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The Impact of Heavy Elements on Public Health

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ABSTRACT

Although many heavy metals have bio-toxic effects on human biochemistry, some of them have bio-importance as trace elements. The most frequent heavy metals to cause human poisonings are arsenic, mercury, lead, chromium, cadmium, and iron. Their wide distribution in the environment and detrimental effects on people are the results of their numerous industrial, domestic, agricultural, medical, and technological applications. These metals' carcinogenicity has been attributed to defects in DNA repair following the induction of oxidative stress and DNA damage by these metals. Metal toxicity is dependent on the dose ingested, the route of exposure, and the duration of the exposure, and it can cause a variety of disorders as well as excessive damage from oxidative stress brought on by the production of free radicals. In this review, their manufacturing and use, potential for human exposure, and molecular mechanisms of toxicity are all examined. The purpose of this article review is to discuss the effects that specific heavy metals may have on human health.

Keywords: *heavy metals, occurrence, uses, potential effect, toxicity mechanism.*

INTRODUCTION

According to reports, certain heavy metals like Fe, Zn, Ca, and Mg are important to human biology. Others, like As, Cd, Pb, and methylated forms of Hg, on the other hand, have reportedly been found to have no known biological significance in human biochemistry and physiology and can be toxic even at very low concentrations [1-6]. Even for foods with bio-importance, dietary intakes must be kept within regulatory bounds because excesses can cause poisoning or toxicity, as shown by a number of reported medical symptoms that can be diagnosed clinically [3]. For male reproductive function, zinc is a "masculine" element that balances copper in the body [3]. Anaemia and growth and developmental delays are brought on by zinc deficiency [2]. A crucial component of human metabolism is calcium. It is the primary component in the development of very strong bones and teeth in mammals, and the body can tolerate higher doses of it because thyrocalcitonin and parathormone hormones effectively control its blood concentration. [4] Magnesium is a significant electrolytic component of blood that is found in interstitial and cellular fluids as well as blood plasma. From infants to adults and from males to females, it needs more food each day, with pregnant and nursing women needing the most. Although arsenic has been claimed to be a trace element important for human nutrition, its biological functions are unclear [7]. According to reports, lead, cadmium, and mercury do not naturally exist in living things and do not have any known roles in human biochemistry or physiology [8]. Because of their bioaccumulation, dietary intake of these metals, even at very low concentrations, can be extremely harmful.

Heavy metals will nevertheless affect cellular organelles and components in biological systems, including cell membranes, mitochondria, lysosomes, endoplasmic reticulum, nuclei, and some enzymes involved in metabolism, detoxification, and damage repair [9].

According to research, metal ions can interact with nuclear proteins and DNA in cells, resulting in DNA damage and conformational changes that can influence cell cycle progression, carcinogenesis, or apoptosis [10]. Reactive oxygen species (ROS) production and oxidative stress have been shown in several studies from our lab to be important factors in the toxicity and carcinogenicity of metals like arsenic [11, 12, 13], cadmium, and lead. [14], chromium [15, 16], lead [17, 18], and mercury [19, 20]. These five elements are among the priority metals with significant public health implications due to their high level of toxicity. They are all known to cause multiple organ damage even at low exposure levels because they are all systemic toxins. The International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (U.S. EPA) both claim that there is a link between exposure to these metals and the development of cancer in both humans and animals.[21]

It is well known that the harmful heavy metals Cd, Pb, Hg, and As deplete cells' primary antioxidants, especially those enzymes and antioxidants with thiol groups (—SH). The production of ROS like the hydroxyl radical (HO_), superoxide radical (O2), and hydrogen peroxide (H2O2) may be increased by such metals. [22,23] Oxidative stress is a condition brought on by increased ROS production that destroys cells' natural antioxidant defenses [24]. In particular in the renal cortex, heavy metals like Cd, Pb, and Hg are nephrotoxic [25]. Image 1. Represent the assault of heavy metals on cells and the equilibrium between ROS production and the ensuing antioxidant defense. [26]. Figure 2 represent, Figure 2. Tropic transfer of heavy metals from freshwater to human food chain.[27]

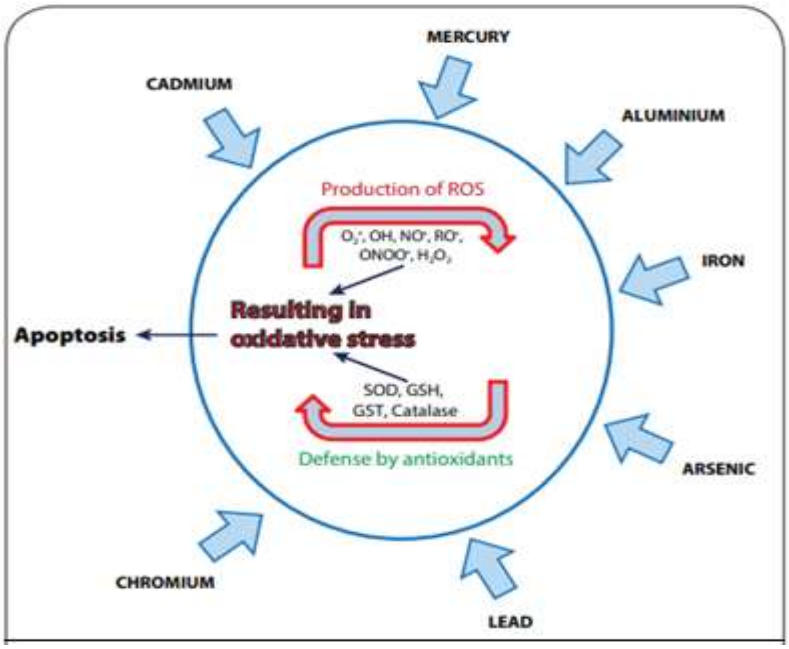

Figure 1. The attack of heavy metals on cell and the balance between ROS production and the subsequent defense presented by antioxidant

[Source: Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda KN. Toxicity, mechanism and health effects of some heavy metals. Interdisciplinary Toxicology. 2014 Jun;7(2):60-72. DOI: 10.2478/intox-2014-0009. PMID: 26109881; PMCID: PMC4427717.]

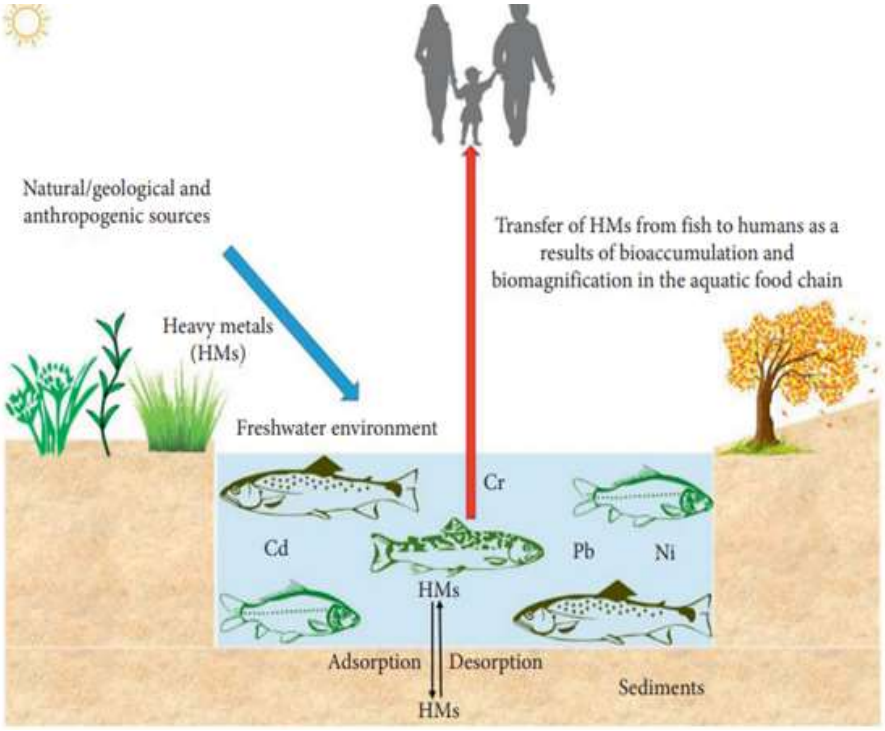

Figure 2. Tropic transfer of heavy metals from freshwater to human food chain.
Source: H. Ali, Ezzat Khan, I. Ilahi. Environmental Chemistry and Ecotoxicology of Hazardous Heavy Metals: Environmental Persistence, Toxicity, and Bioaccumulation. Published 5 March 2019, Environmental Science, Journal of Chemistry

1: Arsenic

1.1. Environmental Occurrence, Industrial Production and Use

Arsenic is a common element that is found in almost all environmental matrices at low concentrations [28]. Trivalent arsenite and pentavalent arsenate are two of arsenic's main inorganic forms. The methylated metabolites monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and trimethylarsine oxide are the organic forms. Arsenic pollution of the environment results from both anthropogenic activities and natural events like volcanic eruptions and soil erosion [29]. Industrial production of several arsenic-containing compounds has led to the development of agricultural products like insecticides, herbicides, fungicides, algicides, sheep dips, wood preservatives, and dyestuffs. They have also been applied to the treatment of tapeworms in sheep and cattle in veterinary medicine. [30]. Syphilis, yaws, amoebic dysentery, and trypanosomiasis have all been treated with arsenic compounds in medicine for at least a century [31]. In veterinary medicine, arsenic-based medications are still employed to treat parasitic diseases like canine filariasis and black head in poultry and turkeys, as well as some tropical diseases like amoebic dysentery and African sleeping sickness [31]. The Food and Drug Administration recently approved arsenic trioxide as a cancer preventative for the treatment of acute promyelocytic leukemia [32]. Its ability to treat disease has been linked to the induction of apoptosis (programmed cell death) in leukemia cells. [33].

1.2 Mechanism of arsenic toxicity

When harmful inorganic arsenic compounds are subjected to arsenic biotransformation, bacteria, algae, fungi, and humans produce monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) as a result. These inorganic arsenic species (iAs) undergo enzymatic conversion to methylated arsenicals, the end products and the biomarker of chronic arsenic exposure, during this biotransformation process. DMA (V) iAs (V) iAs (lll) MMA (V) MMA (lll). [35] Inorganic arsenic that has been methylated and is excreted in the urine as

MMA (V) and DMA (V) is a bioindication of chronic arsenic exposure. Biomethylation is a detoxification process. The intermediate product MMA (III) is, however, not excreted and stays inside the cell. When compared to other arsenicals, the intermediate product monomethylarsonic acid (MMA III) has been found to be extremely toxic. [36]

1.3 Potential Effects of Arsenic on humans

Arsenic contaminations are caused by both man-made activities and natural geological processes on earth. Arsenic comes from anthropogenic sources, such as human activity (ore processing and mining). Arsenic can be released to the air and soil during smelting, an ancient and modern process. [37] These different types of sources can all have an impact on the quality of surface water by using groundwater ejection and runoff, as well as other geologic sources like arsenic minerals and sedimentary and metasedimentary bed rocks. [38]. Arsenic is present in the majority of soaps, dyes, paints, metals, semiconductors, drugs, and semiconductor components. Higher concentrations of arsenic are also released into the environment by some fertilizers, pesticides, and animal feeding operations. However, inorganic forms of arsenic, such as arsenite and arsenate, have been found to be particularly dangerous to human health because they are extremely carcinogenic to people and can lead to skin, bladder, liver, and other types of cancer. [39] Humans are exposed to arsenic through air, food, and water, with drinking water contamination being one of the major contributors to arsenic toxicity in more than thirty countries worldwide. [40, 41]. Arsenical pesticides contaminated the water, arsenical chemicals were improperly disposed of, or natural mineral deposits may be to blame [42]. Arsenic toxicity can be acute or chronic; the latter is known as arsenicosis because it is more difficult to diagnose and most reports of arsenicosis in humans focus on skin manifestations. The specific skin lesions that signify chronic arsenic toxicity in humans are pigmentation and keratosis [43]. Low doses of arsenic exposure can harm blood vessels and cause nausea, vomiting, prickling in the hands and legs, decreased production of erythrocytes and leukocytes, and abnormal heartbeat. Arsenic exposure over a long period of time can cause internal cancers, neurological issues, skin lesions, peripheral vascular disease, pulmonary disease, hypertension, and cardiovascular disease. [44, 45] Because there is no effective early treatment for this lethal toxicity, chronic arsenicosis of arsenic may cause permanent changes in the body's vital organs, increasing the death rate. [46]

2. Mercury

2.1 Environmental Occurrence, Industrial Production and Use

The periodic table's transition element series includes the heavy metal mercury. It is distinctive in that it can be found in nature in three different forms—elemental, inorganic, and organic—each of which has a different toxicity profile [47]. Elemental mercury is a liquid at room temperature with a high vapor pressure that is released into the air as mercury vapor. Additionally, mercury can exist as a cation in the oxidation states of +1 for mercury and +2 for mercury [48]. The most prevalent organic form of mercury found in the environment is methylmercury, which is created when microorganisms in soil and water methylate the inorganic (mercuric) forms of mercury. [49].

Mercury is a common environmental toxin and pollutant that causes serious changes in body tissues and a variety of negative health effects [50]. Mercury is present in the environment in a variety of chemical forms that can harm both people and animals. These include organic mercury compounds, inorganic mercuric, mercuric (Hg+1), and elemental mercury vapor (Hg0) [51]. Because mercury is so prevalent in the environment, it is impossible for anyone to

avoid getting exposed to it. This includes people, plants, and animals. [52].

Mercury is used in many industrial processes, including the production of caustic soda, in nuclear reactors, as antifungal agents for wood processing, as a solvent for reactive and precious metals, and as a preservative of pharmaceutical products [53]. It is also used in the electrical industry (switches, thermostats, batteries), dentistry (dental amalgams), and many other fields of medicine. The federal bans on mercury additives in paints, pesticides, and the reduction of its use in batteries caused the industrial demand for mercury to peak in 1964 and start to sharply decline between 1980 and 1994. [54].

2.2. Mechanism of mercury toxicity

Acute heavy metal poisoning is frequently caused by the toxicity of mercury, a well-known hazardous metal. Methylmercury is a neurotoxic substance that damages mitochondria, causes lipid peroxidation, damages microtubules, and accumulates neurotoxic molecules like serotonin, aspartate, and glutamate [55]. 2,200 metric tons of mercury are estimated to be released into the environment each year [56]. According to the Environmental Protection Agency and National Academy of Science, 8 to 10% of American women have mercury levels that would result in neurological disorders in any offspring they might have. [57].

Mercury continues to be a target organ for the brain, but it can harm any organ and cause problems with nerves, kidneys, and muscles. The membrane potential may be disturbed, and intracellular calcium homeostasis may be interfered with. Due to the high stability constants, mercury binds to readily available thiols. [58] Inhaling mercury vapors can result in bronchitis, asthma, and transient respiratory issues. By attaching to the selenohydryl and sulfhydryl groups, which react with methyl mercury and impair cellular structure, mercury plays a significant role in harming the tertiary and quaternary protein structure and altering cellular function. Additionally, it interferes with transcription and translation, which causes ribosomes to vanish, endoplasmic reticulum to vanish, and natural killer cells to become active. The formation of free radicals is also impacted, which compromises cellular integrity. Although the mercury sulfhydryl bond is stable and divided to the surrounding sulfhydryl-containing ligands, the basis for heavy metal chelation is that it also contributes free sulfhydryl groups to encourage metal mobility within the ligands. [59].

2.3. Potential for Human Exposure Hg on human

Accidents, environmental pollution, tainted food, dental care, preventive medical procedures, industrial and agricultural operations, and workplace activities all expose people to various forms of mercury [60]. Dental amalgams and fish consumption are the main causes of long-term, low-level mercury exposure. Both industrial pollution and natural off-gassing from the earth's crust cause mercury to enter water [61]. Mercury that enters waterways is methylated by bacteria and algae. Then, methyl mercury moves up the food chain, into fish, shellfish, and ultimately, into people [62]. The two species of mercury that are most readily absorbed are methyl mercury (MeHg) and elemental mercury (Hg0). More than 50% of the elemental mercury in dental amalgams [63]. Due to its high lipophilicity, the elemental vapor is efficiently absorbed through the tissues lining the mouth and lungs. Hg0 enters the bloodstream and quickly crosses cell membranes, including the placental barrier and blood-brain barrier [64]. Hg0 is oxidized into the highly reactive Hg^{2+} once it has entered the cell. Due to its solubility in lipids, methyl mercury obtained from eating fish is easily absorbed in the gastrointestinal tract and can cross both the placental and blood-brain barriers. Mercury has a very low excretion rate after being absorbed. A significant portion of what is absorbed builds up in the liver, kidneys, and

nervous system. Mercury is toxic in all its forms, and its side effects include nephrotoxicity, neurotoxicity, and gastrointestinal toxicity. [65, 66]

3. Lead

3.1 Environmental Occurrence, Industrial Production and Use

The earth's crust contains trace amounts of lead, an element that is naturally occurring and bluish-gray in color. Although lead naturally occurs in the environment, human activities like burning fossil fuels, mining, and manufacturing cause high concentrations to be released. Numerous industrial, agricultural, and domestic uses exist for lead. Currently, it is used to make lead-acid batteries, ammunition, metal products (such as pipes and solder), and X-ray shielding gadgets. For various industrial uses, an estimated 1.52 million metric tons of lead were used. [67, 68].

Lead's use in ceramics, caulking, pipe solder, and paints has significantly decreased over the past few years [69]. Despite this development, it was noted that 25% of the 16.4 million households in the United States with more than one child under the age of 6 still had significant amounts of lead-contaminated dust, deteriorated paint, or nearby bare soil [70]. When children play on bare, contaminated soil, blood lead concentrations in those children rise [72], and lead in dust and soil frequently recontaminates cleaned homes [71]. Dust and chips from deteriorating lead paint on interior surfaces are currently the main cause of lead poisoning in children. [73].

3.2 Mechanisms of lead toxicity

Lead toxicity typically manifests as an increase in reactive oxygen species (ROS) and disruption of the production of antioxidants [74]. Lead cannot directly participate in the reactions that lead to the formation of ROS because it is not a redox-active element. It was discovered that the interaction of lead with oxyhemoglobin increases the generation of ROS in erythrocytes [75]. Lead's interference with the enzymes and other cellular elements and mechanisms of the defense system, which are in charge of preventing oxidative damage, is what contributes most significantly to the onset and growth of oxidative stress. [76]. One of the most important substances that guards against ROS damage to cell components is glutathione (GSH), a tri-peptide composed of cysteine, histidine, and glutamate [77]. 90% of GSH is found in reduced form and 10% is found in oxidized form in healthy cells and tissues, where it typically serves as an antioxidant defense mechanism.

Glutathione reductase converts glutathione back into GSH after it has been converted (oxidized) to glutathione disulfide [78]. Lead inhibits the sulphydryl-dependent enzymes (such as glutathione reductase, superoxide dismutase, catalase, etc.) and renders GSH replenishment ineffective by attaching to the sulphydryl group of glutathione. Reactive oxygen species are produced when these enzymes are inhibited, which causes oxidative stress. Lipid peroxidation caused by an increase in oxidative stress causes cell membrane damage. Lead prevents 5-aminolevulinic acid dehydratase from working and causes hemoglobin oxidation, which when combined with lipid peroxidation can result in hemolysis [79]. As soon as it enters the intravascular space, lead binds to red blood cells quickly. Lead's half-life in blood is thought to be 30 days. In the brain, bone marrow, liver, kidneys, and other soft tissues, lead from the blood diffuses. The heavy metal then diffuses into bone, where it is deposited for a longer time and has a half-life of several decades. Blood lead levels rise as a result of increased bone turnover during pregnancy, lactation, menopause, or immobility.

3.3 Potential effect of lead on human

In comparison to other organ systems, the nervous system appears to be the most sensitive and important target for lead-induced toxicity [80]. Lead primarily affects

calcium-based reactions and neuronal signaling in the nervous system. Lead exposure affects both the central and peripheral nervous systems. While lead has remarkable effects on adults' peripheral nervous systems, its effects on children's central nervous systems are more pronounced [81,82]. Encephalopathy is a specific outcome of lead exposure, and the risk of developing this progressive, degenerative brain disease rises with blood lead levels, becoming more likely when they exceed 70μg/dL. [83,84]. The main clinical signs of lead poisoning are irritability, inability to focus, dullness, tremors in the muscles, headaches, hallucinations, and memory loss. More severe symptoms, such as delirium, paralysis, lack of coordination, convulsions, ataxia, and coma, are seen after exposure to very high levels of lead [85]. The peripheral nervous system has also been affected by lead exposure, resulting in peripheral neuropathy, which is characterized by diminished motor activity due to the destruction of the myelin sheath that protects the nerves. This severely impairs the transduction of nerve impulses, causing muscular weakness, especially in the muscles on the outside, lack of muscular coordination, and exhaustion. [86]. Since the developing nervous system absorbs a significant amount of lead, lead exposure-related neurological effects are especially devastating in developing children and offspring. The accessibility of the amount of systemically circulating lead in children's brains is noticeably higher than in adults' [87]. Lead in the cerebral cortex seriously impairs the development of synapses in the developing brain of children. Lead also obstructs the formation of ion channels and the development of neurochemicals such as neurotransmitters. Lead poisoning also impairs neurotransmission, decreases neuronal growth, and results in the loss of the myelin sheath on neurons. Developmental disabilities are more likely to occur in children whose blood lead concentration is greater than 10 μg/ dL. [88]. Lead has a very slight negative impact on children's cognitive abilities [89–91]. There doesn't appear to be a lead concentration below which exposure to the nervous system is safe [92]. Additionally, long-term exposure to lead can destroy hard dental tissues and result in tooth loss [93]. Lead can also pass through the placental barrier, which can affect fetal development, particularly the nervous system of the developing fetus. Lead can also result in stillbirths and abortions. Reduced pollen germination and seed viability, altered community components, decreased growth and reproductive rates in both plants and animals are just a few of the negative effects of polluted ecosystems. [94- 98].

4. Cadmium

4.1 Environmental Occurrence, Industrial Production and Use

A heavy metal of significant environmental and occupational concern is cadmium. It has a low average concentration in the earth's crust, at just 0.1 mg/kg. The environment's highest concentration of cadmium compounds is found in sedimentary rocks, and marine phosphates have a 15 mg/kg cadmium content [99]. Numerous industrial processes frequently use cadmium. Cadmium is primarily used in the manufacturing of alloys, pigments, and batteries [100]. Even though cadmium's use in batteries has increased significantly in recent years, its commercial use has decreased in developed nations as a result of environmental concerns. For instance, the daily intake of cadmium in the United States is approximately 0.4 g/kg/day, which is less than half of the oral reference dose set by the U.S. EPA. [101-103].

4.2 Toxicity mechanism of cadmium

According to some research reports, the exact toxicity mechanism of cadmium is still unclear, but its effects on cells are well known [104]. As cadmium binds to the cystein-rich protein (metallothionein), increasing its concentration by 3,000-fold, a cysteinmetallothionein complex is created.

After building up in the renal tissue, this cysteinmetallothionein complex circulates from the liver, where it causes hepatotoxicity, to the kidney, where it causes nephrotoxicity [105]. Iron deficiency can result from cadmium's ability to bind with the ligands of cystein, aspartate, histidine, and glutamate. Due to cadmium's similar oxidation state to that of zinc, it can replace zinc in metallothionein and prevent it from acting as a cell-disrupting scavenger of free radicals. [106].

4.3 Potential for Human Exposure Cd on human

Ingestion of food and inhalation of cigarette smoke are the two main ways that people are exposed to cadmium. Rare skin absorption occurs. Human exposure to cadmium can occur from a variety of sources, with smoking being the main one [107, 108]. These sources include working in primary metal industries, eating contaminated food, smoking cigarettes, and working in environments that are contaminated with cadmium. Emissions from industrial processes, such as mining, smelting, and the production of batteries, pigments, stabilizers, and alloys, are additional sources of cadmium [109]. Additionally, certain foods like leafy vegetables, potatoes, grains, seeds, liver, kidney, and crustaceans and mollusks contain trace amounts of cadmium [110]. Additionally, consuming cadmium-rich foods can significantly raise the amount of cadmium in human bodies. Examples include dried seaweed, liver, mushrooms, shellfish, mussels, and cocoa powder. The circulatory system is a significant route of distribution, whereas blood vessels are thought to be the primary target organs of cadmium toxicity. Chest radiographs that are consistent with emphysema and changes in pulmonary function are typically linked to chronic inhalation exposure to cadmium particulates [111]. Reduced olfactory function has been linked to workplace exposure to airborne cadmium particles [112]. Numerous epidemiologic studies have shown a connection between osteoporosis and decreased bone mineral density caused by chronic low-level cadmium exposure. [113,114,115] Measurements of cadmium levels in blood or urine are frequently used to determine cadmium exposure. Cadmium levels in the blood indicate recent cadmium exposure, such as from smoking. Cadmium accumulation or kidney burden is indicated by the presence of cadmium in urine, which is typically corrected for dilution by calculating the cadmium/creatinine ratio [116, 117]. According to estimates, 2.3% of Americans have elevated urine cadmium levels (>2 g/g creatinine), a sign of chronic exposure and body burden [118]. Cigarette smokers typically have blood and urine cadmium levels that are higher, intermediate in former smokers, and lower in nonsmokers [119]. Throughout the past century, environmental contamination and human exposure to cadmium have significantly increased as a result of the continued use of cadmium in industrial applications. [120, 121].

5. Aluminium

5.1 Environmental Occurrence, Industrial Production and Use

Aluminium naturally occurs in the air, water, and soil and is the third most common element in the earth's crust [139]. According to some studies on environmental toxicology, aluminium poses a serious threat to the current state of health in humans, animals, and plants [140]. The pH of the water and the amount of organic matter have a big impact on how toxic aluminium is; as pH decreases, toxicity rises. The environment is negatively impacted by the mobilization of the toxic aluminium ions as a result of pH changes in the soil and water caused by acid rains and rising atmospheric acidification. All of this has an impact on the environment by causing crop failure or decline, plant poisoning, the death of aquatic animals, and various imbalances in how well human and animal systems work. The main concern

worldwide is soil acidity, which can result from a soil surface PH below five and affect crop production. Acidic soils cause silicon to leach, leaving behind solid, unstable forms of aluminium such as aluminium oxyhydroxides. These unstable forms of aluminium then release phytotoxic Al3+, also known as Al(OH)63 in soil. Al3+ toxicity results from contact with apoplastic, plasma membrane, and symplastic targets, which also disrupts physical and cellular processes in plants. [141]. The destruction of the plasma and hemolymph ions in high concentrations of aluminium causes osmoregulatory failure in aquatic animals, especially in fish, seaweed, and crawfish [142]. Aluminium has an impact on the phosphorous, fluorine, calcium, and iron metabolic pathways of living things. Additionally, it has been discovered in some research studies that aluminium is extremely harmful to skeletal, nervous, and hemopoietic cells.

5.2 Mechanism of aluminium toxicity

The majority of cellular and physical processes are hampered by aluminium. Uncertainty surrounds the precise mechanism by which the gastrointestinal tract absorbs aluminium. According to literature reviews, it is challenging to specify a precise time frame for aluminium toxicity because different symptoms can be noticed minutes or even hours after aluminium exposure [143]. Aluminium's interaction with plasma membrane apoplastic and symplastic targets is likely what causes aluminium toxicity [144]. Al3+ replaces Mg2+ and Fe3+ in humans, which disrupts many processes like intracellular communication, cellular growth, and secretory functions. Aluminium induces changes in neurons that are comparable to the degenerative lesions seen in Alzheimer patients. The most serious side effects of aluminium toxicity include neurotoxic effects like neuronal atrophy in the striatum, substantia nigra, and locus ceruleus. [145,146]

5.3: Effects of Aluminium on humans

In the environment, aluminium only exists in one oxidative state (3+), and humans primarily consume it through inhalation, ingestion, and dermal contact. Drinking water, alcoholic beverages, food, and medications containing aluminium are its main exposure points [147]. Although it hasn't been thoroughly studied yet, humans absorb aluminium and its compounds poorly. Although these symptoms are said to be mild and transient, higher levels of aluminium in humans can cause nausea, vomiting, mouth ulcers, skin rashes, skin ulcers, diarrhea, and arthritic pain. According to the World Health Organization, human exposure to aluminium may be a risk factor for the development of Alzheimer's disease because it had negative effects on the nervous system and caused memory loss. Balance issues and loss of coordination [148]. Aluminium builds up in the body and is difficult for kidney patients to get rid of, which can harm the bones and the brain. Increased exposure to aluminium can alter the course of secondary hyperparathyroidism and result in other conditions like osteomalacia and dynamic bone disease, both of which have low levels of bone remodeling. For example, a dusty environment, a sedentary lifestyle, long-term intravenous nutrition, decreased kidney function, and hemodialysis could all contribute to the development of aluminium toxicity. [149,150]

6. Iron

6.1 Environmental Occurrence, Industrial Production and Use

In the crust of the earth, iron is the transition metal that is most prevalent. As a cofactor for numerous essential proteins and enzymes, it is the most significant nutrient for the majority of living things from a biological perspective. Most aerobic organisms depend on iron-mediated reactions for their respiration. It can catalyze reactions that result in the production of radicals, which can harm

biomolecules, cells, tissues, and the entire organism if it is not properly shielded. Pediatricians have historically been primarily interested in the subject of iron poisoning. Due to the high amount of iron-containing products that children are exposed to, they are particularly vulnerable to iron toxicity. [151]. Four stages of iron toxicities take place. The first stage, which starts six hours after the iron overdose, is characterized by gastrointestinal symptoms like vomiting, diarrhea, and gastro intestinal bleeding [152]. The second stage, known as the latent period or apparent medical recovery period, advances within 6 to 24 hours of overdose. Between 12 and 96 hours after the onset of specific clinical symptoms, the third stage begins. Shocks, hypotension, lethargy, tachycardia, hepatic necrosis, metabolic acidosis, and occasionally death characterize this stage [153]. Within two to six weeks of an iron overload, the fourth stage takes place. This stage is characterized by the development of strictures and gastrointestinal ulcerations. In developed and meat-eating nations, excessive iron absorption is a serious issue that raises the risk of cancer. Asbestosis, the second most important cause of lung cancer, is a serious risk for workers who are exposed to asbestos, which contains almost 30% iron [154]. Free radicals are allegedly related to cancer caused by asbestos. DNA deterioration can also be encouraged by loose intracellular iron. The process of oxidizing DNA molecules is the main mechanism by which iron can cause cancer. [155].

6.2 Mechanism of iron toxicity

Due to various harmful free radicals that are created when absorbed iron fails to bind with proteins, the concentration of iron in mammalian cells (especially those in the gastrointestinal tract) and biological fluids is severely impacted. Extreme amounts of iron enter the body, cross the rate-limiting absorption step, which becomes saturated, and this free iron enters the liver, heart, and brain cells. After this free iron disrupts oxidative phosphorylation, ferrous iron is transformed into ferric iron, and this ferric iron releases hydrogen ions that raise metabolic acidity. Additionally, free iron can cause lipid peroxidation, which severely harms microsomes, mitochondria, and other cellular organelles [156]. When iron intake is excessive, a variety of free radicals are formed, and these free radicals are thought to have the potential to cause cellular damage, DNA mutations, and malignant transformation, all of which contribute to the development of various diseases. [157,158]

6.3. Effects of Iron on humans

The majority of iron-mediated reactions aid aerobic organisms in their process of respiration. Iron can catalyze reactions that result in the formation of radicals if it is not properly shielded. These radicals can harm biomolecules, cells, tissues, and the entire organism if they are not contained. Pediatricians have long been interested in iron poisoning because children are particularly vulnerable to it due to their high exposure to iron-containing products. [159]. The four stages of iron toxicity (i): Gastrointestinal symptoms (vomiting, diarrhea, and gastro intestinal bleeding) are indicative of iron toxicities after 6 hours of iron overdose. (ii): The apparent medical recovery (latent period) is considered to have occurred within 6 to 24 hours of the iron toxicities. (iii): Hepatic necrosis, metabolic acidosis, shocks, lethargy, tachycardia, hypotension, and occasionally death are symptoms of iron toxicities between 12-96 hours after an iron dose. (iv): gastrointestinal ulcerations and strictures form within 2–6 weeks of an iron dose, indicating iron toxicity [160]. In developed and meat-eating nations, excessive iron absorption is a serious issue because it raises the risk of cancer. Workers who are heavily exposed to asbestos are at a high risk of developing asbestosis; asbestosis is thought to be the second-leading cause of lung cancer. Asbestos contains almost 30% iron. Asbestos-related cancer has been

linked to free radicals, suggesting that they may play a significant role in the development of lung cancer [161]. Different enzymes (superoxide dismutase, catalase, and glutathione peroxidases) actually neutralize free radicals. Iron can be released from ferritin by the superoxide molecule, and this free iron reacts with increasing amounts of superoxide and hydrogen peroxide to produce extremely toxic free radicals like the hydroxyl radical. Hydroxyl radicals are harmful because they can depolymerize polysaccharides, inactivate some enzymes, start lipid peroxidation, and cause DNA strand breaks which can sometimes result in cell death [162-164].

Prospects

A thorough review of the available data reveals that heavy metals like arsenic, cadmium, chromium, lead, and mercury are naturally present. However, anthropogenic activities have a big part in contaminating the environment. These metals are known to be systemic toxins that have negative health effects on people, including cardiovascular diseases, developmental abnormalities, neurologic and neurobehavioral disorders, diabetes, hearing loss, hematologic and immunologic disorders, and various cancers. The three main exposure routes are dermal contact, ingestion, and inhalation. The type of heavy metal, its chemical form, as well as time and dose, all influence how severe the negative health effects are. A significant factor in metal toxico-kinetics and toxico-dynamics is speciation, which is greatly influenced by factors like valence state, particle size, solubility, and biotransformation chemical form, too. Numerous studies have demonstrated that chronic exposure to toxic metals harms human populations' health. Although some metals have known acute and long-term effects, little is known about how toxic elemental mixtures affect human health. Recent studies have noted that these harmful substances may disrupt the metabolism of nutrients like iron, calcium, copper, and zinc [165, 166]. However, there isn't much information in the literature about the combined toxicity of heavy metals. When multiple heavy metals are exposed simultaneously, a toxic effect may result that is either additive, antagonistic, or synergistic.

The co-exposure to metal/metalloid mixtures of arsenic, lead, and cadmium resulted in more severe effects at both relatively high dose and low dose levels in a biomarker-specific manner, according to a recent review of a number of individual studies that addressed metals interactions [167]. It was discovered that the dose, the length of exposure, and genetic factors all mediated these effects. Additionally, cadmium and inorganic arsenic exposure in humans caused more severe renal damage than either element alone did [168]. Chronic low dose exposure to numerous elements is a significant public health issue in many areas of metal pollution. Understanding the mechanistic underpinnings of heavy metal interactions is crucial for assessing health risks and managing chemical mixtures. Research is therefore required to better understand the molecular mechanisms and effects on public health brought on by human exposure to toxic metal mixtures.

Author's Contribution

The author designed the study along with writing the article in line with the Journal's requirements.

The author of this article review is solely responsible for the content thereof. Data, ideas and opinions presented herein do not necessarily represent the corporate views of the Saudi Arabian Oil Company.

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