A review of heavy metal-induced toxicity in fish: Bioaccumulation and manifestations

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Abstract. This general review provides data on the accumulation of heavy metals in the body of fish and the histopathological effects. Fish represent an essential bioindicator regarding the degree of environmental pollution. Heavy metals can induce mutagenic and carcinogenic effects in the body, so their study is very important. Regarding intracellular biochemical processes, they can be blocked due to the increased concentration of heavy metals in the body through the bioaccumulation effect. According to the existing data in the specialized literature, the target organs of the accumulation of heavy metals are represented by the kidneys and liver. The bioaccumulation of heavy metals is a growing concern for humanity because it can influence the entire food chain. The continuous accumulation of heavy metals throughout the environment, especially in the aquatic environment, is increasingly accentuated with the passage of time due to population growth, new technological developments and industrialization. Excessive exposure to heavy metals is an essential risk regarding the etiology of several neurological and neurodegenerative diseases.
Key Words: bioaccumulation, fish, heavy metals, health risk, histopathology.

Introduction. Heavy metal pollution has become an important concern worldwide, with a major role in biological toxicity. According to some authors, knowledge of metals was existent 2000 years BCt, when ores were obtained as a byproduct of the smelting process of silver. Metals were cited in the past by Hippocrates in 370 BC, in the context of abdominal colic to a man. Arsenic and mercury were cited by Theophrastus of Erebus (370–287 BC) and Pliny the Elder (AD 23–79) (Allan & Flecker 1993; Goyer & Clarkson 1996). According to the Environmental Protection Agency (USA) and the International Institute for Cancer Research, heavy metals are considered and classified as toxic, mutagenic and carcinogenic metals.

Metal contamination poses a major risk to the environment. For example, according to existing literature data, lead levels in Greenland's ice sheet have increased significantly especially in recent years, with a peak reached when lead was introduced into gasoline fuel since the 1920s. Nowadays, due to effects on environmental pollution and health, especially children, its use was abandoned (Tinker 1981).

For some time, plants have been used to hyperaccumulate certain metals. These plants can have the role of phytoremediation (removing contamination from the soil) or phytomination (growing plants for metal harvesting). Also, some metals in a certain amount have the role of essential nutrients for the plant (Rascio & Navari-Izzo 2011).

Heavy metals are characterized as natural elements with a high atomic weight and a density at least five times higher than that of water. Regarding the risk of toxicity, it can be influenced by several factors, namely: the concentration of the elements, the route of exposure, the type of chemical elements, the age, sex and health status of the exposed individual (Smith et al 1978; Tchounwou et al 2012). Figure 1 summarizes the main factors that may influence heavy metal toxicity to some extent. These factors can act differently, so the negative repercussions are primarily given by the concentration of metals in organs and tissues. Figure 1 shows the factors influencing the degree of toxicity of heavy metals.

All these factors are correlated with each other and influence the homeostasis of the human and animal body.

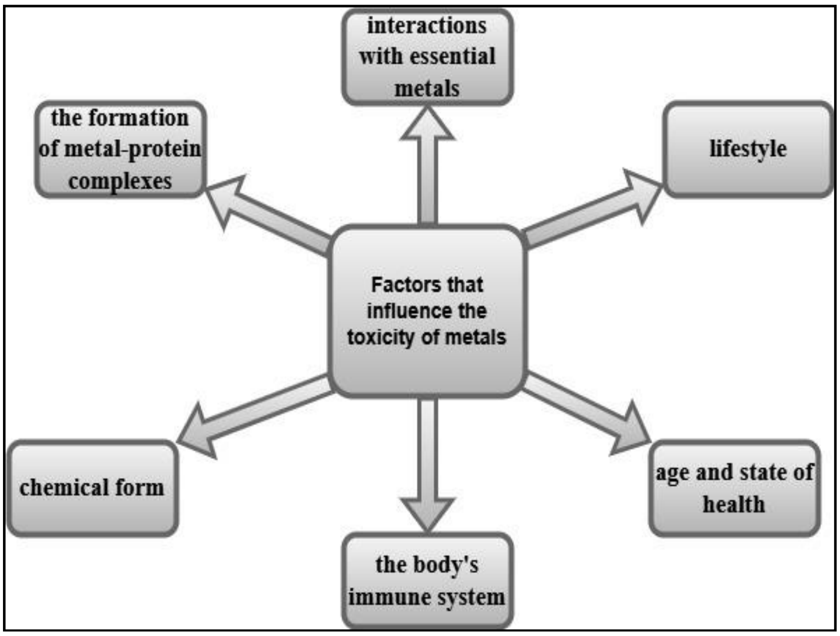

Figure 1. Main factors influencing metal toxicity.

Heavy metal contamination of the aquatic environment is also confirmed in a study carried out from water samples taken from several rivers coming from the Tibetan Plateau. Following the experiment, Mg was in high concentration in all samples, with an electrical conductance of 36 mS m^{-1}. Elements such as Cu, Zn, Ag, Cd and Cr were generally low compared to Pb, which was identified in a few locations and Ni in a few places in the Yangtze River (Huang et al 2008).

The study conducted by Rupakheti et al (2017) evaluates the concentration of heavy metals, the water quality index, the danger coefficient and the risk of cancer in water samples from two urban lakes in the Himalayan region (Phewa and Gosainkunda). Of the two lakes, the lake far from the urban area (Gosainkunda) showed a very good water quality, also confirmed by the content of heavy metals, including the metal index, compared to the lake (Phewa).

In the urban environment, the water quality was very low, results supported by the calculation of the heavy metals index. Rupakheti et al (2017) argue that the origin of manganese (Mn) and iron (Fe) is from natural and geological processes. Lead (Pb), vanadium (V), chromium (Cr), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn) and cadmium (Cd) are the result of anthropogenic processes in the case of the two lakes.

According to a study conducted on water in the Pakistan region, using flame atomic absorption spectrophotometry, large amounts of Ca, Mg and K were observed, and the levels of Cd, Co, Cr and Pb were higher than the national/international allowed values. Analysis of elements such as Cd, Cr, Pb resulted in a value much higher than the acceptable limit (Iqbal & Shah 2013).

Heavy metal contamination was assessed in the Bangaldesh area, where tissue samples were taken from 15 species of fish intended for human consumption. Following the study, Fe concentration was highest, 162.198 mg kg^{-1}, followed by Zn, 113.326 mg kg^{-1} and Ca, 87.828 mg kg^{-1}. The lowest values were Rb, 1.912 mg kg^{-1}, Hg, 1.657 mg kg^{-1}), Ni, 1.467 mg kg^{-1} and Pb, 0.521 mg kg^{-1}.

Euryhaline and benton fish had higher concentrations of metals than stenohaline and demersal fish from the Meghna river and other adjacent rivers (Bangladesh) (Hossain et al 2022).

In a study conducted to identify heavy metal concentrations in fish samples taken from the Warri River (Nigeria), using the method of atomic absorption spectrophotometry, the highest concentrations were identified for Fe, Cu and Pb. Following the study, it was concluded that the pollution of the river was caused mainly by the industries in the nearby areas (Ayenimo et al 2005).

There are several methods to remedy heavy metal pollution, including physical, chemical and biological methods, but phytoremediation would be a better alternative in terms of conventional approaches, due to aesthetics, ecology and profitability. To improve plant tolerance, various methods of approach are needed to reduce the accumulation of heavy metals in the soil (Rajeshkumar & Li 2018; Li et al 2019).

The critical retention point of a metal is characterized by its biological nature, by the degree of elimination, that is the time required for the body or organ to try to partially eliminate it from the body through the process of excretion. Typically, half of an accumulated amount of metal is excreted through an elimination pathway that may differ from one metal to another. Therefore, an important role of the biological half-life is the nature of the metal, but also the target organ or tissue (Tinker 1981). For example, for lithium and arsenic, the partial biological elimination time is several hours compared to cadmium, whose target organ is the kidney, and lead, which enters the bone marrow. Their biological half-life is several years (Singer 1981; Spivey & Rader 1988).

Likewise, we can make a comparison between lead that reaches bone tissue and lead that enters the circulatory system, where the biological half-life is several weeks, much less than for the lead that reaches bone (Rosen 1985). According to specialized literature (Valentino et al 1991), for a recent exposure that usually correlates with acute effects, the following can be used as samples (indicator tissue): blood, urine and hair. However, not all tissues are reliable indicators for all metals. In the case of mercury, hair can be a reliable indicator (Valentino et al 1991).

Stevens & Batlokwa (2017) conducted a study in which they demonstrated a cheap and ecological method of removing heavy metals from the environment with the help of eggshells. In the study, eggshells were treated with acetic acid. The concentrations of nickel and cobalt ions were taken into account for the demonstration. The observed factors that influence adsorption were pH, contact time and biomass dose when releasing Ni and Co from water. The removal of nickel and cobalt was 78.7±1.02% and 76.53±1.21%, respectively. Eggshells treated with vinegar have been proposed as readily available to achieve metal removal from the aquatic environment.

According to the data, toxic metals influence the role of essential metals as cofactors for various enzymes or other metabolic substances. For example, lead interferes with calcium-dependent release of neurotransmitters (DeForest et al 2007).

Bioaccumulation of Heavy Metals in Different Organs and Histopathological Effects. An important taxa regarding the bioaccumulation of heavy metals in various organs is fish. The histopathological manifestations produced by heavy metals at the level of organs are studied more and more in depth, because they have serious repercussions on the state of health (Kaoud & El-Dahshan 2010; Bibi et al 2021). The histological changes represent the final biomarker to evaluate the degree of toxicity induced by metals with toxic potential at the tissue level (Javed et al 2017).

Figure 2 shows the toxicity of these heavy metals on the organism. The histopathological manifestations can be: pyknotic nuclei, vacuolization at the level of the liver, leukocyte infiltration, necrosis, hyperplasia, formation of granulomas at the brachial level, etc. (Topal et al 2017; Rajeshkumar & Li 2018).

Regarding Pb toxicity, in inappropriate concentrations, it acts on the central nervous system, with memory loss and neurodegenerative diseases. All this affects other tissues, including liver and kidneys (Beijer & Jernelov 1986; Alessio & Dell'Orto 1988).

Chromium is a very aggressive element in the body and depends significantly on its oxidation state, causing tissue destruction. Its effects can be carcinogenic with the same action on the liver, kidneys and lungs (ATSDR 2010). In the case of a study, the researchers confirmed the processes of apoptosis at the cellular level, with vacuolization, necrosis and cellular hypertrophy (Hossain et al 2022).

A study carried out in Romania (Mureș River), the well-being of two species of fish was evaluated both downstream and upstream. Liver and gill samples were histopathologically evaluated. Fish showed changes in gill epithelium, focal proliferation of primary and secondary lamella epithelial cells, fusion of secondary lamellae, mucosal cell hyperplasia and hypertrophy, focal inflammation and necrosis of the epithelial cell (Triebskorn et al 2008).

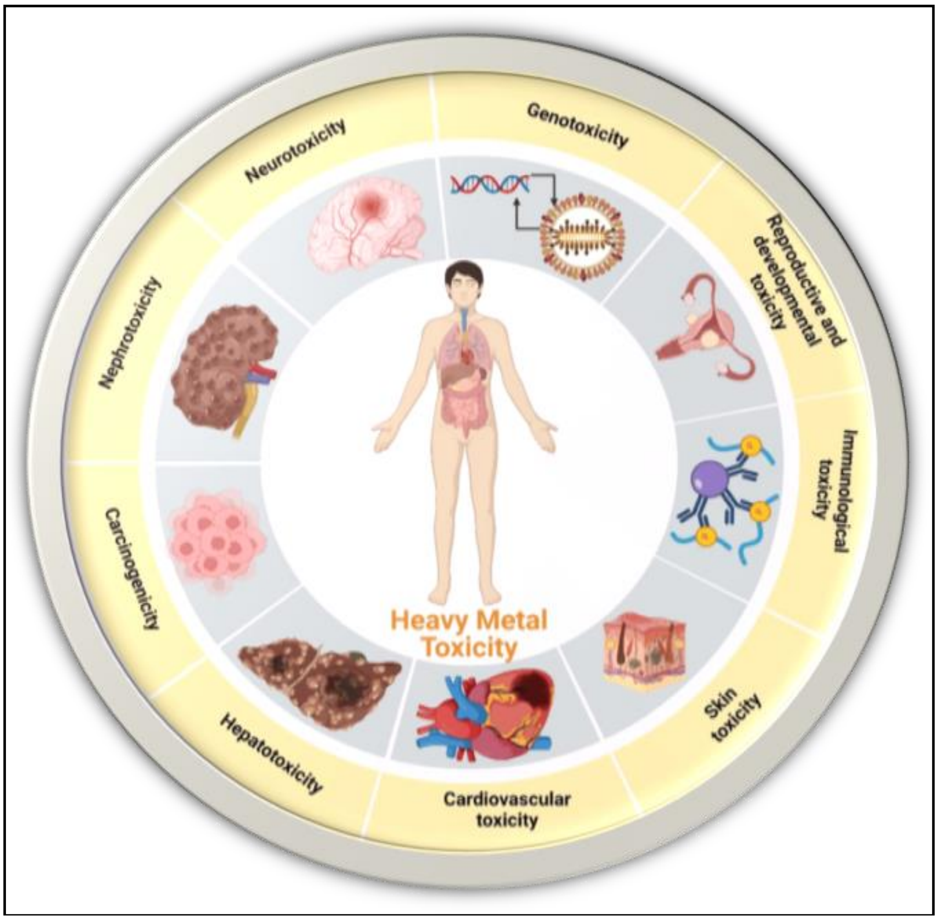

Figure 2. Heavy metal toxicity; source: Singh et al (2023).

The toxicity of heavy metals can be seen in Figure 2, for different tissues or organs. It can be seen according that heavy metals have a major influence on the whole body.

Another experimental study carried out by Purwanti et al (2019) followed the bioaccumulation of nickel under different concentration levels by checking the histopathological effects in the gills and liver of silver barb (*Barbonymus gonionotus*), from the rivers of Indonesia (Java and Sumatra Islands). Changes in lamellar fusion, hyperplasia and oedema have been described in the gills compared to liver tissue where necrosis and congestion processes, including vacuolization, have been initiated.

Awasthi et al (2019) investigated antioxidant responses and changes at the cellular level in different tissues in rainbow trout (*Oncorhynchuss mykiss*). Trout were exposed to nickel chloride for 21 days with a concentration of 1 mg L^{-1} and 2 mg L^{-1}. Following the experiment, peroxidative lesions, lamellar thickening, cellular infiltration in the brachial tissues, hydropic degeneration of hepatocytes in the liver, hyaline accumulation in the glomeruli, tubular degeneration at the renal level and other oxidative damages were observed. It is known that mercury is found in the environment in different elemental, inorganic and organic forms, but all of them have a toxic role for the body. The main organ involved in the regulation of metabolism, homeostasis and detoxification is the liver. Damage to the liver tissue can be confirmed at various low and short-term concentrations. All pathological changes are influenced by the dose. Changes at the liver level described are: cytoplasm vacuolization, hypertrophic, atrophy, cell contraction, decrease in both lipid droplets and glycogen granules, increase in number of mitochondria, increase of rough endoplasmic reticulum and pyknotic nuclei (Macirella et al 2016).

Another study on *Channa punctatus* followed the cell-level effects of mercury chlorides ($HgCl_2$) in different concentrations. After liver and kidney sampling, the authors confirmed major tissue damage and histopathological changes (hypertrophy, cell degeneration, vacuolization, etc.), (Trivedi et al 2022).

Based on data from Cambier et al (2010), following exposure of zebrafish to different concentrations of methylmercury (MeHg) for 25 days (13.5 microg Hg g-food^{-1}), changes occur in skeletal muscles, and mitochondrial respiration did not change.

The major histopathological effects of the action of heavy metals on various organs or tissues are shown in Figure 3. According to the figure, the process of necrosis can be achieved in most organs (kidneys, intestines, gills, brain, muscles).

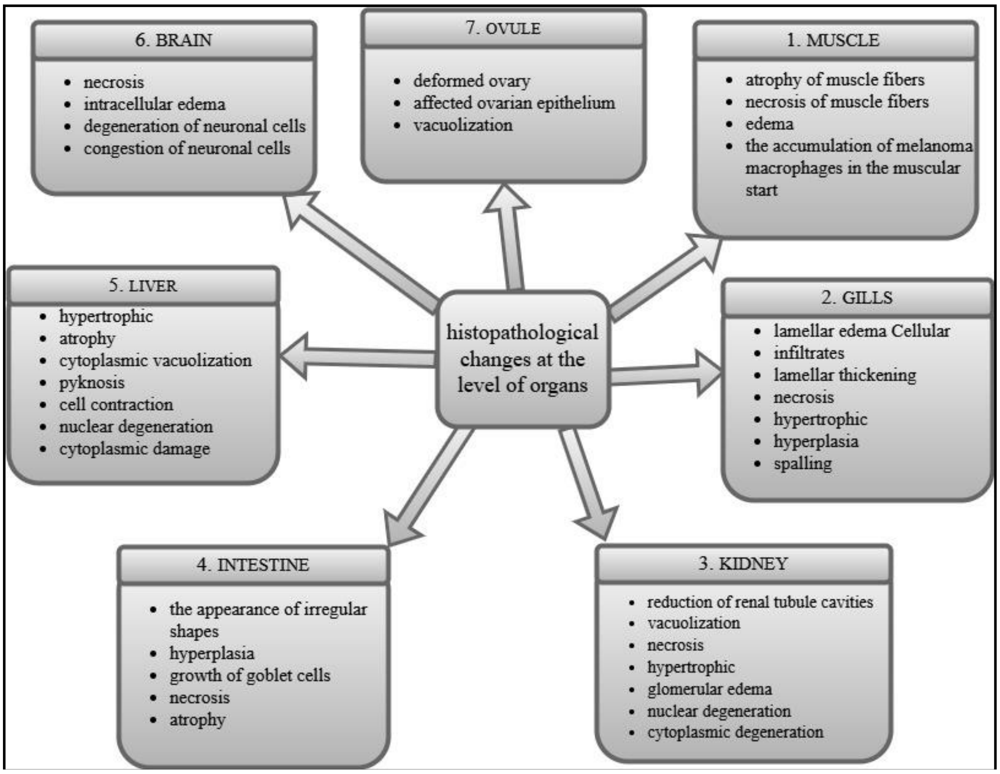

Figure 3. Major histopathological effects of the action of heavy metals on the target organs.

Fish gills have a large external contact area and are particularly sensitive to chemical and physical changes in their aquatic environment.

Regarding a study carried out on *Astyanax fasciatus* and *Cyanocharax alburnus* from Brazil, the authors followed the histopathological changes in the gills, and if there is any relationship between the severity of the changes and environmental pollution (Lopoes & Thomaz 2011). Thus, the gills of 107 specimens of *A. fasciatus* and 116 of *C. alburnus* were collected seasonally and processed by routine histological techniques for fixation and embedding in paraffin and staining the sections with hematoxylin and eosin. The main changes observed in both species were alteration of the structure of the epithelium, vacuolization, hyperplasia of the epithelium of the primary lamella, elevation of the epithelium and alteration of the structure and the appearance of aneurysms in the secondary lamellae. Therefore, following the study, it was concluded that the most severe are related to the most affected environment, indicating the presence of stress factors in the water (Lopoes & Thomaz 2011).

Conclusions. Heavy metals are natural elements that are transported throughout the geosphere. Depending on their quantity, they can cause pollution through natural phenomena, such as volcanic eruptions and rock weathering, but human intervention also plays a major role in the environment in terms of the degree of pollution. Anthropogenic activities leading to the entry of elements into the environment are of major importance, and the widespread use of these activities in recent years has led to dangerously high exposure, affecting both aquatic habitats and more severely the homeostasis of living beings. As a result of the influence of metals on the body of fish, according to existing data, the disturbance of all biochemical and physiological functions of fish is confirmed. Humanity is exposed to different forms of mercury (Hg): elemental (Hg^0), divalent (Hg^{2+}) and methylmercury (MeHg), with different potential health risks being reported.

Conflict of Interest. The authors declare that there is no conflict of interest.

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