1. INTRODUCTION

Environmental problems have increased exponentially in recent decades mainly because of rapid growth in human population and increased demand for several household materials [1]. Water is essential constituent of life support system and its quality play pivotal role in the maintenance of health [2]. Industrial effluents including toxic metal compounds are major source of water pollution besides sewage, agricultural discharges and other household residues [3],[4]. Heavy metals are important environmental pollutants and their toxicity is a problem of increasing significance for ecological, evolutionary, nutritional and environmental reasons [5]. Threatening effect of metals is a serious problem which is increasing at an alarming rate all over the world [6]. Heavy metal poisoning is believed to interfere with metabolic pathways in vital organs through different mechanisms in living organisms. It is believed that metals may exert their effects directly by interfering with endocrine system and/or they may alter many metabolic body processes. However, the study related to the understanding the mechanism of action of toxic metals on vital organs is still at its infancy.

The contamination of fresh waters with a wide range of pollutants has become a matter of concern over the few decades [7]. Natural aquatic resources are extensively contaminated with heavy metals like lead (Pb), cadmium (Cd), nickel (Ni) and copper (Cu) released from domestic, industrial and other man made activities. Among the heavy metals, Cd is one of the most toxic, non-essential heavy metal; known for its corrosive nature and is widely used in paints and dyes, cement and phosphate fertilizers [8]. Cd occurs naturally in the environment in significant amounts but its release in the recent past is steadily increasing due to human activities causing pollution at considerably toxic amounts was reported by earlier workers in various aquatic ecosystems [9]. In aquatic systems, as fish occupy the upper trophic level, there are greater chances of transferring Cd to higher organisms particularly to man.

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Abstract: Man and the biosphere are presently under an increasing risk of heavy metal pollution. Cadmium (Cd), in meticulous, is extremely toxic to humans as well as aquatic organisms. Cd flow to humans is more through aquatic meat. Throughout the world cadmium and cadmium compounds are regulated in the workplace and in the market place. Metal toxicity in various animal species has been well documented; however, their combined action in the regulation of metal stress has never been reviewed yet. Therefore, this review examined the important health, safety and environmental issues associated with the use and disposal of cadmium compounds. Cadmium (Cd) has been in industrial use for a long period of time. Its severe toxicity stimulated into scientific focus throughout the middle of the last century. It is necessary to investigate their toxicity and potential hazards to human and aquatic ecosystems. In this review, we conferred significant and modern developments of toxicological and epidemiological difficulty, including elucidation sources, toxic effects, particularly the acute toxicity and chronic ones, induced by Cadmium in aquatic animals and how it reached through food chain to higher mammals. The toxic effects of selected metal cadmium, as well as the underlying mechanisms of cadmium causing these effects, are also highlighted and described in detail. In addition to acute effects such as mortality, chronic exposure to cadmium can lead to adverse effects on growth, reproduction, immune and endocrine systems, development, and behavior in aquatic organisms.

Keywords: Cadmium toxicity, Food web, Human and Environmental health safety.

Fig. 1. A. Global cadmium refinery production 1950-2000/USGS 2002/1

Fig. 1. B.Mine production and reserves by country, 2000/2001/USGS 2002/2


Fig.1. Statistical data of global cadmium refinery production, mine production and reserves by country [10].
2. SIGNIFICANCE OF THE PRESENT REVIEW:
It clearly shows that the Environmental Protection Agency’s (EPA) national recommended ambient water quality criteria for cadmium replicate the latest scientific information, and existing EPA policies and methods. It is generally EPA’s water quality criteria for cadmium will provide recommendations to states and tribes authorized to establish water quality standards under the Clean Water Act. In adopting water quality standards, states set exposure protections for aquatic life. Although this approach gives significantly more coverage of acute effects such as mortality, chronic exposure to cadmium can lead to adverse effects on growth, reproduction, immune and endocrine systems, development, and behavior in aquatic organisms. To address this problem, Cadmium enters the environment by natural and human processes, however, human sources, such as mining and urban processes, are responsible for contributing approximately 90 percent of the cadmium found in surface waters [11]. This hypothesis is supported by recent findings.

3. CONTEMPORARY RESEARCH ON CADMIUM: INDIA
Many of the rivers, lakes and oceans in our country have been contaminated by pollutants like heavy metals. Some of these pollutants are directly discharged by industrial plants and municipal sewage treatment plants, others come from polluted runoff in urban, agricultural areas and some are the result of historical contamination [12]. Cd is one of the most toxic metals and constitute a real threat to fish because of its wide spread occurrence in the aquatic environment. The effect on fish species related to Cd exposure was damage to people may be caused by fish foods coming from polluted water. Heavy metals like Cd produce adverse effects by causing osmoregulatory stress in fish. The anthropogenic sources add 3-10 times more Cd to the atmosphere than natural sources [13]. Major occupational exposure occurs from nonferrous smelters during production and processing of Cd, its alloys, compounds and the exposure is increasingly common during recycling of electronic waste in various states in India. Some years later, pathological bone fractures and severe pain (named Itai-Itai disease) occurred after World War-II, in Japan, as a consequence of Cd exposure [14]. At present, Cd pollution in India remains largely unassessed.Sporadic reports indicate Cd concentration in unpolluted waters, natural cadmium concentrations are generally less than 1 μg/L or 1 part per billion (ppb) [15]. Above the permissible level of Cd in aquatic systems is a particular concern because metals are both persistent and toxic. Animals that accumulate Cd in their bodies (“body burden”) can be eaten by others, and so on, such that Cd will both accumulate and biomagnify in the food chain. [16] reported that Cd, Pb and Ni in crops in sewage irrigated areas were highest in green leafy vegetables followed by roots and tubers and lowest in cereal crops. For example, Cadmium accumulation level was high in coriander leaves followed by spinach and lowest in garlic. Daily intake of green leafy vegetables by population in sewage water irrigated areas would lead to higher intake of the metals much more than safe limits and may show toxic effects Recently, in the case study of a 32-year old silver jewelry manufacturer, Cd concentration was found to be 20.10 μg/l (normal is <5.0 μg/l). The patient was found to have a polynuropathy due to chronic exposure of Cd [17]. Cd exposure in India is a complex matter and needs to be understood in detail. Though the range of Cd exposure sources in India are extensive and as yet not well understood. The possible and potential sources of Cd toxicity are storage battery factories, mining and smelting processes, tanning, paper and pulp industries, pesticide manufacturing industries and cigarette smoking. Though several studies are available on Cd poisoning in India [18] very few studies were made by Indian Investigators on Cd induced oxidative damage [19] and also on metallothionein formation [20]. Still several studies are underway in determining the characterization of various metal binding and transport proteins and their role in intracellular absorption, transport and storage of metals and also in disease pathology. In the present day scenario Cd in the human diet constitutes a potential chronic hazard to health. In the non smoking general population, diet is the major source of Cd exposure and therefore it is important to monitor the dietary intake of this heavy metal to quantify and improve the understanding of Cd accumulation in the human body. Consumption of a balanced and varied diet was recommended to minimize such imbalances. Thus research on the effects of nutritional supplements on metal toxicity has produced growing evidence in the field of essential trace element intake and reduction of toxicity. However, no consolidated compilation on incidence of Cd exposure in India is currently available, although the potential usage of Cd in unorganized sectors (in Ni-Cd battery manufacturing, electroplating, galvanizing, paint industry and pottery glazing) continues unabated. It appears that the people exposed to Cd contaminated food, dust and fumes are unaware of health hazards associated with it. In India where most of the poor are under risk of malnutrition and exposures to various environmental pollutants, obviously there is need for more focused research on reduction methods and therapeutic strategies of heavy metal toxicity particularly Cd, as it appears on the priority list of “Top 20 Hazardous Substances” according to the Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, Georgia in cooperation with the U.S. Environmental Protection Agency (USEPA).

4. EVENTUAL EFFECTS OF CADMIUM TOXICITY
It is important to examine the toxic effects of metals like Cd, Pb, Hg and Cu etc. on fish since they constitute an important link in food chain and their contamination causes imbalance in the aquatic ecosystem. Among heavy metals Cd is considered as one of the major aquatic pollutant in many parts of the world. Cd is a highly toxic metal, still attracts the attention because it is often detected in the air, water and food products [21]. The toxic effects of Cd have been studied by several authors in different animal species such as the Snail Cleopatra bulimoides[22]; fishes like Channa punctatus [23], Cirrhinus mirigala (Hamilton) [24]; sea bream, Sparus aurata [25]; Ophiocephalus stratus[26]; Tilapia mossambica [27]; Cyprinus carpio [28]; mice [29]; rats [30]; pigs [31] and in humans [32].The liver and kidney are the major target organs following Cd exposure. Cd toxicity depends on the dose, the route of administration, and duration of exposure. [33] reported that Cd causes delayed effects on the renal function in the aquatic animals. They also reported that Cd contamination represents a serious and critical hazard for the renal function of the fish. The Cd administration causes renal toxicity by inducing lipid peroxidation (LPO) with a significant decrease in the antioxidant systems and also altering lipid metabolism in fish. [34] reported that combined exposure of Cr and Cd causes decreased glutathione status and decrease in activity of...
superoxide dismutase (SOD) may induce radicals, injuring the corresponding tissues. They reported that these toxic metals disturb membrane integrity of cells via ROS and classifying mechanism for altered receptor binding, steroidogenesis and hormone production. It can cause osteoporosis, non-hypertrophic emphysema, irreversible renal tubular injury, eosinophilia, anemia and chronic rhinitis. Chronic exposure to inorganic Cd results in accumulation of the metal mainly in the liver and kidneys as well as in other organs causing many metabolic and histological changes, membrane damage, altered gene expression and apoptosis [35]. Cd induced injury to both major target organs (liver and kidney) has been attributed to its ability to enhance free radical formation in vivo [36]. Cd inhibits antioxidant enzymes which protect tissues by either binding to sulfhydryl groups essential for the enzymes, replace the bivalent metals like Cu and manganese (Mn) required by the enzymes or decreases the bioavailability of selenium (Se) required by the enzymes [37], [38]. The importance of Cd as an environmental health problem has become increasingly apparent over the past 50 years. Since the beginning of the industrial revolution, large amounts of Cd have been released from the lithosphere into the environment. Depending upon the dose, route and duration of exposure, Cd can damage various organs including lungs, liver, kidney, bone, pancreas and endocrine system [39]. It was found to be teratogenic, embryo toxic, carcinogenic, nephrotoxic in humans and the risk is greater among smokers. In fact, the low-exposure to Cd is more toxic to stimulate free radical production, protein and DNA oxidative deterioration and initiating various pathological conditions in humans and animals [40]. The cadmium produced enhanced lipid peroxidation in plasma and kidney [41]. These Cd-induced changes were accompanied by a significant rise in renal Fe, Cu and a fall in tissue Zn, Se and also reported that LPO is associated with Cd toxicity and that Se was found effective in attenuation of these renal effects. In fish, the toxic effects of metals like Cd may influence physiological functions, individual growth rates, reproduction and mortality [42]. They also stated that Cd can cause immunotoxicity. The antioxidant enzyme exhibited its own pattern of activation or inhibition upon exposure to different concentrations of Cd, with more oxidative stress observed in the mitochondria in fish liver cells [43]. Earlier studies [44] stated that Cd induces cellular death in cortical neurons in culture. This death could be mediated by an apoptotic and a necrotic mechanism. The apoptotic death may be mediated by oxidative stress with ROS formation which could be induced by mitochondrial membrane dysfunction since this cation produces: (a) depletion of mitochondrial membrane potential and (b) diminution of ATP levels with ATP release. Necrotic death could be mediated by LPO induced by Cd through an indirect mechanism (ROS formation). Recent evidence obtained [45] that Cd toxicity and cellular toxic mechanisms is complex, probably affecting both membrane transporters and tight junction proteins. They also observed that most of the filtered Cd is reabsorbed within the kidney. The chronic Cd intoxication can induce a change in renal handling of ions without altering glomerular filtration rate and supplementation with Ca protects against the renal toxic effects of Cd and inhibiting apoptosis. [46] reported that Cd inhibits enzymes such as Mg²⁺-ATPase and Na⁺-K⁺-ATPase causing metabolic effects and disrupting neurotransmitter uptake. In several situations acetylcholine is not broken and accumulates within synapses causing physiologic impairment and alterations in fish swimming behavior [47]. Cd increases brain AchE activity and decreases brain antioxidant status in animals [48]. Ca and L-cysteine have antagonistic effect on Cd. Apparently, several mechanisms have been proposed to explain the toxic effect of Cd on renal cells. Cd may cause nephrotoxicity by generating free radicals [49] and by inducing necrosis and apoptosis [50]. Interestingly, a protective effect of Se and Ca has been reported in vitro against the cellular toxicity due to Cd. Se protection is probably due to an action on oxidative stress and apoptosis [51]. Other researchers have shown that Cd induces cytochrome c release from mitochondria, leading to apoptosis via the activation of the caspase 3 and 9 cascade [52]. The observed Cd toxicity in rat hepatoma cell line, cellular events mediating DNA damage and stated that Cd induced lysosomal damage is an earlier event than DNA damage and can mediate other cellular events that lead to cell death [53]. Previous publications have already addressed this Cd can cause osteoporosis, non-hypertrophic emphysema, irreversible renal tubular injury, eosinophilia, anemia and chronic rhinitis. Chronic exposure to inorganic Cd results in accumulation of the metal mainly in the liver and kidneys as well as in other tissues and organs causing many metabolic and histological changes, membrane damage and altered gene expression [54]. The observation of supplementation with Se and Ca produces tolerance to several Cd toxic effects [55]. They also reported that Ca-induced protection against the cytotoxicity of Cd in the cells may be related to the maintenance of normal redox balance inside the cell. Humans environmentally exposed to Cd are at risk of tubular damage because Cd causes damage to the organization and function of the nephron [56]. Several structures i.e., endoplasmic reticulum, mitochondrion, lysosome, cellular and intracellular membrane, as well as their biological functions, i.e. aerobic and anaerobic respiration, transport functions and biochemical processes taking place in the endoplasmic reticulum, were affected. Cd damages kidney structurally and functionally even at a relatively low level (5mg/l) corresponding to human environmental exposure, the target for Cd action in the kidney is the tubules (proximal convoluted tubules and straight tubules), and disturbance in their function is the main toxic effect of Cd. An important observation the waterborne Cd level in polluted areas can reach 1 mg/L [57] and a concentration-dependent uptake of Cd in the tissues of aquatic animals has been reported [58]. Sublethal levels of Cd can affect ion regulation and cause physiological disturbances in the fish [59]. For example dietary Cd at 500 µg/g dry weight has been reported to reduce the tubular reabsorption and thereby increase the renal excretion of major ions such as Mg²⁺, Na⁺, Cl⁻, K⁺ and Ca²⁺. Overall, the data are consistent with a high rate of Variability in the Cd induced toxic effects on fish is evident especially in interrupting development and growth [60], anemia, preventing Ca uptake through the gills, disturbing liver functions skeletal deformations and pathological changes in some tissues and organs [61]. In wild birds accumulation of Cd may cause severe pathological changes and physiological dysfunction. In growing Pheasants (Phasianus colchicus) after given food contaminated with 70 µg Cd /g for 21 days, the highest Cd concentration (~ 142 µg Cd/g dry wt) was found in the kidneys and the lowest concentrations found in muscles (0.03-1.08 µg Cd/g dry wt) and severe damage was observed in the kidneys, whereas pathological changes found in liver and gills. The Cd accumulation caused decreasing Fe and Hb levels in the
tissues which leads to stimulate hematopoiesis in the liver [62]. Interestingly in recent years, Cd has been recognized as one of the toxic environmental and industrial pollutants due to its ability to induce severe alterations in various organs and tissues following either acute or chronic exposure [63]. Consequently, extensive studies have been carried out to identify the mechanisms of Cd toxicity [64]. Although information regarding the primary intracellular sequences of Cd toxicity is still lacking, available reports indicate that liver, kidney and gills represent the major target organs of Cd toxicity in aquatic animals [65].

5. CADMIUM TOXIC EFFECTS ON AQUATIC ANIMALS

The fact that beginning in the 1950s, the attention of the scientific community has been focused on the potential toxicity of Cd and on the risks presented by its accumulation in man and animals. In aquatic systems Cd is most readily absorbed by organisms directly from the water in its free ionic form Cd. The acute toxicity of Cd to aquatic organisms is variable, even between closely related species and is related to the free ionic concentration of the metal. Effects of long term exposure can include larval mortality and temporary reduction in growth [66]. Sublethal effects have been reported on the growth and reproduction of aquatic invertebrates; there are structural effects on invertebrate gills. There is evidence of selection of resistant strains of aquatic invertebrates after exposure to Cd in the field. The toxicity is variable in fish, salmonoids being particularly susceptible to Cd. Sublethal effects in fish, notably malformation of the spine, have been reported [67]. The most susceptible life stages are the embryo and early larva, while eggs are the least susceptible. In studies of lake trout exposed to different levels of Cd, researchers found Cd affected foraging behavior, resulting in lower success at catching prey. Decreased thyroid function as a result of Cd exposure has also been documented [68]. Cd has been reported to exert deleterious effects in terms of nephrotoxic, cytotoxic, genotoxic, immunotoxic and carcinogenic [69]. Not only this it also creates disturbances of Ca metabolism, hypercalcuria and takes part in the formation of stones in the kidney. In another study, the lower and long-term exposure to Cd through air or through diet can cause kidney damage. Although the damage is not life-threatening, it can lead to the formation of kidney stones and affect the skeleton, which can be painful and debilitating. Lung damage has also been observed. Animals given Cd-contaminated food and water showed high blood pressure, iron-poor blood, liver disease, nerve damage and brain damage in rats [70]. These effects have not been observed in humans. Studies showed that humans can experience lung irritation after breathing as little as 1.0 mg/cubic meter of air of Cd-contaminated air for a short period of time. Breathing 0.01mg/m³ of Cd-contaminated air over the long-term has resulted in chronic lung and kidney disease in humans. In addition, Background levels of Cd in uncontaminated, nonbiological compartments extended over several orders of magnitude. Concentrations (ppb) of cadmium reported ranged from 0.05 to 0.2 in fresh water [71], up to 0.05 in coastal seawater, from 0.01 to 0.1 in open ocean up to 5,000 in riverine and lake sediments, 30 to 1,000 in marine sediments, 10 to 1,000 in soils of nonvolcanic origin, up to 4,500 in soils of volcanic origin, 1 to 600 in igneous rock, up to 100,000 in phosphatic rock, and 0.001 to 0.005 μg/m³ in air [72]. Where Cd is comparatively bioavailable, these values are very near those that have been shown to produce harmful effects in sensitive biological species. The maximum levels permitted of cadmium in seafood as follows 0.05 mg/kg in fish, 0.5 mg/kg in crustaceans and 1.0 mg/kg in mollusks [73]. Moreover, the Joint FAO / WHO have recommended the provisional tolerable weekly intake (PTWI) as 0.007 mg/kg for Cd (0.420 mg/g/week for a 60-kg person) [74]. The most convincing evidence after absorption, Cd is transported into the blood bound albumin. It is taken up by the liver and due to its similarity to Zn, causes this organ to induce the synthesis of the protein metallothionein (MT) to which it binds. The Cd-MT complex then becomes transported to the kidneys, and it is filtered at the glomerulus, but is reabsorbed at the proximal tubule where it remains stored therefore, the kidney is one of the main target organs for Cd induced toxicity. Within the renal tubular cells, the Cd-MT complex becomes degraded by digestive enzymes, which releases the Cd. Renal tubular cells deal with the release of this toxic substance by synthesizing MT to neutralize it, but eventually the kidneys lose their synthetic capacity for MT. At this point, the Cd has accumulated to a high level in the renal tubular cells, and irreversible cell damage occurs [75]. More recently the toxic effects of Cd are due to its inhibition of various enzyme systems. Like similar heavy metals, Cd able to inactivate enzymes containing sulfhydryl (-SH) groups and it can also produce uncoupling of oxidative phosphorylation in mitochondria. Cd may also compete with other metals such as Zn and Se for inclusion into metallo-enzymes and it may compete with Ca for binding sites on regulatory proteins such as calmodulin [76]. Humans may be contaminated by organic and inorganic pollutants like Cd associated to aquatic systems by consumption of contaminated fish and other aquatic foods from this environment. Additional evidence regarding the connection of Cd is a toxic agent and it is also an environmental contaminant. Cd exposure may be implicated in some human disorders related to hyperactivity and increased aggressiveness [77]. Cd can enter to body by inhalation and other routes and accumulates mainly in the kidneys. At high levels, it can reach a critical threshold and can lead to serious kidney failure. Cd can enter through ingestion, intra peritoneal, subcutaneous, intramuscular and intravenous routes. The Cd retention is generally higher in women than in men. “Ouch-ouch” or itai-itai is mainly a human disease [78]. This disease is caused by long-term exposure of the inhabitants to Cd intoxication. Clinical features of this disease include renal tubular dysfunction, osteomalacia, amino-aciduria, glycosuria and anemia which include decreased Hb, iron deficiency and low serum erythropoietin levels in the human body.

6. CADMIUM IMPACT ON FISH PHYSIOLOGY

There have been a number of reports on Cd is an environmental health problem has become increasingly apparent over the past 50 years [79]. Since the beginning of the industrial revolution, large amounts of Cd have been released from the lithosphere into the environment. Cd like many other heavy metals is antagonistic to essential trace elements like Fe, Zn, Cu, Ca etc. These are Nutrient elements for binding sites as transport and storage proteins [80], metalloenzymes and receptors. For the general population, the two main sources of exposure are the diet (from contaminated water and crops grown on polluted soil) and tobacco smoke [81]. Meat and fish normally contain 5-40 ppb of Cd. Animal tissues such as kidney and liver exhibit high Cd values, up to
1000 ppb, as these are the target organs for Cd toxicity [82]. 
Cd has been found in at least 776 of the 1,467 Nationalpriorities list sites identified by the Environmental Protection 
Agency (EPA). However, previous studies revealed that in 
carp (Cyprinus carpio) Cd inhibits steroid formation and ovarian 
maturatation [83]. Extensive (1.8 and 3.4 µg/l) Cd exposure in trout causes delayed egg formation and it has 
been shown to inhibit egg development into the fry stage direct 
exposure of fish embryos to Cd induces premature hatching 
and developmental abnormalities. Exposure to low levels of Cd 
can cause DNA damage and stress in common carp (Cyprinus carpio) [84]. It is known that chronic exposure to Cd can induce 
severe nephropathy in humans and animals [85]. This 
nephrotoxicity causes reabsorptive and secretory dysfunction 
of the renal tubule. Experimental chronic intoxication with Cd²⁺ 
has been performed at various doses over several weeks and 
causes tubular dysfunction that develops into renal failure. 
Other researchers have shown that Cd enters the environment via 
landfill, inadequate waste disposal methods, and leaks at 
hazardous waste sites. It is produced by mining and other 
industrial activities. Cd particles enter the atmosphere when 
coal is burned for energy and household waste is incinerated. 
Particularly of the reverine system, ponds and small water 
basins that are lying adjacent to the effective zones of 
industrial effluents release suffer drastic changes and the 
habituation of various trophic levels cannot escape these 
detrimental effects of pollution. Animals and plants take up Cd 
when it is in the environment. If the food consumed 
contaminated with Cd, it may alter oxidative stress enzymes in 
fresh water fish, decreased immunity state, change in 
behavior, growth rate and nutritional state, digestive enzyme 
activities, efficiency of food assimilation and state of 
carbohydrate metabolism and disturb osmotic and ion 
regulation [86]. Apparently, the range of its toxic manifestations 
of Cd includes its effect on energy metabolism, membrane 
transport, protein synthesis and cellular necrosis. Chronic 
exposure leads to proximal tubular atrophy and disturbances in 
the antioxidant status. Cd binds to cysteine residues of 
proteins, including metallothionein and reduced glutathione an 
intracellular complex, and is known to be stored primarily in the 
kidneys and liver [87]. Cd can be transported over to great 
distances when it is absorbed by sludge. This Cd-rich sludge 
can pollute surface waters as well as soils. Further studies are 
waranted to confirm that in aquatic ecosystems Cd accumulates in the fish, mussels, oysters, shrimps and 
lobsters etc. The susceptibility to Cd can vary greatly between 
aquatic organisms. Salt-water aquatic species are known to be 
more resistant to Cd poisoning than freshwater organisms. 
Animals eating or drinking Cd sometimes get increased blood-
pressures, liver, kidney, central as well as peripheral nervous 
systems damage. The dominant form of Cd in sediments was 
a carbonate. Levels of Cd in water varied over time and 
between sites, but usually ranged from 0.5 to 2.5 ppb. It is 
possible that significant amounts of Cd are transferred from the 
sediments into rooted aquatic macrophytes and later released into the water after macrophyte death [88]. Water hardness is 
often regarded as the major influencing factor on Cd toxicity. 
The acute toxicity of Cd decreases with increasing water 
hardness [89]. This is believed to be due to the fact that at 
increased hardness levels, the major hardness cation, Ca²⁺, 
out-competes Cd²⁺ for binding sites on the gill and thereby 
reduces toxicity. Waterborne Ca has been found to be a strong 
modifier of Cd accumulation in fish gills under short term (2–3 
h) acute exposure to Cd [90]. Moreover, in many studies 
quotted above the effects of hardness were difficult to interpret 
because of the confounding effects of alkalinity, which co-
varied with hardness levels. In these studies, differences in Cd 
toxicity at various hardness levels may have been caused, at 
least partially, by a difference in carbonate complexation rather 
than by competition with hardness cations only. It has short 
and long-term toxicity to aquatic life.

7. BIOACCUMULATION OF CADMIUM
It is now well established that bio-accumulation is one of the 
important properties of the metal through which they interfere 
with physiological functions. Bio-accumulation can be defined 
as “the net accumulation of a metal in a tissue of interest or a 
whole organism that results from exposure”. The bio-
accumulation of metals arises from all environmental sources 
including air, water, solid phases (organic and inorganic 
phases in soil and sediment) and diet; and also represents a 
steady-state balance of losses from the tissues and the body. Industrial discharges containing toxic and hazardous 
substances, including heavy metals [91] contribute 
tremendously to the pollution of ecosystem. Bioaccumulation 
of metals reflects the amount ingested by the organism, the 
way in which the metals are distributed among the different 
tissues and the extent to which the metal is retained in each 
tissue. This happens either because the heavy metal is taken 
up faster than it can be used or because the heavy metal 
cannot be broken down for use by the organism (i.e. the heavy 
metal, Cd cannot be metabolized).

In addition, Bioaccumulation results from a dynamic 
equilibrium between exposure from the outside environment or 
amount of heavy metal entered into the body after treatment of a 
xenobiotic and uptake, excretion, storage and degradation 
within an organism. The level at which a given substance is 
bioaccumulated, depends on the rate of uptake, the mode of 
uptake, ingestion along with food, contact with epidermis (skin), how quickly the substance is eliminated from the 
organism, transformation of the substance by metabolic 
processes, the lipid (fat) content of the organism, the hydro 
phobicity of the substance, environmental factors and other 
biological and physical factors. As a general rule the more 
hydrophobic substance is the more likely to bioaccumulates in the 
organism. Moreover, increasing hydrophobicity or 
lipophilicity of the heavy metal leads to an increasing 
propensity to bioaccumulation of the substance. Though, the 
amount of heavy metal pollutant might have been little enough 
not to cause any damage in the lowest levels of the food web, the 
biomagnified amount might cause severe harm to the 
organisms that are located in higher levels in the food web. This 
phenomenon is known as bio-magnification. Thus, 
bioaccumulation is often a good integrative indicator of the 
heavy metal exposure of an organism in polluted ecosystems 
[92]. An important observation accumulation of metals and 
metaloids is of particular value as indicators because these 
metals are not metabolized in the organism. Bioaccumulation 
is the gradual build up over time of xenobiotics including heavy 
metals in a living organism. It is a normal process that can 
result in injury of an organism only when the equilibrium alters 
between exposure and concentration of the substance in the 
tissues of an organism. At this stage bioaccumulation is 
overwhelmed relative to the toxicity of the heavy metal. The 
fact that heavy metals like Cd, Pb and Hg have no known 
biological functions and consequently detrimental to essential
life processes [93]. These metals in the form of inorganic compounds from natural and anthropogenic sources continuously enter the ecosystem where they pose a serious threat because of their toxicity, long time persistence, bioaccumulation and bio-magnification in the food chain. It is important to examine the toxic effects of these metals on fish since they constitute an important link in food chain and their contamination by metal causes imbalance in the aquatic system. Cd is considered as one of the most toxic heavy metals. It is a nonessential element to all living organisms. Rivers and lake shores are the areas primarily affected by diluted Cd waste from industrial effluents in big cities. The Cd-related contamination of the aquatic habitat has greatly increased in the last decades, resulting in an increase of Cd deposits in tissues of aquatic organisms in all food chain systems [94]. It is important to note that Cd is a highly toxic element for all mammals and fish. Cd levels have constantly been increasing and consequently, the research on Cd has become quite topical and urgent. Accumulation of Cd in living organisms is a major ecological concern, especially because of its ability to accumulate very quickly. By contrast, the excretion of Cd from living organisms is a slow process [95].

Fig.2. The cycle of cadmium in aquatic ecosystem [97].

In general, they are not biodegraded and therefore, their bioaccumulation in fish, oyster, mussels, sediments and other components of aquatic ecosystems have been reported from all over the world. It appears that problem of heavy metals like Cd accumulation in aquatic organisms including fish needs continuous monitoring and surveillance owing to biomagnifying potential of toxic metals in human food chain [96]. Thus, the bioaccumulation factor (BAF) and bioconcentration factor (BCF) are used as criteria for bioaccumulation in the context of identifying substances that are hazardous to the environment. The BCF / BAF criteria, while developed as surrogates for chronic toxicity and/or biomagnifications of anthropogenic substances, are applied to all substances including metals. Among the various toxic metals, Cd is particularly severe in its action due to tendency of bio-magnification. Studies have shown that the fish are able to accumulate and retain Cd when they were subjected to Cd treatment and it has been shown that accumulation of Cd in tissues of fish is dependent upon mode of entry, concentration and period of Cd treatment [98]. Cd is an environmental pollutant to which animals are exposed, resulting in gradual accumulation in the kidney and liver. It accumulates in different tissues to a different extent but the main storage and action sites are the liver and kidney. Based on the available literature it is clearly indicated that the kidney, liver and gill are the critical targets for Cd in fish [99], [100] in which they have been reported to cause significant metabolic, biochemical and physiological effects. The absorbed Cd caused direct or indirect physiological and histopathological changes in the tissues of various organisms [101]. Cd accumulation and its toxic effects in the tissues of various fish species have been reported or reviewed by several authors viz. Zahedi et al., [101].

8. CADMIUM - OXIDATIVE STRESS

It is notable that environmental contaminants may cause oxidative stress, which is an imbalance between ROS and the organism’s capacity to handle them, by different mechanisms. The dynamic equilibrium can be disturbed leading to enhanced ROS level and damage to cellular constituents which is called “oxidative stress”. It affects numerous cellular components such as DNA, lipids and proteins, through oxidation reactions causing significant changes in their function and may result in pathogenesis [102]. Particularly, the application of Si and NO in combination lowered the oxidative stress markers via up-regulating the antioxidant defense system (particularly AsA-GSH cycle) suggesting the increased efficacy of Si+NO against the Cd toxicity in wheat seedlings as compared to their alone treatments [103]. Oxidative lipid injuries termed LPO produce a progressive loss of membrane fluidity thus reducing membrane potential and increasing its permeability to metal ions. Active oxygen species are continuously produced in tissues by the action of mitochondrial electron transport system. Exposure of fish to metals may result in increases in ROS such as hydrogen peroxide, superoxide radicals, and hydroxyl radicals leading to impairment of normal oxidative
metabolism and finally to oxidative stress [104]. The importance of antioxidant enzymes is generally emphasized in the prevention of oxidative stresses by scavenging of ROS. The antioxidant system comprises several enzymes such as SOD, Catalase (CAT), and Glutathione Peroxidase (GPx). Superoxide radicals that are generated are converted to H₂O₂ by the action of SOD, and the accumulation of H₂O₂ is prevented in the cell by CAT and GPx. Excessive ROS production in response to heavy metal pollution detoxification can overwhelm natural defense mechanisms leading to cumulative damage to biomolecules. When the antioxidant enzymes fail or are insufficient, an increase of ROS production may originate oxidative damage [106].

![Fig. 3.2. Schematic representation of selected cadmium (Cd)-related cellular pathways and nuclear interactions.](image)

At the cellular level, many adverse effects of Cd were shown to be mediated by an over production of ROS [107] associated with a decrease in glutathione (GSH) levels [108] and oxidative damage to lipids [109], DNA [110], [111] and proteins [112]. At present, oxidative stress has been considered as an important possible mechanism of Cd toxicity [113]. Moreover, it induces systemic DNA damage [114], interferes with DNA repair processes and enhances genotoxic damage [115]. Cd is readily distributed in tissues after exposure and interferes with intracellular signaling network and gene regulation at multiple levels and induces LPO. Lipid peroxides that accumulate due to LPO are known to be harmful to cells and tissues. Thus Cd induces oxidative damage in liver and kidney by enhancing peroxidation of membrane lipids and altering the oxidant system of the cells. Although, Cd is a redox-inactive metal, it is reported to increase ROS in many cell types [116]. Even when the mechanisms responsible for Cd induced oxidative stress are not well understood, free radicals overproduction may result from indirect interactions of Cd at critical cellular sites or as a consequence of protective mechanisms inhibition. It can cause oxidative stress by inducing ROS synthesis, such as hydrogen peroxide (H₂O₂), hydroxyl radical (OH·), superoxide radicle (O₂⁻) and singlet oxygen (¹O₂) as well as disturbances in antioxidative systems for the detoxification of ROS [117]. They act as mediators in apoptosis as well as in cell proliferation and may induce cell death by themselves or act as intracellular messengers during cell death induced by various other kinds of stimuli. Increased LPO and alteration in GSH levels in Cd exposed animals indicate that oxidative stress is also implicated in Cd induced apoptosis [118]. The conformity strongly suggests that the Cd inhibits the activity of various oxidative stress enzymes such as CAT, SOD, GPx, glutathione-s-transferase (GST) and GSH [119]. As a result of this inhibition, the electron transport chain becomes highly reduced, electrons are transferred directly to available oxygen and lead to enhanced formation of ROS [120]. ROS may lead to increased oxidative stress in tissues, cellular damage, peroxidation of membrane lipids and loss of membrane bound enzymes [121]. At the cellular level, Cd induces oxidative stress in many organisms [122] which might result in histological changes and physiological damage to different organs [123]. Intake of Cd results in consumption of GSH and protein binding -SH groups and subsequently the levels of free radicals such as H₂O₂, OH· and O₂ are highly increased [124]. One of the most important effects of free radicals is oxidation of polyunsaturated fatty acids (PUFAs). As a result of free radical attack, lipids are oxidized and hence membranes are damaged [125]. However, free radicals may be used as an indicator of cell membrane injury. Sulfhydryl – rich, metal binding protein, MT may function in a manner similar to GSH, wherein MT provides an intracellular `nucleophilic sink’ to trap free radicals, electrophiles and alkylating agents.

![Fig. 4. Effect of Cd on various antioxidant enzymes and their cofactors leading to inactivation of enzyme activity](image)

9. MECHANISM OF CADMIUM TOXICITY

New approaches and attempts for Cd absorption in fish is carried out along the gill surface and gut tract, followed by blood transport to other organs [126]. With regard to the distribution of Cd in tissues, following oral absorption, Cd is initially transported via the portal circulation, to the liver where it is efficiently taken up by hepatocytes. In the hepatocytes, Cd induces the synthesis of MT, which binds and sequesters Cd, thereby buffering its toxic effects in the cell. However, as the hepatocytes in which Cd is sequestered die off, either through normal turnover or as a result of Cd injury, the Cd-MT complex can be released into the blood stream [127]. Even though the Cd-MT complex is non toxic to most organs, it can have the paradoxical effect of facilitating the delivery of Cd from the liver to the kidney. Likewise, any Cd that is bound to low molecular weight molecules in plasma, such as cysteine and glutathione, can be filtered at the glomerulus and Cd either as the free ion (Cd²⁺) or as the sulfhydryl conjugates, can be taken up by the
proximal tubule epithelium. There is evidence that the peritubular capillaries, which are fenestrated, can deliver Cd and Cd-thiol conjugates to the basolateral surface of the proximal tubule epithelial cells from where Cd can then be taken up [128]. After it is taken up by the epithelial cells of the proximal tubule, the Cd-metallothionein complex initially accumulates in lysosomes, where the complex is degraded, resulting in the release of Cd within the cell [128]. The released Cd, most likely rapidly associates with intracellular -SH groups, either on proteins or low molecular weight compounds such as glutathione. The interaction of Cd with –SH groups on proteins can result in the direct alterations in protein function. These interactions along with alterations in glutathione metabolism can result in the induction of oxidative stress [130]. The intracellular Cd²⁺ also induces the synthesis of additional MT [131], and can interfere with the actions of essential metal ions and disrupt various signaling pathways [132].

10. CONCLUSION:
This comprehensive review on Cadmium heavy metal dictates that we can easily be exposed to heavy metals from surroundings until proper management has been implied throughout the world to reduce environmental pollution by heavy metals. The cadmium is a heavy metal with high toxicity. It is toxic at very low exposure levels and has acute and chronic effects on aquatic organisms health and environment. Cadmium is not degradable in nature and once release to the environment, stay in circulation. Cadmium and cadmium compounds are, compared to other metals, relatively water soluble therefore also more mobile in soil, generally more bioavailable and tend to bioaccumulate. It is accumulates through food chain in the human body and especially in the kidneys. According to the current literature kidney damage is probably the critical health effect. There have been some reports cadmium toxicity to freshwater fish can be altered by water chemistry variables, such as alkalinity, hardness and organic matter. Finally, Cadmium could pose a large threat to fish in the polluted areas. The evaluations should continue after seasons commences. In conclusion, heavy metals cause diverse effects, including oxidative damage, inhibition of AchE activity, biochemical changes, histopathological changes as well as developmental changes, mutagenesis and carcinogenicity. Though we cannot avoid the use of heavy metals, measures should be taken for the conservation of the water quality.

Conflict of Interest Statement:
The authors declare that the present review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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