms in various studies (Patel et al. 2021; Boopathi et al. 2024a; Rezaei et al. 2024; Garg and Bandyopadhyay 2025). The mechanism of the neurotoxic effects of heavy metals is shown in Fig. 1 below.

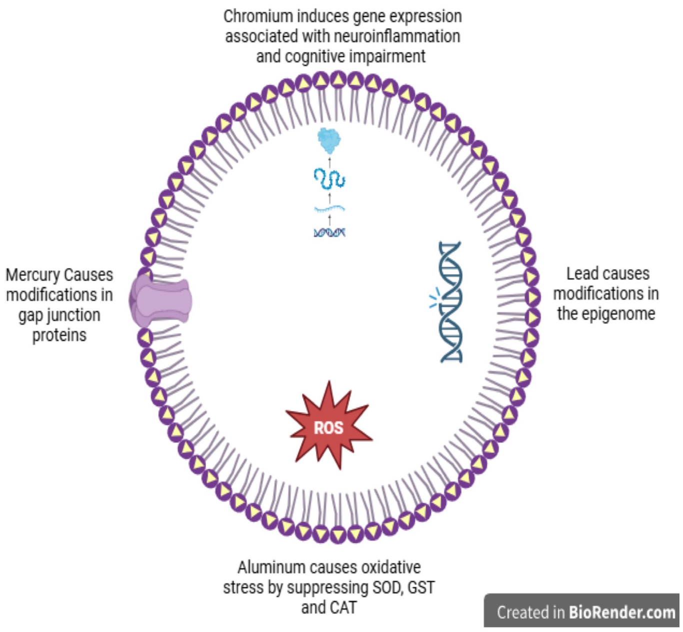

***Fig. 1**: Mechanisms of heavy metal-induced neurotoxicity in freshwater fish (ROS – Reactive oxygen species; SOD – Super oxide dismutase; CAT – Catalase; GST – Glutathione S-transferase)*

3. General mechanisms of hepatotoxicity in fish

The liver is known for its metabolic detoxification and xenobiotic metabolism processes (Wu et al. 2024). Therefore, it comes under the category of organs most influenced by pollutants and contaminants (Wu et al. 2025). Several hepatotoxic effects can be seen in freshwater fish exposed to heavy metals. Oxidative stress is a key factor that is triggered by structural and functional modifications in catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) (Jomova et al. 2024; Sozen et al. 2024). This oxidative damage causes biochemical changes such as elevated lipid peroxidation that disrupts the hepatocyte membrane and may be linked to developing necrotic regions in the liver (Bashir et al. 2024). These biochemical changes lead to histopathological alterations such as the occurrence of sinusoidal dilation and congestion, squamous-like hepatocytes, necrosis, the proliferation of fibrotic tissues around muscles, vacuolization, eosinophilic bodies, and infiltration. All these factors lead to the development of histopathological lesions and ultimately liver damage (Rajkumar 2022; Elumalai et al. 2023). Mechanism of toxicity in fish is show in Fig. 2.

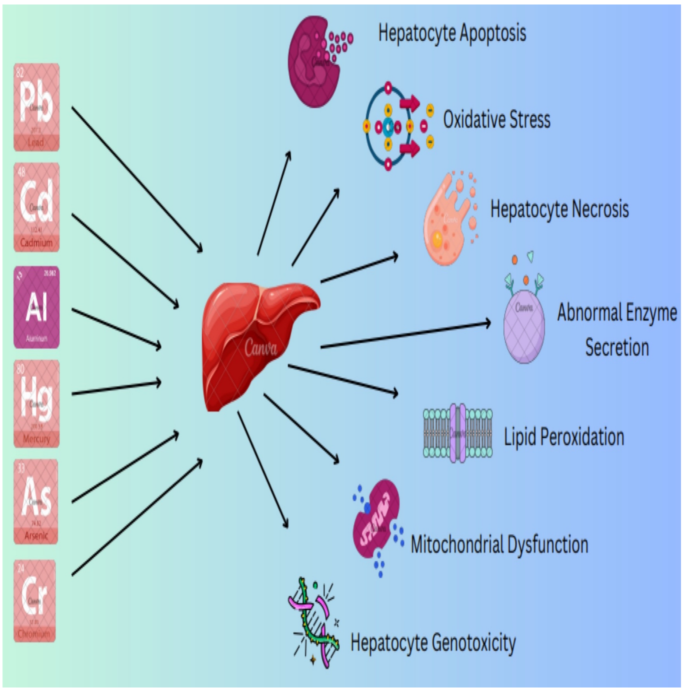

***Fig. 2**: Mechanisms of heavy metal-induced hepatotoxicity in freshwater fish*

4. Various metals that cause neurotoxicity and hepatotoxicity in freshwater fish

4. 1 Cadmium (Cd)

Despite being a non-essential, persistent, and non-biodegradable element, cadmium is extremely harmful to people, animals, and plants, even in low quantities (Sable et al. 2024). As the seventh most abundant element on Earth, Cd is found in rocks, soils, plants, and volcanic dust. Numerous freshwater fish species, such as *Danio rerio*, *Pimephales promelas*, and *Oncorhynchus mykiss*, have been examined for their neurological effects at lower concentrations of Cd (Oleinikova et al. 2024). According to these studies, Cd causes alterations in social and flight behavior, boosts auditory thresholds, impairs the neuromast and sensory macula, and builds up in the olfactory bulb (Patel et al. 2021; Rani et al. 2022; Xu et al. 2022; Naz et al. 2023; Nalivaikienė et al. 2024). Cd can accumulate in the brain of adults and upregulate the expression of apoptotic genes, including Jun proto-oncogene, AP-1 transcription factor subunit, and detoxifying genes such as metallothionein 1 (mt1) and metallothionein 2 (mt2), even at very low levels of exposure (Hu et al. 2022; Al Marshoudi et al. 2023). By increasing the concentration levels, upregulation of the nuclear factor erythroid 2-related factor 2 in the telencephalon and olfactory bulb can be observed when the exposure period is less than 24 hours (Xu et al. 2023; Alharbi et al. 2024). It also increased the expression of mt1 and mt2 in the brain, as demonstrated by another study (Liu et al. 2024). Nuclear factor (erythroid 2-related factor 2) and metallothioneins (mt1 and mt2) are considered defenses that aid in reducing oxidative stress and regulating cellular homeostasis. However, these protective mechanisms appeared to be overcome after exposure to elevated duration and concentration of Cd, resulting in the downregulation of the antioxidant enzyme heme oxygenase 1 (HO-1) and metal-responsive transcription factor 1 (MTF1) pathway. Consequently, symptoms of tissue degeneration become evident due to elevated oxidative stress and inflammation (Choudhury et al. 2021; Min et al. 2021; Patel et al. 2021; Talukder et al. 2021; Banaee et al. 2023; da Silva et al. 2023; Motta et al.2025). These disruptions comprise alterations in the structure of retinal neurons, intensified light sensitivity, reduction in glial fibrillary acidic proteins, and increased concentrations of malondialdehyde, nitric oxide, and ROS. In general, Cd triggers oxidative stress reactions and stimulates the induction of detoxification genes in adults and embryonic larvae. Moreover, during the embryonic and larval phases, the maturing sensory system was more vulnerable to Cd toxicity (Khan et al. 2023). Similarly, Cd at higher concentrations accumulates in the liver, the primary organ for metal detoxification, and causes damage (Rasin et al. 2025). For instance, Wu et al. (2019) reported that Cd induces hepatocyte necrosis by disrupting the lipid metabolism in *Gobiocypris rarus* when exposed to higher concentrations. Moreover, Rahmi et al. (2024) reported severe liver damage in *Oreochromis niloticus* when exposed to Cd by excessive secretion of aspartate transaminase (AST) and alanine aminotransferase (ALT) enzymes, downregulating total protein levels, upregulating total lipid levels that lead to the disruption of metabolic processes and ultimately liver dysfunction. Hence, Cd increases the morbidity and mortality of freshwater fish due to its direct influence on its nervous system and liver.

4.2 Mercury (Hg)

High Hg levels are more toxic to both animals and humans. Studies demonstrate that *D. rerio, P. promelas, and Diplodus sargus* show neurologically damaging effects when exposed to it. For instance, studies on adults have revealed that Hg activates the metallothionein gene in the brain at concentrations below 200 ppb, but otherwise does not impact other neural transcripts (Alam et al. 2021; Zhu et al. 2022). On the other hand, minimal inorganic concentration exposure led to impaired foraging ability, suppression of membrane adenosine deaminase, and abnormal swimming patterns (Albers et al. 2022; Jeong et al. 2024). Intermediate concentrations revealed a notable accumulation of Hg in the brain (Zhang et al. 2023) which cause high mortality, late hatching (Barst et al. 2022), reduction in dopamine, neurotransmitters, and serotine associated with the onset of hyperactive behavior (Nielsen et al. 2017; Chen et al. 2021; Solakhiyah et al. 2023). Exposure to elevated levels of Hg modifies amino acids associated with oxidative phosphorylation and gap junctions, causes mitochondrial dysfunction, and upregulates the metallothionein gene expression (Rasinger et al. 2017; Trivedi et al. 2022; Singh et al. 2024). Notably, this disruption may be associated with the modifications in the mammalian target of the rapamycin (mTOR) pathway activated by oxidative stress triggered by Hg. Another investigation specifically on zebrafish embryos demonstrated its sensitivity toward low concentrations of Hg resulting in modification at cellular, molecular, and behavioral levels. For example, exposure at the embryonic development stage to Hg levels below 30 ppb caused adult vision impairments, hyperactivity, suppression of neural tube cell growth, and higher mortality (Bakar et al. 2017; Cano-Viveros et al. 2021; Henriques et al. 2023). Significant harmful effects, such as delayed hatching, reduced head size, modified cAMP signaling, and mortality, can be observed at levels above 50 ppb (Bakar et al. 2023; Henriques et al. 2023). Similarly, Hg caused hepatotoxicity in freshwater fish. For instance, according to a study conducted by Lei et al. (2025), exposure of *D. rerio* to low levels of Hg caused liver damage evidenced by oxidative stress in hepatocytes leading to the activation of intrinsic apoptotic pathway, the uncontrolled activity of kinases and nuclear receptors, mitochondrial dysfunction and abnormal endocrine secretions. Another study demonstrated the hepatocyte disruption in *Geophagus brasiliensis* by elevating lipoperoxidation in response to oxidative stress and impaired activity of antioxidant enzymes, including catalase (CAT) and glutathione peroxidase (GPx) (Monteiro et al. 2024). Furthermore, Mohamed et al. (2019) reported severe hepatotoxic impacts of mercury along with lead on *Clarias gariepinus* including severe hepatic cords, excessive hepatocyte necrosis, melanomacrophage aggregation, and hemolysis. Lastly, Pervaiz et al. (2019) reported liver damage in *O. niloticus* after exposure to sublethal concentrations of Hg. The disruption included hepatocyte destruction, the occurrence of karyolysis and pyknotic nuclei, sinusoids, tissue degeneration, vacuolization, and cellular necrosis. In conclusion, mercury causes severe damage to freshwater fish by inducing neurotoxic effects including hyperactivity, delayed hatching, reduced head size, and increased mortality rate, and hepatotoxic effects such as reduced activity of antioxidant enzymes, hepatocyte necrosis, and hemolysis.

4.3 Lead (Pb)

Pb is known as a natural element of the geological crust and is present in micro-concentrations in plants, water, and soil. However, anthropogenic activities have caused its high accumulation which is dreadful for aquatic life. It is mainly because of the increased affinity of Pb for a particular protein due to its capacity to develop a stable complex with oxygen and sulfur atoms in protein (Lee et al. 2019). For instance, numerous genes responsible for the development of the nervous system are modified by Pb at low concentrations, such as elevated protein expression of the GABA gene during embryonic maturation (Paduraru et al. 2023). These modifications were due to incomplete nerve development, resulting in slower neuronal signaling and inefficient communication between the neurons due to reduced axon length (Liu et al. 2024). Moreover, zebrafish showed changed color preferences and reduced adult learning at concentrations of more than 100 ppb (Paduraru et al. 2021; Thawkar and Kaur 2021). However, lasting learning impairment for three generations after first exposure revealed the ability of Pb to cause modifications in the epigenome (Wang et al. 2022a). Also, Pb above 100 ppb concentrations caused hyperactivity, trembling, abnormal swimming, muscle tremors, and rapid breathing in *Coregonus lavaretus* and *Cyprinus carpio* (Gashkina et al. 2022; Habib et al. 2024). Lastly, elevated levels of Pb disturbed cognitive functions and motor activity in zebrafish by suppressing neurexin 2 expression, which is essential for neural development (Tu et al. 2017). Similarly, Pb affects the health of freshwater fish by inducing hepatotoxicity. For instance, a novel study on superoxide dismutase (Sod) deficiency in *D. rerio* liver caused by Pb revealed that like Cd, Pb toxicity triggered oxidative stress in the cell by disrupting the activity of SOD by shifting Zn and Cu ions from its catalytic pockets (Wang et al. 2022b). Hence, oxidative stress can be a key factor in Pb-induced abnormalities in freshwater fish (Guo et al. 2021; Shafiq et al. 2024). Moreover, Dey et al. (2024a) demonstrated hepatotoxicity in *D. rerio* when exposed to 5 ppm concentration levels. It triggered severe oxidative stress, resulting in lipoperoxidation and, ultimately, apoptosis. However, activation of the Nrf2-Keap1 signaling pathway in response to oxidative stress was the cellular defense mechanism that has been observed. A similar pattern of activation of the Nrf2-Keap1 defense mechanism has been seen in *Anabas testudineus* when exposed to 43.4 ppm Pb concentration (Dey et al. 2024b; Helmizuryani et al. 2024). Similarly, Giri et al. (2021) indicated that the Pb-induced impairment of the cytochrome P450 detoxification system results in the slow detoxification of pollutants in *C. carpio,* causing liver dysfunction by reducing liver enzyme aspartate aminotransferase through its leakage into the blood. Hence, Pb contamination causes serious neurotoxic and hepatotoxic effects in the freshwater fish and risks their survival.

4.4 Aluminum (Al)

Al makes up 8.1% of the Earth's mass and so categorized as the most frequent natural metallic element and the third most common mineral in the crust (Upadhyay 2025). Al affects aquatic organisms adversely (Botté et al. 2022). Al-induced oxidative stress is a key factor that targets the cognitive functions and behaviors of fish by interrupting cellular metabolism. For instance, long-term exposure suppressed the antioxidant enzymes produced in response to oxidative stress, such as brain catalase activity (CAT) in *Channa punctatus, Oreochromis mossambicus,* and *Ctenopharyngodon Idella* (Closset et al. 2021; Aydin et al. 2024). This suppression in CAT was explained by the inhibition of gene expression and the binding of Al ions to enzyme thiol groups (Rahimzadeh et al. 2022). Similarly, Temiz and Kargın (2022) reported the significant suppression of glutathione S-transferase (GST), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in *O. niloticus* leading to lipid peroxidation due to elevating oxygen radical levels. Moreover, a significant production of AChE was reported in *D. rerio* on exposure to 50 μg/L $AlCl_3$, which diminished the locomotor activity, including lowering maximum speed, elevating the absolute angle of rotation, and reducing traveled distance (Kaur et al. 2022; Nadiga and Krishna 2024; Zhang et al. 2024). Furthermore, there are reports of swimming impairment in *D. rerio* larvae when exposed to Al at concentrations below 100 μM, including lowering the time and velocity of movement, reducing average traveled distance and number of headings due to modification in glucose metabolism and restricted neuroblast differentiation due to decreasing numbers of neural stem cells (Wei et al. 2018; Capriello et al. 2019, Gao et al. 2022). Boopathi et al. (2024a) reported that in *D. rerio* after being exposed to Al witnessed a decline in their spatial learning abilities. Cognitive deficiencies were linked to a reduction in the forebrain's neuronal plasticity and Neurogenic differentiation factor 1 (NeuroD1) expression in the telencephalon (Tutukova et al. 2021). Several studies have revealed the hepatotoxic effects of Al on freshwater fish. For instance, the exposure of *O. niloticus* to 2.6 ppm concentration levels of Al_2O_3 induced severe liver damage by triggering oxidative stress through elevating levels of thiobarbituric acid reactive substance (TBARS) and consequently, damaging hepatocyte cell membrane (Temiz and Kargın 2022). It also caused genotoxicity by upregulating the biomarker of DNA oxidative damage known as 8-hydroxy-2-deoxyguanosine (8-OHdG). In another study, *O. niloticus* exposed to 4 mg/L concentration of Al_2O_3 NPs indicated irreversible liver damage due to the induction of melanomacrophage aggregation leading to necrosis of hepatocytes (Massoud et al. 2021). Aluminum exposure of freshwater fish exhibits neurotoxic and hepatotoxic effects by causing cognitive deficiencies and genotoxicity in hepatocytes.

4.5 Arsenic (As)

As is regarded as an environmental contaminant. Different countries have restricted As concentration to conserve aquatic biodiversity (Saxena 2025). For instance, according to Brazilian law, the highest amount of As tolerable for aquatic fauna is 10 μg/L (de Souza et al. 2019). However, As toxicity in the nervous system gained minimal recognition compared to its impacts on cellular disruption, genetic toxicity, and cancer (Chuong et al. 2024; Garkal et al. 2024). Neurotoxic effects of As has been observed in *D. rerio* when exposed to 50 μg/L and 500 μg/L of sodium arsenate for 30 days (Ma et al. 2024). Consequently, neurobehavioral dysfunctionalities can be observed including reduced social interaction and cognition, long-term memory impairment, and lower aggression levels. In another study, low performance of *D. rerio* in the latent learning task and disrupted memory due to alteration in dopamine-associated genes in the brain when exposed to high (100 μg/g) and medium (60 μg/g) doses of As were observed (Rachamalla et al. 2023). Moreover, the disruption of neurotransmitter AChe in *C. carpio* after 30 days of arsenite exposure at 2.83 mg/L resulting in disrupted coordinated behavior, slowed reflexes, and memory loss was observed (Wang et al. 2021). In a study on *Labeo rohita* the exposure to As (20.25 mg/L) induced severe liver damage due to severe oxidative stress, excessive secretion of ALT, AST, and ALP, and upregulation of cytochrome P450 gene expression (Khalid et al. 2024). Similarly, the histopathological and metabolic damage in the liver of *D. rerio* exposed to arsenic was reported (Ragupathi et al. 2022). Likewise, in another study within 48 hours of exposure to the nonlethal As doses, *C. punctatus* hepatopancreas developed severe degenerative alterations (Chandel et al. 2024). *C. batrachus* exposure to sodium arsenate caused babbling of the nucleus and necrosis of hepatocytes, infiltration, and abnormalities in the original architecture (Pichhode et al. 2022). Lastly, arsenic hepatotoxicity in *C. gariepinus* led to several histopathological modifications comprising of liver cell enlargement and cell proliferation, lymphocytic accumulation, dilated blood vessels, reduction in cellular glycogen levels, necrosis, and melanomacrophage clustering (Moneeb et al. 2020). Hence, arsenic can alter the

Table 1 Prevalence, effective concentration, and mechanisms of heavy metal neurotoxicity in different freshwater fish species

Heavy metal	Prevalence	Effective concentration	Species	Neurotoxicity	Reference
Cd	Low	1.9 ppb –1000 ppb	*D. rerio*, *P. promelas*, *O. mykiss*,	♣Social and flight behavior, ♣Boosts auditory thresholds, ♣↑ Expression of detoxifying genes and apoptotic genes	(Xu et al. 2022; Naz et al. 2023; Nalivaikieė et al. 2024)
Hg	Low	200 ppb - 13 ppm	*D. sargus*, *D. rerio*, *P. promelas*, *O. niloticus*, *P. flavescens*	♣Activation of the mT2 gene in the brain ♣Impairing foraging ability ♣Abnormal swimming patterns ♣Mitochondrial malfunction	(Alam et al. 2021; Zhu et al. 2022; Albers et al. 2022; Jeong et al. 2024; Usman et al. 2024)
Pb	Low	10 ppb to 2 ppm	*S. gairdneri*, *S. fontinalis*, *T. pavo*, *G. mirabilis*, *D. rerio*	♣↑ GABA gene and protein expression ♣Modifications in the epigenome ♣Learning impairment ♣Hyperactivity ♣Trembling ♣Abnormal swimming ♣ Muscle tremors ♣ Rapid breathing	(Paduraru et al. 2023; Liu et al. 2024; Habib et al. 2024)
Al	Low	Less than 100 μM	*C. punctatus*, *O. mossambicus*, *C. Idella*, *D. rerio*, *S. salar*	♣Inducing oxidative stress by suppressing CAT, GST, SOD and GPx ♣Increased lipoperoxidation ♣Diminished locomotor activity	(Capriello et al. 2019; Closset et al. 2021; Rahimzadeh et al. 2022; Temiz and Kargın 2022)
As	Low	0.001 mg/L – 100 mg/L	*D. rerio*, *C. carpio*	♣Impaired long-term memory ♣Impaired cognitive performance	(Wang et al. 2021; Rachamalla et al. 2023; Ma et al. 2024)
Cr	Medium	2 mg/L – 19.7 mg/L	*D. rerio*, *S. schlegelii*, *C. punctatus*	♣Severe oxidative stress in brain cells ♣Gene expression associated with neuroinflammation and Alzheimer's disease ♣Cognitive impairment	(Shaw et al. 2020; Yadav 2023; Boopathi et al. 2024b)

neurobehavioral patterns and histopathology of the liver in freshwater fish.

4.6 Chromium (Cr)

According to the US Environmental Protection Agency, Cr is one of the most prevalent heavy metal pollutants and is regarded as a dangerous element (Sable et al. 2024). The most toxic state of Cr is Cr [VI] due to its property of rapid accumulation in the living cells (Muddin et al. 2024). For instance, the neurotoxic effect of Cr on zebrafish and snakehead fish included severe oxidative stress, blood-brain barrier injury, and ferroptosis (Li et al. 2024). Another study reported severe oxidative stress in brain cells, gene expression associated with neuroinflammation, and cognitive dysfunction in *D. rerio* on exposure to Cr (Boopathi et al. 2024b). Additionally, Xu et al. (2021) demonstrated the suppression of neurogenesis in the embryo of zebrafish by suppressing the activity of proneuronal genes, including zash1a, zash1 b, and ngn1, when exposed to a 9 μM sub-lethal dosage of Cr for one day. Consequently, incomplete development of the nervous system causes cognitive dysfunction, abnormal swimming patterns, increased heart rates, and disturbances in reward pathways. Moreover, irregular swimming patterns and lethargy were observed in *C. punctatus* as a result of DNA damage triggered by excessive production of micronuclei in interphase cells (Yadav 2023). A similar pattern of DNA damage was observed in *D. rerio* when exposed to 2 mg/L Cr [VI] with the activation of the Nrf2-ARE signaling pathway in response to oxidative stress. Consequently, abnormal behavior patterns included irregular swimming patterns, slow activity, and cognitive impairment (Shaw et al. 2020). Similarly, the exposure of *O. niloticus* to 4.57 mg/L hexavalent chromium Cr (VI) caused hepatotoxic effect by triggering oxidative stress, impairing the detoxification mechanism through suppressing GST and CYP450, which are involved in clearing reactive oxygen species and metabolizing heavy metals in the cells and induced apoptosis through upregulating caspase-3 and downregulating Bcl-2 (Mohamed et al. 2020; Shafqat et al. 2023). The histopathological changes in *Ctenopharyngodon idella* after exposure to sublethal concentrations of Cr (VI), including dilation of sinusoidal space, intracellular vacuolation, glycogen depletion, dilation of rough endoplasmic reticulum, lymphocyte infiltration, hemorrhage, and hepatopancreas degeneration, were observed (Handa and Jindal 2021). Moreover, Awasthi et al. (2018) reported adverse effects of Cr^{6+} on the liver of *Channa punctatus* when exposed for a longer time, and at higher dosages through oxidative stress, DNA damage, and apoptosis. All these destructive mechanisms were evident in hepatic cells through increased activity of CAT, SOD, NOX-1 and GSR genes, increased number of micronuclei, and increased activity of apoptotic genes including apaf-1, casp3a, and bax. The synergistic effects of arsenic and chromium on liver damage in *D. rerio* has been reported (Kamila et al. 2024). Lastly, in a study on *C. carpio*, the exposure to a sub-lethal concentration of Cr led to excessive production of Serum glutamic pyruvic transaminase (SGPT) and Serum glutamic-oxaloacetic

Table 2 Prevalence, effective concentration, and mechanisms of heavy metal hepato-toxicity in different freshwater fish species

Heavy metal	Prevalence	Effective concentration	Species	Hepato-toxicity	Reference
Cd	Medium	0.0001- 5.03 mg/L	*R. quelen, G. rarus, O. niloticus*	♣Development of liver lesions due to ♣Alterations in GST ♣ ↑ Lipoperoxidation ♣↑ Hepatocyte necrosis ♣↑ AST and ALT enzymes ♣ ↓ Total protein levels ♣ ↑ Total lipid levels.	(El-Sabbagh et al. 2022; Liu et al. 2023)
Hg	Low	0.25 – 539 µg/L	*D. rerio, H. malabaricus, C. gariepinus*	♣Liver damage evident by oxidative stress in hepatocytes ♣Activation of the intrinsic apoptotic pathway ♣Uncontrolled activity of kinases and nuclear receptors ♣Mitochondrial dysfunction ♣Abnormal endocrine secretions.	(Mohamed et al. 2019; Pervaiz et al. 2019; Monteiro et al. 2024)
Pb	Medium	5 ppm -43.4 ppm	*D. rerio, A. testudineus, C. gariepinus*	Induction of severe oxidative stress, resulting in lipoperoxidation and ultimately leading to hepatocyte apoptosis.	(Giri et al. 2021; Dey et al. 2024a; Dey et al. 2024b)
Al	Medium	0.1 mg/L -8 mg/L	*O. niloticus, C. auratus*	♣Trigger oxidative stress through elevating levels of TBARS. ♣Caused genotoxicity by upregulating the biomarker of DNA oxidative damage known as (8-OHdG). ♣Induction of melanomacrophage aggregation leading to necrosis of hepatocytes ♣Panhypoproteinemia	(Massoud et al. 2021; Temiz and Kargın 2022)
As	Medium	3 ppm	*O. mossambicus, C. punctatus*	♣Hepatocyte vacuolation and apoptosis ♣Pyknosis in numerous necrotic cells ♣Tissue peliosis hepatitis.	(Ragupathi et al. 2022; Pichhode et al. 2022; Khalid et al. 2024)
Cr	Low	Sublethal doses	*O. niloticus, C. idella*	♣Inducing oxidative stress ♣Impairing detoxification mechanism through suppressing GST and CYP450 ♣Induces apoptosis through upregulating caspase-3 and downregulating bcl2.	(Mohamed et al. 2020; Handa and Jindal 2021; Kamila et al. 2024)

transaminase (SGOT), indicating liver damage (Ali et al. 2021). In conclusion, all the above studies proved the neurotoxic and hepatotoxic effects of Cr exposure in freshwater fish. The mechanisms of neurotoxicity and hepatotoxicity caused by heavy metals are given in Tables 1 and Table 2, respectively, along with effective concentrations.

5. Conclusion

These findings demonstrate the adverse effects of heavy metals on freshwater fish, with compelling evidence of hepatotoxicity and neurotoxicity. These metals bioaccumulate in the nervous system, resulting in impaired cognitive functions and abnormal behavior, while hepatotoxic effects disturb detoxification and metabolic processes and ultimately influence the health of the ecosystem. Toxicity induced by heavy metals not only has adverse effects on fish but also influences aquatic food webs and human food security. Therefore, the focus should be on the detoxification of the heavy metals by developing proactive assessment and mitigation strategies. Upcoming studies should focus on sustainable pollution control measures and the prolonged effects of heavy metal toxicity on aquatic life to understand the mechanism of toxicity and develop permissible environmental limits.

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