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Review Article
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Effects of potentially toxic metals on fish physiology, histopathology and impact on human health

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ABSTRACT

The present review aimed to summarize the concentration of potentially toxic metals in water bodies and in the gills, kidneys, and livers of fish and other seafood. Histopathological and haematological alterations and the impact of these metals on the growth and reproduction of fish are also documented. For sustained global development, fish and seafood must be protected from these pollutants, as they damage food quality and human health. These pollutants lower body weight, body length, survival rate, feed intake and decrease reproductive capacity. These pollutants are distributed in the gills, kidney, liver and muscle of fish and other seafood from the bodies of water and cause several histopathological changes such as severe necrosis, hypertrophic hepatocytes, vacuolated cytoplasm, sinusoids dilation in the liver, haemorrhage due to epithelium cell break, lamellar artery wall weakening, the fusion of all the lamellae, and rupture of lamellar epithelium in gills, lowering the number of the hematopoietic tissues, expansion of the connective tissues; damage of the renal tubuli; and glomerular contraction in the kidney. In the muscle tissue, shortening and elongation of muscle bundles are observed. Consumption of such contaminated fish and other seafood directly transfers these metals into the human body which expedites the number of diseases. This toxic metal in human disrupts the endocrine functioning, damages antioxidants, inhibits the functioning of enzymes, retards the DNA repair mechanism, and causes protein dysfunction. Some of these metals are well-known to be carcinogenic.

Keywords: Pollution, Potentially Toxic Metals, Fish, Histopathology, Liver, Kidney, Public health risks.

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Introduction

Water, the lifeblood of the biosphere, is an ingenious solvent in which most of the pollutants/chemicals are dissolved. These pollutants contaminate not only the water but also inhabitant organisms. Due to increasing urbanization, industrialization and climate change, potentially toxic metals are continuously accumulating in most of the bodies of water and underground water globally (Singh et al., 2020; Bansal,2020a). Globally, most of the rivers, lakes, and drains receive agricultural drainage water, industrial and municipal effluents, and solid waste.These potentially toxic metals are very easily and quickly accumulated in surface water (Olayinka-Olagunju et al., 2021, Hossain et al., 2021). The degree of accumulation of these toxic metals in the water bodies besides other factors depends on the type of activities in the area (Sharma and Chatterjee, 2017). Cu, Zn, Co, Fe, Mn, and Cr are essential metals for the entire living organism including humans, to survive in the biosphere, whereas the metals As, Cd, Pb, and Hg are non-essential. As these metals are non-biodegradable and easily bio-accumulated even in low concentrations, these metals (As, Cd, Pb, Hg) show several adverse health effects on living organisms, including humans. Globally, hundreds of millions of people are affected by toxic metal contaminated water and air, and about 25% of the population drinks potentially contaminated water, Hindu Business in its edition of Feb 20, 2019, has reported that more than forty million people in rural India drink potentially toxic metal contaminated water.

In coastal countries, seafood (fish, shellfish, and other molluscs) is one of the main food and economic resources. Food scientists have estimated that fish provides approximately 20% of animal protein to 33 billion people across the world. The consumption of fish twice a week has been recommended by the American Heart Association to minimise heart problems. The global human population is continuously increasing and there is a stress on agricultural production. It has attained its threshold point, so to cater to 9.7 billion people by 2050 (U.N., 2015) more agricultural, fish, and seafood production is required. So, globally for food system sustainability and economic growth, the consumption of fish and seafood by humans is essential. Worldwide, India is positioned in fourth place for exporting fish and seafood, and its turnover is approximately 7billion US dollars. Globally, fish is consumed and is considered a valuable food item and is recommended in a balanced diet as it is the major source of animal protein (17%), all the proteins (7%) long-chain omega-3 fatty acids, high level of unsaturated fatty acids (which prevents the heart disease), low amount of cholesterol, vitamin D, B_{12}, A, and E needed for bones; red blood cells, neurological functions and for the synthesis of nucleic acids; for the care of vision and respiratory tract and defence of antioxidants (Tamele and Loureiro, 2020); iron (for transportation of oxygen to the blood); iodine (for thyroid proper functioning); Ca (for bones and teeth), Zn (enzymatic activities and immune system), P, Mg and K. A number of medical researchers (Acharya, 2020, Acharya et al, 2019, Akinrotimi and Ukwe, 2019, Kron, 2022; Lange, 2020; Vallerand et al., 2019) have found that the risk of Alzheimer's disease, symptoms of depression, probability of rheumatoid arthritis, risk of autoimmune diseases, and chances of PMS symptoms are lowered by the regular consumption of fish. The longer lifespan of Japanese and Nordic populations has been significantly positively correlated with the amount of fish consumed. Recent studies have shown that the global average per capita consumption of fish is 21.4 kg with a maximum consumption of 200 kg per capita, though in India consumption per capita is low and is 5-9 kg. The FAO Agricultural Outlook has predicted that by 2029, the consumption of fish worldwide will be 180 million tonnes and production will be about 200 million tonnes. Accumulation of these toxic metals in fish and their environment (water, sediments, and aquatic plants) interrupts communication between fish and their aquatic environment, resulting in a negative impact on fish survival, growth rates, and reproduction, causing physiological disorders and excessive stress.

Sources of potentially toxic metals within the bodies of water and sediments:

Due to natural activities such as volcanic eruptions, forest fires, rock erosion, wind-borne soil particles and anthropogenic activities such as industrial activities (such as cement production, iron industry, steam power plants, glass production, paint, textile industries, and tanning industries), agricultural activities (use of pesticides, fertilizers, sewage sludge, sewage water), urban runoff, leaching to groundwater from dumping sites, mine drainage, smelting activities, these potentially toxic metals enter in environment.

Routes of Contamination:

Aquatic animals uptake these potentially toxic metals by direct exposure or by indirect exposure (Mustafa, 2020; Maurya et al. 2019)

(i) Direct exposure (Ingestion): This occurs when toxic metals are consumed orally i.e. through the gastrointestinal route.

(ii) Indirect exposure: occurs in two ways:

(a) Dermal/via permeable membrane: Absorption through the skin is called dermal uptake.

(b) Inhalation: When aquatic animals inhale polluted air as dust fumes or contaminated vapours containing toxic metals, these toxic metals are accumulated in the body of the animal. Potentially toxic metals are also present in the sediments, which act as a habitat for a number of small aquatic organisms. From these sediments toxic metals become available to other animals and humans who take them as food.

Potentially toxic metals in the water bodies and sediments:

The accumulation of potentially toxic metals due to anthropogenic activities such as erosion of landfills, agricultural cultivation, sewage from domestic and industrial waste, corroded underground pipes, smelting, and vehicles is posing a severe health concern globally, especially in developing countries. These toxic metals are non-degradable (persistent), and easily bio-accumulated in the aquatic flora and fauna, causing severe problems in the aquatic system as well as in the ecosystem. Many researchers (Yousif et al., 2021; Guo et al., 2018) have reported that the concentration of these pollutants was higher in the sediments than in the water. When the concentration of these metals exceeds the tolerable limit, it affects the normal ecological and physiological activities in the aquatic environment, causing toxicities to aquatic animals and plants, and the ultimate threat to humans. The concentration of these pollutants in groundwater, surface water, river water, lake water, seawater, and sediments is documented (Table 1).

Potentially toxic metals in fish and other aquatic organisms:

The ecosystem's water quality is the main factor that controls the health of fish and seafood. The presence of potentially toxic metals beyond their permissible limit causes stress in the aquatic system. Fish fauna, which is not only an important source of human food but also an important part of the aquatic system, easily assimilate these toxic metals via the food they consume other organic matter and suspended sediments present in the water body. These potentially toxic metals are accumulated in the different tissues (gills, liver, kidney, brain, lungs, and intestine) of the aquatic organisms (Sarkar et al., 2022; Akter et al., 2021). The accumulation of these toxic metals depends on the concentration and other properties of the pollutant, the length of exposure, and the type of aquatic animal (Bansal, 2020b). The concentrations of the potentially toxic metals in fish and other aquatic organisms are recorded in Table 2.

Impact of Potentially toxic metals on aquatic organisms:

The accumulation of the potentially toxic metals in the water bodies and surroundings adversely affects the health of aquatic flora and fauna as these animals and plants cannot escape from the water bodies. Bioaccumulation of these metals in aquatic organisms beyond the allowable limit causes deformities in the fish, a decline in fish populations, and a reduction in their growth rates with abnormal behaviour (Islam et al., 2020; Yan et al., 2020).

Histopathological Consequences: Potentially toxic metals present in the water affect the growth, nutritional value and reproduction, of the fish. As gills, kidneys and liver of the aquatic organisms which control the vital functions of the body i.e. respiration, excretion, accumulation, osmoregulation, acid-base balance, gas exchange and biotransformation are most affected (Abdel-khalek et al., 2016; Yancheva et al., 2015). The damage to these organs depends on the nature of the toxic metal, its concentration, and the length of exposure. Histopathological changes in the aquatic animals denote the degree of pollution by these toxic metals (Hussain et al., 2021; Sahid et al., 2021; Rehman et al., 2021; Dai et al., 2020). Based on the review of the literature, it can be inferred that the effect of these toxicants on gills, liver, and kidney can be divided into three grades: i) Grade 1: When the concentration of these metals in water is just beyond permissible limits; ii) Grade 2: When the concentration of these metals in water is moderate; and iii) Grade 3: When the concentration of these metals in water is very high.

Table 1: Histopathological changes based on severity

Tissue	Grade	Changes in Fish
Gill	1	Epithelial lifting of the lamellae, lamellar disorganization, blood congestion, gill epithelium hyperplasia and hypertrophy
	2	Abnormal epithelium break, fusion of the secondary lamellae, peeling of cells of epithelium
	3.	Haemorrhage due to epithelium cell break, lamellar artery wall weakening, fusion of all the lamellae and rupture of the lamellar epithelium
Kidney	1.	Dilated renal tubuli
	2	Contraction of tubular epithelial cells with dilation
	3	Lowering the number of the hematopoietic tissues, expansion of the connective tissues, damage of the renal tubuli, glomerular contraction
Liver		Dilation of sinusoids,
		Expansion of connective tissues with sinusoids dilation
		Hypertrophic hepatocytes, vacuolated cytoplasm and sinusoids dilation

Onita et al (2021) studied the effects of Cr and Zn on freshwater fishes of different feeding habits and found that in the gills there was lamellar fusion and epithelial necrosis with epithelium filament proliferation. In the kidney, there was glomerular contraction, disruption of the hematopoietic tissues, and renal epithelial cell damage with atrophy of renal tubular lumens, while no visible significant histopathological changes were observed in the liver. In the presence of Cd and Pb gills of the freshwater fish, *Luciobarbus xanthophores* showed an increase in the number of mucous cells, detachment of the epithelial cells, blood congestion, and necrosis in the primary and secondary lamellae; in the liver, there was blood congestion, mononuclear cell infiltration, and nuclear pyknosis, with cytoplasmic vacuolation. Necrosis of renal tubules with infiltration of protein substances, nuclear pyknosis, aggregation of melanomacrophase, and hydrophobic degeneration with detached epithelial cells were the histopathological changes in the kidney of the freshwater *fish Luciobarbus xanthophores* in the presence of Cd and Pb (Mustafa, 2020).In their studies Puntoriero et al. (2018) found that arsenic in water causes congestion in hepatic sinusoidal and blood vessels, hemosiderin, degeneration of cells, no proper contact between hepatocytes and pancreocytes, focal necrosis areas and cellular apoptosis with coagulative necrosis areas in the liver of the fish *Odontesthes bonariensis*. They also reported Oedema in secondary lamellae, epithelial detachment, curling of secondary lamellae, congestion and telangiectasia in blood vessels of gill filaments with hyperplasia of mucous cells. Several researchers (Khalid et al., 2020;Faheem et al., 2016; Cuevas et al., 2016) during their studies on the effects of potentially toxic metals reported inflammation, oedema, central vein congestion, cytoplasmic disorganization, cytoplasmic vacuolation, dilation of the sinusoid, necrosis of hepatic cells, pyknotic nuclei, and vacuolation of cells in the liver part of the studied fish, while in the kidney part there was necrosis in renal tubular cells, tubular haemorrhage, and Oedema, degeneration of the glomerulus tissue, collecting duct damage,blood congestion and damage of collecting duct.

Gopinathan and Binukumari (2021) during their studies on the effect of heavy metals on the gill histopathology of the fish *Labeo rohita* found that lamellar fusion and epithelial lining degeneration occur at low concentrations and shorter periods of exposure, while on prolonged exposure, structural alterations, viz., lamellar fusion, epithelial proliferation, and necrosis occur. On prolonged exposure, atrophy of secondary lamella, dilation and congestion of the blood vessels were also reported. Dilation of the blood capillaries, extensive aneurism, necrotic changes, and rupture in the epithelial cells of lamellae in the gills; extensive congestion of hepatocytes, destruction of the cell membrane, hepatic cord disorganisation in the liver; and extensive damage of renal tubules, glomeruli in the kidney were observed by Abdel-Kader and Mourad (2019) in the fish *Clarias gariepinus*. Exposure of the fish to toxic metals causes epithelium separation from the base, lifting of the secondary lamellar epithelium, increase in the diffusion distance between blood and oxygen in gills; dilated intercellular space, degeneration in pancreatic tissues, loss of cord structure, infiltration of red blood cells, vacuolar degeneration, damage of parenchymal cells in the liver; necrosis, tubular degeneration, glomerular shrinkage with splitting, haemorrhage, and melanomacrophages in the kidney were observed by a number of the researchers (Zaghloul et al., 2020; Yancheva et al., 2015; Omar et al., 2013). Elwasify et al. (2021); Sahid et al., (2021) observed that accumulation of the potentially toxic metals in the fish *Tilapia zillii* causes several histopathological changes in the liver and kidney; congestion in the interstitial blood vessels, necrosis in renal tubules occurring in the kidney part and compressed blood sinusoids, vacuolated hepatocytes, dilated central vein, vasculitis hepatoportal blood vessel in the liver part. Jasim (2017) during their research studies found that the potentially toxic metals destroy the morphology of gill epithelium, which in turn disturbs the osmoregulation, respiration, and growth rate. It also impedesliver function by decreasing the blood supply through the hepatic artery, degenerating hepatocytes and lowering the levels of antioxidant enzymes levels. uring their work on *Chanos chanos*Maftuch et al (2017) found fusion, hyperplasia and necrosis in gills; degeneration of cells, congestion and necrosis in the liver; and cloudy swelling, glomerular hyalinization and atrophy in the kidney due to accumulation of the toxic metals. Due to the accumulation of potentially toxic metals in water and sediments in the fish *Lutjanus monostigma*, variations like separation of respiratory lamellae, increased mucous secretion, swelling and fusion of secondary lamellae, hypertrophy, and complete dissolution of blood sinusoids were observed in the gills, while increased mucous cells, vacuolar degeneration, separation of the mucosal epithelial layer of the intestinal villus, lymphocytic infiltration due to disintegration of muscular layer, nuclei pyknosis and karyolysis, and lipid droplet accumulation were observed in the intestine part by Bin-Dohaish (2018).Pervaiz et al. (2019) found that mercury at a sub-lethal level causes hepatocyte destruction, sinusoids, pyknotic nuclei, and hepatic cord disorganization in the liver part of Oreochromis niloticus, while a high concentration of mercury there causes bile duct degeneration, necrosis, and vacuolization.

Impact of potentially toxic metals on the growth and reproduction of fish: Proper nutrition is essential for the growth, health status and reproductive performance of all aquatic animals, including fish (Rohani et al., 2022).Zn, Cu, Cr, Co, Fe, and Mn are essential for the proper nutrition of aquatic animals as they play a significant role in the growth and number of physiological and metabolic processes (Rohani et al., 2022). Accumulation of these toxic metals in fish and aquatic environments negatively affects the reproductive performance of the fish. These metals affect fertilization, hatching, and survival of larvae. The excess accumulation of these toxic metals in the fish body impacts the formation and activities of some tissues and organs, including reproductive organs.

Several scientists (Fazio et al., 2022; Paul and Small, 2021; Zheng et al., 2016; Giri et al., 2021) have reported that cadmium accumulation in water retards growth and lowers body weight, body length, survival rate, and feed intake. Chromium in lower amounts improves the metabolism and physiology of some aquatic animals, including fish (Akter et al., 2021), lowers the triglycerides, and cholesterol levels in the blood, affects glucose metabolism, and lipogenesis (Ren et al., 2018). Growth is retarded when there is an excess accumulation of chromium in the animal and water (Ko et al., 2019). Copper is an essential metal for all animals as it plays an important role in bone formation, and haemoglobin controls the myelin activity in the nervous system and impacts the enzymatic activities of the enzyme, lysyl oxidase, tyrosinase etc (Mohseni et al., 2014). Copper accumulation in fish that exceeds the permissible limit slows growth, reduces feed efficiency and increased feed conversion ratio (Zebral et al., 2018). The metal zinc is an essential micronutrient as it acts as a co-factor for a number of metalloenzymes viz., alkaline phosphatase, carbonic anhydrase, etc. These enzymes stimulate the digestion and metabolism of nutrients in the body. Zinc regulates fish nucleic acid metabolism, protein synthesis and functions of anti-oxidative enzymes, according to Ye et al. (2021). Excessive zinc accumulation causes retardation of growth and reproduction as well as oxidative stress. Zinc in the fish also causes delayed hatching, growth defects, and bone malformations (Salviggio et al., 2016). Gárriz and Miranda (2020) found during their studies on the effects of metals on sperm quality, fertilization and hatching rates, and embryo and larval survival of pejerrey fish (*Odontesthes bonariensis*) that the presence of Cd, Cr, Cu, and Zn in aquatic environments beyond their permissible limits for the protection of aquatic life reduces sperm mobility and velocity. They also found that there was a significant reduction in hatching rate and embryo and larval survival. The accumulation of arsenic in aquatic organisms, including fish, reduces egg and sperm quality and quantity, decreases fertilization rate, alters embryo viability, alters enzymatic processes and causes teratogenesis, was the findings of Ghosh et al., (2022).Gautam and Chaube (2018) found that growth, development, reproduction, and survival of the fishes as well as of all the aquatic flora and fauna are adversely affected by the accumulation of toxic metals in the aquatic environment. Cadmium metal in the fish body causes shrinkage of spermatic lobules and fibrosis in testis, abnormal oocytes structure, condensation of cytoplasm, and reduction in a GSI which results in difficulties in reproductive performance (Garriz et al., 2019; Hayati et al., 2017). Long- term chromium exposure impairs the sperm motility, causes fibrotic and pyknotic changes in testis, reduction in GSI, and reduces the number of oocytes and matured spermatozoa in fish (Ni and Shen, 2021; Chen et al., 2016). Gupta et al., (2021) have reported that accumulation of zinc in the fish body reduces the hatching rate, fertilization performance and success and GSI. Similar effects have been reported for the accumulation of copper, lead and mercury (Gariz et al., 2019; Santos et al., 2021; Luszczek et al., 2014).

Other Effects of Potentially Toxic Metals on Fish and other Seafood: Accumulation of the potentially toxic metals in fish via contaminated water also causes haematological alteration in the fish. During their studies on the different fishes under different conditions Fazio et al., (2020); Tabassum et al., (2020) found an alteration of the fish plasma glucose level and disruption in hepatic expression. An increase in the serum glucose of

Clarias gariepinus due to the accumulation of toxic metals has been reported by Zaghloul et al (2020).

The activity of the acetylcholinesterase (AChE) synaptic transmitter of nerve instinct, present in the brain, heart, liver, and muscle tissues of the fish decreases in the presence of the studied pollutants, causing pathological changes in the organs and tissues (Tabassum et al., 2020; Kumar et al., 2017; Han et al., 2016).

A survey of the literature revealed that continuous accumulation of the potentially toxic metals in fish and surroundings induces cellular oxidation in fish and alters the activities of the enzymes superoxide dismutase (SOD), catalase (CAT); glutathione peroxidase (GPx); glutathione S-transferase (GST); and malondialdehyde (MDA) resulting in the change of antioxidant activity in fish. Hossain et al. (2021) found that prolonged exposure of fish to these toxic metals alters the muscle and hepatic tissues, which increases the glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activity which sometime may also cause death. Rehman et al., (2021) discovered that toxic metals in fish *Oreochromis niloticus* significantly decrease the activity and quantity of antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD) in the tissues of the brain, liver and gills, while increase the activity and quantity of enzymes peroxidase (POD) and Glutathione-S-transferase (GST) significantly increases.An increase in the activities of the enzymes GOT and GPT was observed in *Cirrihinus mrigala* by Jasim (2017). Jasim (2017) also reported that copper metal in *Cyprinodon vaiegatus* retards the glucose level and enzyme activity; cadmium metal in fish, *Oncorhynchus mykiss* increases the T_4 level of the thyroid gland; drops electrolytic concentration in *Oncorhynchus mossambicus*; and alters the ATPase activities in *Symphysodon sp.* Chromium damages DNA in *Cyprinus carpio,* according to Ambreen and Javed (2016), and retardation of growth was reported by Shaheen and Jabeen (2015). Cadmium in fish stimulates reactive oxygen species production with a decrease in the electron transfer chain in the mitochondria (Garai et al., 2020). Yu et al. (2021) during their studies found that Zn affects the growth, body composition and activites of anti-oxidant enzymes in *Oncorhynchus mykiss*.

Abdunabi (2020) studied the impact of toxic metals on haematological parameters of the lake fish *Oreochromis niloticus* and reported that the number of red blood cells, white blood cells, neutrophils, thrombocytes, haemoglobin (Hb), haematocrit (Ht) and mean capuscular haemoglobin (MCV) levels decrease with the accumulation of these metals. They also reported that accumulation of these metals in *Oreochromis niloticus* enhances aspartate transaminase (AST), alanine transaminase (ALT) and creatinine phosphokinase levels in plasma. Similar results were reported by Hassan et al (2018) during their studies of the impact of cadmium metal on *Catla catla* fish. Shah et al (2020) reported that Chromium lowers the haemoglobin and RBCs level in *Ctenopharyn godonidella* blood. Exposure of *Oreochromis niloticus* to cadmium Ahmed et al. (2016) observed an initial increase in the activity of renal CAT followed by retardation. Cadmium accumulation in *Wallago attu* decreases protein levels (Batool et al., 2018). In their studies on the effect of cadmium attanayak and Behera (2020) found that accumulation of cadmium decreases glycogen, lipids, total proteins, and amino acid composition in the liver, kidney, gill, muscle, heart, brain, ovary, testis, and stomach tissues of the fish *Clarias batrachus*, while the level of glucose increases. The accumulation of Hg and Zn beyond their permissible limit decreases the carbohydrate content and increases the protein and lipid content in the marine fish of Tuticorin according to the findings of Roja Madhuvanthi and Sasikala (2019).

Toxicity of Potentially hazardous Metals:

Environmental pollution by potentially toxic metals is a major concern worldwide as these metals are bio-accumulated in humans via the food chain. These metals in the human body disrupt the endocrine system and negatively affect the metabolism of living cells in the body (Bansal, 2020b; Bansal, 2021; Fu and Xi, 2019). The potentially toxic metals even at very low concentrations harm the human body and affect the normal functioning of the human central nervous system (Jiang et al. 2018; Kim et al. 2015; Núñez et al. 2016). Exposure of mammals to these toxic metals adversely affects immune and Hematopoietic systems. One of the major causes of human bone diseases is the accumulation of these toxic metals in water beyond permissible limits Li et al. (2018). Some potentially toxic metals are carcinogenic. Cytotoxicity (Hernández-García et al., 2014); oxidative stress; antioxidants damage; enzyme inhibition; apoptosis (programmed cell death); loss of DNA repair mechanism; protein dysfunction and damage to lipid peroxidase and of the membrane occurs in the living cells (Fu and Xi, 2019) due to overexposure to the potentially toxic metals.

Arsenic: Arsenic is a non-essential carcinogenic metalloid. The sources of arsenic in the environment are natural as well as anthropogenic activities. Accumulation of arsenic in the human body causes cardiovascular dysfunction as it damages capillary endothelium (Balali-Mood et al., 2021), and skin and hair changes as it affects thiol bonding. Arsenic in the human body inhibits ATP formation, causing CNS injury and altering neurotransmitters which give GI discomfort. Besides lung, liver, kidney, and bladder cancer, accumulation of arsenic in the human body also causes enlargement of the kidney, nuclear, mitochondrial, and liver damage as it causes homeostasis (Livertox 2017; Bhattacharya et al., 2016), histological changes, and decreased antioxidant power of the kidney (Orr and Bridges, 2017; Shen et al. 2013). This metalloid in the human body is also responsible for cognitive dysfunction, Alzheimer's disease, cognitive impairment, deafness, hypertension, anemia dementia, neuron cell death and hematemesis (Prakash and Verma, 2021). Prolonged exposure of humans to arsenic also disturbs the normal functioning of the central nervous system.

Cadmium: The uptake of cadmium by humans which is a non-essential metal for them is via food. Cadmium in humans is an endocrine disrupter causing neurodevelopmental toxicity and affecting the immune system, kidneys, reproductive system, liver, central nervous system, and cardiovascular system. Accumulation of cadmium in humans causes degenerative bone diseases, GI disorders, a disorder in the Zn and Cu metabolism in the human body, and breast and prostate cancer (Yousif et al., 2021; Bhattacharya et al., 2016). Abdominal pain, vertigo, painful spasm, and loss of consciousness are some of the signs of cadmium toxicity in humans. Cadmium causes bogging down of the psychomotor function of the brain and replacement of vitamin C and E from the metabolically active sites of cells are among other impacts of cadmium.

Chromium: Chromium metal in trace amounts is essential for human and aquatic animals. The global production of Cr is approximately7.5 million tons. In the human body accumulation of Cr causes kidney dysfunction (due to DNA damage); GI disorders, dermal diseases (due to oxidative stress and ROS generation), lungs, larynx, bladder, kidney, bone, thyroid, and testicular cancer, and delays in healing of fractured bone are due to a reduction in the secretion of Collagen-type I). The deficiency of Cr disturbs glucose, lipid, and protein metabolism in humans (Akoto et al., 2014).

Cobalt: Cobalt an essential trace metal plays an important biological role as it is the metal constituent of vitamin B_{12}. Excessive exposure causes many adverse effects, viz., vomiting and nausea; vision problems; heart problems; thyroid damage, sterility; hair loss; bleeding; diarrhoea; coma; decreased pulmonary function; asthma; interstitial; lung disease, and nodular fibrosis. Respiratory tract hyperplasia, pulmonary fibrosis, increases in the number of red blood cells, emphysema, and paralysis of the nervous system, seizures, and growth retardation occur in human when the bio-accumulated amount of cobalt is very high.

Copper: Copper is a vital trace metal for both plants and animals, including humans as copper is involved in haemoglobin synthesis. A healthy human requires approximately 0.9 mg of copper daily for different catabolic and metabolic processes. Vomiting, nausea, abdominal pain, and/or diarrhoea occur when a high amount of copper is ingested via liquid intake. Excessive accumulation of copper in humans besides genetic diseases Wilson's and Mense diseases also cause severe mucosal irritation and corrosion, capillary damage, hematemesis, jaundice, and melena, hepatic and renal damage, and irritation of the central nervous system. The deficiency of copper causes anaemia, a low number of leucocytes, disorders in animal tissue in adults, and osteoporosis in infants.

Lead: Lead, which is a natural and industrial-produced metal, has no known benefits for humans. The annual global industrial discharge of lead in to the environment is approximately three million tons. The uptake of lead by humans is either via the digestive tract or via the respiratory tract. More than 90% of the insoluble lead is accumulated within the bones as lead phosphate, causing calcium deficiency. Accumulation of lead in humans affects the digestive system, bones, reproductive system, nervous system, urinary system, immune system, and gene expression. Hypertension, cardiovascular dysfunction, liver damage reduced pulmonary function; haematological changes have also been reported by the accumulation of lead (Orr and Bridges, 2017).The level of active vitamin D_3 and parathyroid within the plasma decreases which results in the lowering γ–carboxyglutamic acid-containing protein secretion. The secretions and activities of the enzymes delta-aminolevulinic acid dehydratase, delta-aminolevulinic acid synthase, and ferrochelatase crucial for human body functioning (helps in biosynthesis of haemoglobin, cytochromes, and myoglobin) are retarded even at the level 5ug/dL of blood lead. The impact of lead accumulation is greater in children than in adults.Lead inducesneurological, musculoskeletal, and renal disorders, nephrotoxicity, and cognitive impairment are caused by the excessive accumulation of the lead (Tamele and Loureiro, 2020).

Mercury: Mercury is not only a non-essential metal but also the most toxic metal present in the aquatic environment. The kidney and brain are two organs which are most affected by the accumulation of Hg. Because Hg disrupts the endocrine gland function the foetal development and maternal-foetal balance are disrupted. Death of neuronal cells, cognitive dysfunction, Alzheimer's disease, gastrointestinal upset, joint and muscle pain, fatigue, heart rate disturbance, hair thinning, memory loss, skin, and nose irritation, hearing loss and visual disorders also occur due to accumulation of mercury, due to formation of reactive oxygen.Some other adverse effects of Hg on humans are Minamata disease, renal dysfunction, hepatotoxicity, and damage to the central nervous system (Zhang et al., 2020; Chen et al., 2019).

Nickel: Nickel, an essential trace metal found in the environment, water, soil, and air, is derived from natural sources as well as from the steel and other metal products industry, pigments industry, valves industry, batteries industry, liquid and solid fuels, municipal and domestic sewage water, and chocolate industry. Vegetables such as legumes, spinach, lettuce, and nuts are the natural sources of nickel.Allergies, cardiovascular and kidney diseases, lung fibrosis, asthma, pneumonia, and skin rashes are caused by the accumulation of nickel metal. Excessive accumulation enhances the chances of miscarriage, lung and nasal cancer, and prostatic adenocarcinoma. Excessive accumulation of nickel in humans induces the loss of calcium and zinc ions, urinary phosphate, urinary glucose output and nitrogen, whilein women, urinary protein, β2-microglobulin, and retinal binding protein N-acetyl-β-D-glucosaminidase levels are enhanced. Nickel in the human body causes mitochondrial dysfunction and oxidative stress.

Zinc: All plants and animals, including humans, require zinc in a small amount for different activities in the body. Zinc can bind more than 300 enzymes and acts as a cofactor in a number of metalloenzymes such as dehydrogenase, alkaline phosphatase, carbonic anhydrase, leucine amino peptidase, and superoxide dismutase. Zinc plays an important role in the synthesis of protein and collagen (which helps in wound healing and healthy skin). Cellular functions, such as DNA replication, DNA damage repair, cell cycle progression, and apoptosis, occur with the help of Zn. Prolonged exposure to zinc causes low levels of high-density lipoprotein (HDL), decreased immune function, copper deficiency (decrease in the activity of copper metalloenzyme), nausea, vomiting, stomach aches, diarrhoea, headaches, and gastrointestinal disorders. The deficiency of zinc, which is reported in about 17% of the global population, causes humoral and cell-mediated immunity dysfunction, cardiovascular disease, and poor pregnancy (Chasapis et al., 2020)

Conclusions

- Globally, most of the bodies of water (rivers, lakes, groundwater, and ponds) and seas are contaminated with potentially toxic metals. Due to rapid urbanization and industrialization in developing countries, this problem has become more severe. The toxic metals enter the bodies of water via leaching from industrial waste dumps, municipal landfills, municipal and sewage wastewater, leaching from soils, and agricultural run-off.
- Some toxic metals are essential for different biological processes in the body. Excess or deficiency disturbs the metabolic pathways, causing serious illness.
- Consumption of fish and other seafood which is considered globally a well-balanced diet for humans as it contains a sufficient amount of vitamins and minerals besides proteins is increasing. Due to population growth, the demand for fish and other seafood is continuously increasing. The global average per

capita consumption of fish in 2020 was 21.4 kg, with a maximum consumption of 200 kg per capita.

- As fish and other seafood provide more and better protein than agricultural products or animal husbandry products, fish provides approximately 20% of animal protein to 33 billion people across the world.
- Accumulation of these toxic metals in the aquatic environment causes histopathological, alterations like the epithelial lifting of the lamellae, lamellar disorganization, blood congestion, gill epithelium hyperplasia, dilation of sinusoids, contraction of tubular epithelial cells with dilation; an alteration of the fish plasma glucose level and disruption inhepatic expression. Haematological alterations are an increase in the serum glucose, a decrease in the number of red blood cells, white blood cells, neutrophils, thrombocytes, haemoglobin (Hb), haematocrit (Ht), and mean capsular haemoglobin (MCV) in fish different organs. These impacts result in the retardation of the food value of the fish/seafood. The bioaccumulation of these metals in aquatic fauna disturbs the growth and reproduction of these aquatic animals.

These pollutants pose a substantial threat to consumers, including humans. When these pollutants are bio-accumulated in the human body via the food chain, they cause several adverse effects. Most of these toxic metals are endocrine disruptors, acetyl cholinesterase enzyme activity inhibitors, causing cardiovascular diseases, reproductive problems; behavioural changes; neurological and immunodeficiency disorder, nasopharyngeal congestion etc. Metals like As, Cd and Hg are carcinogenic and may expedite breast, prostate, and lung cancer. Developmental abnormalities occur in children due to these metals.

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