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Review

A Comprehensive Review on Metallic Trace Elements Toxicity in Fishes and Potential Remedial Measures

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Abstract: Metallic trace elements toxicity has been associated with a wide range of morphological abnormalities in fish, both in natural aquatic ecosystems and controlled environments. The bioaccumulation of metallic trace elements can have devastating effects on several aspects of fish health, encompassing physiological, reproductive, behavioural, and developmental functions. Considering the significant risks posed by metallic trace elements-induced toxicity to fish populations, this review aims to investigate the deleterious effects of prevalent metallic trace elements toxicants, such as mercury (Hg), cadmium (Cd), chromium (Cr), lead (Pb), arsenic (As), and copper (Cu), on the neurological, reproductive, embryonic, and tissue systems of fish. Employing diverse search engines and relevant keywords, an extensive review of in vitro and in vivo studies pertaining to metallic trace elements toxicity and its adverse consequences on fish and their organs was conducted. The findings indicate that Cd was the most prevalent metallic trace elements in aquatic environments, exerting the most severe impacts on various fish organs and systems, followed by Cu and Pb. Moreover, it was observed that different metals exhibited varying degrees and types of effects on fish. Given the profound adverse effects of metallic trace elements contamination in water, immediate measures need to be taken to mitigate water pollution stemming from the discharge of waste containing metallic trace elements from agricultural, industrial, and domestic water usage. This study also compares the most common methods for treating metallic trace elements contamination in water.

Keywords: metallic trace elements; toxicity; growth; body systems; fish; remedial approaches

Citation: Naz, S.; Chatha, A.M.M.; Téllez-Isaías, G.; Ullah, S.; Ullah, Q.; Khan, M.Z.; Shah, M.K.; Abbas, G.; Kiran, A.; Mushtaq, R.; et al. A Comprehensive Review on Metallic Trace Elements Toxicity in Fishes and Potential Remedial Measures. *Water* **2023**, *15*, 3017. https://doi.org/10.3390/w15163017

Academic Editors: Andrea Santulli, Concetta Messina, Eleonora Curcuraci, Simona Manuguerra and Junhong Bai

Received: 21 June 2023
Revised: 7 August 2023
Accepted: 17 August 2023
Published: 21 August 2023

1. Introduction

Recent advancements in industrialization and increased human influence on the environment have caused an exponential increment of different pollutants, such as dyes, metallic trace elements, pharmaceuticals, pesticides, fluoride, phenols, insecticides, and detergents which enter into water resources [1]. These toxicants are serious health concerns for humans and water-living organisms [2]. Similarly, surface water contamination by pesticides is also a serious health-related and environmental issue highlighted at different forums [3]. Bioaccumulation of pollutants in an aquatic ecosystem affects humans and marine life directly and indirectly through the food chain [4]. Metallic trace elements like Cd, Co, Ni, and Pb have been found to impact fishes and other aquatic organisms directly [5]. Majority of metallic trace elements also act as environmental toxins. Some of these metallic trace elements, such as Cu, Zn, Cr, Pb, Cd, Hg, and As affect the health of living beings more adversely as these could quickly transfer from one trophic level to another and hence show higher persistence in the food web [6]. Moreover, the ions of trace elements in water bodies have also become a serious concern globally, as these metallic ions have shown adverse effects on the aquatic ecosystem, and human health [7]. Therefore, simple but effective methods are required for their detection and to maintain water quality to solve water scarcity and further its reuse [8,9]. Despite being able to cause serious damage, these metals are not being identified easily due to insufficient methods and limited laboratory facilities. The present detection methods like UV–Visible spectroscopy, atomic emission spectroscopy (AAS), gas chromatography/mass spectrometries (GC/MS) are not economic and user-friendly [10]. For instance, the technological advancements have raised major concern over environmental safety, due to increasing generation of toxicants [11]. To overcome this and provide ease of analysis, with accuracy and cost effectively, "biosensor" came to existence. A biosensor has a readable biological element, responsible for providing and transforming the information that is used to detect the concentration of a particular analyte in environment. The bio-element based sensors are qualitative, quantitative, and semi-quantitative and can be used against conventional methods [12]. Biosensors possess unique features that make them more adept at measuring the level of metallic trace elements concentration on-site and therefore are advantageous in water quality control. For instance, ligand-rich membranes like tannin-reinforced 3-aminopropyltriethoxysilane crosslinked polycaprolactone (PCL) based nanofibrous membrane have shown effective and quick response to trace elements' toxicity as compared to uncross linked membranes [13].

The biosensor is a relatively small hand-held device that is feasible for in situ applications and can be used for rapid identification of various organic and inorganic analytes and metal(loid)s [14]. Metal organic frameworks (MOFs) are gaining immense attention in enhancing the stability and sensing capability of biosensors. An efficient biosensing platform requires a minimum amount of sample volume and consumables; MOFs, which bridges metal ions with organic ligands, assist these devices and increase their detection potential [15].

Assessing the effects of metallic trace elements and the extent of their prevalence in both environmental and residential settings is essential. Additionally, significant measures need to be taken to limit and decrease their detrimental impact on human health and the environment [16]. As trace elements and their ions are becoming a serious global threat for aquaculture and aquatic ecosystem, it is very important to explore various methods for water purification and removal of trace elements and their ions from the water [17]. Apart from trace elements, various bacteria are also very common pollutant of water. Therefore, we should use various methods to remove bacteria from the water to make it safe for human consumption. In order to treat water to remove bacteria, phages are strong antibacterial agents commonly used in the food industry and have a strong potential to be used for water treatment as well [18]. One of these phage treatment methods is MXene–laden bacteriophage, which has shown promising results to purify water up-to 99.99% from bacteria [19].

This study aims to review metallic trace elements accumulation in diverse fish species and their adverse effects on different body systems and physiological processes, including the nervous system, reproductive system, embryonic development, and various body tissues.

2. Metallic Trace Elements-Induced Toxicity

In aquatic ecosystems, metallic trace elements demonstrate lasting persistence as they do not undergo natural degradation even after their sources have been eliminated. This persistent nature renders them especially hazardous in toxicological studies concerning aquatic life [20]. The metals Cr, Cu, Pb, Hg, and Zn are commonly found in surface water, and although they are essential, excessive concentrations of these metals in the aquatic ecosystem can cause stress to fish and act as pollutants. While metal contaminants occur naturally, human activities such as industrial operations and pollution can significantly increase their concentration in the environment [21]. It is crucial to note that not all metals are harmful to fish or humans, as some are necessary for human health. Nevertheless, it is important to recognize the significance of metallic trace elements in the environment, as exceeding safe limits can have deleterious environmental effects [22]. Pollution from metallic trace elements poses a serious threat to aquatic ecosystems and organisms if the concentration exceeds the safe limit [23]. This article specifically focuses on the abundance of selected metals found in nature and their natural environmental sources. Copper, for instance, exists in two oxidation states +1 (cuprous) and +2 (cupric); while natural concentrations of copper in water are generally less than or equal to 5 μg/L, it can enter aquatic systems through human-related sources such as industrial discharge, pipeline corrosion, municipal drainage/sewage, coal combustion, mining, and the use of copper-containing fertilizers and fungicides [24]. Cadmium is present in the Earth's crust at an abundance of 0.1–0.5 ppm and is frequently found alongside zinc, lead, and copper ores. Natural cadmium emissions into the environment can occur due to volcanic eruptions, forest fires, the generation of sea salt aerosols, or other natural phenomena. In surface water and groundwater, cadmium can exist in the form of a hydrated ion or as ionic complexes with other inorganic or organic substances [25]. Mercury (Hg) is released into the environment by numerous human activities. However, mercury can also occur naturally in the Earth's crust, especially in Hg mineral belts that are distributed globally and in areas of altered rock that have high Hg concentrations. During its transportation in the environment, Hg can enter aquatic environments through various means, including diffuse and point sources [26]. At pH levels below 7.5, lead may exist partially as the divalent cation, but it can form insoluble $PbCO_3$ through complexation with dissolved carbonate under alkaline conditions [27]. Even small amounts of carbonate ions generated during the dissolution of atmospheric CO_2 are sufficient to maintain lead concentrations in rivers at the solubility limit of 500 μg/L. Lead forms robust complexes with humic acid and other organic matter [28]. Inorganic arsenic (As) is categorized into two types: trivalent (As III) and pentavalent (As V). Arsenic oxide is the most important As compound. Although As is occasionally found naturally, its primary source of economic value is arsenopyrite. Mining activities have mainly contributed to the contamination of soil and water with elevated As concentrations. However, other human activities that use As, such as agriculture, forestry, and industry, have also caused localized soil and water contamination [29].

2.1. Metallic Trace Elements' Sources in Aquaculture Systems

Metallic trace elements occur naturally in the environment, but human activities such as mining, agricultural practices, and municipal sewage sludge can also contribute to their presence in the aquatic environment. Erosion, rock weathering, and volcanic eruptions are among the natural sources of metallic trace elements in the aquatic environment. Metallic trace elements in wastewater sludge, urban compost, and phosphate fertilizers can be carried through the soil to groundwater [30]. Fertilizers containing nitrogen and phosphorus compounds are commonly used in fish farming to enhance plant nutrient concentrations, stimulate phytoplankton growth, and ultimately increase fish or crustacean production.

These fertilizers may also contain some metallic trace elements [31]. Additionally, metallic trace elements-contaminated crops grown in soil may be used as animal feed in aquaculture, leading to the transfer of the metals to the system through sediments [32]. Sediments are known for their high metallic trace elements content, which can be carried downstream by tributary rivers and released into the overlying water, causing harm to aquatic organisms [33,34]. Metallic trace elements on the surface of the sediment can also enter the food chain through flora and fauna consumption [35]. Some water sources used for fish farming, such as dams, rivers, and streams in developing countries, may contain metallic trace elements above permissible limits, making them potential metallic trace elements sources [32]. Sewage-fed aquaculture, a process that involves the reuse of sewage-treated wastewater for aquaculture, may also introduce metallic trace elements from residual wastewater into the system [36]. Finally, the accumulation of metallic trace elements in fish can occur through food ingestion. Formulated feeds are crucial for successful aquaculture production, but they may also contain metallic trace elements [34,37]. Figure 1 summarizes different sources of metallic trace elements and their accumulation. It shows the biodilution of metallic trace elements across the trophic levels. Biodilution, also known as biomagnification dilution, is a process that occurs in ecological food chains, where the concentration of certain substances, such as pollutants or toxins, decreases as it moves up the food chain.

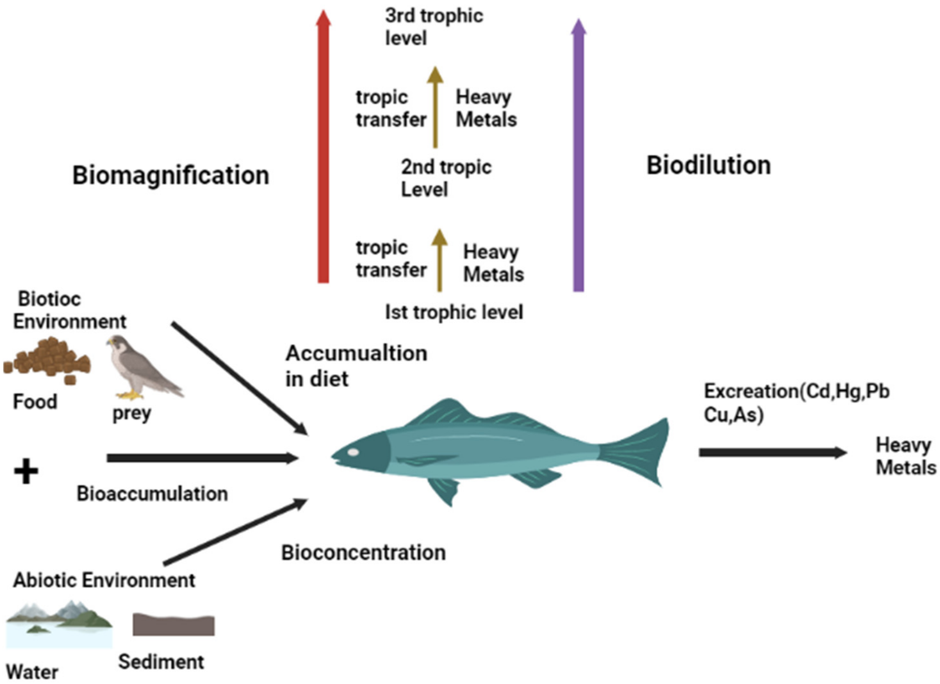

Figure 1. Sources of metallic trace elements in aquatic ecosystem.

2.2. Comprehensive Literature Review and Selection Criteria

To provide a detailed and comprehensive review, original research articles and review articles were initially downloaded from different search engines, e.g., Google Scholar, Semantic Scholar, ISI Web of Knowledge, and PubMed. This review includes articles published between 1975 and 2023, which were searched using various keywords such as metallic trace elements toxicity, fish nervous system, sperm motility, embryonic fish development, histopathological alterations, fish reproductive system, sperm analysis, fish size, fish length, metal deposition, and fish reproduction. The Higher Education Commission (HEC) of Pakistan's digital library granted access to full-length articles. Even so, not all selected publications were completely accessed, making it impossible to include those studies in the review article.

This study included articles, reports, and documents that specifically detailed the impact of metallic trace elements on the nervous system, reproductive system, embryonic development, fish size, and various tissues. Any articles not focusing on these topics were excluded from the study.

3. Effect of Metallic Trace Elements on Fish Physiology and Biochemistry

This review thoroughly examined and discussed the effects of various metallic trace elements. Figure 2 illustrates the impact of metallic trace elements on fish from different sources. These selected metals belong to the first transition series of the periodic table and are known to trigger the production of reactive oxygen species (ROS) in living systems, which contribute to their toxicity [38,39]. Exposure to sub-lethal or lethal concentrations of metallic trace elements can lead to stress in fish, which eventually accumulates in various tissues and organs such as gills, kidneys, liver, skin, muscles, etc. [40]. Fish have their defence mechanism to cope with the stressful conditions caused by metallic trace elements exposure by utilizing more energy from reserved carbohydrates, proteins, and lipids in their body. Metallic trace elements such as As, Cd, Cr, Cu, Fe, Hg, Ni, Pb, and Zn are active redox components that contribute to the formation of ROS, which play an essential role in certain physiological functions in fish [39].

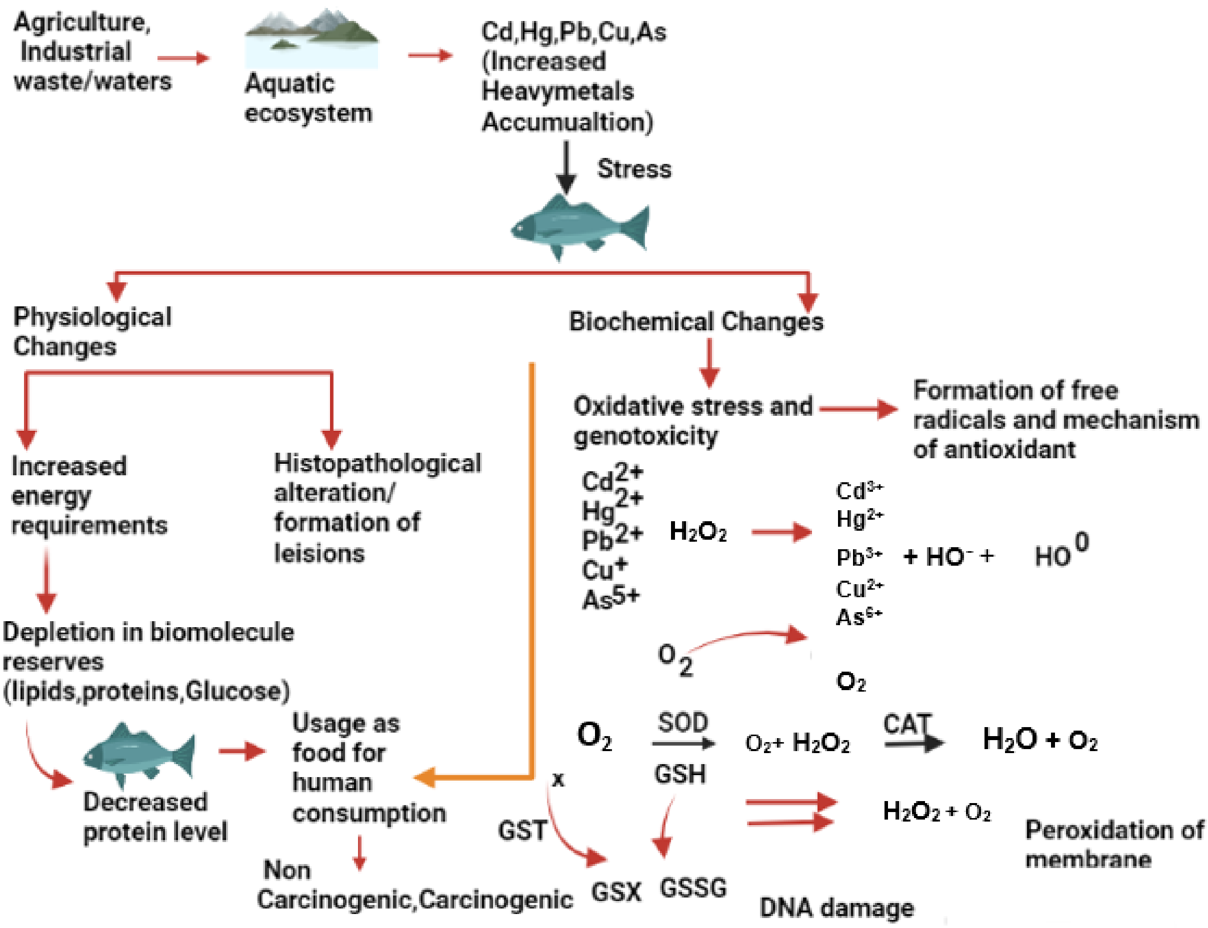

Figure 2. Effects of metallic trace elements on the fish physiology and biochemistry.

The excess of ROS Indicates an imbalance in the production of ROS and causes oxidative stress, which eventually interferes with cellular function by damaging lipids, proteins and DNA [41]. Enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione S transferase (GST), and non-enzymatic compounds such as reduced glutathione (GSH) are essential in maintaining the dynamic balance of ROS through detoxification. SOD converts superoxide free radicals into hydrogen peroxide, which is further broken down into non-toxic oxygen and water by the CAT enzyme [42]. GST aids in detoxification by catalysing the conjugation of electrophiles to GSH. However, electrophilic substances (free radicals and ROS) can also oxidize GSH non-enzymatically to glutathione disulfide. Any hindrance in the enzymatic reaction can generate excess ROS that accumulates in fish tissues, leading to oxidative stress. ROS can degenerate the cell membrane through lipid peroxidation, causing genotoxicity through DNA damage [41]. There is a wealth of information on the effects of metallic trace elements on fish physiology in various fish species. However, this review focuses on the impact of specific metallic trace elements on particular fish systems, such as the nervous system, reproductive system, etc.

3.1. Effect of Metallic Trace Elements on Fish Collected from Contaminated Sites

Estuaries are highly sensitive zones that serve as a natural conduit for transferring agricultural, industrial, and urban pollution to the sea [43]. Rapid industrial growth during the past century has led to an increase in industrial effluents [44] and anthropogenic run-off in coastal and estuarine environments [45]. The fate of metallic trace elements in water is mainly influenced by their initial concentration and several chemical, physical, and biological factors [46]. Table 1 provides details on the effects of metallic trace elements on fish collected from various contaminated sites.

Table 1. Effects of heavy metals on fish collected from different contaminated sites.

Fish Specie	Location	Metal Detected	Organ Affected	Effect on Fish	References
Channa striata, *Heteropnuestes fossilis*	Yamuna Barrage (India)	Cr, Ni, Pb	Kidney, gills, liver, muscle	Ruptured veins, hemorrhages in the liver, necrotic urinary tubules.	[47]
Clarias gariepinus	Abuja (Nigeria)	Pb, Cd, Cu, Zn, Cr	Liver, gill, kidney, spleen	Congested central veins in the liver, interstitial hemorrhages in the kidney, congested splenic vein.	[48]
Cyprinus carpio	Slovak University of Agriculture in Nitra, University Farm Kolíňany	Cu, As, Pb, Cr, Cd, Hg	Testes	Reduced sperm DNA fragmentation, reduced motility of spermatozoa.	[49]
Cyprinus carpio and *Capoeta*	Kor River (Fars Province)	Hg, Cd, As, Pb	Blood cells, liver, kidney	Hyperemia, cellular degeneration, and vacuolation.	[50]
Oreochromis niloticus	Challawa River (Kano, Nigeria)	Zn, Cd, Fe, Pb	Muscles	Higher bioaccumulation in muscles compared to bioaccumulation factor.	[51]
Clarias gariepinus	Lake Maryout (Egypt)	Cd, Pb, Hg, As	Gonads	The ovary exhibits lytic characteristics with oocytes at various stages, a decreased quantity of germinal cells, and an augmented interstitial space in the testes.	[52]
Auchenoglanis occidentalis	Tiga Dam (Nigeria)	Zn, Cd, Pb, Fe	Gills, liver, kidney	Lesions in the gills, liver, and kidney.	[53]
Hypophthalmichthys molitrix, *Ctenopharyngodon idellus*, *Carassius auratus*, *Cyprinus carpio*, *Silurus asotus*	Yangtze River	Cd, Cr, Cu, Hg, Pb, Zn	Fish size	Positive and negative relationships were observed between fish size and metal concentration.	[54]
Channa striatus, *Heteropneustes fossilis*	Kali River (India)	Cr, Cd, Pb, Ni	Liver, kidney, gill, muscle, brain	Decreased level of glutathione (GSH), increased oxidative stress.	[55]
Etroplus maculates, *Cirrhinus reba*, and *Ompok bimaculatus*	Bhadra River (Karnataka)	Cu, Zn, Cd, Ni, Fe, Pb	Liver, kidney, muscle, gills	Degeneration of the hepatocytes in liver, vacuolar degeneration in the tubular epithelium in kidney.	[56]

Table 1. *Cont.*

Fish Specie	Location	Metal Detected	Organ Affected	Effect on Fish	References
Oreochromis niloticus, *Geophagus brasiliensis*, *Hoplias malabaricus*, *Astyanax altiparanae*, *Rhamdia quelen*	Sao Francisco do Sul River (Brazil)	Cr, Mn, Fe, Ni, Cu, Zn, As, Se, Pb	Muscle, liver, and gonads	Metals accumulated in the gonads, liver, and muscle, with chromium levels in the muscle reaching fifty times the maximum limit set by Brazilian legislation.	[57]
Oligosarcus spp., *Chyphocharax voga*	Sinos River (Brazil)	Al, As, Cd, Co, Cr, Cu, Fe, Mn, Zn, Pb	Liver	Detritivores species accumulated more metals than carnivorous species.	[58]
Salminus franciscanus	Paraopeba River (Brazil)	Cu, Pb, Cd, Zn, Cr, Hg, Fe	Liver, spleen, and muscle	Hepatocytes exhibited fat accumulation along with pigmented macrophages in the liver. Fibrosis was observed in the spleen, and contaminated fish showed decreased oocyte diameter and increased follicular atresia.	[59]
Pseudoplatystoma corruscans	Paraopeba River (Brazil)	Hg, Cd, Zn, Cr, Pb	Liver, muscle, and spleen	The liver and spleen showed higher concentrations of metals compared to the muscle. Additionally, liver fibrosis was observed.	[60]
Bryconamericus iheringii	Ilha River (Brazil)	Al, Cd, Mn, Ni, Fe, Pb, Cr, Zn	Blood—micronucleus analysis, gills, and muscle	In rural areas, a higher frequency of micronuclei, nuclear abnormalities, and mucous cells was detected. Conversely, urban areas exhibited a lower condition factor, higher frequencies of lamellar alterations, and higher concentrations of chromium (Cr) and nickel (Ni) in muscle.	[61]

Table 1. *Cont.*

Fish Specie	Location	Metal Detected	Organ Affected	Effect on Fish	References
Prochilodus magdalenae, *Pimelodus blochii*	Magdalena River (Colombia)	Cd, Pb, Ni	Gills, liver, and muscle	Pimelodus Blochii showed a higher accumulation of metals, particularly an increased concentration of cadmium (Cd) in the liver.	[62]
Aequidens metae, *Astyanax bimaculatus*	Ocoa River (Colombia)	Hg, Cd	Blood and liver	There was a decrease in the number of erythrocytes, lymphocytes, and neutrophils, as well as a decrease in hemoglobin concentration and hematocrit percentage.	[63]

3.2. Effect on the Nervous System

Deposition of various metallic trace elements in fish can cause serious damage to the nervous system, affecting behaviour, response to stimuli, and recognition patterns among fish [64]. Mercury is known to cause numerous disorders, primarily on the biochemical level in the central nervous system of fish. For example, exposure to HgCl caused a significant increase in lipid peroxidation and depletion of total lipids in the brain of catfish (*Heteropneustes fossilis*) [65]. Copper-induced morphological abrasions are evident in the sensory organs of fish [64]. Copper is a vital metal and a fundamental component of many enzymes, but it can be extremely toxic to fish when its concentration exceeds normal levels [66], especially in freshwater due to the high ionic copper content [67]. Increased Cu concentration in cellular membranes reduces the antioxidative capacity of lipids, causing lipid peroxidation and severe damage to cellular membranes [68].

As the formation of free radicals and lipid peroxidation increases, they can cause serious cellular trauma. In Cu-exposed marbled electric ray (*Torpedo marmorata*), ultrastructural analysis of neurons in the central nervous system showed an increased number of lipofuscin granules erosion of mitochondria [69] and a reduction in Golgi apparatus as well [70]. Long-term exposure to Pb can cause neurochemical changes in the brain of walking catfish (*Clarias bathrachus*). For instance, Pb increases the histamine and serotonin levels while decreasing the gamma-aminobutyric acid (GABA), monoamine oxidase (MAO), and acetylcholinesterase (AChE) contents. Furthermore, cholesterol, brain lipid, and protein contents are also decreased [71]. We compared the adverse effects of different metals on the nervous system (CNS and peripheral) from various studies (Table 2).

Table 2. Effects of heavy metals on nervous system of different fish species.

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Cadmium (Cd)						
Danio rerio	0.970	Cd †	Juvenile	12 h	Elevated immunotoxicology.	[72]
Danio rerio	0.040	$CdCl_2$	0–168 hpf	7 days	Increased rotational movement, Hyperactivity, and decreased size of otolith.	[73]
Pimephales promelas	0.003	$Cd(NO_3)_2$	Adult	4 days	Elevated auditory threshold.	[74]
Pimephales promelas	0.060	$CdCl_2$	Adult	21 days	Decreased vitellogenin gene expression and increased estrogen receptor beta.	[75]
Danio rerio	0.112	$CdCl_2$	0–96 hpf	4 days	Immunotoxicity, behavioural alteration, and oxidative stress.	[76]
Effect of Mercury (Hg)						
Diplodus sargus	0.002	$HgCl_2$	Juvenile	7 days	Increased anxiety, decreased number of optic tectum cells, and altered swim behaviour.	[77]
Pimephales promelas	0.720	MeHg	Adult	30 days	Decreased levels of dopamine and hyperactivity.	[78]
Danio rerio	10	MeHg	Adult	56 days	Mitochondrial dysfunction, and oxidative phosphorylation.	[79]
Danio rerio	0.720	MeHg	Adult and embryo	30 days	Decreased level of dopamine and hyperactivity.	[80]
Danio rerio	0.027	$HgCl_2$	5–72 hpf	~3 days	Hyperactivity causing mortality.	[81]

Table 2. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Lead (Pb)						
Danio rerio	0.010	$Pb(CH_3COO)_2$	0–72 hpf	3 days	10 Gene expression changes in 89 genes associated with nervous system development.	[82]
Danio rerio	0.020	$Pb(CH_3COO)_2$	0–144 hpf	6 days	Decreased axon length and decreased locomotion (speed).	[83]
Danio rerio	0.100	$Pb(CH_3COO)_2$	2–120 hpf	~5 days	Altered color preference (adults).	[84]
Danio rerio	0.207	$Pb(CH_3COO)_2$	2–24 hpf	~2 days	Decreased learning (adults).	[85]
Danio rerio	1.730	$Pb(CH_3COO)_2$	0–24 hpf	24 h	Decreased Nrxn2a gene expression.	[86]
Effect of Copper (Cu)						
Cyprinus carpio	0.60	Cu	Juvenile	96 h	Increases in brain ROS production, lipid peroxidation, and protein oxidation.	[87]
Capoeta umbla	3.0	$CuSO_4{\cdot}5H_2O$	112 ± 5 g	96 h	Induce astroglial response accompanied by modulations of NF-kB and PARP-1 expression.	[88]
Danio rerio	0.100	$CuSO_4{\cdot}5H_2O$	Adult	10 days	Negatively affect the associative learning capabilities.	[89]
Oreochromis niloticus	120	$CuSO_4{\cdot}5H_2O$	Adult	96 h	Loss of balance and exhaustion.	[90]

Table 2. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Arsenic (As)						
Danio rerio	15	Na_2HAsO_4	Adult	96 h	Alteration in behaviour and ectonucleotidase activities.	[91]
Danio rerio	0.050	As_2O_3	Juvenile	96 h	Antagonistic effects on brain.	[92]
Danio rerio	0.500	As^{+}	Larvae, juvenile and adult	96 h	Alteration in motor function (embryo-adult), effects on associative learning.	[93]
Clarias batrachus	20	As_2O_3	Adult	96 h	Increased body discoloration, excessive mucous secretion, loosening of the skin, and complete loss of skin (head region and fins).	[94]
Effect of Zinc (Zn)						
Anguilla anguilla	0.12	Zn	Juvenile	28 days	Cholinergic neurotoxicity did not occur, only liver GST increased significantly.	[95]
Leporinus obtusidens	4.57	$ZnSO_4{\cdot}5H_2O$	Adult	45 days	Significantly increased AChE activity.	[96]
Danio rerio	1750	$ZnCl_2$	Adult	25 days	Significant decrease in acetylcholinesterase activity and abnormal neural signaling.	[97]

Note: † Metallic trace elements written without their respective chemical formulas were administered in their metallic forms.

3.3. Effect on the Reproductive System

The adverse effects of metals on the fish reproductive system are increasing every day, mainly due to increased water pollution and the usage of polluted water for fish culture. Healthy eggs and sperms are essential for the process of successful fertilization. However, the quality of eggs and sperm is affected by induced spawning, gamete storage methods, and more importantly, water pollution. The motility time of spermatozoa is very important for effective fertilization. According to the literature, sperm motility is affected by metallic trace elements. For example, although the sperm morphology of mummichog (*Fundulus heteroclitus*) was not affected by methylmercury (CH_3Hg), it triggered a significant loss in the motility of sperms [98,99]. Lead, Cd, and Cu caused a significant decrease in the motility of European carp (*Cyprinus carpio*) spermatozoa [100–102].

Similarly, Cu toxicity caused adverse effects in the spermatozoa activity in *C. carpio* [103], while Sionkowski et al. [104] showed that the higher concentration of Cu and Pb caused reduced spermatozoa motility in grass carp (*Ctenopharyngodon idella*). Likewise, the effects of Zn on the sperm motility of some common carp were also explored. Metallic trace elements are also responsible for several endocrine complications among fish. For example, Cd decreased the thyroid hormone level, inhibited the estrogen receptors, and interrupted the expression of growth hormone [105]. On the other hand, iodine metabolism interruption by Pb was also recorded to inhibit thyroid synthesis [106]. Prooxidative possessions of the metal ions could also cause oxidative harm to the cell membrane. They can also induce oxidative stress in fish. Lead, Pb, and Cu can also trigger the genotoxic effects on the fish [107–109]. A tabulated review of different references is provided to show the deteriorating effects of different metals on fish's reproductive system (Table 3).

Table 3. Effects of heavy metals on reproductive system of different fish species.

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Cadmium (Cd)						
Heteropneustes fossilis	0.050	$CdCl_2$	Adult	24 h	Decreased ovulation.	[110]
Pimephales promelas	0.005	$CdCl_2$	12 months	21 days	Reduced egg production.	[75]
Oryzias melastigma	0.010	$CdCl_2$	5 months	30 days	Decreased gonadal development.	[111]
Prochilodus magdalenae	24.90	$CdCl_2$	2 years	7 days	Reduced fertility rate.	[112]
Effect of Mercury (Hg)						
Heteropneustes fossilis	0.050	$HgCl_2$	Adult	24 h	Increased germinal vesicle breakdown.	[110]
Cyprinus carpio	4.990	$HgCl_2$	3 years	12 h	Decreased motility and fertility of sperms, damaged eggs.	[113]
Oncorhynchus mykiss	10.00	$HgCl_2$	3 years	4 h	Reduced motility of sperm.	[114]
Danio rerio	0.015	$HgCl_2$	Adult	5 days	Delayed gonadal development, imbalanced sex hormone.	[115]
Danio rerio	0.030	$HgCl_2$	Adult	30 days	Decreased testosterone level.	[116]
Clarias gariepinus	0.119	$HgCl_2$	Adult	30 days	Disruptive effect on gamete development.	[117]
Effect of Lead (Pb)						
Heteropneustes fossilis	0.050	$(Pb(NO_3)_2$	Adult	96 h	Increased germinal vesicle breakdown.	[110]
Clarias gariepinus	140.0	$Pb(C_2H_3O_2)_2$	Adult	96 days	Reduced sperm motility.	[118]
Oryzias melastigma	0.050	$PbCl_2$	5 months	30 days	Decreased gonadal development.	[111]
Effect of Copper (Cu)						
Danio rerio	0.040	$CuSO_4$	Adult	30 days	Damaged structure of gonads, altered steroid hormone level.	[119]
Pimephales promelas	0.075	$CuCl_2$	12 months	21 days	Decreased abundance of post-vitellogenic follicles, increased follicular atresia.	[120]
Daphnia magna	1.041	$CuCl_2$	Adult	21 days	Reduced rate of reproduction.	[121]
Poecilia reticulata	45	CuO	Adult Larvae	96 h	Decreased reproduction success.	[122]
Poecilia reticulate	0.026	$CuSO_4$ $5H_2O$	2.5–3 months	56 days	Gonadosomatic index, offspring production decreased.	[123]
Effect of Arsenic						
Gobiocypris rarus	40.00	$NaAsO_2$	3 months	96 days	Accumulation in testis.	[124]
Daphnia magna	0.049	$NaAsO_2$	Adult	48 h	Stable reproduction rate.	[125]
Gambusia affinis	0.075	$NaAsO_2$	Juvenile	30 days	Lower gonadal-somatic indices.	[126]

Table 3. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Zinc (Zn)						
Odontesthes bonariensis	0.021	$ZnSO_4$ $7H_2O$	Adult	10 days	Reduced embryo and larval survivability.	[127]
Danio rerio	500	Zn	Adult	4 days	Majority of eggs were dead, larger hatching time.	[128]
Clarias magur	300	$Zn(CH_3COO)_2$	Mature	60 days	The highest GSI and fecundity.	[129]
Oryzias melastigma	0.010	$ZnSO_4 \cdot 7H_2O$	Adult	30	Irregular oocytes, partly adhesion, empty follicle, and increased follicular atresia, loose follicular lining.	[111]

3.4. Effect on Embryonic Development

The influence of water-borne metals can disrupt the embryonic development of spawners. [130] found elevated levels of Cd, Zn, and Pb in the female gonads of stone loach when exposed to toxic concentrations of these metals. Ellenberger et al. [131] investigated the levels of Cu in the reproductive organs of European perch (*Perca fluviatilis*) exposed to Cu-polluted ponds. White suckers in polluted lakes exhibited higher amounts of Cu and Zn in their testicles and female gonads compared to fish in uncontaminated water [132,133]. Common carp exposed to Cu, Cd, and Pb showed decreased egg swellings in a concentration-dependent manner, contrasting with about 40% expansion in egg width observed in the untreated groups [134]. Copper and Cd accumulation in the gonads of Mozambique tilapia (*Orechromis mossambicus*) was found to be elevated when fish were kept in metal-polluted water, and blue tilapia (*Oreochromis aureus*) exposed to Cd and Pb for seven days showed metal accumulation in the testicles and female gonads, particularly Cd levels in the ovaries [135]. Metal exposure to spawners can result in the deposition of metallic trace elements accumulated in eggs and sperm, severely affecting the survival of fertilized eggs and the embryonic development of fish [103].

Metals can also influence the physical characteristics of an egg's outer surface. Benoit and Holcombe [136] observed that eggs of Zn-exposed fathead minnow (*Pimephales promelas*) became sticky and more prone to breakage soon after egg laying. Fathead minnow embryos rapidly absorb Hg from surrounding water sources, with concentrations in juveniles increasing to 2.80 μg per gram humid mass after four days of exposure to 25 μg per cubic decimeter of methylmercury [137]. Chromium was found to accumulate in the outer protective coatings of *Cyprinus carpio* eggs at pH 6.3 [138]. Copper can alter selective membrane permeability, disrupting cation trade between the liquid in the yolk membrane and the outside water [139]. During the early development of fish eggs in a toxic (metallic trace elements) environment, the outer protective coating of the egg blocks most of the metal concentration, but a significant toxic amount still enters the fluid inside the egg membranes, while only a small amount infiltrates the embryo [140]. Beattie and Pascoe [141] found that eggs of Atlantic salmon (*Salmo salar*) exposed to 10 mg per litre of Cd at 22 h old retained 98% of the metal in the outermost membrane. Similarly, the outer membrane of Japanese rice fish (*Oryzias latipes*) eggs retained 94.4% of Cd [142]. In Zn-treated Atlantic herring (*Clupea harengus*) eggs, 30% to 50% of Zn accumulated in the outermost membrane, while the rest accumulated primarily in the yolk sac and in lower quantities in the embryos. However, even a small amount of metals penetrating the egg can significantly influence fish embryonic growth [141,143]. Devlin [137] observed significant abnormalities in fathead minnow embryos treated with Hg, including spinal curves, heart damage, and abnormal growth of the heart cavity. Samson and Shenker [144] reported tissue anomalies in zebrafish (*Danio rerio*), including abnormalities in fin overlaps and caudal parts.

The first 24 h of fish embryonic development are the most vulnerable to metallic trace elements toxicity. A study found that during the first 24 h after insemination in contaminated water, almost 20% of developing embryos died, even in a controlled environment [145]. The blastula stage had the highest mortality rate (15%), and metal exposure during this stage significantly affected the life span of developing embryos. Embryos exposed to 0.1 mg/L of Cu had significantly decreased survival rates compared to the control group, and at 0.3 mg per litre, all embryos died. Copper exposure caused most fish embryo deaths during the blastula stage (25%), followed by the stage of body division (15%). However, embryo mortality decreased significantly at later developmental stages [103]. Slominski et al. [145] also reported that mortality significantly declined during organ formation, the division of the body, and eye coloration phases. Most fetuses (5%) expired during organ formation before the eye coloration phase. Metallic trace elements toxicity also increases the death of fish hatchlings in various species, including rainbow trout (*Onchorynchus mykiss*), Atlantic salmon, common carp, and grass carp. Freshly inseminated ovum of *Oncorhynchus mykiss* were more susceptible to Ni than the embryo at the organogenesis stage, while goldfish (*Carassius auratus*) eggs' mortality was greater during the blastula stage than at the eyed stage when exposed to Cd or Hg. Rainbow trout (*Oncorhynchus mykiss*) fetuses were more vulnerable at the eyed stage than newly inseminated eggs when presented with a mixture of metals. The abnormalities caused by different metallic trace elements at the embryonic stages of fish are reviewed in Table 4.

Table 4. Effects of heavy metals on embryonic development fish species.

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Cadmium (Cd)						
Leuciscus idus	0.1000	$CdCl_2$	Egg, sperm	21 dpf	Reduced larval survival, growth, and delayed development.	[102]
Oryzias latipes	0.0019	$CdCl_2$ $2H_2O$	Embryo, larva	20 dpf	Morphological abnormalities were observed.	[146]
Cyprinus carpio	0.06	$CdCl_2$	Eggs	60 dpf	Retardation in the developmental stages of eye pigmentation and spine curvature, lack of tail formation and head.	[147]
Danio rerio	34.8	$CdCl_2$	72 hpf	72 h	Neuromast damage, coagulated egg, increased mortality rate.	[148]
Danio rerio	0.8018	$CdCl_2$	6 hpf	24 h	Increased apoptotic event and induced cell death in brain of embryo.	[149]
Leuciscus idus	0.1	$CdCl_2$	Embryonic and larval	21 days	Reduced embryonic survival, increased frequency of malformation, and delayed hatching.	[102]
Danio rerio	0.8909	$CdCl_2$	Embryonic and larval	96 hpf	Increased heartbeat rate of larvae and decreased brain size.	[150]
Leuciscus idus L.	0.1	$CdCl_2$	Embryos and newly hatched larvae	2 h	Reduced egg swelling, slowed the rate of development (especially body movements), and delayed hatching.	[151]
Odontesthes bonariensis	0.00025	$CdCl_2$	Advanced-stage embryos and newly hatched larvae	10 days	Decreased hatching rate and survival of embryo and larvae.	[127]
Effect of Mercury (Hg)						
Danio rerio	0.016	$HgCl_2$	Adult	2 hpf	T3 and T4 content in larvae increased.	[152]
Danio rerio	0.016	$HgCl_2$	Adult	168 hpf	Decreased hatching rate, increased mortality, increased malformation rate in larvae.	[116]
Cyprinus carpio	0.00001	$HgCl_2$	Embryo	96 h	SOD and GPx reduced up to 85%.	[153]

Table 4. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Lead (Pb)						
Danio rerio	0.100	Pb $(C_2H_3O_2)_2$	Adult	30 dpf	Distance moved by juvenile zebra fish decreased, and swimming activity alterations in larvae and juvenile fish.	[154]
Danio rerio	0.005	Pb $(CH_3COO)_2$	Adult	144 hpf	Delayed hatching, spinal and tail deformity, pericardial edema, and yolk swelling was observed.	[155]
Danio rerio	99.885	Pb $(C_2H_3O_2)_2$	Adult	72 hpf	Deformed CNS, increased levels of Gamma-aminobutyric acid (primary inhibitory neurotransmitter).	[156]
Danio rerio	1.6	Pb $(NO_3)_2$	Embryo	120 hpf	Spinal malformation.	[157]
Pterophyllum scalar	20	$PbCl_2$	Embryo	3 days	Tilt, loss of vision or the lack of effect on growth delay.	[158]
Effect of Copper (Cu)						
Leuciscus idus	0.100	$CuSO_4{\cdot}5H_2O$	Egg, sperm	21 dpf	Reduced larval survival, growth, and delayed development.	[102]
Oryzias latipes	0.0185	$CuCl_2$ H_2O	Embryo, larva	20 dpf	Percentage of deformed larvae significantly increased.	[146]
Poecilia reticulata	1.50	$CuSO_4{\cdot}5H_2O$	Embryo	15 days	Abnormalities in blastodisc to middle-eyed stages of development.	[159]
Danio rerio	0.018	$CuSO_4$	72 hpf	72 h	Neuromast damage, coagulated egg, increased mortality rate.	[148]
Leuciscus idus	0.10	$CuSO_4{\cdot}5H_2O$	Embryo and larval	21 days	Reduced embryonic survival, increased frequency of malformation.	[102]
Leuciscus idus L.	0.10	$CuSO_4$	Embryos and newly hatched larvae	2 h	Reduced egg swelling slowed the rate of development (especially body movements) and delayed hatching.	[151]
Odontesthes bonariensis	0.00025	$CuSO_4$	Advanced-stage embryos and newly hatched larvae	10 days	Decreased hatching rate and survival of embryo and larvae.	[127]
Carassius auratus	1	Cu^{2-}	Embryo	24 h post-hatching	Scoliosis and tail curvatures.	[160]

Table 4. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Arsenic (As)						
Danio rerio	360.32	$NaAsO_2$	Adult	120 h	Tail bud deformation in embryo.	[161]
Danio rerio	0.5	$NaAsO_2$	Adult	120 hpf	No effect on mortality and developmental deformations.	[162]
Labeo rohita	198.18	$NaAsO_2$	Adult	120 hpf	Reduced survival rate with abnormal development.	[163]
Danio rerio	0.5	$NaAsO_2$	Embryo	14 dpf	Thinning of the retinal pigmented epithelium (RPE) layer in embryos.	[164]
Effect of Zinc (Zn)						
Odontesthes bonariensis	0.021	$ZnSO_4$ $7H_2O$	Hatchling	10 days	Cumulative embryo survival was significantly reduced.	[127]
Pagrus major	2.5	$ZnCl_2$	2 years	10 days	Low hatching rate, high mortality, abnormal pigmentation, hooked tail, spinal deformity, pericardial edema, and visceral hemorrhage.	[165]
Melanotaenia fluviatilis	33.3	Zn	Embryo	2 h	Spinal deformities.	[166]

4. Effect of Hazardous Metal Ions

Metallic trace elements are stable and non-biodegradable compounds that pose a lethal threat to fish species due to their ability to bioaccumulate and biomagnify in living tissues. Furthermore, these metals cannot be effectively eliminated from fish organs through oxidation, precipitation, or bioremediation methods [167]. Kidneys and liver are considered the most important tissues for monitoring metallic trace elements levels because they exhibit elevated concentrations of metal-binding proteins such as metallothioneins [168]. Antioxidant enzymes play a critical role in mitigating the oxidative stress caused by various toxicants [169]. Studies have shown that Cd and Pb can disrupt the antioxidant balance in animal tissues by increasing the production of superoxide radicals [170]. In the case of Channa punctatus ovaries, histopathological studies have revealed that exposure to Cr can damage the ovaries and significantly impair vitellogenesis, the process of yolk formation [171].

Histopathological changes induced by different metals have been extensively examined in various fish species, revealing significant alterations in the liver, gills, blood vessels, nervous system, muscles, and kidneys of the examined fish. Numerous cellular mutations have been reported in various fish organs over the years, including incomplete loss of the spiral direction of liver plate, cytoplasmic granularity, deflation of liver aggregate cells in hepatocytes, genetic alterations in cell nuclei, decay and cytoplasmic vacuolation in the kidneys, and changes in gill lamellae and fibres. Additionally, morphological variations, red blood cell (RBC) levels, and complete blood cell count (CBC) have been observed in focal vessels and veins [172]. Exposure to Malathion, for example, has been shown to cause histopathological changes in the ovary, such as modified ovigerous lamellae, decay of capillary cells, increased presence of atretic egg cells, cytoplasm accumulation, rupture of capillary epithelial lining, and shrinkage of genetic materials. These mutations have been associated with endocrine and hormonal irregularities. Similarly, exposure to carbofuran has been linked to connective tissue degradation, mutations in follicular membranes, and the formation of vacuoles in egg cytoplasm during the secondary and third phases of development [173,174]. Different mutations in the ovaries have also been observed following exposure to diazinon, including abnormalities in the grip of basic follicles, increased presence of atretic female gametocytes, cytoplasmic disruption in the oocyte, oocyte damage, degeneration of the yolk-forming layer, and cytoplasm rich in vacuoles [175]. Deka and Mahanta [176] reported that Malathion alters the histopathology of the kidney, liver, and ovaries in stinging catfish (*Heteropneustes fossilis*). Likewise, exposure to sodium cyanide (NaCN) has been found to cause various histopathological alterations in the tissue structure of the kidneys, including decay, destruction of glomeruli, infiltration of lymphocytes, vacuole formation in cytoplasm, blood clot formation, damage to collecting tubules, and variations in the size of the tubular lumen in common carp when exposed to a partially lethal dose [177]. Numerous studies have documented the harmful effects of different pesticides on the various tissues and organs of various fish species. These include atrazine on *Labeo rohita* [178], cypermethrin on *Tor putitora* [179], formalin on *Corydoras melanistius* [180], dimethoate on *Putius ticto* [181], hostathion on *Channa gachua* [182], and malathion on *Heteropneustes fossilis* [183]. Table 5 provides a detailed analysis of the effects of metallic trace elements on different fish tissues.

Table 5. Effects of heavy metals on tissues of different fish species.

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Cadmium (Cd)						
Cyprinus carpio	0.075	$CdCl_2$	6 months	4 weeks	Increase in the number of blast cells, proliferating cell nuclear antigen (PCNA), and apoptotic cells of brain.	[184]
Oncorhynchus kisutch	0.347	Cd	Adult	48 h	Impaired skin extract avoidance behaviours.	[185]
Channa punctatus	5.00	$CdCl_2$	Adult	45 days	Loss of sensory cells, impaired olfactory functions.	[186]
Clarias batrachus	0.1198	$CdCl_2$	Adult	30 days	Distortion of the gill, liver.	[187]
Effect of Mercury (Hg)						
Cyprinus carpio	0.01	$HgCl_2$	Adult	96 h	Oxidative stress and genotoxicity in gills, blood, and liver.	[188]
Clarias batrachus	0.0299	Hg	Adult	30 days	Distortion of the gill, liver.	[2]
Oreochromis niloticus	0.03	$HgCl_2$	Fingerlings	21 days	Lesions in the epithelial cells, focal proliferation, edema, mucous secretion, vacuolization, or almost empty, congestion, and haemorrhage in gills	[189]
Danio rerio	0.0385	$HgCl_2$	Adult	96 h	Induced severe morphological and ultrastructural changes in the gill apparatus.	[190]
Danio rerio	13.50	MeHg	Adult	25 days	Brain mitochondrial impairments.	[80]
Oreochromis niloticus	0.3	$HgCl_2$	Fingerlings	96 h	Edema, mucous secretion, vacuolization, lesions in the epithelial cells, focal proliferation, or almost empty, congestion, and haemorrhage.	[189]
Effect of Lead (Pb)						
Cyprinus carpio	4.295	$Pb(NO_3)_2$	Fingerling	28 days	Distortion of the lamella in gills, large polyhedral cells within the network of minute canaliculus in liver.	[191]
Labeo rohita	11.40	$Pb(NO_3)_2$	Fingerlings	60 days	Upliftment of gill rakers, hyperplasia.	[192]
Cyprinus carpio	4.50	$Pb(NO_3)_2$	Adult	96 h	Loose epithelial lining of cartilaginous core, necrosis, and deformed secondary gill lamellae	[193]
Cyprinus carpio	6.20	$Pb(NO_3)_2$	Adult	15 days	Fusion of gill lamellae, vessel dilatation, hyperaemia, and hyperplasia of gill epithelial cells.	[194]

Table 5. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Copper (Cu)						
Oreochromis niloticus	0.40	Cu^{2+}	Adult	21 days	Inhibition of Na^{+}/K^{+}-ATPase activity in gills.	[195]
Cyprinus carpio	55.00	CuO NP	Adult	4 days	The observed effects included curvature, edema, hyperplasia, dilated marginal channel, lamellar fusion, dilated and clubbed tips, epithelium shortening, aneurysm, necrosis, increased mucous secretion, and haemorrhage at the secondary lamellae.	[196]
Oncorhynchus mykiss	0.1.00	$CuSO_4$	Juvenile	10 days	Hyperplasia, aneurysms, and necrosis in secondary lamellae of the gills.	[197]
Catla catla	0.300	$CuSO_4$	Fingerling	3 weeks	Cytolysis, necrosis, pyknosis, and fibrosis in liver.	[198]
Cyprinus carpio	0.075	$CuSO_4$	6 months	4 weeks	There was an increase in the number of blast cells, proliferating cell nuclear antigen (PCNA), and apoptotic cells.	[184]
Effect of Arsenic (As)						
Oreochromis mossambicus	49.90	$NaAsO_2$	Adult	192 h	Gills were characterized by epithelial hyperplasia and necrosis, liver tissue showed focal lymphocytic and macrophage infiltration.	[199]
Ctenopharyngodon idella	89.00	As_2O_3	Adult	28 days	Decrease in glycogen levels in gill, liver, kidney, and brain.	[200]
Channa punctatus	99.80	$NaAsO_2$	Adult	20 h	Fragmentation of liver chromosomal DNA.	[201]
Effect of Zinc (Zn)						
Cyprinus carpio	16	ZnO	120 d	96 h	Hyperplasia of epithelial cells, lamellar fusion, aneurism, lamellar disorganization and curling in gills.	[202]
Oreochromis niloticus	6	$ZnCl_2$	Adult	28 days	Hepatocyte degeneration, nuclear pycnosis, cellular swelling, and congestion of blood vessels.	[203]
Oreochromis mossambicus	0.02	ZnO NPs, ZnO	Adult	96 h	lesions in the gills, disorganization of gill lamella, cartilaginous core disruption, lifting of epithelium, loss of secondary gill lamellae, blood congestion, fusion of secondary gills lamellae, shortening of secondary gills lamellae, atrophy, and curling.	[204]
Sparus aurata	1	ZnO-NPs	Juvenile	96 h	Hyperplasia of epithelial cells and fusion of secondary lamellae in gills. Lipid vacuolation in various degrees, necrosis of hepatic and pancreatic tissues. Degeneration, atrophy, and necrosis of muscle fibers with edema in muscles.	[205]

4.1. Effect on Immune System

Immunotoxicity is defined as the adverse effects of xenobiotics (e.g., drugs and chemicals), including the dysfunction and/or structural damage of the immune system and can be induced directly or indirectly [206]. The immune system is indispensable for host defence and the maintenance of homeostasis in the body. The intricate immune system requires close involvement of multiple components which can be reluctantly disrupted by environmental chemicals such as pesticides and polycyclic aromatic hydrocarbons (PAHs) [207]. Evidence has indicated that toxicants can cause the diversity of possible immune responses, resulting in not only immune suppression or immune stimulation but also immune diseases, e.g., allergic or autoimmune diseases [208]. In addition, even those unremarkable impairments of immunity might result in enhanced susceptibility to infection, with possible lethal consequences [209]. However, due to the vague mechanism and unclear mode of action (MOA), immunotoxicity has long been an underused but sensitive endpoint for chemical risk assessment with insufficient attention [208]. Conventional immunotoxicity evaluation based on animal experiments was limited by low sensitivity, low throughput, a long duration, and high costs; in vitro tests have consequently emerged. However, due to the complex characteristics of the immune system, it is challenging to develop accurate and convincing in vitro detection immunotoxicity methods [210]. In this review, Table 6 provides a detailed analysis of the effects of metallic trace elements on immune system of fish.

Table 6. Effect of heavy metals on immune system.

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of Cadmium (Cd)						
Cyprinus carpio	0.5932	$CdCl_2{\cdot}5H_2O$	Juvenile	30 days	Reduced levels of antioxidant enzymes (SOD, GSH-Px).	[211]
Labeo rohita	0.65	$CdCl_2$	Mature	28 dpe	Reduced lysozyme activity, alternative complement pathway activity, phagocytic activity, phagocytic activity.	[212]
Danio rerio	1.000	Cd	Adult	96 h	Increase in the protein levels of (TNF-α), increase in the mRNA levels of NF-E2-related factor 2 (Nrf2) and nuclear transcription factor κB (NF-κB), increase in ROS, NO, and MDA.	[213]
Oreochromis niloticus	1.22	Cd $(NO_3)_2{\cdot}4H_2O$	Adult	96 h	Significant reduction in antioxidant levels, significant decrease in hematological parameters, increase in neutrophils.	[214]
Effect of Mercury (Hg)						
Danio rerio	0.016	$HgCl_2$	Adult, embryos	168 hpf	Transcription levels of several representative genes involved in innate immunity were upregulated.	[215]
Pylodictis olivaris	0.010	$HgCl_2$	Juvenile	42 h	mRNA levels of immune-related genes were upregulated.	[152]
Pseudosciaena crocea	0.040	MeHg	Juvenile	30 days	Genes related to immunity (TCTP, GST3, Hsp70, Hsp27 mRNA) were all upregulated.	[209]
Sparus aurata	0.010	CH_3HgCl	Mature	30 days	Leukocyte, peroxidase activities significantly increased.	[216]
Effect of Lead (Pb)						
Sebastes schlegelii	240	Pb $(NO_3)_2$	Juvenile	28 days	Lysozyme activity significantly increased	[217]
Hypophthalmichthys molitrix	0.00384	Pb $(NO_3)_2$	Adult	96 h	Immune factors genes were upregulated, increasing the goblet cells' number, causing the intestinal leukocyte infiltration.	[218]
Carassius carassius	1	Pb·(CH_3COO_2) $3H_2O$	Adult	60 days	Significant decrease in lysozyme and the content of immunoglobulin M.	[219]
Pelteobagrus fulvidraco	0.050	Pb·(CH_3COO_2) $3H_2O$	Adult	60 days	Significant decrease inlysozyme (LYZ), complement 3 (C3), and immunoglobulin M (IgM) levels.	[220]

Table 6. *Cont.*

Fish Species	Metal Concentration (mg L^{-1})	Metal Composition	Stage of Exposure	Exposure Duration	Effect Observed on Fish	References
Effect of copper (Cu)						
Oreochromis niloticus	0.040	Cu	Adult	60 days	Increased levels of lysozymes (LYZ), respiratory burst activity (RBA), and myeloperoxidase (MPO).	[221]
Takifugu fasciatus	0.010	Cu NPs	Juvenile	30 days	Physiological indicators of immune response increased.	[222]
Pseudobagrus fulvidraco	0.0011	$CuSO_4$	Adult	42 days	Lysozyme and phagocytosis in the blood were significantly decreased.	[223]
Effect of Arsenic (As)						
Labeo rohita	15	$NaAsO_2$	Fingerlings	12 days	Immune-suppressive effect leading to down regulation of both Th1 and Th2 cytokines, regulation of HSP genes.	[224]
Sebastes schlegelii	0.040	$NaAsO_2$	Juvenile	20 days	Increased levels of immunoglobulin M (Ig M) and lysozyme.	[224]
Sparus aurata	0.988	As_2O_3	Adult	30 days	Leucocyte peroxidase, respiratory burst, and phagocytic activities were significantly increased.	[225]
Danio rerio	0.08	As_2O_3	Adult	30 days	Hyperactivation of the immune system.	[226]
Danio rerio	0.060	$Na_2HAsO_4 \cdot 7H_2O$	Larvae (7 dpf)	24 h	Immune suppression due to increased neutrophils, decreased lymphocytes.	[227]
Effect of Zinc (Zn)						
Danio rerio	0.060	$ZnSO_4$	Larvae (7 dpf)	24 h	Significant increase in number of neutrophils.	[227]
Danio rerio	0.020	Zn	3 months	42 days	Significant increase in CAT activity, upregulation of stress-related and immune-related genes.	[228]
Acanthopagrus schlegeli	0.040	ZnO	Adult	28 days	Increased phagocytosis and lysozyme, increased immune responses.	[229]
Oreochromis mossambicus	5	$ZnSO_4 \cdot 7(H_2O)_x$	Adult	14 days	Decreased phagocytic activity, increase in lysozyme and myeloperoxidase activities.	[230]

While all metallic trace elements are toxic to some extent, certain metals pose an exceptionally high risk to fish. Some of the highly toxic metals are described below:

4.2. Mercury (Hg)

The accumulation of mercury in various organs of fish has been linked to several abnormalities in fish species. For instance, elevated levels of Hg in *Heteropneustes fossilis* have been found to disrupt the biochemical balance in its central nervous system (CNS) and lead to a significant increase in lipid peroxidation and depletion of total lipids [65]. Mercury exposure has also been shown to cause a noticeable reduction in sperm motility in mummichog [98]. Furthermore, when Fathead minnow embryos were exposed to Hg, they exhibited gross irregularities and histopathological changes, such as spinal curves, impaired heart conditions, and abnormal growth of the heart cavity [137]. Even lower levels of dietary Hg have been observed to hinder the development of adolescent yellow pike (*Sander vitreus*) [231].

4.3. Lead (Pb)

Prolonged exposure to lead (Pb) can have significant neurochemical effects on the brain of walking catfish (*Clarias batrachus*). This exposure can lead to increased concentrations of histamine and serotonin, as well as a decrease in levels of Gamma-amino butyric acid (GABA), Monoamine oxidase (MAO), and Acetyl cholinesterase (AChE). Additionally, the brain's cholesterol, lipid, and protein contents are reduced [71]. Lead exposure also affects the motility of mature sperm cells in Grass carp, reducing their percentage of motility. Lead levels impact the permeability of the outer cell membrane by binding mucopolysaccharides, thereby altering ion exchange between the perivitelline fluid and the environment [139]. Furthermore, lead interferes with iodine metabolism, which hinders the synthesis of thyroid hormones [106].

4.4. Cadmium (Cd)

Cadmium disrupts the antioxidant balance in animal tissues by increasing the formation of superoxide. For example, in goldfish exposed to cadmium or mercury, higher mortality of eggs was observed at the germinal disc/blastodisc stage compared to the eye stage [232]. Cadmium also decreases thyroid hormone levels [105], reduces the number of estrogen receptors [233], and affects the expression of growth hormones [234]. Furthermore, cadmium exposure damages the genetic material (DNA, RNA) of fish, compromising its integrity [107–109].

4.5. Copper (Cu)

The survival of embryos exposed to Cu (0.1 mg per dm^3) 24 h after insemination was significantly reduced compared to the control group, and complete mortality occurred at a concentration of 0.3 mg per litre [235]. Cu, Pb, and Cd caused a decrease in the motility rate of spermatozoa in pejerrey fish (*Odontesthes bonariensis*) [127]. Exposure to Cu led to a decrease in the duration of sperm motility in Grass carp [236]. In common carp exposed to Cu, Cd, and Pb, there was a 40% decrease in egg growth (as measured by the increase in egg diameter) compared to the control groups [103].

4.6. Zinc (Zn)

Zinc (Zn) is the key element for the control of several functions, including immune functions, fertility, metabolism, catalyst for the several enzymes, wound healing, growth performance, reduction of oxidative stress in animal and fish [237]. However, despite all its beneficial properties, at a relatively high concentration, zinc can cause adverse effects that are manifested as changes in the function of internal organs, delays in the transmission of nerve impulses, and decreased mobility of the organism [238]. Along with their direct toxic effects, zinc compounds, which can show the ability to accumulate in aquatic organisms, cause long-term embryotoxic, genotoxic, cytotoxic, and carcinogenic effects in organisms [239].

By setting maximum allowable levels for specific metallic trace elements, the WHO aims to provide governments, regulatory bodies, and water management authorities with a framework for effective water quality management and pollution control. Table 7 shows such limits of metallic trace elements, which are discussed in this paper.

Table 7. Permissible limits of metallic trace elements.

Metal Ion	Permissible Limits by WHO (ppm)
Hg	0.001
Cd	0.005
Cu	1.5
As	0.05
Pb	0.05
Cr	0.05
Zn	5.0

5. Treatment of Metallic Trace Elements–Contaminated Aquaculture

The accumulation of pollutants in water-body sediments and the subsequent release of these substances play a crucial role in regulating the concentration of aquatic pollutants. As these concentrations continue to rise and persist, the removal of pollutants like metallic trace elements from water and marine sediments becomes exceedingly expensive and technically challenging [240]. Contaminated aquaculture systems affected by metallic trace elements can be treated using various wastewater treatment methods. These methods encompass chemical approaches (precipitation, ion exchange, electrochemical, reduction/oxidation treatments), physical techniques (reverse osmosis, filtration, membrane technology, flotation, coagulation-flocculation, adsorption), and biological methods (biosorption, phytoremediation) [241]. However, except for adsorption, the chemical and physical methods have proven to be problematic, as they tend to be costly, generate sludge and toxic waste, and exhibit limited effectiveness, particularly when dealing with metal concentrations below 100 mg/L. Additionally, most metallic trace elements are soluble in water, making their complete removal through conventional methods challenging. On the other hand, adsorption offers several advantages over other techniques, as it can effectively treat low-concentration pollutants such as metallic trace elements, is relatively cost-effective, allows for regeneration and reuse, and does not produce toxic residues [17].

Studies have demonstrated the effective use of natural products in mitigating the detrimental effects of metallic trace elements pollution on water bodies and their resident organisms [242]. These natural products predominantly consist of medicines derived from plants and herbs. As they are derived from readily available environmental resources, these products offer efficiency, minimal adverse effects on aquatic organisms and the surrounding environment, and most importantly, cost-effectiveness. Moreover, laboratory experiments have substantiated the efficacy of these products. For instance, research has shown that naturally available herbs and plant-based medicines effectively reduce induced metallic trace elements toxicity in laboratory animals [243].

In addition to natural remediation approaches, nanotechnological methods have gained popularity for their ability to alleviate the adverse effects of metallic trace elements in water. Since the advent of nanotechnology, various nanomaterials have been developed and tested to mitigate metallic trace elements accumulation and the resulting damage to aquatic organisms [244]. For example, nanomaterials based on metal oxides have been engineered to remove toxic metallic trace elements ions from contaminated water due to their unique physical and chemical properties [245].

5.1. Metal Oxides Nanoparticles

Recent studies have revealed that metal oxide nanoparticles have great potential for the removal of toxic metal ions wastewater. Only a few metallic nanoparticles are analysed for sorption due to their instability in agglomeration or separation. Furthermore, the separation of single metallic nanoparticles from wastewater is a difficult process [246]. Therefore, to stabilize their property and aggregate them in a simple way, they need to be functionalized. However, the field of nanoscience has introduced superior water purification techniques. The role of significant nanomaterials used in the water purification process includes the elimination of toxic metal ions and minute pollutants less than 300 nm and certain smart reagents with mechanical stability that can remove the toxic metal ions. Nanotechnology has been observed with more interest in the field of environmental application because of its higher surface area and tenable physicochemical properties [247].

5.2. Magnetite Nanoparticles

In recent years, there have been significant advancements in the development of green chemical methods for producing magnetic nano-adsorbents aimed at the therapeutic treatment of metallic trace elements pollutants. These strategies offer several notable advantages, such as low cost, easy availability, higher biodegradability, and strong affinity for metal ions [248]. For example, in a recent study, CuO nanoparticles were synthesized with various structural modifications, demonstrating effective adsorption properties for metals like Arsenic (As), Lead (Pb), and Chromium (Cr) [23].

Surface coatings applied to magnetic iron oxide nanoparticles (Fe_3O_4) have also shown promising results in reducing aggregation, oxidation, and enhancing selectivity for specific targets. These coatings facilitate the rapid separation and enrichment of mercury ions Hg^{2+} in various matrices [249]. Another noteworthy example is the hybridization of Fe_3O_4 with polyaniline and MnO_2 (Fe_3O_4/PANI/MnO_2) [250,251]. This approach offers an economically viable and environmentally friendly production method while exhibiting a high capacity for adsorbing metallic trace elements ions, including lead (Pb^{2+}), zinc (Zn^{2+}), cadmium (Cd^{2+}), and copper (Cu^{2+}) [211]. It is important for researchers and official organizations to develop large-scale therapeutic treatment plants or units to mitigate metallic trace elements pollution in various effluents before they reach our freshwater bodies.

Magnetite nanoparticles have been subjected to tremendous attention because of their unique physicochemical properties, especially their high magnetization, unique electrical features, high surface area, small size, and high adsorption capacity [252]. Due to strong magnetic properties, they can easily be removed from water by using a magnet and its surface can easily be functionalized with different surfactants. Some of the most applied surfactants and polymeric coatings are polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), oleic acid, lauric acid, sulfonic acids and phosphonates, octanoic acid and chitosan, etc. Above all, these nanoparticles are cost-effective and easy to prepare at a large scale. These unique properties make them an ideal candidate for the treatment of wastewater. Iron oxide magnetite nanoparticles coated with polyvinylpyrrolidone (PVP–Fe_3O_4-NPs) have been successfully applied for the removal of metallic trace elements; Cd^{2+}, Cr (VI), Ni^{2+} and Pb^{2+} have been removed from synthetic soft water and seawater, both in the absence and presence of fulvic acid. The PVP–Fe_3O_4 NPs were found to remove 100% of all metal ions at the concentration of 167 mg/L within 2 h and the kinetics were found to follow the pseudo-second-order. The material is useful for the removal of metallic trace elements under different environmental conditions, in the presence or absence of oil [253].

6. Future Perspectives

Advancements in sensor technologies are expected to revolutionize real-time detection of metallic trace elements in environmental samples. Miniaturization, improved sensitivity, and selectivity of sensors will enable on-site monitoring with enhanced accuracy and efficiency. Integration of Internet of Things (IoT) and cloud-based systems will facilitate real-time data transmission and analysis, allowing for immediate responses to contamination events [254].

Future perspectives may entail integrating various remediation techniques for synergistic effects. For example, combining phytoremediation with nanomaterial-based sensors could facilitate real-time monitoring of plant health and metallic trace elements uptake, guiding better management decisions [218].

The presence of metallic trace elements in water can cause oxidative damages, oxidative and non-oxidative types of DNA damages, and rupture of the cell wall or membrane of organisms. The toxicity of concurrently existing contaminants restricts or inhibits the growth of bioremediating organisms or agents and reduces the performance of treatment systems. Using several microorganisms or applying various pollutant-tolerant microbes may be a more efficient means of treating concurrent metal and organic pollutant-contaminated wastewater. However, the entire potential of biotechnology use has to be uncovered [255].

Simple but effective methods are required for their detection and to maintain water quality to solve water scarcity and further its reuse [8]. The technological advancements have raised major concern over environmental safety, due to increasing generation of toxicants [256]. Further development of biosorption technologies based on immobilized algae will require detailed life-cycle analysis to assess environmental impacts, and the field-scale analysis of algal immobilization may significantly advance the field and provide techno-economic insights [257].

Overall, future perspectives on remedial measures and real-time detection of metallic trace elements align with a multidisciplinary and holistic approach. A combination of technological advancements, nature-inspired solutions, regulatory support, and public engagement is poised to drive innovative strategies for managing metallic trace elements pollution effectively and safeguarding water resources for future generations.

7. Conclusions

In conclusion, extensive research conducted through original studies and reviews has revealed that while metallic trace elements generally have detrimental effects on living organisms, certain metals are particularly toxic and pose a significant threat even at low concentrations, leading to adverse impacts on various physiological systems and behaviours. Aquatic animals, such as fish, are particularly vulnerable to the harmful effects of metallic trace elements due to the contamination of water sources such as rivers, lakes, and marine environments. These metals have profound consequences on the overall health, growth, and development of aquatic organisms. Therefore, it is imperative to prioritize the reduction and control of water contamination originating from agricultural, industrial, and domestic sources in order to mitigate the serious problems faced by aquatic organisms and the aquaculture industry.

Author Contributions: S.N., A.M.M.C., Q.U., B.A. and Z.A.K. designed the study and wrote the manuscript; S.U., G.A., M.Z.K., M.K.S., A.K., R.M. and G.T.-I. helped in the collection of data resources and editing of the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: Research was supported in part by funds provided by USDA-NIFA Sustainable Agriculture Systems, Grant No. 2019-69012-29905. Title of Project: Empowering US Broiler Production for Transformation and Sustainability USDA-NIFA (Sustainable Agriculture Systems): No. 2019-69012-29905.

Data Availability Statement: All the data is available in the manuscript.

Acknowledgments: We express our gratitude to the Higher Education Commission (HEC) of Pakistan for granting access to their digital library, which enabled us to conduct extensive literature searches and obtain full-text articles, thus facilitating the completion of this review.

Conflicts of Interest: The authors declare no conflict of interest.

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