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Review Article

# A Review on Histopathological Alterations Induced by Heavy Metals (Cd, Ni, Cr, Hg) in Different Fish Species

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SB and SS collected the data and wrote the manuscript. SN, AMMC and SS conceived the study and approved the article.

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Histopathology, Toxicity, Bioaccumulation, Toxic metals, Heavy metal pollution

**Abstract** | Industrial, domestic and other human activities are responsible for heavy metal toxicity of aquatic bodies. Metals are the major stimulators for variety of diseases in aquatic organisms mainly fishes. Chromium (Cr), mercury (Hg), nickel (Ni) and cadmium (Cd) causes histopathological variations and several diseases in various fishes of Pakistan. Extensive histopathological variations in gills, liver, kidney and skin of different fishes were noticed when exposed to heavy metals, thus indicating severity of heavy metal toxicity. The current study was focused on the toxicological effect of Cr, Hg, Ni and Cd in different type of fishes and it would be useful for the scientific community to restore different metals contaminating water.

**Novelty Statement** | Histopathological alterations in target fish organs functioned as fundamental indicator to assess metal toxicity in different fish species as it provides accurate data on effects of different contami-nants on fish. Hence, histopathology must be consider to monitor contaminated aquatic systems.

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## Introduction

In natural environment, pollution owing to heavy metals is a major issue. Heavy metal toxicity and their bioaccumulation easily enter humans via food chain (Tahir *et al.*, 2017) and also affect other organisms. In an ecosystem, metal residual distribution revealed contaminated area. Toxicity can easily be determine by considering various factors as to measure the level of feed and water pollution, bioaccumulation and toxicity of heavy metals along with bio magnifications in living beings (Has-Schön *et al.*, 2006; Saleemi *et al.*, 2019).

Heavy metals intake is a main reason for metal accumulation in different fish organs (Javed, 2015). In aquatic environment, metal toxicity not only effect aquatic life (Fish) but also humans as they are consumers in food chain (Faiza *et al.*, 2015; Perera *et al.*, 2015). Various fish species are used to measure health conditions of aquatic life and their ecosystem, as metal pollution is increasing day by day (Abbas and Javed, 2016). Gills and food web are directly associated for the entry of heavy metals in aquatic life and also get entry in other organs. When accumulated, metals brings oxidative stress, thus causes genotoxicity (Khan *et al.*, 2015a, b). Different biological techniques are used to evaluate metal toxic levels and their impact on fish and other organism's behavior, their physiological sensitivity as well as morphological indices (Yang *et al.*, 2014; Kousar and Javed, 2015).

Different metals greatly effect cell organelles as well as metabolic and detoxifying enzymes (Wang and Shi, 2001). Metals also effect DNA and nuclear proteins,

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hence causes apoptosis or carcinogenesis (Beyersmann and Hartwig, 2008). Liver plays an important role in toxic material transformation (Udotong, 2015). Mercury (Hg) is a lethal metal and exists naturally in earth crust. Erosion, volcanic eruptions and anthropogenic activities (Industrial, agricultural and municipal wastes) may contaminate environment. As fish is on the top of aquatic food chain so metals from the water can easily enter the body. Increase mercury level in water brings more accumulation is fish organs.

More the amount of mercury in aquatic environment, greater will be its accumulation in fish tissues, and also in human beings (Gilbertson and Carpenter, 2004; Guilherme *et al*., 2008). Due to methyl mercury rapid swimming was noticed in Zebra fish (Zamorano *et al*., 2016). Cadmium (Cd) has teratogenic, carcinogenic and mutagenic effects on aquatic life. Freshwater ecosystem is effected by Cd owing to higher sensitivity towards aquatic life compared with mammals (Burger, 2008; Jia *et al*., 2011).

Nickel (Ni) also possess toxic behavior and its greater concentration causes complications in blood, respiratory system, tissues as well as mucus membranes and effect different cells and chromosomes. Thus, the European Union had offered World Trade Organization (WTO) to consider nickel as a hazardous element (Purwanti *et al*., 2019). Nickel can also cause metal toxicity in organs, contact dermatitis, allergy, morphological alterations in cellular systems and even chromosomal abnormalities (Coen *et al*., 2001; Palaniappan and Karthikeyan, 2009). Literature on nickel accumulation in fish is limited compared with other metals (Palermo *et al*., 2015). Chromium (Cr) toxicity may cause mucus discharge, color changes, erratic motion and even abrupt swimming as in *Danio rerio* (Zebra fish) (Nisha *et al*., 2016). Thus, the aim of current work was to estimate the effect of different heavy metals i.e. mercury, cadmium, nickel and chromium on fishes that brings histopathological variations and also causes various diseases. In Pakistan, fish species are going to reduce due to heavy metal accumulation and present study reveals that heavy metal exposure in aquatic life increases damage to fish tissues and organs.

## Materials and Methods

Present study was designed to review the studies from 2000-2020 and it was based on the histopathological alterations on fish. Various articles were searched from Google Scholar and PubMed using keywords as histopathology, heavy metals, toxicity, bioaccumulation, aquatic life, fish species, and histopathological abnormalities. Latest research papers and articles were selected to avail some relevant data. All the papers were cited along with their proper references.

*Aquatic toxicity*

*Industrial effects*

Countries being developed are in front of many issues and one of them is water pollution. This is just because of industrialization which is spreading very quickly and civilization as well. Very huge number of pollutants and polluting products are released from these industries. From these pollutants, various heavy metals are on top of the list which is continually being released into adjacent water bodies without treating them. Hazardous impacts of heavy metals on water ecosystem have been considered as a global issue (Yousafzai *et al*., 2008). These toxic metals are allowed to be released in the environment through anthropogenic and natural activities i.e., industrial and urban discharges, mining combustion processes and mining etc. (Barone *et al*., 2013; Ambreen *et al*., 2015).

*Biochemical toxicity*

Chromium is considered to be exerting its toxic effects on intestinal epithelial cells and brings changes in functions regarding glucose transportation. A study on the intestine of rainbow trout revealed shortage of glucose absorption by the epithelial cells of intestine (Stokes and Fromm, 1965).

Various fish species' osmoregulatory functions have been affected by the impact of trivalent chromium ($Cr^{3+}$). A fish species named *Cyprinus carpio var. communis* upon chromium sulphate [$Cr_2(SO_4)_3$] exposure brought variations in osmoregulation functioning in fish (Subashini *et al*., 2005). Heavy metals exposure up to different levels might cause various behavioral and morphological aberrations in fish (Qadir and Malik, 2011). Cd is considered as a toxic heavy metal and also have disrupting properties of endocrine (Afridi *et al*., 2011; Chouchene *et al*., 2011).

Some metals like Cd, Cr, Pb, Hg and As being non-essential elements can exert toxic effects even at very low concentration. While Co, Mn, Zn, Cu, and Ni are the essential metals producing lethal effects at high concentrations (Couture and Rajotte, 2003).

*Bioaccumulation of heavy metals*

Fish attained the ability of heavy metals bioaccumulation in their tissues via absorption, while humans can come into exposure of these metals by the food chain. As fish is the prior in human's diet thus affecting humans in different ways (Dogan and Yimaz, 2007). Heavy metal's bioaccumulation and their bio-magnification is linked with the pathway of transformation of pollutants from one trophic level to another (Ghannam *et al*., 2015).

In marine biota, the accumulation of Cr needs to be discovered. Marine biota which uses gill tissues for absorption is more affected by its concentration. As per known, marine organisms uses gills for the absorption process as major and main part of their body. Cr might deposit at different concentrations in different tissues. Fish gills, kidney and liver were found to be containing high concentration of Cr and muscles were not found to be affected and accumulated by the metal. However, Cr cannot be accumulated at higher trophic levels in marine food webs (Pourahmad *et al*., 2005).

*Histopathological alterations*

Histopathological studies are thought to be consistent and comprehensive biomonitoring tool to analyze the fish health and its survival rate in accumulated aquatic ecosystems (Deore and Wagh, 2012). Effects of metals i.e. Cd, Cr, Ni and Hg in different fish species present in Pakistan were noticed along with their histopathological changes (Table 1).

*Heavy metals and diseases*

*Cadmium*

Metals uptake primarily occurs by gills but it can also occur through intestinal epithelium (Mohamed, 2008). Some of the aberrations were observed in the intestine of *Oreochromis nioticus* and *Lates niloticus*. It was noticed that there were various severe degenerative and necrotic alterations in their intestinal mucosa. Kaoud *et al*. (2011) studied some pathological changes in the intestine of *Oreochromis niloticus* exposed with Cd along with atrophy in muscularis, necrotic and degenerative alterations in mucosa and sub mucosa. As the liver is associated with biotransformation and detoxification processes so due to these functions, its location, and its access to the body supply, it is an organ which is mostly affected by the water contamination (Camargo and Martinez, 2007; Mohamed, 2009).

*Nickel*

Generally, Ni present in trace amounts in the fish, if its concentration increases; it would be a risk for the survival of water organisms (Rauf *et al*., 2009). An extensive use of Ni, in various activities like, ceramic, steel industries and electroplating which are making Ni containing products, releasing waste materials into adjacent water channels without treating them (Jabeen and Javed, 2011). Fish accumulates heavy metals in its body by various ways i.e., through respiratory system, digestive system and skin directly (Ma'ruf, 2007). One of a fish named *Barbonymus gonionotus*, is considered to be sensitive to the environmental fluctuations and that's why they act as bio indicator of environmental changes in the aquatic ecosystem (Wajiya and Yazid, 2009).

*Chromium*

Cr has deteriorating effects on fish survival and its growth (Shaheen *et al*., 2012). It just not only damage fish fertility but also produces aberrations in their progeny as well. Breeders' exposure before spawning induced cumulative impact on fish gonads and it results in meager, weak and retarded off-springs just because of the malfunctioning of trophic hormones (Kobayashi and Okamura, 2005). It was noticed that, any decrease in activation of mitogen induced lymphocytes and a noticeable change in shape and phagocytic functions of neutrophils. These alterations may reflect the reduced power of resistance to pathogens chronic exposure of Cr in fish (Steinhagen *et al*., 2004).

*Mercury*

Studies revealed that, Hg ions increases the formation of vacuole in hepatocytes and hepatic disintegration occurs in severe cases. Damage increases with persistent exposure of Hg, indicating its accumulation in fish body. This study also in the favor of Kuang *et al*. (2007), who studied the roles on heavy metal's ions in *A. japonica* under the water. Toxicity of heavy metals may lead to various pathological alterations in various fish tissues and these changes also has been addressed in *Labeo rohita* when exposed to mercuric chloride and *Channa puntatus* when exposed to phenyl mercuric acetate (Karuppasamy, 2000). Some major diseases caused by heavy metal toxicity are:

*Necrosis*

Hepatocytes necrosis and its degeneration might be due to the cumulative effects of metals and an increase in their concentrations in liver. Liver cellular degeneration might be due to oxygen deficiency as a result vascular dilation along with intravascular haemolysis was noticed in blood vessels (Mohamed, 2001). Lesions as degeneration, blood vessels dilation and necrosis in hepatocytes were detected in *Mugil cephalus*, *Tilapia mossambicus* and *Clarias gariepinus* (Ibrahim and Mahmoud, 2005).

*Oedema*

*Labeo rohita* gills when exposed to tannery effluent indicated fusions and primary lamellar epithelium clumping (Fanta *et al*., 2003). Some degenerative alterations in edema and lamellar were observed in fish gills when exposed to heavy metals (Osman *et al*., 2009). The lamellar epithelium lifting is a change of tissues, might be induced by any incidence of severe edema (Pane *et al*., 2004; Schwaiger *et al*., 2004).

*Hyperplasia*

Epithelial cells which undergo the lamella fusion and hyperplasia can go on to cause a huge decrease in gill surface area for respiration. It also disrupts blood flow in gills, alters the functioning of metabolism and may cause fish mortality (Purwanti *et al*., 2019). Recently, some of the researchers demarcated the gill injuries of two types. First type of injury comes from defense response and it includes hyperplasia of gill epithelium filaments while the second type is direct injuries which include shedding and necrosis of gill epithelium (Fanta *et al*., 2003).


Links Researchers

**Table 1: Effects of metals (cadmium, chromium, nickel and mercury) in different fishes of Pakistan.**

| Fish species | Metal | Concentration | Exposure type | Exposure time | Organ | Histopathological changes | References |
|---|---|---|---|---|---|---|---|
| *Wallago attu* | Cadmium | 1/3, 1/4, 1/5 of LC50 | Sub-lethal | 14days | Liver | Protein level decreased | (Batool *et al*., 2018) |
| *Catla catla* | Nickel | 70.40 mg/L | Sub-lethal | 60days | ….. | Total length, fork and weight increased | (Safina *et al*., 2020) |
| *Labio rohita* | | 71.99 mg/L | | | | Weight increment | |
| *Cirrhinus mrigala* | | 79.9 mg /L | | | | Weight increment | |
| *Channa striata* | Nickel | 1/3, 1/4, 1/5 of LC50 | Sub-lethal | 14days | …. | CAT activity reduced | (Arshad *et al*., 2018) |
| *Catla catla* | Cadmium | ….. | Acute | 96hrs | Blood | Hemoglobin, hematocrit and RBCs decreased | (Hassan *et al*., 2018) |
| *Channa marulius* *Mystus seenghala* *Wallago attu* | Cadmium | 101.25mg/L | Acute | 96hrs | Liver | Liver sensitivity increased | (Javed *et al*., 2016) |
| *Ctenopharyngodon idella* | Chromium | 25.5mg/L 22.5mg/L 20mg/L 18mg/L | Acute | 24hrs 48hrs 72hrs 96hrs | Gills, muscle tissues | Swelling in gills cells, fusions, inflammation. muscle cells necrosis, RBCs and hemoglobin decline. | (Shah *et al*., 2020a) |
| *Oreochromis niloticus* | Mercury | 0.044 mg/L | Sub-lethal | 48hrs | Liver | Hepatocytes destruction, sinusoids, pyknotic nuclei | (Pervaiz *et al*., 2019) |
| | | | | 96hrs | | Cellular necrosis, melano-macrophages centers appearance, pyknotic and karyolosis nucleus, hepatic cords disorganization. | |
| | | 0.055 mg/L | | 48hrs | | Tissue degeneration, hepatic cords disorganzation, bile ducts degeneration, pyknosis | |
| | | | | 96hrs | | Bile duct inflammation, cellular necrosis, pyknotic nuclei, hemopoietic tissue degeneration. | |
| | | 0.073 mg/L | | 48hrs | | Pyknotic nuclei, hemopoietic tissue degeneration, bile duct degeneration, vacuolization, necrosis. | |
| | | | | 96hrs | | Pyknosis, necrosis, degeneration of tissue, bile duct inflammation, vacuolization. | |
| *Carassius auratus* | Chromium | 4ppm 6ppm 8ppm 12ppm | Sub-lethal | 24hrs 48hrs 72hrs 96hrs | Gills Intestine Skin | Increased breathing rate. Increased mucus secretion. Tissue residues. | (Fawad *et al*., 2017) |
| *Oreochromis niloticus* | Cadmium mixture | 183.4 ml | Chronic | 2weeks | Kidney | Renal CAT activity increased firstly, decreased finally. | (Ahmed *et al*., 2016) |
| *Ctenopharyngo-donidella* | Chromium | 45.5, 43.5, 41.5, and 39 mg /L | Lethal | 96hrs | Blood | RBCs and hemoglobin level decreased | (Shah *et al*., 2020) |
| *Labeo rohita* | Nickel | 0.32 - 1.22 mg/L | Sub-lethal | River water | Gills | Hyperplasia, necrosis, Blood vessels congestion | (Sultana *et al*., 2016) |
| | | | | | Intestine | Atrophy, | |
| | | | | | Liver | Necrosis | |

*Table continue on next page.....................*

| Fish species | Metal | Concentration | Exposure type | Exposure time | Organ | Histopathological changes | References |
|---|---|---|---|---|---|---|---|
| *Tilapia nilotica* | Cadmium-cobalt mixture | 37.93 mg/L | Acute | 96hrs | Tissues | Exhibited sensitivity higher | (Ambreen and Javed, 2016a) |
| *Cyprinus carpio* | Chromium | 5 mg/Land 10mg/L | Sub-lethal | 16 days | Liver | Blood congestion, necrosis, parenchyma cell degeneration. | (Rana *et al.*, 2015) |
| | | | | | Kidney | Pyknotic nuclei reduction, haemolysis. | |
| *Gibelion catla* | Chromium | 1/3rd of LC50 | Chronic sub-lethal | 12 weeks | Liver | Growth performance affected. | (Azmat *et al.*, 2018) |
| *Labeo rohita* | | | | | Kidney | | |
| *Cirrhinus mrigala* | | | | | Gills | | |
| *Cyprinus carpio* | Chromium | 25 to 150mg/L | Sub-lethal | 30days | ….. | Deleterious effects on growth produced. | (Shaheen and Jabeen, 2015) |
| *Cyprinus carpio* | Cadmium | 10.42, 7.81, 6.25 and 5.21mg/L | Sub-lethal | 30days | Blood | DNA damage | (Ambreen and Javed, 2016b) |
| *Cyprinus carpio* | Cadmium-lead mixture | 78.94 and 82.22 $\mu gg^{-1}$ | Lethal | 96hrs | Kidney | Higher accumulation, increase sensitivity. | (Ambreen *et al.*, 2015) |

## Results and Discussion

Different metals (Hg, Cr and Cd) are considered as systemic toxicants, thus affect various organs even at low level (Olsson *et al.*, 1998). Cellular organelles as well as enzymes involved in detoxification, damage repair and metabolic process are greatly influenced by heavy metals (Wang and Shi, 2001). Metallic ions effect nuclear proteins and DNA molecule, hence brings apoptosis or carcinogenesis (Beyersmann and Hartwig, 2008).

Histological biomarkers regarding fish organs toxicity are important indicators of environmental pollution. Biomarkers permits to examine specific target organ (gills) that are responsible for their vital function as respiration (Gernhöfer *et al.*, 2001; Peebua *et al.*, 2008). Gills are mainly involved in entry of heavy metals that brings lesions and gill damage and structural variations in gills of exposed fish are responsible for deaths (Bols *et al.*, 2001; Obomanu *et al.*, 2007). A study indicated that histopathological changes in gill tissues of Channa might cause hypoxic disorders, thus affecting their locomotory ability (Begum *et al.*, 2006). Various organic compounds causes toxicopathic lesions in liver of fish. Cloudy swelling, hydropic degenerations as well as karyolysis, pyknosis and karyorrhexis of nuclei occurs due to acute toxic injury (Paul *et al.*, 2014; Jiraungkoorskul *et al.*, 2003). Cytoplasmic vacuoles of hepatocytes containing glycogen and lipids are associated with normal liver functioning (Camargo and Martinez, 2007). Hepatocytes vacuolation brings metabolic changes when exposed to contaminated water. Similarly, histopathological variations with Cu and Cd were noticed in liver of teleostean fishes (Pacheco and Santos, 2002; Ibrahim and Mahmoud, 2005; Tayel *et al.*, 2008).

Fish can even cope with increased level of heavy metals in their bodies but is not safe for human consumption. Thus, time duration of contact with toxic elements and fish species as well as concentration rate must be considered before establishing basics for tolerable levels in ecological studies (Usero *et al.*, 2004). The oedema can lead to tissue swelling due to fluid accumulation and cause cell organelles to decrease cell permeability (Rennika and Nurlita, 2013). Oedema may cause hyperplasia occurrence which may lead to interlamellae being clogged, thus causing the entire space to be filled with new cells and thicken the epithelium present at lamellae base (Robert, 2001). Epithelial degeneration, inflammatory cell infiltration in sub mucosa along with sub mucosal edema was detected in the intestine of tilapia when exposed to carbofuran (Soufy *et al.*, 2007). Histopathological changes in the intestine of *Oreochromis niloticus* and *Lates niloticus* indicated severe degenerative and necrotic variations in the intestinal mucosa. Edema may be due to absorption of toxic metals (Hanna *et al.*, 2005). Thus, various studies reported heavy metal accumulation in different fish organs and changes were noticed regarding particular heavy metal.

## Conclusions and Recommendations

The current review indicates that exposure of heavy metals such as Cr, Cd, Ni and Hg at various concentrations brings histopathological changes in different fish organs. Such histopathological variations would be supportive to determine effect of heavy metals on fish species. Hence, present research served as experimental tools for the estimation of environmental pollution.

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*Conflict of interest*

The authors have declared no conflict of interest.

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