Effects of Metals on Human Health and Ecosystem

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Contents

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Abstract Heavy metals are one of the main constituents of the earth and have played an important role in living organisms. However, ingestion of large amounts of even essential heavy metals can cause serious damage and continue to cause many sufferings as pollutants in the environment. This chapter outlines the toxicity common to the general properties of heavy metals, and then details the effects of individual heavy metals on living organisms, mainly human health. And finally, it also describes the effect of reducing the antioxidant heavy metals that coexist with the adverse health effects of these heavy metals.

Keyword Co-exposure, General properties, Heavy metals, Lethal dose, Reactive oxygen species, Toxicity

1 Introduction

Heavy metals are important biologically as trace nutrients, however, the toxic effects of the heavy metals in human physiology are very concerning. Thus, for comprehensive understanding of metals' mechanism of actions, there is a need to know about involving functions and actions, such as their concentrations, speciation, and toxicokinetics which make them detrimental [1]. There is an urgent need to address properly their environmental sources, leaching criteria, chemical alterations, and their modes of action that contaminating the surrounding environment and ecosystem, where life persists. Several researches depicted that these metals are released into the environment by two pathways: one is natural and the other is anthropogenic means, especially mining and industrial activities, and automobile exhausts [2]. Metals accumulate into the groundwaters, by passing along water pathways and ultimately assembling in the aquifer, or they are washed away by run-off into surface waters, as a result water and soil pollution occur. The toxicity and poisoning level of metals are being triggered by their exchange mechanism. When metals are ingested, they form several cellular stresses including formation of reactive oxygen species (ROS), altering their structures, and inhibit the biomolecular reactions and functions in biological systems. This chapter focuses on certain heavy metals and their effects on human and ecosystem [3]. Metals are crucial components of the environment. Their presence in the environment is quite unique because it is troublesome to dispel them from the environment entirely once they enter in the environment. Metal comprises such toxic substances which are visible in several environmental and occupational conditions. The effect of these toxic metals on human health currently is of great interest due to the omnipresence of metal exposure [4]. For decades, various metals are being evicted from the Earth and utilized in industries and production worldwide. So, the problems raising in the environment from these toxic metal usages have such serious aspects. Metals are natural material (except for Plutonium and Uranium) also categorized as globally-distributed pollutants. Metals are being depressive now-a-days creating environmental disruptions such as they accumulated in the human body. Even if their exposure level is minor, they could be potentially toxic [5]. For example, Iron (Fe) and Copper (Cu) are vital for life and play a vital role in enzyme system functioning. Other metals are xenobiotics in nature, they do not have any crucial benefits for human and other living organisms, e.g., lead (Pb) and mercury (Hg) at trace level exposure can be toxic. Though these metals are of great importance, they can be detrimental at high exposure. The very basic tenet of toxicology follows as: "the dose makes the poison" [6]. U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 2017) lists all the metals with their potential hazards, disposal, and toxicity level. According to the list, the order of three most hazardous metals is Pb, Hg, arsenic (As), respectively. Cadmium (Cd) is the sixth most hazardous metal according to ATSDR [7]. The metal exposure has several routes such as inhaling tiny particulate matter, ingesting them through foods, metals can be vaporized and inhaled [8]. The amount of metals that was accumulated in the digestive tract could be different based on the metal's chemical form and individual's nutritional condition. After metal accumulated in the tract, it spreads throughout the organs and tissues. Metals usually accumulated in some storage areas such as liver, kidneys, and bones for decades, as through kidneys and digestive tract, excretion primarily occurs. Metal toxicity mainly affects the brain and kidneys, though some corresponding metals such as As are able to cause cancer [9]. An individual with acute dose of metal toxicity has some symptoms which involves hypertension (exposure to lead), headache, renal toxicity (exposure to Cd), and weaknesses in body. Also these toxicities might occur even the individual has no symptoms. The diagnosis of this kind of toxicity level can be so difficult otherwise the technical body must have that expertise and knowledge to able to do correct diagnosis [10]. Due to metal toxicity, the genetic factors may become vulnerable and that study needs much intensive inquisition. A diagram of sources of heavy metal and human exposure has been presented in Fig. 1. It is also concerning that metals exposures now at low condition can cause several chronic diseases and hinder necessary functioning [11].

Dose-response relationship is an important part of the principles of pharmacokinetics and pharmacodynamics. In this relationship, the required dose and frequency with the therapeutic index for a drug are determined for a population. The therapeutic index is the ratio of the minimum toxic concentration to the median effective concentration. This index helps to measure drug's efficacy and safety. Increasing the drug dose with a minimal therapeutic index enhances the toxicity probability or drug ineffectiveness. Thus, this relationship differs by population and it is influenced by patient-related factors such as age, pregnancy, and organ function [12]. Dose-response curve has been shown in Fig. 2.

In fish, metals can transport through various pathways [12]:

– Through gills as diffusion occurs in membranes into bloodstream
– Skin contact as diffusion occurs in the bloodstream
– By drinking water
– Ingesting sediments
– Transportation in food chain

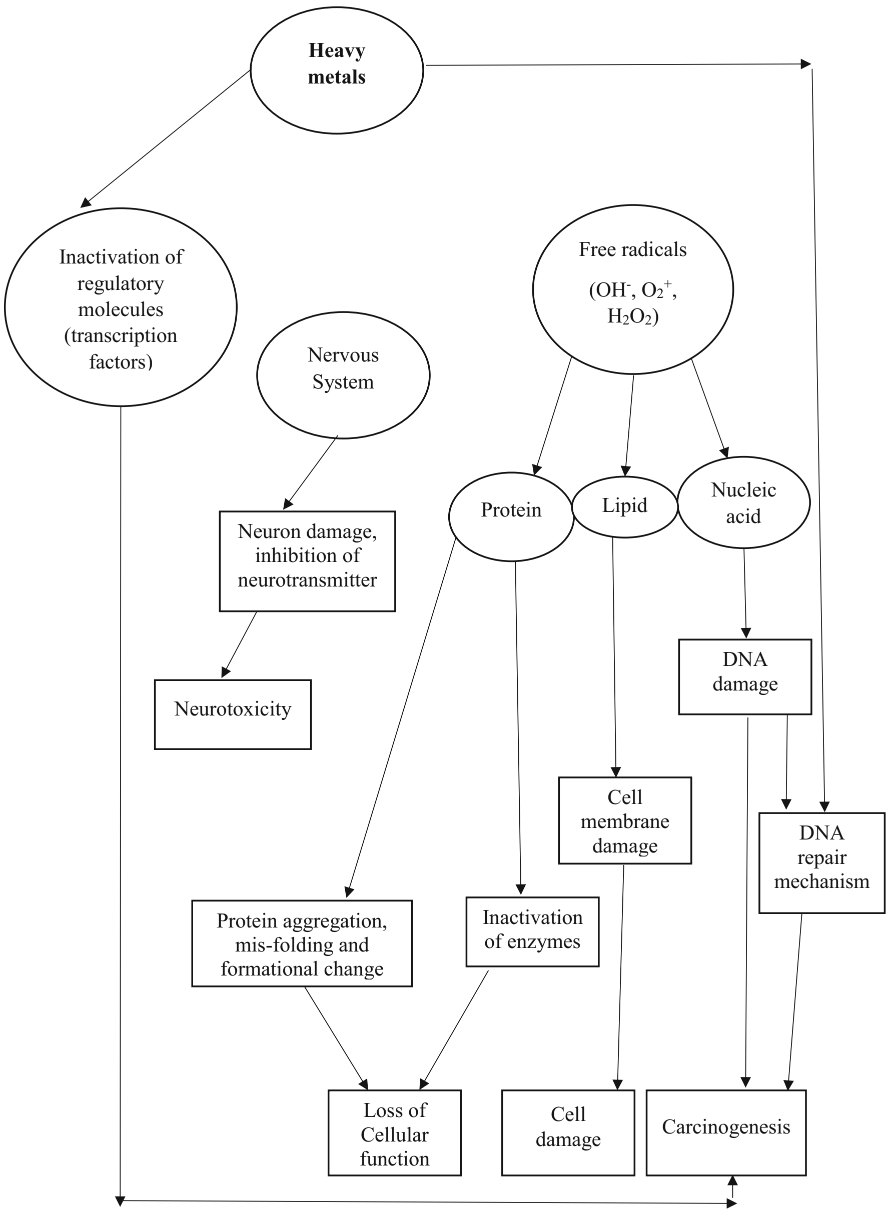

Fig. 1 Sources of heavy metals and human exposure (Modified after [2])

In humans, metals are transported through several pathways such as through lungs when humans inhale lead dust and particulate matters, through skin, by drinking metal-polluted water, through food chain, by eating contaminated food

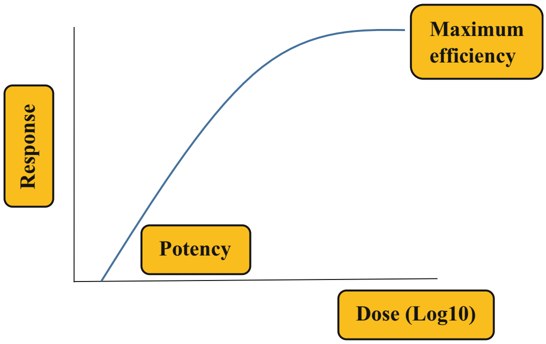

Fig. 2 Dose-Response curve

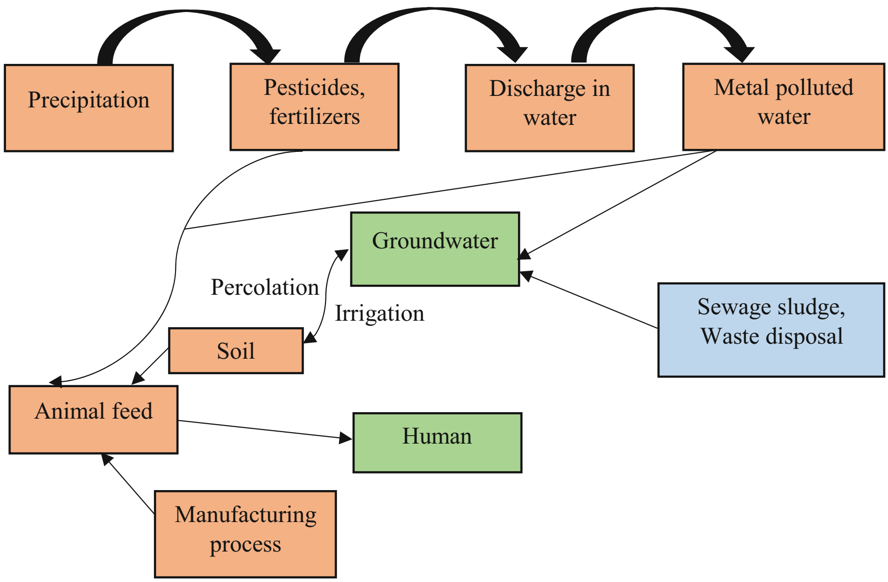

Fig. 3 Human exposure to metals through food chain (Modified after [13])

(such as for Pb, acidic juices and foods will liquefy lead from the food and juice containers). Children playing with toys that may contain Pb paint [12]. Human exposure to metals through food chain has been illustrated in Fig. 3.

The categories of metals are bit different in case of concentration. It can be essential and non-essential. Metals in low concentrations are crucial for good health and in high concentrations these are lethal [12]. Some essential metals are: chromium (Cr), Cu, zinc (Zn), nickel (Ni), manganese (Mn), and selenium (Se). Non-essential metals are: aluminum (Al), Pb, As, Hg, Cd, gold (Au), silver (Ag), and tin (Sn).

Many factors are responsible for metal toxicity in body such as metal solubility, metal's ability to bind with the biological sites, extent of metabolized metal complex formation, and much more [14]. Thus, this metal toxicity can cause severe impacts on human health as well as on the environment.

2 Properties of Metals

Metals have some notable properties which make them crucial and also make them globally-distributed pollutant [12]. Some mentionable properties are:

– Metals have luster, malleability, and ductility.
– They are the elements of rocks and mineral ores in low concentration.
– Anthropogenic activities trigger erosion, as a result metals are released in the environment.
– They remain solid at room and normal temperature.
– They form cations (positively charged ions).
– They are good conductors of electricity and heat.
– They dissolve in water and are easily concentrated in aquatic organisms.
– They trigger point and non-point source pollution.

3 Sources of Metal Pollution

Metals (toxic) can be accumulated in the environment through discharging industrial effluents, organic wastes, refuse burning, power generation, and transportation. Wind can also be a major metal pollution source because metals can be steered many places even miles away through this force, if metals are in particulate (gaseous) form [5]. Metal pollutants are then finally carried out from the air into the ground and the surface of waterways. In this way, air is also an important source for the metal pollution in the environment. Metals which are released from industrial effluents are severe pollution causing source of hydrosphere. Also the movement of drainage water from contaminated catchment areas is responsible for such pollution [15].

Mining is one of the major sources of metal pollution. Because of the mining activities, the mine tailing is being disposed in the waterbodies, which forms acid rock drainage (ARD). And then from both abandoned and operating mines, the mine tailing and ARD are released into the groundwater and surface water [12]. Some toxic metals used in industrial production [5] are shown in Table 1.

Other mentionable sources are agricultural activities which involve use of fertilizers; soil amendments from bio-solids; coal combustion such as As, Cd, Se, and Zn; urban run-off such as Cu, Pb, and Zn; industrial waste; solid waste disposal such as batteries, tires, and appliances [16]. Regulatory limits of heavy metals are given in Table 3.

Table 1 Toxic metals used in industrial production

Metal	Manufacturing purposes
As	Fertilizer, metal hardening, paints, textile
Cd	Fertilizer, electronics, paints
Cr	Metal plating, tanning, rubber
Cu	Plating, rayon, electrical
Pb	Paints, battery
Ni	Electro-plating, iron steel
Zn	Galvanizing, iron plating, steel
Hg	Chlor-alkali, scientific apparatus, chemicals

Table 2 The favorable organs of some toxic metals

Metal	Favorable organs
As	Skin and pulmonary nervous system
Cd	Skeletal, pulmonary, and renal system
Cr	Pulmonary system
Mn	Nervous system
Pb	Nervous system, renal system, hematopoietic system
Ni	Pulmonary system and skin
Sn	Nervous and pulmonary system
Hg	Renal system and nervous system

4 Metal Toxicity

Metals have impacts on human, animals, and aquatic organisms. There is an adverse biological effect of metals on organism's survival, activity, growth, metabolism, and reproduction. Mainly, the chemical activity of metal ions with the enzymatic and membrane system often causes metal ions toxicity to mammal species. Toxic metals usually target those organs which have the possibility to persist highest metal concentration such as brain and bone marrow, etc. This possibility depends on the exposure route and chemical characters of metal compounds such as lipid solubility and molecular size. Human exposure to toxic metals can also be carcinogenic such as chromium and nickel are associated with cancer causing agent [17]. The favorable organs of some toxic metals are shown in Table 2. Metals can cause both acute and chronic poisoning in human and animals [12].

Toxicity can be measured in two ways: LC_{50} and EC_{50}. LC_{50} is the lethal concentration 50 which causes death in 50% of the organisms of exposed population. EC50 is the effective concentration 50 which causes nonlethal negative effect in 50% of the exposed organisms. If there is lower amount of LC_{50} or EC_{50}, then the metal has more toxicity [12]. Regulatory limits of some heavy metals according to EPA Environmental Protection Agency, OSHA Occupational Safety and Health Administration, FDA Food and Drug Administration have been presented in (Table 3).

Table 3 Regulatory limits of some heavy metals (*EPA* Environmental Protection Agency, *OSHA* Occupational Safety and Health Administration, *FDA* Food and Drug Administration, *ppm* parts per million, *mg* milligram)

Metals	EPA regulatory limit in drinking water (ppm)	FDA limit in food or bottled water (ppm)	OSHA limit in air (workplaces) (mg/m^3)
Arsenic	0.01	–	10
Cadmium	0.005	0.005	5
Chromium	0.1	1	1
Selenium	0.05	–	0.2
Manganese	0.05	–	5
Mercury	0.002	1	0.1
Sliver	0.0001	–	0.01
Zinc	5	–	5
Lead	0.15	–	0.15
Aluminum	0.2	–	5
Barium	2.0	–	0.5

4.1 Modes of Action

Metals cause structural damage to organs especially to the tissues such as Hg injures brain. Metals inactivate the enzyme and the enzyme co-factors [18]. Metals interact in three ways as follows;

- Additivity where two metals have twice the effect of either metal (1 + 1 = 2);
- Synergism where two metals have more effect than twice the effect of either metal (1 + 1 = 3), such as Cd and Cu, Cd and Cr, Cu and Ag, and Zn and Ag;
- Antagonism where two metals have less than twice the effect of either metal (1 + 1 = 1.5), such as Zn and Cd, Zn and Pb, Hg and Se, and Hg and Cd [18].

Heavy metal toxicity mechanism in human has been illustrated in Fig. 4.

4.2 The Factors Affecting Metal Toxicity

Some factors [6, 12, 19] that affect metal toxicity in human and animals are given below:

- *Metal concentration:* In high concentration metals can cause acute effects. And in low concentration they may cause chronic effects.
- *Time of exposure and mood of exposure:* Furthermore, the continuous exposure is more hazardous than discontinuous exposure.
- *Bioavailability or speciation:* Metal concentration is not an indicator of its biological effect. Metals need to be present in the dissolved form to interact with the surface or tissues for better detection of its biological system. Metal

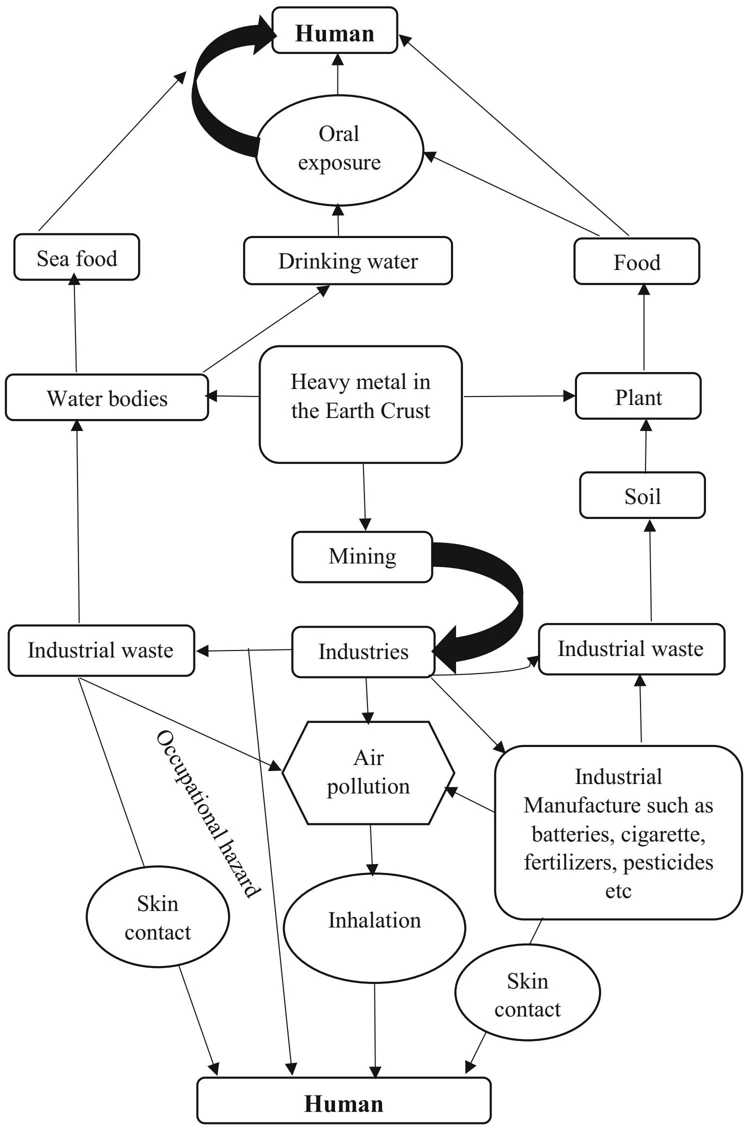

Fig. 4 Heavy metal toxicity mechanism in human (O figures → exposure routes)

bioavailability is affected by speciation. Speciation refers to different chemical forms where metal exists as its neutral element, ions, and organic forms. For example: organic and inorganic mercury, Cr^{+6} and Cr^{+3}.

– *pH:* At low pH metals are more toxic. Concentration of hydrogen ion has an impact on the metal speciation such as aluminum. In sediment, metals are being

released due to lower pH levels. On the other hand, metals are being bound in the sediment due to higher pH levels.
- *Buffering capacity*: Buffering capacity of waterbodies relies on the carbonate and bicarbonate ions concentration and affects the aquatic ecosystem susceptibility to ARD. In the buffered waterbody, metals are less lethal.
- *Salinity*: Comparing with saltwater, metals are more toxic in the freshwater because they are more bioavailable in freshwater. Chemical speciation of metal is affected by salinity, for example: Cd in the form of Cd^{+2} is more bioavailable than its elemental form and dominant in freshwater. On the other hand, Cd creates chloride complexes, which makes them less toxic and bioavailable.
- *Water temperature*: If water temperature increases, then metal toxicity also increases. $\mathbf{Q10 = 2}$ (in coldblooded animals metabolism rate is doubled with every 10°C water temperature increase). With increasing water temperature, respiratory rate, membrane permeability, and absorption rates also increase.
- *Hardness*: In soft water, metals are mostly toxic. Whereas the toxicity depends on calcium (Ca) ion concentration (Ca^{+2}), it gives protective effect. Water quality criteria for metals are based on water hardness in US, Canada, and Europe.
- *Species and individual differences*: Aquatic animals are more delicate than aquatic plants. Daphnia is planktonic freshwater crustacean where shrimp is impressible marine crustaceans. In each species, there are sensitivity differences.
- *Age and body size*: Young animals are more sensorial than adults. Young animals don't have developed detoxification enzymatic system. They have high metabolic rate, as a result more toxic metals are taken faster by them.
- *Persistence*: The time required for 50% of the metals dose to be reduced from organisms is termed as half-life. Metals such as Hg, Cd, and Pb have longer half-lives in mammal species and ultimately can create prolonged effects.
- *Detoxification*: Metal exposure can lead to metallothionein (low molecular weight protein), it has the ability to bind with some metals such as Cd, Cu, and Zn and thus lessen their toxicity. The system can be submerged if concentration of metal is too high and also if there is a continuous metal exposure.

One of the notable phenomena of metal toxicity is bio-concentration or bioaccumulation. Bioaccumulation is the phenomenon which is responsible for the increase of metal concentration in the organisms comparing with their concentrations in sediments or water. All the metals sustain bioaccumulation. Animals which live in sediment are more susceptible to metal exposure at high level [20].

Bio-magnification is another phenomenon which is responsible for metal toxicity. The term "bio-magnification" refers to the increase of metal concentration gradually in the higher trophic levels of food chain. Usually, predators sustain more metal concentration than the preys. Animals on higher trophic level have the highest metal concentration, mainly pertaining to mercury and cadmium, manganese, and selenium also [20].

Biotransformation refers to the metal alteration by the organism. Thus, the metal toxicity can be both increased and decreased. For examples, converting organic Hg with inorganic Hg can increase Hg toxicity whereas the conversion of inorganic As to organic As can decrease the As toxicity [21].

5 Metals and Their Effect on Human and Environment

There are some concerning metals that can cause residential and occupational hazards. Out of 35 metals, 23 metals are considered as heavy metals, such as As, Cd, cesium (Cs), Cr, cobalt (Co), Cu, Fe, Pb, bismuth (Bi), antimony (Sb), Au, Mn, Ni, platinum (Pt), Ag, Hg, Sn, Zn, uranium (U), vanadium (V), and tellurium (Te) [22]. They can be naturally occurring. Though some of them are required in trace amount for health, higher concentration of these can be dangerous for health. Metal can affect the human body and environment in several ways [23]. Heavy metals can damage energy levels, hinder the human body function, even damage organs such as liver, kidneys, brain, and blood, and cause Parkinson's disease, Alzheimer's disease. It can induce either acute or chronic health effects. Long-term exposure of such metals can even cause cancer [24]. Some heavy metals above the tolerable concentration can be found in the environment. For proper defensive measure to avoid excessive exposure, the knowledge of heavy metals is required [25]. Some important metals such as Pb, Hg, Cd, Cu, As, Cr, Mn, Al, and Ag with their effects on human health and the environment are discussed here in the below.

5.1 Pb and Its Effects

For decades, intensive focus has been provided on Pb in environmental health research. Pb is mined and used in industries and production for millennium, thus modern industrialization introduced mass production of household products, paint, candies, toys, ceramics, cans and other products in the twentieth century. For the past 60 years, Pb has been used as antiknock vehicle fuel additives, which is major source of environmental disruption worldwide [26]. The annual production rate of Pb is raising from 5.4 million tons currently. Around 60% Pb has been used in battery manufacturing, rest of them are used in solder, cable, gasoline additive and plastic production etc. Such productions are posing a considerable risk to individuals as well as the prevailing communities. Because of the risks, several developing countries have taken necessary actions which have limited the actual exposure of Pb over the last 25 years [27]. Several sources are responsible for Pb pollution in the environment such as gasoline and pigments, factory chimneys, ore smelting, pesticides and fertilizers, metal plating, battery wastes, soil wastes, automobile exhaust and so on. Pb accumulation pathway in human are diverse such as inhaling Pb dust, drinking Pb contaminated water, eating contaminated food (acidic juices and foods will liquefy Pb from the food and juice containers. Children playing with toys that may contain Pb paint [13, 28]. Pb is easy to find and mine, has multipurpose. Pb undergoes corrosion and stain, delivers brightness to paint dye, gives support to be attached on the woods. Pb^{+2} is the most bioavailable form of Pb and successfully binds with sediments [27]

Several factors are responsible for the Pb exposure effects, such as water having low pH (acid rain water) can release more Pb from Pb solder plumbing in respect of high pH water [29]. In soil environment, Pb tends to persist in root vegetables like onions and vegetables such as spinach [30]. If people do not have enough Ca, Zn, or Fe in their diets, then there is a high possibility to absorb more Pb in their diets [28].

For the toxicity level measurement, humans have focused on the method development such as GFAAS (Graphite Furnace Atomic Absorption Spectroscopy), a technique used for surveillance and research, which can be used for the precise Pb measurement in blood (mg/dL). According to general dose, children and adults Pb exposure can create a great health problem such as coma, renal failure, effects on metabolism, intelligence (low exposure) and even death (at high dose) [31]. Children are particularly vulnerable to neurotoxic effects of Pb. According to epidemiologic studies, Pb exposure at low level in children (<5 years) was found in the range of 5–25 mg/dL which may hinder their intellectual development [28]. Because of that Centers for Disease Control (CDC) has lowered the allowable concentration of Pb in children blood ranging from 25 to 10 mg/dL. And it is also recommended that children from 6 months to 5 years old must do universal blood Pb screening [32].

Impacts of Pb on Human Health Even at markedly low level exposure, Pb is very viral for humans. Pb can cause both chronic and acute health effects depending on the dose and exposure condition. Pb mainly targets the nervous system, hematopoietic system and renal system, thus causing anemia, neurological, cardiovascular, renal, gastrointestinal, hematological, and reproductive effects. Through blood examination, Pb exposure to human can be measured. Pb tends to persist in the bones in re-mobilized form hence can cause Pb exposure late in the individual life [2]. Primary sources of Pb exposure are industrial dust and fumes inhalation and contaminated food consumption. Inhalation is one of the most prominent exposure pathway for human triggering point source pollution such as Pb contaminated sites and generated waste from production contains Pb which is then burnt. Another major source of Pb pollution is drinking contaminated water [28]. Home dusts can contain Pb paint which can be inhaled by both adults and children and ingested by children through eating behavior. Pb can have several deleterious effects on human health such as by accumulating in teeth and bones, Pb can persist there and can act as transporter of Pb in the bloodstream because half-life of Pb is around 20 years [4]. Pb mainly targets the bone marrow and brain as reservoir. So, Pb toxicity is much more severe if the diet is calcium deficient. There is no safe level for children. By measuring Pb concentration in blood, Pb exposure can be evaluated. Around 250 parts per billion (ppb) was taken into account as safe level till 1970. And then according to the revised recommendation, the safe level of Pb was checked from 50 to 100 ppb [12]. Pb has some neurological impacts also such as hyperactivity, imperfect attention span, and low IQ in children. Pb interferes with Ca transportation in the neuron membranes. The linkage between Pb exposure and cancer is yet to be evaluated though more studies are needed to address the probable linkage between Pb exposure and several cancers [33].

Impacts of Pb on Aquatic Organisms Pb can be found in water up to 500 ppb injures algae. Pb obstructs the necessary enzymes to perform photosynthesis, lessen the absorption capacity of water, inhibits growth (greater than 50 ppb injures fishes) [12].

Impact of Pb on Animals Pb creates poisons for animals, which is termed as avian plumbism for birds. This disease is caused by high concentration of exposure in animals. Pb enters into animal's body through several processes [2]. Pb is toxic for several organs such as kidneys, heart, bones, hematopoietic system, nervous system, and reproductive system. Pb also affects the red blood cell formation by inhibiting aminolevulinic acid dehydrogenase (ALAD). Pb affects the enzymes of sulfhydryl group and erythrocyte thiol contents. It is viral for domestic animals such as cattle, dogs, and small animals. In animals, Pb poisoning can be acute and chronic which can readily cause death [19].

Physiological and Biochemical Impacts of Pb Pb also interferes in the enzymatic process for hemoglobin synthesis. Pb causes birth defects, kidney dysfunction, anemia (usually found in children having Pb concentration $>$ 400 parts per billion in bloods). Around 1,200 toys were tested by using X-ray fluorescence analyzer. It was found that Pb levels were at 12–23 ppt in weight [10].

5.2 Hg and Its Effects

Hg is a naturally occurring metal which is an odorless liquid, colorless as vapor and has silver-white shiny feature. It is very viral and also bioaccumulative. It has severe impacts on the environment, particularly in the water environment. Primary sources of Hg pollutions are some man-made activities such as wastewater discharge, incineration, mining, agriculture, and so on [34]. Hg can be toxic for biological system even if they prevail in trace amount. Hg is used in several activities worldwide such as: in chlor-alkali 13%, batteries 9%, dental amalgam 9%, electronic equipment (5%), vinyl chloride monomers 21%, lamps (4%), measuring devices 9%, gold mining 22%, and others 8%. Hg toxicity is based on the form in which it accumulates in body such as elemental form, organic or inorganic form (alkyl-Hg compounds: methyl-Hg, dimethyl-Hg, and ethyl-methyl Hg). Hg remains in nature in these forms: elemental, organic, and inorganic Hg, having their own different toxicity levels. These three forms can be found in water environment such ocean, river, lakes where it is taken up by the microorganisms and converted to methyl-Hg within them, thus causing bio-magnification and aquatic environment disturbances. Human methyl-Hg exposure mostly occurs due to consuming these contaminated aquatic lives [15]. In case of methyl-Hg (potential neurotoxin), ingestion of contaminated food is one of the major reasons of Hg toxicity exposure, mainly for fishes. About 80% of inhaled elementary Hg vapor is accumulated in the lungs tissue where they enter in the blood-brain barrier causing neurological and renal effects [35]. Neurological effects are considered as hindering human brain development. Though elemental Hg ingestion does not cause high level of toxicity but deaths have been recorded. Elemental Hg vapor inhalation has caused some severe symptoms such as insomnia, memory loss, thyroid, headache, shivering, also damages kidney [19]. Also, organic and inorganic Hg toxicity can be triggered by using fairness creams, soaps, and medicines. Hg passes easily through the placental barrier and blood-brain barrier causing severe exposure during pregnancy. According to International Agency for Research on Cancer, methyl-Hg is regarded as a potential carcinogen [7].

Hg Speciation Speciation of Hg can be in various forms such as elemental Hg or metallic Hg (Hg^0), inorganic Hg (Hg^{+2}), organic Hg (methyl-Hg). As bacteria (methylate Hg^{+2}) at water–sediment interface, methylation is forwarded by low pH and high dissolved organic carbon. Methyl-Hg (CH_3Hg^+) is the most persistent, lethal, and lipophilic form [12].

Impacts of Methyl-Hg on Fish Fishes are relatively impassible to toxic effects of methyl-Hg and can endure up to 10 times as much methylmercury as humans. Methylmercury storage in muscle tissue can detoxify methyl-Hg. If the levels of methyl-Hg are high, then unfavorable conditions may arise such as decreasing rates of egg hatching, impairing growth, and development [15].

Impacts of Methyl-Hg on Human Health Hg exposure may cause Alzheimer's disease [36]. This disease is considered as one of the top four death causing diseases, particularly responsible for mortality in the USA. This disease has affected over five million people, which will increase to 16 million affected by 2050 [37]. Methyl-Hg exposure may cause autism spectrum disorder which is a neurological disorder [17]. Several impacts can be seen due to methyl-Hg exposure such as memory loss, weak muscles, hand paralysis, disability in eye-hand coordination, vision and speech loss, impairment in consciousness. Children are at higher risk of methyl-Hg exposure, birth defects, cause cancer, prolonged exposure can damage kidneys even death [2]. Methylmercury toxicity mechanism in human body and affected organs (critical) has been illustrated in Fig. 5.

Impact of Hg on Animals Hg has detrimental effects on neurological and reproductive systems of wildlife. This effect has been for a while as contaminating source of freshwater bodies [12]. Hg enters into the animal's body, persists in the tissue for prolonged period, affecting their physiology. Fish from the water body, the birds (eagles and loons) which eats these fishes all are interconnected in this process [5]. A recent study by New York State scientists and other researchers in the Adirondack region reiterated this problem by showing that common loons (below) with high Hg levels exposure produced fewer off-springs (chicks) [18].

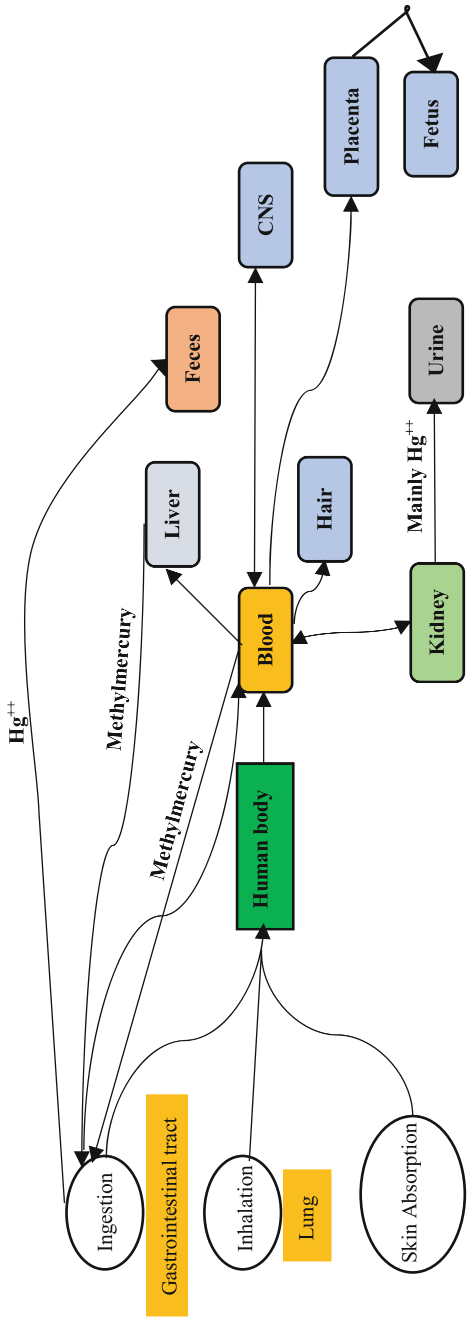

Fig. 5 Methylmercury toxicity mechanism in human body and affected organs (critical)

Minamata Bay Incident In 1907, Chisso factory near Minamata Bay started to produce acetaldehyde and vinyl chloride. And then in 1932, mercuric oxide (HgO) catalyst started to be used in production. Because of this continuous discharge, around 150 tons of Hg was discharged from the period of 1932 to 1968. Hg was present in that the bay in the form of bacteria methylated Hg^{+2}. Minamata Bay had many fishes, so people and seabirds ate those fishes from the bay. Methyl mercury concentration is millions of times stronger in top food chain than water. As a result, such disease called "Minamata disease" was occurred. In 1956, a completer linkage between the Minamata disease and methyl mercury was identified [38].

5.3 *Cd and Its Effects*

Cd is not such crucial element for human biological functions. Cd exposure has some effects on human health and ecosystem [39]. Mammal species can be exposed to Cd through inhalation (tobacco smoking) and ingestion pathway. Cd mainly targets renal and pulmonary system. Major health impacts from Cd exposure were recorded through dietary exposure. These exposures can cause kidney, lung, and bone damage [40]. Around 90% of Cd exposures through dietary intakes recorded for non-smokers. Cd can be viral for animals, organisms, and plants. Cd deposited in toxic form in the environment causes bioaccumulation in the kidneys and liver of both vertebrates and invertebrates. Cd can enter into the environment from various man-made sources. Wastewater is one of the notable sources of Cd contamination in the environment [41]. Industrial air emissions and worldwide use of fertilizers in soil for agricultural activity are also some emerging sources of Cd. Iron and steel production (20% Cd exposure), fossil fuel (33% Cd exposure), waste incineration (2% Cd exposure), cement, and other (1.2% Cd exposure) such human activities are responsible for human Cd exposure [42]. Plants such as rice and tobacco which are grown in contaminated soils can take up Cd and Pb through inhalation and human dietary exposures. Furthermore, Cd contaminated soil can cause human exposure when it is disturbed, and the Cd dust inhaled by humans [43].

Cd Toxicity Cd hinders Zn metabolism, disturbing Zn containing enzymes. Thus, gastrointestinal absorption occurs and ultimately replaces Zn in metallothionein. It also binds with Ca which may cause osteoporosis, Cd deposition in bones may cause hypercalciuria. It decreases Cu concentration in liver and decreases ceruloplasmin concentration in plasma. It also binds with Fe, decreases the concentration of hemoglobin and hematocrit, thus causing [44]. Cd exposure toxicity has been illustrated in Fig. 6.

Effects of Cd on Human Health Cd can cause acute and chronic health effects such as anemia, deformation in skeletons, loss of bones, kidney dysfunction, obstructs necessary enzymes to perform absorption in tubules of kidney. It can be a potential carcinogen on higher dose [46]. Diets such as rich in red meat, sea fishes can often contain high Cd intakes, cause kidney and liver damage, elevated

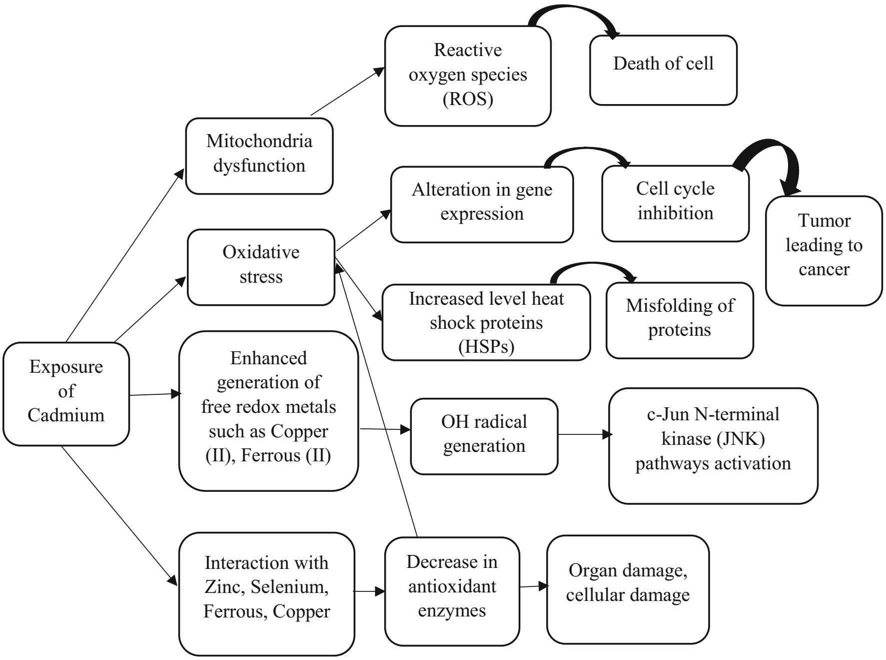

Fig. 6 Cd exposure toxicity mechanism in human body (Modified after [45])

frequency of stone (kidney) formation. Smokers are marked as the higher risk bearer than people with less iron levels. The secondary health effects of Cd are skeletal damage which is caused by the damage in kidney through Cd exposure [47].

Effects of Cd on Aquatic Organisms Cd can also affect aquatic organism's health: Such as Cd impairs the growth of aquatic plants, deformities in skeleton of fishes (in bones Cd replaces Ca), reduces the survival rate of shell fish, as well as causes kidney tubules dysfunction in fishes [46].

Effects of Cd on Animals In animals, prolonged inhalation or ingestion exposure of Cd causes detrimental effects on the liver, lung, kidney, bone, nervous system, immune system, and blood. Cd can affect the bone tissues on young animals [43].

Cd and Itai-Itai Disease Kamioka Mine situated 40 km away of Fuchu Town had discharged untreated effluent containing Cd to the rice paddies from 1920. Rice plants absorb Cd spontaneously. So, people of the area consumed those contaminated rice for around 30 years and were disclosed to 600–1,000 mg of Cd everyday which exceeds twice the toxicity level. In 1950, people from Fuchu Town, Japan (near Toyama City in Jinzu River Basin) confronted several pains in joint, muscle, and bones, also they faced severe dysfunctions in kidney. Even caused death of some people living there [48].

5.4 Cu and Its Effects

Cu is categorized by the USEPA as Group D carcinogen though it has not been listed in new cancer classification category. Cu is an essential natural metal, needed in trace amount (5–20 ppm) as nutrient [5]. Cu presents in soil at an average concentration of 50 ppm. It is found in plants and animals. It acts as an essential nutrient for human and for animal where it is needed in small quantity. It is an important component of human body because it reacts with iron and creates red blood cells in body. It is a component of enzymes which helps to form hemoglobin and hemocyanin and also supports carbohydrate metabolism. It is responsible for functioning of more than 30 enzymes. It helps to grow healthy hair in humans. Moreover, at concentration of more than 20 ppm, Cu^{+2} is viral [49]. The chief sources of Cu releasing in the environment are mining, sanitary fittings, containers, smelting, birth control pills, and Cu refining, industrial production such as wires, pipes, and fossil fuel combustion. Water line pipes are usually made of Cu and bath settings also are made from bronze and brass alloys which comprise Cu [12]. The chief source of Cu in drinking water is Cu leaching from water pipes and bath settings because of acidic water. Even Cu in water leaves some blue-green spots in bath settings. The other primary sources are as pesticides in agricultural field, used to remove algae from waterbody. Some metabolic studies recorded that oral ingestion of Cu ranges from 24 to 60%. The absorption capacity of Cu depends on some factors such as dietary condition, Fe and Zn presence in food. No studies have been conducted to measure the skin and inhalation exposure of Cu. Though few studies depicted that skin absorption of Cu was very low, the Recommended Allowance (RA) of Cu for adults is 0.9 mg/day. The highest safe level of Cu intake for a lasting period of time (chronic exposure) is 10 mg/day. Metals, beans, cocoa, shell fish are rich in Cu [50].

Toxicity of Cu Cu is able to bind with sediments and organic matter in soil. Cu is highly viral for aquatic organisms. Adrenaline, aldosterone, and cortisol are released due to stress. Adrenal gland is also affected by stress, retaining Cu and reduces Zn. Aldosterone mechanism follows by Na and Cu which secretion increase the reduction of Zn and Mg. Zn is important for toxic heavy metal removal (Cu). Mood swing and mind can become troubled when brain starts to be saturated by Cu. Cu saturation may limit the presence of important neurotransmitters in brain which helps to keep brain Cu functioning static [51]. Cu binds with necessary protein-enzymes such as ceruloplasmin and metallothionein to enter into the cell and mitochondria use these proteins in the Krebs cycle to form ATP. Liver mainly receives adrenal glands signal to form these proteins. Any dysfunction in adrenal glands and liver may relate to unbound and release Cu thus Cu will start to accumulate in blood [12]. Cu may also accumulate in lysosomes, mitochondria causing necrosis and cellular degeneration. Higher Cu level in blood may cause erythrocyte membrane weakness causing fragility thus hemolysis (hemolytic crisis). Cu may cause hemoglobin oxidation forming methemoglobin (cannot carry oxygen). Fish species such as shell fish and fin fish are around ten to hundred times more susceptible to Cu than mammal species [12]. Algae are more sensitive to Cu mammal species (around

1,000 times). When dissolved organic carbon is present in the waterbody then Cu is less viral. The Cu level in blood, hair, liver biopsy are some reliable indicators of copper toxicity. Hemoglobin level, serum copper, and serum ceruloplasmin can be helpful for the diagnosis, as Cu accumulates deep in the liver and brain [5].

Impact of Cu on Human Health and Animals Cu plays an important role in human body function. For example, in bones and connective tissue, Cu is necessary to bind with Ca to form connective tissue and repair them all. Such imbalances may cause osteoporosis, skin, nails and hair damage also. Cu plays an important role in cell's energy production. Cu is required in the electron transport system which is termed as energy cycles final stage and produces cellular energy. Any imbalances here may cause depression, fatigue, and low energy Cu [51]. For immune system, Cu must be in balance with Zn. Any imbalance may cause infections such as yeast and fungal infections. Cu can affect thyroid gland, glandular system, adrenal system. Cu imbalance may cause premenstrual syndrome, cysts, miscarriages, sexual malfunction, even hyperthyroidism, Wilson disease, Menkes disease, and Grave's disease [52]. These all can occur because of stress and Hg exposure as well. It may affect reproductive system, for example Cu is related to estrogen metabolism which is necessary for pregnancy and women's fertility and man's potency. It can affect the nervous system also. Cu increases the production of the neurotransmitters such as epinephrine, dopamine, and norepinephrine. Cu imbalance may affect psychological and neurological conditions such as loss of memory in young people, schizophrenia, anxiety, and depression. Cu deficiency may cause anemia, hindering white blood cells formation, osteoporosis in infants and children, and defects in tissue, skeletal problems. There is relatively low copper toxicity in humans because of Cu detoxification process by metallothioneins in kidney and liver [53]. The drinking water standards for Cu are developed depending on the taste, not on the toxicity risk. Acute or short-term effects of Cu are: more Cu ingestion may cause temporary gastrointestinal distress with nausea, abdominal pain, and vomiting. High Cu dose can damage liver, even can cause death. High level Cu exposure may cause red blood cells decimation, ultimately causing anemia [49]. Chronic or long-term effects of Cu are: kidney and liver damage (high dose), mammal species have versatile mechanism to store Cu in the body that they are usually protected from over plus dietary copper levels. Wilson's disease is a genetic inherited disorder in which Cu stores in liver. Liver toxicity has some severe symptoms such as jaundice, swelling, headache usually does not appear at young age [2]. It can be a potential carcinogenic, causing cancer. Studies have showed that Cu has high cancer risks, especially in workplaces, as workers are exposed to chemicals having carcinogenic capacity. Though in animal, Cu cancer risk has not been found. Cu has some reproductive and developmental effects also. Though the developmental effects have not been recorded in human but in animals some effects have been occurred such as animal growth and developmental processes can be hampered at high Cu dose, hinder bone formation, lessen the body mass and litter capacity [51] Copper toxicity mechanism in human body and their outcome have been illustrated in Fig. 7.

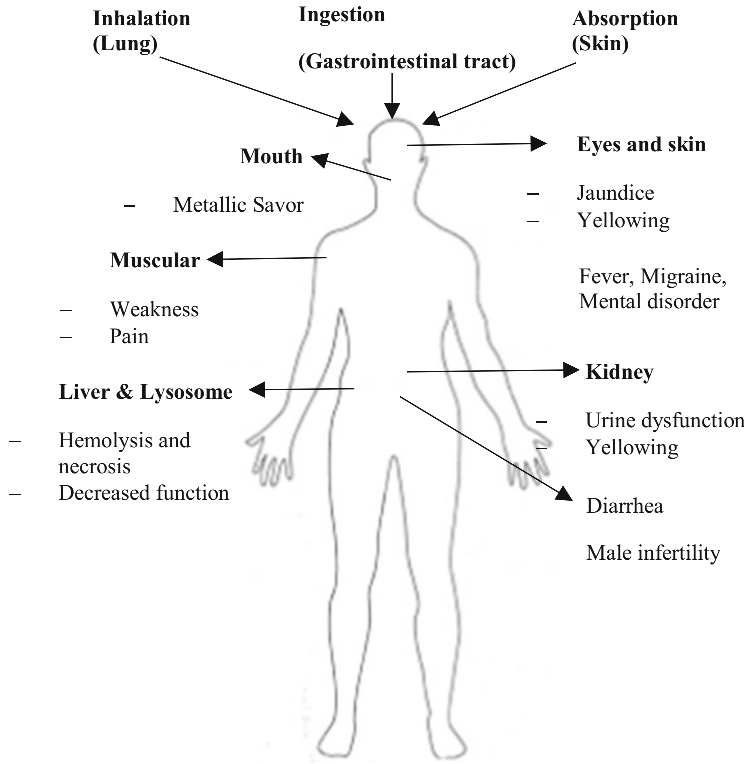

Fig. 7 Copper toxicity mechanism in human body and their outcome

Impact of Cu on Fish Fish species such as shellfish have some considerable individual effects of Cu such as it lowers the metabolism rate of clams especially in estuaries. It also affects shell fish population by lowering the egg and sperm production is sea, exposing to Cu concentration around 10–20 ppb [12]. In fin fish, Cu inhibits osmoregulation by intervening the sodium uptake process in the gills. Cu also has some neurotoxic effects such as it meddles with olfaction, as a result disrupted olfaction process obstructs migration, salmon habitation, and predator avoidance. Cu has effects on their food intake and growth, damages kidney, lessens the survival rate of juvenile fish. Cu has some sub-fatal effects on rainbow trout also. Stress in rainbow trout occurs at relatively low Cu exposure (1.4 ppb), causes hyperactivity in population, increases cortisol level in bloodstream, in liver it forms metallothionein [54].

Cu Effects on Ecosystem Cu limits the algal growth, responsible for death of beneficial insects such as mayflies, causes emergence of insects which can undergo water pollution. These variations will have an impact on fish species appearances. Cu has continuing effect throughout the ecosystem [5].

5.5 As and Its Effects

As can be present in three allotropic forms: grey, yellow, and black. The stable form is silver-gray and brittle-crystalline solid. As rusts easily in air and at high temperatures, thus, it forms As trioxide. Non-metallic form of As is not that much reactive. As and its compounds are widely used in special type of glass manufacturing, also in wood preservation [2]. As gas AsH_3 is an important dopant gas in micro-chip industry, although it is extremely viral which requires strict guidelines. China is the chief exporting country of As worldwide. World resources of As in Cu and Pb ores are around 10 million tons. In the nineteenth and twentieth century, As and its compounds were used in medicine. As is found in small concentration naturally on Earth's crust. It is found in minerals and soil and thus enter into the air, land, and water through run-off and dust. As originates from various sources such as micro-organisms that release volatile methyl-arsines to around of 20,000 tons per annually and from volcanoes that release about 3,000 tons of As annually. Anthropogenic activities are more responsible for such As pollution. By burning fossil fuel, man-made activities release around 80,000 tons of As annually. As is known as potential poison though it is needed in trace amount for human (maybe) and animals. The required intake of As is around 0.01 mg/day which is as much as low. As is a hard component that can't be turned to water-soluble form or volatile form easily. As is an unstable metal, so for that high concentration does not actually stay at a site for a longer period. Despite this characteristic, it might have some negative impacts too because it disperses easily. Because of human encroachment activities, such as melting and mining, the As forms, which were immobilized, have started to mobilize now. As a result, they can be found in many places where it is not supposed to be found. Many As forms may be found in combination with minerals and sulfur such as Arseno-pyrite (AsFeS) and orpiment. From As's oxide form, the worldwide production of As is around 50,000 tons annually, excessively used in industries [55].

As Toxicity As toxicity may arise from bio-transformation activity, where detrimental inorganic As compounds are methylated by microorganisms such as bacteria, algae, fungi, and even by human forming mono-methylarsonic acid (MMA) and dimethyl-arsenic acid (DMA). In this process, inorganic As is enzymatically transformed to end metabolite (methylated arsenicals), which is responsible for chronic As exposure [18].

$$\begin{aligned}\text{Inorganic Arsenic (V)} &\rightarrow \text{Inorganic Arsenic (III)}\\ &\rightarrow \text{Mono} - \text{methylarsonic acid (V)}\\ &\rightarrow \text{Mono} - \text{methylarsonic acid (III)}\\ &\rightarrow \text{Dimethyl} - \text{arsenic acid (V)}.\end{aligned}$$

In bio-methylation process, the end products are mono-methylarsonic acid and dimethyl-arsenic acid. These compounds are excreted through urine, which indicates chronic As exposure. Under specific conditions, mono-methylarsonic acid (MMA) in the form of MMA (III) generally is not excreted and stays as intermediate product in the human cell. It is highly toxic compared with other forms, which can ultimately cause As related carcinogenesis [56].

Effects of As on Human Health As has some toxic effects though inorganic form of As is found naturally. Humans can be exposed to excessive As concentration through eating contaminated food, inhalation of polluted air, and drinking contaminated water. Through skin absorption or skin contact with water and soil, humans and animals can be exposed to As [50]. Soluble form of inorganic As may have immediate toxic effects. So, ingesting large quantity can cause severe gastrointestinal problems such as vomiting, dysfunction in blood, impairment in nervous system, and even death. If not that deadly, these large doses may diminish blood cell formation, disruption in red blood cells formation in the blood circulation, liver enlargement, skin colorization, limbs sensation impairment and can cause brain damage. The interrelationship between As exposure and health effects is of great concern [33]. From the studies it is depicted that As causes high blood pressure, heart attacks, and other circulatory disease. Though in case of diabetes and reproductive effects, As sensitive is not recorded yet, it causes long-term neurological effects and causes cancer at sites other than lung, bladder, kidney, and skin. Also, it causes skin changes such as hyperkeratosis and colorization. These effects have been visible in several studies [50]. Dose–response relationships and As risks have been demonstrated in various studies. Drinking-water having As concentrations of 50 μg/L can cause As related skin damage. Inhaling As through occupational exposure can cause lung cancer. It has also been recorded that the risk of As related health effects increased at cumulative exposure levels ≥ 0.75 (mg/m^3) $\times$ year (e.g., 10 years of exposure to a work area air concentration of 50 μg/m^3 As) [12].

In food, As can find in lower amounts, but in fish and sea food As concentrations can be high because in water fishes absorb As through discharge. Fishes that absorb high amount of inorganic As can be dangerous for human health. At workplace, people can be exposed to higher levels of As due to occupational exposure. Also, in houses (furniture), farmlands (pesticide use), people can be exposed to As. Inorganic As exposure may cause several health problems such as stomach irritation, less formation of red and white blood cells, lung irritation, skin type change. Also several studies have concluded that exposing to high amount of inorganic As may develop the chance of several cancer formation such as lymphatic cancer, lung cancer, skin cancer, and liver cancer. Also a very alarming exposure to inorganic As may cause skin irritations, increased infections, heart failure, miscarriages, infertility in women, brain damage, and more. Ultimately, inorganic As can cause DNA damage. A toxic dose of As oxide is considered as 100 mg. Organic form of As does not harm DNA or cause any cancer. But exposure to significant concentration of organic As can have impact on human health such as stomach aches and nervous system damage [57].

Effects of As on Plants and Animals Human interferences prolongs As cyclic process in the environment. As a result, huge amounts of As are being discharged in the environment, animals, and aquatic organisms. Pb, Zn, and Cu producing industries may produce As [5]. In agricultural processes As can be released in the environment, once it is entered in the environment, it can't be removed, so the amount increases over time by both anthropogenic and natural activities. Thus, causing prolonged health effects to plants and animals everywhere. Plant absorbs As readily, in these foods, high concentration of As might be present. Inorganic As is very toxic. So, toxic inorganic As concentration is found in surface water which readily changes the genetic mechanisms of aquatic animals, especially of fish populations. This kind of toxicity is being generated by As accumulation in bodies of organisms that eat those fishes from freshwater. Generally, bird eats these fishes that have high concentration of As presence causing As poisoning to aquatic organisms, fish populations start to die and decompose [58].

5.6 *Cr and Its Effects*

Cr is a hard metal with silver-gray color. It does not rust in air, when it is heated, it forms chromic oxide (green). Cr is impermeable to oxygen. According to International Agency for Research on Cancer (IARC), Cr and its trivalent compounds have been listed within Group 3 (it is not classified as carcinogenicity characteristics to human). OSHA does not consider Cr as a carcinogen [2]. Cr is an essential metal that is found in coal, petroleum, steel, catalysts, fertilizers, pigment oxidants, and metal plating tanneries. Cr is used in industrial production such as electroplating, coating of silver mirror, metallurgy, paint and pigment production, dyeing catalyst, leather tanning, mold making for bricks, paper and pulp production. Cr in the form of Cr (IV) oxide- (CrO_2) is used to produce magnetic tape. As a result, the industrial activity plays a concerning role in Cr releasing in the environment causing harmful effects to human, plants, animals, and ultimately to ecosystem. Anthropogenic activities such as sewage disposal, fertilizer usage trigger the chromium release in the environment. As well as agricultural practices are responsible for the Cr contamination. In recent year, Cr in hexavalent form Cr^{+6} is severely responsible for environmental Cr contamination [12]. Cr is mined in the form of Cr which is $FeCr_2O_4$ ore. Cr ores are mined worldwide. Around 14 million tons of chromite ore are being extracted. Worldwide reserves of Cr ore are 1 billion tons [3].

- *Cr ions on Human Health:* Through breathing, drinking, eating or skin absorption, human can be exposed to Cr and its compounds. In air and water, Cr is found in lesser amount. In drinking water, its concentration is low also. But contaminated water might contain Cr (IV) or Cr (VI). The main route of Cr exposure to human body is through food that contains Cr (III). This form of Cr is readily found in fruits, vegetables, yeasts, meats etc. The way of food packaging, preparation, and storage may change the Cr quantity in food. Food storing in cans and tanks may increase the concentration of Cr in the food. Cr (III) acts as nutrient for humans and its deficiency can cause heart diseases, diabetes, metabolic activity disruptions. But human exposure to high amount of Cr (III) may affect human health such as causing skin rashes. Unlike Cr (III), Cr (IV) is very toxic to human health. Especially at workplace, people working in textile and steel factories may expose to this compound. Also tobacco users have the highest chance of Cr (IV) exposure. This compound can cause severe health impacts such as from leather items, allergy and skin reaction may happen (skin rashes). Inhalation of Cr (VI) may cause nose bleeding and irritations. Some severe health problems of Cr (VI) are: skin rashes, liver damage, kidney damage, genetic mechanism alteration, immune system damage, ulcer, stomachaches, respiratory diseases, cancer (lung), and even death. The human health problems to Cr exposure depend on the Cr's oxidation form. Cr in its metal form has low toxicity. Cr in hexavalent form is very toxic. Some adverse health effects of the Cr (VI) form are: ulcer formations, nasal septum's mucous membrane perforation, bronchitis, edema, allergic reactions, skin irritations, dermatitis, and respiratory diseases (breathing shortness, nasal itchiness) [12, 59]. According to National Toxicology Program (NTP), Cr and its trivalent compounds can be considered as carcinogen. NTP provided evidence of Cr carcinogenicity in animals. Some forms of Cr that can show carcinogenicity are: Cr (VI): Calcium chromate, chromium trioxide, strontium chromate, and zinc chromate. Hexavalent form (Cr^{+6}) of Cr is the most viral, though some other forms of Cr such as Cr (III) compounds are less toxic and cause little or no health problems. On the other hand, Cr (VI) tends to be corrosive, thus cause swelling and redness of skin (allergic reactions) to the body. Furthermore, inhalation of Cr^{+6} may cause anemia, nose lining irritation, and nose ulcers. It may cause stomach ulcers (mostly in chromate worker), sperm damage in male reproductive system. Therefore high Cr^{+6} dose can cause severe respiratory, hepatic, gastrointestinal, and neurological effects and even death. High chromium exposure can cause inhibition of erythrocyte glutathione reductase, which readily lessens the ability to convert methemoglobin to hemoglobin. In both in vivo and in vitro experiments, it has been seen that in several ways chromate compounds can cause DNA damage and chromosomal aberrations and DNA transcription. Human can be exposed to higher dose of Cr (VI) through drinking water. Also, some potential evidences show that Cr can induce carcinogenicity to human, in animals chromium can cause stomach tumors [60].

5.6.1 Effects of Cr in Plants and Animals

Cr and its compounds differ in characteristics and cause effects on plants and animals. Through anthropogenic process and natural processes, Cr in the form Cr (III) and Cr (VI) enters in the soil, water, and air and ultimately in the entire environment. Steel, textile, and leather production industries are main responsible body for this high concentration Cr (III) exposure to living things. Thus, Cr level in the water has been increased by discharging industrial effluents in the water body [16]. Man-made activities such as coal combustion are also responsible for the high concentration dispersal of Cr in the air. Waste disposal will eventually increase its amount in the soil. In the air, Cr is end to persist and then goes to soil or water. Cr readily attaches with the soil particles as a result Cr does not flow through the groundwater. Sediment would absorb Cr in water and produce unstable form. Finally, only smaller amount of Cr can be dissolved in water. Cr (III) is a crucial element for organisms which can disrupt sugar metabolism causing heart diseases, when the daily uptake is too low [61]. Cr (VI) is dangerous to organisms. Cr (IV) can change the genetic mechanisms and can cause different type of cancer. Crops have some system which regulates the Cr concentration in a significant way that it remain at low level and did not cause any impairment. If there are higher concentrations of Cr in soil, that will eventually increase the Cr concentration in crops too. Cr uptake of crops is influenced by soil acidification process. Plant usually takes up only Cr (III). This is an important chromium form, but negative effects can occur when concentration will be much higher [5]. In fish, Cr does not accumulate in their body. Metal products disposal may trigger the high Cr concentration in surface water. That can damage fish gills present at the point of disposal. In animals, Cr can cause severe health hazards such as birth defects, infertility, weakness, ulcer, tumor, respiratory diseases, and disability to fight disease [3].

5.7 Mn and Its Effect

Mn is a very important element for iron and steel production. In present days, steel making comprises 85–90% of total demand and other most of the demand. Mn is the basic component of cheap stainless steel formation and widely used in aluminum alloys. Mn in the form of Mn dioxide is used as a catalyst. Mn is widely used to de-colorize glasses and create violet color glasses. Potassium permanganate is one of the strong oxidants and is used as disinfectant widely. Manganese oxide (MnO) and manganese carbonate ($MnCO_3$) are used in fertilizers and ceramics and $MnCO_3$ is used especially for making other Mn compounds [1].

Mn is a crucial element for all and found readily in soils, where it remains as oxides and hydroxides, and it moves through its different oxidation states. Mn's principal form is pyrolusite (MnO_2) and also present in the form of rhodochrosite ($MnCO_3$). In around 25 million tons of mining activities, five million tons of the metal are being recovered, and reserves exceeds around 3 billion tons metal. Some organisms, such as diatoms, mollusks, and sponges, store manganese. Fish can store up to 5 ppm Mn and mammals can store up to 3 ppm in their tissue, though they have already around 1 ppm [2].

Effect of Mn on Human Health and Animals Mn is one of the three toxic essential trace metals, which is not only necessary for survival but also can be toxic when high Mn concentration will prevail in human body. When people do not make up to the recommended daily allowance (RDA) or exceed the limit, in both conditions it starts to decrease the health condition. Human can be exposed to manganese through several routes such as eating food, for example eating spinach or tea or the food which contains highest concentrations of grains and rice, soya beans, oyster, eggs, nuts, olive oil, and green beans. After Mn absorption in the body, it will transport to the blood and then liver, kidney, pancreas, and finally to the endocrine glands. Mn has severe impact on brain and respiratory tract. The symptoms of high dose manganese exposure are: forgetfulness, dullness, nerve damage, and hallucinations which can cause Parkinson's, bronchitis, schizophrenia, paralysis, sleepiness, emotional disturbance, insomnia, headache, and lung embolism. Especially impotence in men can occur if men are exposed to Mn for prolonged period. Other alarming health effects of Mn are: glucose intolerance, blood clotting, fatness, skeleton disorder, birth defects, hair color changes, depressed cholesterol level, neurological effects. Long or chronic health effects of Mn can be triggered by dust and fume inhalation. From these kinds of diseases, nervous system becomes weak and may cause physical disability. Severe pneumonia and other respiratory infections have been recorded among workers who are exposed to Mn dust or fume and experimental suspicious tumorigenic agents [62].

So, Mn is a crucial metal for body but in recent days it has been listed as global toxic metal. Mn was introduced as gasoline additive in the form of methyl-cyclopentadienyl Mn tri-carbonyl (MMT). MMT is considered as occupational manganese hazard and connected with Parkinson's disease with several syndromes such as tremor, gait disorder, cognitive disorder, and postural instability. High dose of manganese exposure can cause neurotoxicity. Mn can cause neurological disease termed as "Mn" by forming Mn rigidity, tremor, mass formation, mood disorder, and memory dysfunction. The symptoms of Mn are quite similar to the symptoms of Parkinson disease. Therefore, the main differences between Mn and Parkinson disease are the symptoms and disease progression and also Mn is not susceptible to levodopa ($_{L}$-DOPA) administration [2].

Effect of Mn on the Ecosystem Mn and its compounds are found in the soil and water as small particles. Also they can be in the air as dust particles. They tend to settle on the land within few days. Mn and its compounds are released in the environment through industrial activities and fossil fuel burning. From the human exposure, manganese can penetrate into the surface, groundwater, and sewage water. Mn accumulates in the soil easily because it is used as pesticides [63].

Effect of Mn on Animals For animals Mn is an important element for animals of around 36 enzymes, used for carbohydrate, fat, and protein metabolism. Even at low level exposure, Mn can interfere with bone formation, reproduction and growth of animals [64]. Ultimately it could be viral for animal even at low level. Mn compounds can cause brain, lung, and liver damage, vascular disturbances, low blood pressure, inhibit the development of animal fetuses. Then Mn skin absorption may cause tremors [8]. From several studies on test animals, it has been depicted that acute Mn poisoning can develop tumor in animals [5].

Effect of Mn on Plants In plants, after the uptake from the soil, Mn ions are transported to the leaves. Even at low level Mn absorption, it can cause disorder in plant mechanisms. Mn plays an important role in division of water into hydrogen and oxygen for plant uptake. Mn may trigger both toxicity and deficiency problems in plants. Mn deficiency is common in low pH soil. Both deficient and high toxic level of Mn in soils may cause cell wall swelling, leaf withering, and creating brown spots on leaf. The interconnection between deficient and toxic concentration can be measured by detecting optimal Mn concentration for plants [11].

5.8 Al and Its Effects

Al has only one naturally occurring isotope which is Al-27 and that is not radioactive. Al is a poor metal, mainly found in the form of ore bauxite and is versatile for its light weight, strength, and counteraction capacity to oxidation. Meanwhile, Al is oxidized but remains in unstable form than most other metals. Al is used in industrial productions of various products which is very significant for the worldwide economy. Metal recovery from scrap through recycling has become a vital element of the Al industry. Metal industrial production is around 20 million tons per year and also the same quantity is recycled. The Al ore reserves are around 6 billion tons worldwide. Al is used as building material, electrical transmission wire, in packaging, transportation material because of its durability, strength, and lightweight. Al is also utilized as structural components which is emergent for aerospace industry. Al is the second most usable metal after iron. The pure aluminum usually forms alloys with other metals such as Cu, Mn, Zn, and silicon. Al is highly conductive and cheap comparing with Cu. Al was first used for household electrical lining in 1960 [2]. Al is also used in telescope mirrors and modern mirror as thin reflective coating [64]. But Al tends to be sensitive towards thermal expansion as well as can't sustain pressure, because of these characteristics galvanic erosion occurs. The most recent Al technology development is the Al foam production through adding to molten metal usually a metal hybrid, from which hydrogen gas is released. So, for this phenomena, the molten Al need to be thickened by consolidating silicon carbide or Al oxide fibers before this is performed. Thus this Al foam is widely used in space shuttle and traffic tunnels [5].

Effect of Al on the Environment Al is abundant in the earth's surface, present in the percentage of around 7.5% to 8.1% of earth crust. Al can't be found readily in its free form. Al in the form of Al hydroxide provides benefits to the soil properties. Al being a reactive metal is extracted from its ore, Al oxide (Al_2O_3). Comparing with other metals, Al is quite hard to refine because Al is oxidized very easily and that oxidized compound is very stable. And because of these characteristics, Al is used in several applications. It can cause acidifying problems. Al oxide (crystal from) helps to form gemstone which is called as "Corundum." Al oxide with other metals creates some versatile compounds such as with cobalt it makes blue sapphires and with chromium it makes red rubies, with iron traces it makes topaz which is a yellow Al silicate. They all can be easily produced artificially [65].

Effect of Al on Human Health Due to the abundance, human can expose to Al at an alarming rate. At high concentration exposure, Al can cause health disorders. Al's water-soluble form (ions) such as Al chlorine may cause detrimental health effects. In humans, Al exposure may occur through skin absorption and ingestion such as eating contaminated food. Some chronic or long-term effects of Al are: central nervous system damage, memory loss, acute trembling, dementia, and much more. Al is considered as occupational hazard causing metal, as it can create water-soluble form. Workers who are exposed to Al and are being used in production procedure may undergo lung disorders. Also, pulmonary diseases and kidney damage may occur by inhaling Al oxide powder and Al dust. Inhalation of silica and iron oxide air can cause severe diseases such as "Shaver's disease". Especially, in kidney dialysis process, Al can also penetrate in kidney patient's body [66].

Effects of Al on Animals and Plants Al can store in plants and can create health hazards for animals which take these plants as food. In acidic lake, Al concentration is high. In high acidic condition, fish and amphibian population cannot sustain because of the reaction of Al ions with fish protein of gill and embryos of frog. It has been observed that high Al concentration has impacts on fishes, birds, and other animals which take these insects and fishes and also on the animals that take in Al through air inhalation. Animals that take in Al through air may incur lung disorder, loss in weights, and activity downfall [2]. Another notable adverse effect of Al in environment is the Al ions that make reaction with phosphates, thus there are lesser amounts of phosphate available for water organisms to intake. Also, in groundwater of acidified soil, Al concentration can be found at a higher level. Thus indicating, Al can injure the tree roots that are connected to groundwater [27].

5.9 Ag and Its Effect

Ag is a rare metal in the Earth crust as the 67th naturally abundant metal. Pure Ag is very ductile, malleable, and lustrous form of Ag. With nanotechnology development, Ag nanoparticles (Ag-NanoParticles) are being used widely in various sectors [67]. Ag is not chemically active but it can react with nitric acid and sulfuric acid. It is stable in water. It has greater cost and highest electrical conductivity. In crude oil and steam well, Ag concentration can be high. Ag can be found as monovalent in its every form, the predominant forms are its oxide, fluoride, and sulfide. It can react with hydrogen sulfide in the air and creates tarnish (Ag sulfide). Ag is a precious metal, especially Ag nitrate is widely used in electronic manufacturing, appliances, mirror and jewelry making, and photography. Ag bromide and Ag iodide both are used from the very beginning of photography era, also applicable for black and white image. It is used as a catalyst in several oxidation reactions. Ag and its compounds are also used in dentistry and battery manufacturing [8].

Anthropogenic activities can increase the concentration of Ag in the environment such as mining of metal, photo-processing, hazardous waste disposal, smelting, and lots more. Several studies have demonstrated that the few forms of Ag are much more toxic than other metals, because both soluble and insoluble forms of Ag can cause toxicities which also include the occurrence of occupational exposure [5].

Effect of Ag in the Environment In mineral rich soil, Ag can be found in high concentration around 44 ppm. Ag can be absorbed by plants in the range of 0.03–0.5 ppm. Ag metals are natural crystals and its deposits are found worldwide. The major Ag ores “Stephanite” and “Acanthite” can be found in Bolivia, Mexico, and Honduras. Refining of several metals can form some by-product in the form of Ag compounds. Around 17,000 tons of Ag are mined annually [68].

Effect of Ag on Human Health Ag and its compounds are being used worldwide which allows the Ag exposure to human health through various routes such as inhalation, ingestion, and skin absorption. According to ATSDR (2008), human can be exposed to Ag dust or fume through occupational exposure. Skin contact occurred through using different kind of burn creams and jewelry. Through needles and dental amalgams, Ag can also enter into human body. Soluble Ag compounds are more easily absorbed than insoluble Ag [69], causing potential health hazard. Chronic exposure to Ag mainly affects some key organs of human body such as kidney, eye, liver, lung and brain, and causes damage to them. Similarly, prolonged exposure to Ag nitrate can lower blood pressure and lower respiratory rate. Ag in its salt form, $AgNO_3$, can be lethal in the concentrations of more than 2 g. Soluble Ag compounds have the ability to accumulate the muscle and brains in smaller quantity [70]. Soluble Ag compounds are absorbed by tissue slowly (prolonged period), creating blacking pigmentation on skin, which termed as “Argyria.” Such permanent pigmentation developed due to argyria (on skin) and argyrosis (on eyes). This is mainly the result of inhalation and Ag solid material attack on the skin and eyes. It can be severe corneal harm, when it comes to eye contact. Through skin absorption, it can cause skin irritation. This disease can also be occurred by using medicine containing Ag and colloidal Ag. Localized agrarian caused direct skin absorption of Ag, where it enters in the body in very slight amount through sweat glands. This deposition causes small round patches (light brown or black color) on the skin. It mainly affects the hands, mucous membranes, and eyes [71]. In eyes, Ag fine particles may enter through air and form localized agrarian over time. Generalized agrarian causes skin, eye, and nail pigmentation through Ag compound ($AgNO_3$) ingestion, inhalation, and skin surface contact. Once it enters into the body, it passes through the bloodstream and accumulates in the several tissues. Sun-exposed areas are more vulnerable to these types of exposure. Long-term Ag exposure can cause allergy and dermatitis. Inhalation of Ag vapor can cause throat or lungs irritation, headache, breathing difficulties and respiratory problems, unconsciousness, confusion, drowsiness, weakness, and even death [71]. Excess concentration of Ag may be very detrimental. Comparing with other route, ingestion of Ag is much hazardous for health because it can accumulate in the lung for prolonged period. Thus, it can cause anemia, pneumonia, narcosis, nausea, vomiting, stomachache, and diarrhea. Long-term overexposure can cause permanent nervous system and brain damage. Continuous exposure of methyl ethyl ketone through inhalation can form hexane (neurotoxin) [67]. According to ATSDR, Ag in any of its form is not considered as carcinogen and viral to nervous, immune, and reproductive system.

6 Combined Effects of Heavy Metals

Living organisms in nature are exposed to not only one xenobiotic substance, but also a combination of toxic substances through multiple routes of exposure. Combinations of exposure depend on the environmental factors and occupational variability. Though abundant information on the effect and toxicity of single metal are widely available, studies on effects of multiple metals are relatively very few.

Tabacova et al. [72] examined placental As and Cd in relation to lipid peroxides and glutathione levels in 49 maternal-infant pairs from a copper smelter area and reported that combined exposure of metals resulted in lower glutathione antioxidant protection and higher concentrations of lipid peroxides [72]. Dimitrova et al. [73] studied the combined effect of Zn and Pb on the hepatic superoxide dismutase-catalase system in carp *(Cyprinus carpio),* and it was found that superoxide dismutase and the catalase activity were increased at a 24-h exposure and decreased at a 5-day exposure.

Combined effect of Cu and Cd on *Chlorella vulgaris* growth and photosynthesis-related gene transcription was explored by Qian et al. [74]; and it was found that the combination of these two metals decreased cell growth and chlorophyll content, and increased ROS content synergistically. The transcript abundance of *psb*A and *rbc*L were reduced, though not in a synergistic interaction; however, the transcript abundance of *psa*B was increased synergistically by metal combination [74].

Combined treatment of Pb and Cd is reported to be additive type of toxicity in Sprague–Dawley rats, when administrated orally [75]. Yuan et al. [75] informed that combined treatment of Pb and Cd in acute toxicity studies significantly altered physiological and biological properties of blood, resulted in microcytic hypochromic anemia and damages of different intensities to the liver and kidney, where target organs of the metals were testicles, liver, and kidneys. The minimum dose to observe adverse effect was suggested as less than 29.96 (29.25 + 0.71; $Pb(NO_3)_2 + CdCl_2$) mg/(kg bw day) oral administration for 90 consecutive days. Similar additive toxicity of Pb and Cd was reported by Hambach et al. [76], depicting Pb increased the effect of Cd on early renal biomarkers (e.g., retinol binding protein, N-acetyl-β-d-glucosaminidase, intestinal alkaline phosphatase) in metallurgic refinery workers.

According to Hernández-García et al. [77] the major cell death process was apoptosis when isolated red blood cells of common buzzard were exposed to a mixture of Pb and Cd (1:10). It was reported by Wu et al. [78] that Pb and Cd significantly inhibit cellulase activity on earthworm (*Eisenia fetida*) in a combined exposure. The combined toxic effects of Pb and Cd were complex, and probably influenced by the competitive adsorption and bioavailability of both metals [78].

The effect of Hg and Cd on the packing and elasticity of biomimetic lipid monolayers was investigated by Le et al. [79] using various lipid combinations. It was shown that the metal-mixture ($HgCl_2$:$CdCl_2$; 1:1) showed alterations in the lateral lipid packing as depicted by area expansion and enhanced film rigidity.

Antagonistic effect was reported by Smith et al. [80], while investigating the influence of Cd on Pb accumulation in pregnant and non-pregnant mice by exposing them to Cd and Pb contaminated soil. The existing Cd depicted a major influence on the Pb and Fe accumulation in the kidneys and liver, respectively. Cd reduced Pb accumulation in all mice irrespective of status [80]. Vellinger et al. [81] investigated the interactive effect of As and Cd in a freshwater amphipod (*Gammarus pulex*) and reported similar antagonistic interaction between metals on mortality. Metal concentrations in tissues were lower in binary mixtures than in single metal exposures at similar concentration [82]. In another research Vellinger et al. [82] observed that mobilization of the detoxification systems (such as reduction in glutathione content, γ-glutamyl-cysteine ligase activity, and metallothionein concentration) were increased in *G. pulex* in response to the binary exposure. They suggested that this response indicates the changes in energy reserve utilization, as well as a possible energy reallocation from locomotion to detoxification [81].

Jadhav et al. [83] examined the sub-chronic exposure of metal-mixture (As, Cd, Pb, Hg, Cr, Mn, Fe, and Ni) via drinking water in male rat. It was observed that contaminants can alter systemic physiology of rats by altering the functional and structural integrity of kidneys, liver, and brain [83]. The mixture decreased body weight and water consumption and increased weights of brain, liver, and kidneys. Moreover, necrotic changes were observed in those organs. The same research group [84] in a similar study reported that the sub-chronic exposure of metal-mixture (As, Cd, Pb, Hg, Cr, Ni, Mn, and Fe) via drinking water can induce immune toxicity in male rats, and found that the hematopoietic and immune systems of male rats were toxicologically sensitive to joint mixtures. It was also suggested that it leads to anemia and suppression of humoral and cell-mediated immune responses [84].

Low doses of Pb, Cd, and As in a mixture increase delta-aminolevulinic acid (ALA), Fe, and Cu in male Sprague Dawley rats [85]. It was also observed to increase a significant amount of Cu in kidney [85]. Exposure with a mixture of Pb, As, and Cd to BALB/C 3T3 cells resulted in miRNA and mRNA expressions which could be responsible for the cellular death, growth disruption, and inhibited proliferation [86].

Tully et al. [87] investigated the effects of As, Cd, Cr, and Pb on gene expression regulated by a battery of 13 different promoters in recombinant HepG2 cells. They informed that Cd, Cr, and Pb exhibited significant dose-dependent induction of the stress-responsive promoter human metallothionein-IIA (hMTIIA).

Combined effect of Cu, Cd, and Pb on *Cucumis sativus* growth and bioaccumulation was evaluated by An et al. [88]. Binary combinations of Cu + Cd, Cu + Pb, and Cd + Pb resulted in all three types of interactions: additive, synergistic, and antagonistic responses on growth [88]. Ternary combination of Cu + Cd + Pb produced an antagonistic response for the growth. The bioaccumulation of one metal was influenced by the presence of other metals in metal mixtures [88]. Similarly synergistic, antagonistic, or additive effects of the toxicity were reported in different metal mixtures by Lin et al. [89], when the combined toxicity of eight common heavy metals (Pb, Cd, Hg, Cu, Zn, Mn, Cr, Ni) mixtures were studied in HL7702 cells.

The bioaccumulation of heavy metals and growth response of rice plants after exposure to combined contamination by Cu, Cd, and Pb was conducted [90] in a pot experiment. Yizong et al. [90] showed that Pb promoted both root and shoot absorption of Cu and Cd, and Cu affected Cd and Pb absorption in the root, but Pb concentrations in both root and shoot were not affected by Cd application.

The features of morphological changes in the urinary bladder of mature rats were investigated under combined influence of heavy metals (Zn, Cu, Fe, Mn, Pb, and Cr) by Romaniuk et al. [91]. This metal combination caused intense morphological alterations in all structures of the urinary bladder of rats, which may initiate the dysfunctions of bladder; and these alterations rely on the period of heavy metals intake [91].

Antonio et al. [92] reported that in pregnant rat the mixed exposure of Cd and Pb has additive influence on decreasing Na^+/K^+-ATPase function, where Cd activity was effected by Pb to cause inhibition of the Na^+/K^+-ATPase pump. This inhibition results in intracellular K^+ depletion, intracellular Na^+ accumulation, and intracellular free Ca^{+2} increase, causing intense cognitive dysfunction [92]. Another research group [93] reported binary exposure of Pb and As in brain and informed that in the presence of As, action of Pb drastically enhanced and affects the hippocampus. Moreover, the ternary mixture of Pb, As, and Cd triggers intracellular Ca^{+2} release, ROS generation, encourages the extracellular signal-regulated pathway (ERK), c-Jun N-terminal kinases (JNK), and mitogen-activated protein kinase3 (MAPK3) pathway, causing neuronal oxidative stress [94].

The complex interaction of metals (As, Cd, Hg, and Pb) can change the essential neuronal cell integrity by down-regulation of neuronal nitric oxide synthase (n-NOS), metallothionein-3 (MT-III), catalase, superoxide dismutase (SOD), brain-derived neurotrophic factor (BDNF), glutathione peroxides (GPx), glutathione (GSH), and glutathione S-transferase (GS) and results in oxidative stress [14]. The oxidative stress by various cellular signaling pathways results in programmed neuronal cell death and cognitive dysfunction [94].

Vinodhini and Narayanan [95] evaluated the impact of toxic heavy metals (Cd + Pb + Cr + Ni) on the hematological parameters in common carp (*Cyprinus carpio L.)*. They reported decreased hemoglobin and PCV as well as elevated RBC count and blood glucose [95]. Chandanshive et al. [96] studied the effect of heavy metal model mixture on blood hematological parameters in the laboratory acclimatized fish Labeo rohita, where a significant reduction of erythrocyte count and hematocrit level was reported.

Combined effects of Cd, As, and Pb in a comparative study using conceptual models and the antioxidant responses in the brackish water flea were examined by Yoo et al. [97]. Yoo et al. [97] reported that the combinations of As+Pb and Cd + Pb showed synergistic effects, whereas Cd + As+Pb and Cd + As combinations showed additive, but antagonistic effects were not observed in any combinations.

Interestingly, in several combined treatment experiments one metal exhibited protective effect against another metal toxicity. For instance, Fırat and Kargın [98] investigated the combined effects of heavy metals on serum biochemistry of Nile Tilapia (*Oreochromis niloticus*) and found that concentrations of Cd and Zn metals in the serum were lower in combined metals-exposed fish than in fish exposed to individual metals, thereby exhibiting protective effect.

Examining the combined effect of Cd and Zn in PC12 cells, Rahman et al. [99] reported that Zn effectively inhibited Cd-induced apoptotic cell death via suppressing mitochondrial apoptosis pathway and reserving Cd-induced production of reactive oxygen species (ROS). Zn limited Cd-induced apoptosis by decreasing cytochrome c release from the mitochondria, and down-regulating the pro-apoptotic protein caspase 9 and Bax, as well as up-regulating anti-apoptotic Bcl-x [99]. Similarly, evaluating the effect of Zn in the presence of Hg in PC12 cells, Hossain et al. [100] reported Zn triggers glutathione and Nrf2-mediated protection against inorganic Hg-induced cytotoxicity and intrinsic apoptosis. Combined exposure of Hg and Zn exhibited improvement in cell viability, cell membrane, DNA damage, ROS amount, and apoptotic cells, along with a significant increase of pro-survival mTOR, akt, ERK1, Nrf2, HO1, Bcl-2 and Bcl-xL, and decrease in apoptotic p53, Bax, cytochrome *c* and cleaved caspase 3 [100].

Alike Zn, Selenium (Se) also expressed ameliorative actions against As-induced cytotoxicity via modulating autophagy/apoptosis [101]. Rahman et al. [101] explained that Se modulates As-induced intrinsic apoptosis pathway via enhancing mTOR/Akt autophagy signaling pathway by retaining antioxidant molecules and hindering the cellular accumulation of As in the cells. Similar Se-amelioration was reported by Hossain et al. [102, 103] against Cd and Hg influenced toxicity in PC12 cells. Co-presence of Se with Cd protects against Cd-induced cytotoxicity in PC12 cells through inhibition of Cd-induced oxidative stress and suppression of mitochondrial apoptosis [102]. Co-exposure also displayed increased antioxidant glutathione and glutathione peroxidase 1 (GPx1) levels, and decreased DNA fragmentation and cell membrane damage [102]. Hossain et al. [103] also reported that Se attenuates inorganic Hg-induced cytotoxicity and intrinsic apoptosis in PC12 cells modulating antioxidant properties and ROS generation.

These studies in biological system indicate that the interaction among different metals is very complex. These complex interactions depend on environmental factors, exposure time, and exposed animals. Intensive understanding on the associated mechanism of action and exploration of the substantial impact on biological system is needed.

7 Concluding Remarks

There are still many unknown parts about the biological effects of heavy metals. It has been reported that even heavy metals that are recognized as harmful to health, such as Cd and As, have a negative effect on living organisms if they are not completely present. The general understanding is that excessive intake or excess exposure of heavy metals is harmful, even in the case of absolutely essential heavy metals for physical and biological activities such as Cu and Zn. Heavy metal exposure to human, animals, and plants involves several different routes such as by water and food consumption, skin absorption, inhalation of metal dust and fume in the air and especially at workplace through occupation exposure. Usually many heavy metals are considered as toxic even at low level. The chief heavy metal toxicity mechanism is influenced by the free radical formation which can cause biological molecule (lipid, protein, nucleic acid) damage, oxidative stresses, DNA damage. Ultimately these metals act as potential carcinogens and neurotoxins. Some metals can be chronic where other metals can be acute even after prolonged exposure, ultimately causing organ damage and diseases in the body such as liver, brain, kidney and lungs damage and connected diseases. Recently, there have been many reports that the toxicity of these heavy metals can be alleviated by simultaneous or pre-administration of essential heavy metals such as Se, Zn, or Cu. These heavy metals also induce oxidative stress and show toxicity when administered in large amounts. However, these metals can help in relieving oxidative stress under permissible and proper dose. Many studies have various discussions about the mechanism, but it seems that more detailed research is needed in the future.

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