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Toxicological effect of arsenic on organs of fishes: A review

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Abstract
Arsenic (As) is a hazardous contaminant in the aquatic world, existing in inorganic and organic forms. Of inorganic forms arsenic exists as arsenite and arsenate in aquatic bodies like oceans, sea, rivers, lakes, ponds, and groundwater. In oxygenated water, trivalent arsenite is easily oxidized to arsenate. Arsenic being, most common heavy metal pollutant in fresh water, comes from mining, smelting, chemical manufacturing, and other anthropogenic sources. Due to release of acid mine drainage in the aquatic bodies, the pH falls and increasing metal solubility causes devastating effects to the aquatic organism. Arsenic gets locked up in the bottom sediments for many years causing damage to aquatic life and fishes. Generally ionic forms of a heavy metals are more toxic because it can form toxic compounds with other ions. Electron transfer reactions connected oxygen can form toxic oxyradicals. Some anions such as oxyradicals (O_2-) and the hydroxyradicals (OH-) can cause serious cellular anionic damage. Ionic forms of arsenic are readily available to fish, resulting in considerable amount of metal accumulation in fish tissue, those living in polluted water. Relationship between the metal accumulation in fish organs and in water has been studied in field and laboratory both. The present paper reviews, the toxicological effects, and histopathological alterations due to arsenic on the important organs of fishes, like liver, kidney, gills, skin, muscles, bones, heart, and brain.

Keywords: arsenic, toxicity, fish, and organs

Introduction
Arsenic occurs in the environment in inorganic and organic forms, both in trivalent and pentavalent state. Toxicity of trivalent arsenic compounds is more than pentavalent forms because trivalent are more soluble in aquatic environment. According to the data inorganic forms (arsenite and arsenate) shows highest toxicity level compared to the organo-arsenicals (Duker *et al.*, 2005) [25]. Arsenic is released into the aquatic environment through anthropogenic activities such as metal smelting, chemical manufacturing, and agriculture (Singh and Banerjee, 2008) [75]. Although it is toxic trace element but release of large amount as result of industrial and agricultural activities (Canivet *et al.*, 2001) [15] of it becomes threat to ecosystem. In aquatic environment (oxygenated water), trivalent arsenite is oxidized to arsenate and get 'locked up' in the sediments, existing for longer period causing damage to the aquatic life. Groundwater with high concentration of arsenic is reported in many countries like China, India, Bangladesh, Nepal, Vietnam, Japan, and other south Asian countries along some parts of United states (Yoshida *et al.*, 2004; Anwar *et al.*, 2002; Chowdhury *et al.*, 2000) [86, 7, 19].
Heavy metal contamination has devastating effects on the ecological balance of recipient environment and diversity of aquatic organisms (Farombi *et al.*, 2007) [30]. Among animal species, fishes are the inhabitants that cannot escape from the detrimental effects of these pollutants (Olaifa *et al.*, 2004: Kovendan *et al.*, 2013) [63, 47]. Environmental toxins can induce physiological, and biochemical changes in fish that lead to inhibition of growth and death in case of acute poisoning (Beyers *et al.*, 1999; Farkas *et al.*, 2002) [13, 29]. Arsenic enters inside the fish body by its absorption through skin, gastrointestinal tract, gills, and arsenic contaminated food. In gills, it enters the blood through extensive gill surface where the barrier between the blood and metal is very thin (Kumar and Banerjee, 2012b) [49, 50]. Arsenic exposure in the aquatic environment causes bioaccumulation in aquatic organisms which in long run causes deleterious effects on skin, gastrointestinal tract, circulatory system, liver, gill, kidney, muscles and to some extent heart and brain. They change the hematological, biochemical, and ionoregulatory parameters adversely (Lavanya *et al.*, 2011) [54]. Arsenic bioaccumulation led to biochemical disorders such as poisoning, liver lesions, decreased

fertility, cell damage and cell death (Bears *et al.*, 2006; Ribeiro *et al*., 2005) [11, 69]. Min *et al.*, (2014) [58] reported that toxicity level of arsenic also depends on physiochemical factors such as pH, temperature, salinity, turbidity, and water hardness of aquatic body. Toxic effects of arsenic at higher temperature increases both on growth and blood parameters (Han *et al.*, 2019) [36].

Used as surveillant for biomonitoring of pollution in aquatic medium, fish are ideal organism to study the toxicogenomic of toxicants as they are established biomarkers of exposure (Das *et.al*., 2012) [21]. When exposed to toxic substances, hematological levels increase or decrease beyond the normal range acts marker of physiological changes and fish health (Alwan *et al.*, 2009) [6]. Arsenic is one of WHO's 10 chemicals of major public health concern. The current recommendation of arsenic in drinking water is 10µg/ L(ppb). Fish contains various contaminates because of their environment. The arsenic is persistent in fish, although they have different mechanism to bio-transform it to fewer toxic forms for excretion (Bears *et.al*., 2006) [11]. Fish being top consumer in the aquatic food chain accumulate large amount of arsenic which are stored in bones, liver, kidney, gills, fat etc. (Dural, 2007) [26]. Arsenic accumulation variability is observed in fish species. Contaminated fish consumption led to variety of complications in body organ system along epigenetic changes (in utero) and genetic mutations leading to cancer (Abdul *et al.*, 2015) [2]. This review deals with arsenic chemistry, its environmental occurrence, its bioaccumulation, and effects on different organs of fish.

Chemical Forms of Arsenic

Arsenic with atomic number-33 and relative atomic mass 74.92, has chemical properties intermediate between a metal and a non-metal, and often referred to as a metalloid or semi-metals. Arsenic has a complex chemical structure and exists in four oxidation states of -3, 0, +3 and +5 (WHO, 2001; IARC, 2004) [84, 41]. It is widely distributed throughout Earth's crust, most often as arsenic sulfide, or as metal arsenate and arsenites. In water, it is most likely to be present as arsenate, with the oxidation state of 5, if the water is oxygenated. However, in reducing conditions (<200mV), it is more likely to be present as arsenite, with an oxidation state of 3 (IPCS, 2001) [43]. From biological and toxicological perspective, there are three major groups of arsenic compounds, inorganic arsenic compounds, organic arsenic compounds and arsine gas. Inorganic arsenic compounds are arsenic trioxide, sodium arsenite and arsenic trichloride as commonest trivalent compounds and arsenic pentoxide, arsenic acid, and arsenates (lead arsenate and calcium arsenate) are commonest pentavalent compounds. Common organic arsenic compounds include arsanilic acid, methyl arsenic acid, dimethyl arsenic acid (Cacodylic acid) and arsenobetaine (WHO, 2000) [83]. The compounds of arsenic and their physiochemical properties are given in the table no.1 below.

Table 1: Physiochemical properties of arsenic and its compounds (IARC,1980) [40]

Compound	Molecular formula	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Water solubility (g/l)
Arsenic	As	613	-	5.727 at 14 °C	insoluble
Arsenic trioxide	As_2O_3	312.3	465	3.738	37 at 20 °C
Arsenic pentoxide	As_2O_5	315 (decompose)	-	4.32	1500 at 16 °C
Arsenic sulfide	As_2S_3	300	707	3.43	$5x10^{-4}$ at 18 °C
Dimethylarsinic acid (DMA)	$(CH_3)_2AsO(OH)$	200	-	-	829 at 22 °C
Monomethylasrsonic acid (MMA)	$(CH_3)AsO(OH)_2$	-	-	-	-
Lead arsenate	$PbHAsO_4$	720 (decompose)	-	5.79	Very slightly soluble
Potassium arsenate	KH_2AsO_4	288	-	2.867	190 at 6 °C
Potassium arsenite	$KAsO_2HAsO_2$	-	-	-	soluble
Sodium dimethyl arsenate	$(CH_3)_2NaHAsO_2$	-	-	-	Readily soluble
Sodium methane arsonate (MSMA)	$CH_3NaHAsO$	-	-	-	soluble

Sources of Arsenic

Arsenic is the 20th most common element in the earth's crust, and it is emitted in the environment as result of volcanic activity and industrial activities. Mining, smelting, of non-ferrous metals and burning of fossil fuels are major anthropogenic sources arsenic contamination of air, water, and soil (WHO, 2000, 2001) [83, 84]. It also occurs in sulfide form in complex minerals containing silver, lead, copper, nickel, antimony, cobalt, and iron commonest is arsenopyrite. Terrestrial arsenic abundance is 5mg/kg, concentration is high (2900mg/kg) in sulfide, phosphate, iron, and manganese depots (WHO, 2001) [84].

Arsenic and arsenic compounds are produced and used commercially for centuries. Arsenic was used in some medicinal applications until 1970s. Inorganic arsenic was used in the treatment of leukemia, psoriasis, and chronic bronchial asthma, and organic arsenic was used in antibiotics for the treatment of spirochetal and protozoal disease (ATSDR, 2007) [8]. Inorganic arsenic is an active component of antifungal wood preservatives. In agricultural industry it is used in pesticides, herbicides. Insecticides, cotton desiccants, defoliates and soil sterilant. In 2009 US Environmental Protection Agency issued cancellation orders for use of organic arsenical pesticides with exception of monosodium methanearsonate (MSMA). Many organic arsenicals (roxarsone, arsanilic acid and derivatives) are used as feed additives for poultry and swine to increase weight gain and disease treatment (EPA, 2006; FDA, 2008a, b) [27, 31, 32]. Elemental arsenics are used in manufacture of alloys, gallium arsenide and arsine are used in semiconductors, electronic industries, crystals for computer chip and fiber optics (IARC, 2006) [42].

Arsenic Exposure Levels in Aquatic System

Arsenic, from both natural and anthropogenic sources, is mainly transported in the environment through water. Naturally it is introduced through the dissolution of rocks, minerals, and ores, and anthropogenically by agriculture, forestry, industrial effluents, including mining wastes, and via atmospheric deposition (Smith *et al.*,2003) [78]. The form and concentration of arsenic depends on several factors. In well oxygenated surface water, arsenic(V) is generally the most

common species present; under reducing conditions, such as those often found in deep lake sediments or ground water, the predominant form is arsenic (III) (Hughes *et al.*, 2011) [39]. An increase in pH may increase the concentration of dissolved arsenic in water. In water generally arsenite (As^{III}), arsenate (As^{V}), monomethylarsonic acid and dimethylarsinic acid are present. Water with high degree of biological activity is associated with the conversion of inorganic arsenic to methylated arsenic acids, a less toxic form.

The concentration of arsenic in surface freshwater sources, like rivers and lakes, is typically less than 10µg/l (range of 0.15- 0.45 µg/l) (Bissen & Frimmel, 2003) [14]. Although, in areas containing natural sources it can be as high as 12mg/l and near anthropogenic sources, such as mining and agrochemical manufacture and in geothermal waters ranges from 500µg/l - 25mg/l. Concentrations of arsenic in open seawater generally ranges between 1-2µg/l (Ng, *et.al.*,2005) [62], although groundwater concentration can be up to 3mg/l in the areas with volcanic rock and sulfide mineral deposits (WHO, 2001) [84].

Exposure to high levels of arsenic in drinking-water has been recognized for many decades in some regions of the world, notably in China and some countries of Central and South America. More recently, several other regions have reported to have highly arsenic contaminated drinking ground water resources due to geological formations. High concentration of arsenic in water is reported in Bangladesh, West Bengal in India and smaller areas in Australia, Chile, Mexico, Taiwan, Vietnam. In USA and Japan (35- 25.7 mg/l of dissolved arsenic in hydrothermal area) due to geological formation and industrial activity shows high range of arsenic contamination in drinking water (IARC, 2004) [41].

Arsenic Species in The Aquatic System

Arsenic exists in variety of chemical forms in aquatic system. As^{V} is the major and thermodynamically stable form in oxic conditions and is observed mostly in marine waters while the unstable As^{III} is transformed by marine phytoplankton and bacteria. Rahman and Hassler (2014) [68] reported photosynthetic microorganisms (e.g., phytoplankton and cynobacteria) take up $As^{V,}$ biotransforms it to As^{III}, then biomethylate it to methylarsenic (Met As) forms. Although As^{III} species is more toxic than As^{V}, As^{III} is much more easily excreted from the cells then As^{V}. The biomethylation process results in the conversion of toxic inorganic arsenic to less toxic pentavalent MetAs forms (mnomethylarsonate; MMA^{v}, dimethylarsonate; DMA^{v}, trimethylarsonic oxide; $TMAO^{v}$) and trimethyl arsine (DMA^{III}). However, biomethylation also produces monomethyl arsenite (MMA^{III}) and dimethylarsenite (DMA^{III}), which is more toxic than inorganic arsenic. In general about 85 to > 90% of arsenic found in edible portions of marine fish are AsB (arsenobetaine), arsenocholic (AsC), and DMAA and approximately 10% are iAs (inorganic arsenic) species. However, less is known about the forms of arsenic in freshwater fish, but available evidence suggests that AsB and DMAA are the main species in freshwater fish (Slejkovec *et al.*, 2004) [77].

Bioaccumulation and Biomagnification of Arsenic in Fishes

Site of absorption of dissolved arsenic and other dissolved contaminants are skin (dermal exposure or transcutaneous uptake), gills (respiratory system), ingestive intake (gastrointestinal tract). Bioaccumulation of arsenic in fish body occurs due to its uptake from the surrounding water, diet, and other sources.

Behavioral Effect of Arsenic Toxicity

Fish are key constituents of aquatic ecosystem. Contamination in natural systems is often too low to cause mortality but sufficient to interfere with normal functioning. Behavioral perspective links the physiology and ecology of an organism with environment it is living (Little and Brewer, 2001). Alteration of complex, naturally occurring fish behaviors such as foraging, and aggression are ecologically relevant indictors of toxicity and ideal for assessing sublethal impacts. Magellan *et al.*, (2014) [57] reported that mosquito fish (*Gambusia holbrooki*) when exposed to arsenic in lab condition showed significant increase in aggression, slight decrease of operculum movement but food capture efficiency and consumption was unaffected. He also reported increase in bioaccumulation of arsenic and weight gain possibly because increase in aggression facilitated the food resource defense, a reason for weight gain. Acute sodium arsenate exposure causes abnormal behaviors in fish like erratic movement, rapid movement of the opercula, jumping out of the test media, lateral swimming, loss of equilibrium and excessive mucus secretion (Baldissarelli *et al.*, 2012) [9]. Fish exposed to the 2.250 mg/l concentration of sodium arsenate, gives visible reactions within few minutes, but concentration below 0.08 mg/l, behavioral changes are insignificant. Neurotoxic effects and irritation of sensory system led to abnormal behavior while back and forth jumping indicates avoidance reaction. Sinha and Kumar (1992) [76] loss of equilibrium and lateral swimming may be due to impairment of nervous system.

Mechanism of Action of Arsenic Toxicity

The mechanism of arsenic toxicity is related to its effects on enzyme systems within the cell, primarily by binding to sulfhydryl groups on enzymes and other cellular proteins. The accumulation of arsenic in mitochondria results in the inhibition of pyruvate oxidase and phosphatases, interference with NAD-linked substrates within mitochondria, inhibition of succinate dehydrogenase activity, and uncoupling of oxidative phosphorylation by replacing phosphate in high-energy phosphorylated substrate (arsenolysis). The consequences of these effects are functional and morphological cellular abnormalities secondary to the impairment of cellular respiration and depletion of energy stores. Tissues affected most severely by arsenic toxicity are those rich in oxidative enzymes i.e., alimentary tract, liver kidney, gills, endothelium, and epidermis (Hughes, 2002) [38]. At biochemical level, inorganic arsenic in pentavalent state may replace phosphate in several reactions and in trivalent state inorganic and organic (methylated) arsenic may react with critical thiols in proteins and inhibit their activity. In cancer condition it include genotoxicity, altered DNA methylation, oxidative stress, altered cell proliferation, carcinogenesis and tumor promotion (Hughes, 2002) [38].

Effect of Arsenic on Fish Major Organs and Organ System

Arsenic produce toxicity in fish organs. In case of acute toxicity of fish there is difference in the 96-h LC_{50} values among fish species. There are many other factors which influence the 96-h $LC_{50\ like}$ arsenic species, fish species, temperature, and experimental conditions. Acute toxicity effects liver, gill, brain, kidney, blood glucose as stress

biomarkers (catalase, superoxide dismutase, glutathione-s-transferase) were reported to be increased in *Pangasianodon hypophthalamus* (Kumar *et al.,* 2019) [48]. Marker enymes of brain (neurotransmitter enzyme; AchE), immunological status, cellular metabolic enzymes were significantly altered by arsenic (Kumar *et al.,* 2019) [48]. Acute and sub-acute toxicity of arsenic effects respiratory, gastrointestinal, cardiovascular, nervous, and hemopoietic systems on long term exposure.

Skin

Skin is the outermost protection barrier in organism's body. Skin and gill tissue of fish is unkeratinized and have mucous coating due to presence of club and mucous cells in tissue. Due to continuous hydration, it is vulnerable to different water dissolved toxicant. Singh and Banerjee (2008) [75], reported that in *Clarias batrachus* (L.) (1 mg/l of sodium arsenate) skin faces direct contact stress of the toxicants and exhibit extensive damage, including massive wear and tear, sloughing of epithelial cells (ECs), with degeneration of club cells (CCs) whose contents squeezed out onto the body surface. This causes altered histomorphology of epidermis. The mucous cells show great hyperplasia and hypertrophy at most exposure periods and show periodic alteration. Skin and gills of fish, get covered with very thick layer of slime for protective measure (Kumar & Banerjee, 2012b; Chandra and Banerjee, 2003) [49, 50, 18]. The epidermis also exhibits periodic and independent fluctuations in its protein, RNA and DNA contents. Damage in the epidermis become more pronounced with increasing exposure period and certain places, most of the cells in the lower layer of the epidermis, lost their integration and cell boundaries with neighboring cells (Singh and Banerjee, 2008) [49, 50]. Lipid and glycogen contents of skin progressively decreases (Kumar and Banerjee, 2012b) [49, 50]. Hypopigmentation and hyperpigmentation are reported in *Heteropneustis fossilis* L. on arsenic exposure (Kumari *et al.*, 2013) [52].

Gills

Gills are the respiratory organs in fishes, which are continuously exposed to water. They are first organ after skin, affected by contamination of pollutants and chemicals. Arsenic affects antioxidant response in gills even at safer concentrations (Lima *et al.,* 2009) [55]. Exposure to 12.0 mg/l of arsenic trioxide, gills of *Channa punctatus* showed degenerative changes in cartilaginous bars of gills, increase in mucous secretion between the space of primary gill lamella, degeneration of basal lamellar region, vacuolization at tip of primary gill ray and destruction of epithelial cells of secondary gill lamella (Agnihotri *et al.,* 2010) [4]. Tilapia (*Oreochromis mossambicus)* when exposed to different concentration of arsenic then changes in gill were characterized by epithelial hyperplasia, epithelial lifting and oedema, lamellar fusion, aneurism, desquamation, and necrosis (Das and Goswami, 2018) [22]. Fish exposed to arsenic exhibited stress in breathing due to clogging of gills by coagulated mucous and suffered direct damage of arsenic ions to blood vessels, resulting in vascular collapse in gills and anoxia (Mondal & Samanta, 2015) [59]. Decrease in glycogen, protein, and triglyceride is reported when Mystus *vittatus* exposed to arsenic trioxide (Prakash and Verma, 2020) [67].

Gastrointestinal tract

Intestinal barrier function regulates (micro-) nutrient absorption and host defense mechanism at the mucosal interface with the external environment. Different fish species (*C. clupeaformis, S. vitreum, Esox lucius, C. commersoni, Catostomus catostomus*) in arsenic polluted water have very high concentration of arsenic in intestine, liver, and muscles (Zang *et al.,* 2011) [87]. *Channa punctatus* when exposed to sodium arsenite at the concentration of 100µl- 200µl/30 kg bodyweight, showed degenerative and necrotic changes in the intestinal mucosa and submucosa, atrophy in the muscularis and submucosa and aggregations of inflammatory cells in the mucosa and submucosa with edema between them with increase in the duration of exposure cytoplasm demonstrated vacuolization, peliosis, coagulation, apoptotic, aggregation of tissue, necrotic cells in greater number (Hossain, 2012) [37]. Arsenic causes considerable changes in the digestive enzyme of *Anabas testudineus*. Digestive enzyme activity increased considerably, differently in stomach and intestine (Kole *et al.*, 2017) [45]. Gallbladder in white fish fed with arsenic showed lesions affecting liver function (Pedlar *et al.,* 2002) [65]. Das and Goswami (2020) [23], reported in *Channa punctatus* intestine of arsenic treated group revealed severe degenerative changes in the intestinal mucosa, elongated lumen in villi, fusion of villi and atrophy in muscularis. The cytoplasm demonstrated vacuolization, apoptotic, and necrotic cells in the fish intestine exposed to arsenic.

Liver

Liver plays a great role in metabolic regulation by detoxifying metabolites, synthesizing proteins, and helping in digestion. Liver is a major target organ of arsenic toxicity and fish liver plays major role in uptake, accumulation, biotransformation, and excretion of arsenic (Pedlar and Klaverkamp, 2002) [65]. Arsenic is actively metabolized in the tissue of fishes especially in liver and intestine and have tendency to accumulate in fishes e.g., green sun fish (Sorensen *et al.*, 1983) [79] and *Tilapia mossambica* (Suhendrayatna *et al.*, 2002) [80]. Its accumulation and detoxification cause alteration in liver such as irregular-shaped nuclei, nuclear hypertrophy, nuclear vacuolation and the presence of eosinophilic granules in the cytoplasm hepatocytes. Bile stagnation was identified as brownish-yellow granules in cytoplasm. Melan-macrophages were identified as rounded aggregates of cells with dark yellowish granules. Increase in arsenic dose, increases the severity and cellular rupture, pyknotic nucleus, and bile stagnation (Hossain, 2012) [37]. Tilapia (*Oreochromis mossambicus)* liver, when exposed to different concentration of arsenic showed, focal lymphocytic and macrophage infiltration, congestion, vacuolization and shrinkage of hepatocytes, dilation of sinusoids, cloudy swelling, vacuolar degeneration, focal necrosis, and nuclear hypertrophy. Sodium arsenite causes liver chromosomal fragmentation and expression of certain proteins (Das *et al.,* 2012) [21]. Kumar and Banerjee (2012b) [49, 50] reported decrease in liver protein and glycogen but increase in lipid content of arsenic exposed *Clarius batracus*. Gender-specific responses in liver proteome of zebra fish was reported in low-dose (50µl/l) exposure of sodium arsenite (Carlson *et al.*, 2013) [16]. Severe degenerative responses in *Channa punctatus* hepatopancreas was observed on non-lethal exposure to arsenic (Roy and Bhattacharya, 2006) [71]. Hepatic lesions in the form of cloudy swelling of hepatocytes, congestion, vacuolar degeneration, karyolysis, dilation of sinusoids and nuclear hypertrophy were observed in the liver tissue of *Channa punctatus* and *Clarias batrachus* (Das and Goswami, 2018; 2020) [22, 23].

Kidney

Kidney along gills is one of the main routes of excretion of waste in fish body. Histopathological changes appears when fish is exposed to arsenic contaminate. Kidney enzyme species glutathione reduces on arsenic treatment (Allen *et al.*, 2004) [5]. *Channa punctatus* (Bloch) exposed to non-lethal concentrations (3.8mg/l and 7.6 mg/l) of arsenic causes shrinkage of the glomerulus and increase in the Bowman's space consequently increase in urine amount. Irregularities in the renal tubule including apoptotic and necrotic cells. Decreased intratubular space and enlargement of the height of the brush border cells (Roy and Bhattacharya, 2006) [71]. Chronic exposure of *Clarias batrachus* to arsenic causes its accumulation in head kidney resulting in reduction of head kidney macrophage number and head kidney somatic index, increased hemosiderin accumulation. Head kidney macrophage revealed prominent endoplasmic reticulum, chromatin condensation and loss in structural integrity of nuclear membrane. A significant level of superoxide anions and suppressed the production of pro-inflammatory 'IL-1 beta like 'factors acting as immunotoxic to fish and interference in humoral response was observed (Ghosh *et al.*, 2007; Dutta *et al.*, 2009) [34, 24]. Glomerulus shrinkage, congestion of vessels and raptured bowman's capsule was reported in *Clarias batrachus*. *Channa punctatus* exposed to sub-lethal concentrations of sodium arsenite brought ultrastructural changes in renal tissues. Hypertrophy of the epithelial cells of renal tubules along with reduction in the size of the tubular lumens was seen in the kidney tissue of the fishes with acute exposure. Hypertrophied nuclei, dilation, oedema was seen in the renal tubules. Vacuolization due to integration of cytoplasm was quite evident (Das and Goswami, 2020) [23].

Muscles

Muscles aids in locomotion of fish and made up of protein. Arsenic accumulation in fish is comparatively less than other vital and soft tissues in fish body. Few researches reported a positive correlation between arsenic concentration and its accumulation in muscles (Nevàrez *et al.*, 2011) [61]. Arsenic accumulates in fish muscles when exposed to heavy metal contaminated water, but its concentration varies with fish inhabiting different strata. Fish from bottom strata have higher arsenic concentration in muscles than upper and middle strata and its accumulation increases with age (Zhang *et al.*, 2007; Cossa *et al.*, 1992) [87, 20]. *Clarias batrachus* exposed to arsenic shows decreased protein content in the muscles. The DNA content significantly decreased. RNA and lipid content showed fluctuations due to toxicity, they first increased but decreased later period of exposure. The glycogen content of the muscles decreased significantly during the entire period of exposure (Kumar and Banerjee 2012b; Pazhanisamy and Indra, 2007; B. Kumari, 2011b) [49, 50, 64, 51]. Heavy metal exposure showed prominent changes like shortening of muscle bundles, edema, and necrosis in *Labeo rohita*. Destruction and vacuolization in muscle cell in fish was observed on exposure to heavy metal contaminated water (Abbas and Ali, 2007; Kaur *et al.*, 2018) [1, 44]. Arsenic exposure during embryogenesis can initiate to molecular changes that appears to lead to aberrant muscle formation (Gaworecki *et al.*, 2012) [33]. *Heteropneustus fossilis* when exposed to 7 and 20 mg/l of arsenic, degeneration in the muscle bundles accompanied with focal areas of necrosis as well as atrophy and vacuolar degeneration resulted (Begum *et al.*, 2013) [12].

Heart

Heart is a vital organ of body and a part of circulatory system, pumping blood in the body distributing important components and collecting waste for excretion to outside of body. Arsenic affects fish liver, heart and intestine bringing many histological changes in exposed fish (Sorenson, 1991). The most common lesions were ventricular, in which both the spongy and compact layers were infiltrated by mononuclear cells, comprising macrophages, lymphocyte- and plasma like cells. The inflammatory cells were localized within and around myocytes in diffuse or focal pattern which is most evident in the compact layer. Hearts were focally hypercellular and high dose of arsenic cellular infiltration was diffuse and extensive, and large number of necrotic myocytes were observed (NRCC, 1978; Hossain, 2012) [60, 37]. Arsenic treated zebra fish showed increased resting heart rate during larval developmental stage (Hallauer *et al.*, 2016) [35].

Brain

Arsenic exposure effects fish brain. It has capacity to cross blood brain barrier and accumulate in the brain causing degenerative changes (Rodriguez *et al.*, 2002) [70]. Arsenic induced protein depletion has also been observed in the brain of rat (Sameul *et al.*, 2005) [72]. Thirumavalavan & Samipillai (2010) [81] also noticed decreased amount of proteins in the brain of *Catla catla* exposed to 0.1 ppm of arsenic trioxide. the nucleic acid content (DNA and RNA) of the brain and liver decreased throughout the period of exposure indicating malfunction and degenerative changes of these vital organs. Due to high oxygen consumption rate and high level of polyunsaturated fatty acids and relatively high rate of oxygen free radical generation without commensurable level of arsenic (B. Kumari *et al.*, 2017) [53]. Lipid and glycogen content of brain decreased due prolonged arsenic exposure (Kumar and Banerjee, 2012; Thirumavalavan & Samipillai, 2010) [49, 50]. Glycogen decrease might be associated to meet energy requirement under arsenic stress. The reduction in protein content may be due to the higher affinity of metal compound towards different amino acids residues of protein (Kumar and Banerjee, 2012b) [49, 50]. Arsenic toxicity brings alteration in behavioral parameters and brain endonucleotidase activity (Baldissarelli *et al.*, 2012) [9]. Zebra fish treated with chronic arsenic demonstrate dysfunction in their neurological disorder, which is reflected by reduction in locomotive activity (Hallauer *et al.*, 2016) [35].

Gonads

Colisa fasiatus (Bl. and Sch.) were exposed for 15 and 30 days with Arsenic (III) oxide (2.0mg/l, 14.0mg/l). After 15 days no marked histological alteration in ovary was observed during its mature phase, whereas after 30 days exposure decreased development of oocyte (II and III stage), reduced the number and diameter of nucleoli and increased number of atretic follicles (Shukla and Pandey, 1984) [74]. Yamaguchi et.al. (2007) [85] reported a negative correlation between gonad development and accumulation of arsenic in catfish *Pangasianodon hypophthalamus*. Study on Japanese eel (*Anguilla japonica)* suggest that arsenic may inhibit spermatogenesis via steroidogenesis suppression while high dose induce oxidative stress-mediated germ cell apoptosis (Celino *et al.*, 2009) [17]. He reported arsenic treatment provoked a dose-dependent inhibition of hCG-induced germ cell proliferation as revealed by 5-bromo-2-deoxyuridine immunochemistry. The hCG-induced synthesis of

progesterone from pregnenolone was significantly inhibited by low doses of arsenic (0.1-1microM), implying an inhibition of 3beta-hydroxysteroid dehydrogenase activity. Heavy metal toxicity reduces the number of mature oocytes with larger follicular spaces (Barraich & Jangu, 2015) [10]. Effect of arsenic on fish reproduction are not well clarified and need more research.

Blood

Oreochromis mykiss exposed to arsenic concentrations showed fall in no of lymphocytes due to decrease in non-specific immunity of fish. Leucocytes are involved in the regulation of immunological function in many organisms and increase in the white blood cells in stressed animals indicates a protective response to stress (Kotsanis *et al.,* 2000) [46]. The decrease in white blood cells count during acute and sub-lethal treatment, may be due to the toxic effect in head kidney of fish being primary site of hematopoiesis. Blood parameters (hematocrit, hemoglobin concentration, red blood count, mean cell volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) were not affected when, adult lake white fish exposed to 0,1,10, and 100 microgram of arsenic/ g food (Pedlar *et al.,* 2002) [65]. Low levels of arsenic toxicity fishes cause reduction in red and white blood cells (Abernathy *et al.,* 2003) [3]. Tripathi *et al.,* (2003) [82] reported decreased level of hemoglobin and packed cell volume in *Clarias batrachus* exposed to arsenic. *Cyprinus carpio* when exposed to arsenic showed decrease in granulocytes, erythrocyte, hemoglobin, hematocrit values (Selamoglu Talas *et.al.,* 2012) [73]

Conclusion

Contamination of water bodies by arsenic and its compound, is big threat to all the aquatic organism specially fishes. They enter inside the body via skin, gills, and gastrointestinal tract and gest accumulated in vital organs once carried by the blood. Aquatic organisms accumulate arsenic mainly as inorganic forms but few organisms like bacteria, phytoplankton etc. transform inorganic arsenic species into organic forms like $MMAA^{V}$, $DMAA^{V}$, and other organic spp. These arsenic compounds undergo bioaccumulate and biomagnification via food chains and concentrate at higher tropic level of aquatic body i.e., fish and humans on consumption. Once entered inside the body via food and drinking water, they produce many deleterious effects on organism such as enzymatic, genetic, reproductive, and immune system failure, hampering the normal body functions. These arsenic contaminated fishes when consumed by humans produce diseased condition, altering human health. Government of different countries should monitor anthropogenic sources which are contaminating aquatic body and increase public awareness.

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