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Highlights of Heavy Metals: Molecular Toxicity Mechanisms, Exposure Dynamics, and Environmental Presence

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ABSTRACT

Elements denser than water are known as heavy metals, and they are a major global danger to the environment and human health. The ubiquity of each metal in diverse environmental matrices is highlighted by its existence in both natural and industrial sources. Human exposure pathways include everything from food consumption to work environments, and they all contribute to a variety of health effects and organ system damage. Notably, long-term exposure to these metals is associated with increased cancer incidence rates, which can impact the neurological systems, lungs, kidneys, skin, liver, and other organs. The molecular details of the toxicity and carcinogenicity of individual metals reveal a variety of processes, such as DNA damage, oxidative stress induction, disruption of cellular respiration, disruption of signal transduction pathways, and changes in gene expression. Priority heavy metals (cadmium, chromium, arsenic, lead, and mercury) have distinct toxicological profiles, but this review emphasizes the urgent need for comprehensive strategies to reduce environmental contamination and human exposure. It does this by highlighting the complex interactions between environmental events, anthropological sources, and the molecular basis of heavy metal-induced carcinogenicity and toxicity.
Keywords: Environmental Contamination, Heavy Metals, Environmental Health Impacts, Molecular Mechanisms, Metal Toxicity

INTRODUCTION

Heavy metals are metallic elements denser than water. Metalloids that are hazardous at low exposure levels, such as arsenic, are also classified as heavy metals if toxicity and heaviness are associated [1]. These metals' poisoning of the environment has become an increasingly serious worldwide ecological and public health issue in recent years. Furthermore, human exposure has significantly increased as a result of the exponential growth in the number of industrial, agricultural, household, and technical applications of these compounds [2]. Known sources of heavy metals in the environment include geogenic, industrial, agricultural, pharmaceutical, domestic effluent, and atmospheric [3]. Major sources of pollution to the environment are metal-based industrial operations and point sources such as foundries, smelters, and mines [2, 3]. The main ways that humans contaminate and come into contact with naturally existing elements like heavy metals are through mining, industrial production, and agricultural use. Air deposition, soil erosion, leaching, sediment re-suspension, metal evaporation, and metal corrosion are additional sources [3, 4]. It has also been noted that weathering and volcanic eruptions are examples of natural events that greatly contribute to heavy metal contamination [5]. Paper processing factories, plastics, textiles, microelectronics, wood preservation, metal processing in refineries, coal

burning in power plants, petroleum combustion, nuclear power plants, and high tension lines are examples of industrial sources [5]. According to reports, metals including zinc (Zn), cobalt (Co), copper (Cu), chromium (Cr), iron (Fe), manganese (Mn), magnesium (Mg), molybdenum (Mo), nickel (Ni), selenium (Se), and zinc (Mg) are necessary nutrients needed for a variety of physiological and biochemical processes [6]. Numerous deficiency illnesses or syndromes are brought on by an inadequate intake of certain micronutrients [6]. Physical factors that affect heavy metals include temperature, phase association, adsorption, sequestration, complexation kinetics, lipid solubility, and chemical variables. Heavy metals are present in trace levels in a variety of environmental matrices [7, 8]. Additionally, biological elements such trophic relationships, species traits, and physiological and biochemical adaptability are crucial [9]. In both plants and animals, the important heavy metals perform physiological and metabolic roles. They are crucial components of a number of essential enzymes and are involved in a number of different oxidation-reduction processes [6]. Ferroxidases, catalase, and peroxidase are among the enzymes linked to oxidative stress for which copper is an essential co-factor. For the creation of hemoglobin, the metabolism of carbohydrates, the manufacture of catecholamines, and the cross-linking of collagen, it is integrated into metalloenzymes. Cuproenzymes make use of the reduced and oxidized forms of copper [10]. But because superoxide and hydroxyl radicals can be produced during the switches among Cu(II) and Cu(I), this feature of copper also gives it the potential to be poisonous [11]. Additionally, Wilson disease in humans has been related to cellular damage caused by high copper exposure [10, 11]. Like copper, a number of other elements are necessary for biologic functioning; however, an excess of these elements results in damage to cells and tissues, which can lead to a variety of negative effects and human diseases. For some, like copper and chromium, there is a very narrow range of concentrations between beneficial and toxic effects [11, 12]. Other elements, like aluminum (Al), antinomy (Sb), arsenic (As), barium (Ba), beryllium (Be), bismuth (Bi), cadmium (Cd), gallium (Ga), germanium (Ge), gold (Au), indium (In), lead (Pb), lithium (Li), nickel (Ni), platinum (Pt), silver (Ag), strontium (Sr), tellurium (Te), thallium (Tl), tin (Sn), titanium (Ti), vanadium (V), and uranium (U) have no known biological functions and are regarded as non-essential metals [12]. The effects of heavy metals on cellular organelles and components in biological systems have been documented. These consist of the endoplasmic reticulum, mitochondria, lysosome, cell membrane, nuclei, and specific enzymes that are involved in damage repair, metabolism, and detoxification [13]. Metal ions can cause damage and conformational changes to DNA and nuclear proteins, which can lead to apoptosis, cancer, or abnormalities in the cell cycle. Some laboratory research has shown in multiple studies that the generation of reactive oxygen species (ROS) and oxidative stress are important factors in the toxicity and carcinogenicity of metals including arsenic [14], cadmium [15], chromium [16], lead [17], and mercury [18]. These five elements are considered priority metals of major public health relevance due to their high degree of toxicity. Even at lower exposure levels, these are all recognized to be systemic toxicants that can cause damage to various organs. There are numerous mechanistic components to heavy metal-induced toxicity and carcinogenicity, some of which are not fully understood or clarified. Nonetheless, it is well recognized that every metal has distinct characteristics and physicochemical qualities that give rise to particular toxicological modes of action. The environmental occurrence, production and usage, human exposure potential, and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity of arsenic, cadmium, chromium, lead, and mercury are all reviewed in this article using relevant published articles from various scholarly databases.

Arsenic

Arsenic Occurrences in the Environment, Industrial Production and Use

Arsenic whose two main inorganic forms are trivalent arsenite and pentavalent arsenate is a common element present in a variety of environmental matrices. It is a significant cause of environmental contamination brought on by both human activity and natural processes. Compounds containing arsenic are utilized in veterinary care, agriculture, and medical therapies for illnesses such as trypanosomiasis, syphilis, yaws, and amoebic dysentery. Arsenic trioxide has just received approval to treat acute promeylocytic leukemia as an anticancer treatment [19, 20].

Arsenic Potential for Human Exposure

With millions of people being chronically exposed to arsenic, arsenic exposure is a major global health concern. In isolated areas, its concentrations in the air, water, and soil can reach up to 100 ng/m3, but in urban areas, they are less than 10µg/L. It can be found in foods ranging in concentration from 20 to 140 ng/kg [21]. With an average consumption of approximately 50 µg per day, food is the main source of exposure. Higher amounts can be encountered by workers in sectors such as semiconductor production, wood preservation, pesticide manufacture, glass-making, ceramics, smelting, and refining. 781 hazardous waste sites have been found to contain arsenic contamination; humans can be exposed by breathing in airborne dust, consuming tainted water or soil, or coming into contact with it through the food chain. People exposed to high arsenic levels in their drinking water experience various health issues, including development abnormalities, diabetes, hearing loss, and cancer. Arsenic affects various organ systems and has been linked to higher death rates for bladder, kidney, skin, and liver cancers [20]. The degree of negative consequences on health is time- and dose-dependent [22].

Mechanisms of Arsenic Carcinogenicity and Toxicity

Because of arsenic's oxidation state, solubility, and other characteristics, its harmful effects are multifaceted. Toxicology is also influenced by biological species, age, gender, genetics, nutritional state, individual susceptibilities, exposure dose, frequency, and genetics. Pentavalent arsenate is 2–10 times less hazardous than inorganic arsenic, especially As [III] [23]. Because arsenic can inhibit mitochondrial enzymes and uncouple oxidative phosphorylation, it can disrupt cellular respiration, which is why it is hazardous. Enzymes such as thiolase and dihydrolipoyl dehydrogenase are rendered inactive by its interactions with the sulfhydryl groups of proteins and other substances. Human methylation is the main metabolic pathway for inorganic arsenic, producing MMA and DMA, which may be more hazardous than arsenite if they contain trivalent forms [23]. In both human and rodent cells, arsenic chemicals cause chromosomal abnormalities and hinder DNA repair. Additionally, they are weak mutagens in animal and bacterial cells due to their clastogenic qualities in a variety of cell types. Studies on in vitro cell transformation shed light on the cytotoxic effects of arsenic toxicity on a variety of cell types and provide information on the carcinogenic pathways of the metal [24]. In human lymphophytes and mouse leukocytes, arsenic trioxide causes DNA damage, amplifies genes, stops mitosis, prevents DNA repair, and increases the expression of the c-fos gene. It is believed to act as a comutagen and promoter of hazardous substances. According to recent studies, it is cytotoxic and causes stress genes to be induced in liver cancer cells [25]. Arsenic may function as a carcinogen by causing DNA hypomethylation, which in turn promotes abnormal gene expression, according to Zhao et al. [26]. According to theories, prolonged exposure to arsenic accelerates the development of cancer by activating extracellular signal-regulated protein kinase Erk1 and AP-1, altering gene expression, and hypomethylating DNA. Although it is unknown how JNK activation contributes to tumor development or cell

transformation, arsenic stimulates the expression of the c-jun and c-fos genes [27]. According to Trouba et al. [28] exposure to arsenic heightens a cell's receptiveness to mitogenic activation, which may be a factor in the carcinogenic effects of the substance. According to recent research, arsenic disrupts cell signaling pathways, which causes tumors to spread in both human and animal models [29]. Arsenic trioxide has demonstrated therapeutic value in treating acute promyelocytic leukemia in recent clinical studies; its efficacy in treating other cancers is being investigated [30]. Arsenic is a tumor-specific drug that can be used to treat myeloma by specifically causing apoptosis in acute promyelocytic leukemia cells. Research indicates that arsenic can cause cancer cells to undergo apoptosis and cell-cycle arrest [31].

Cadmium

Cadmium Occurrences in the Environment, Industrial Production and Use

Occurring in sedimentary rocks and marine phosphates, cadmium is a heavy metal with a concentration of 0.1 mg/kg that presents serious environmental and occupational risks. In several different industrial processes, cadmium is often utilized. Cadmium is mostly used in the manufacturing of alloys, pigments, and batteries [32]. Environmental concerns have led to a fall in the commercial usage of cadmium in industrialized countries, despite a notable increase in its use in batteries in recent times. For instance, the daily cadmium intake in the United States is less than half of the oral reference dose recommended by the U.S. EPA, at around 0.4µg/kg/day. More general limits on cadmium use as well as more stringent effluent limits from plating enterprises have been connected to the decline in cadmium consumption in a number of countries [32].

Cadmium Potential for Human Exposure

The main ways that people are exposed to cadmium are by eating, inhalation, and cigarette smoke; skin absorption is uncommon. Some of the causes are working in the metal industry, eating tainted food, smoking, and doing jobs where cadmium is present [33]. Trace levels of cadmium can also be found in some meals and can improve blood vessel concentration. Changes in pulmonary function, olfactory function, bone mineral density, and osteoporosis can result from long-term exposure to cadmium [34]. Testing for cadmium in the blood or urine is a popular method of determining cadmium exposure. Recent cadmium exposure, such as smoking, is reflected in blood cadmium levels. Cadmium exposure to humans and environmental contamination have grown significantly during the past century due to the ongoing use of cadmium in industrial applications [35].

The Molecular Basis of Cadmium Carcinogenicity and Toxicity

Severe respiratory and gastrointestinal symptoms, such as nausea, vomiting, convulsions, and abdominal pain, can be brought on by the strong irritant cadmium [36]. Depending on the poisoning route, chronic exposure can cause prostatic proliferative lesions, including adenocarcinomas, as well as depressive effects and lung adenocarcinomas [37]. It is believed that cadmium toxicity damages cells by producing reactive oxygen species that interfere with the synthesis of nucleic acids, proteins, and DNA. Studies both in vivo and in vitro demonstrate cytotoxic effects and changes in male reproduction [38]. By generating inositol polyphosphate, raising calcium levels, and obstructing calcium channels, cadmium affects signal transduction pathways. In addition, it binds to proteins, increases cytokine production, inhibits DNA repair, and triggers protein degradation [39]. Regulatory groups have classified cadmium compounds as carcinogenic to humans. The most conclusively shown site of cadmium-induced lung cancer in humans is the lung [40]. The hemopoietic system, testes, adrenals, and injection sites are other target tissues. Metals known to cause cancer, such as arsenic, cadmium, chromium, and nickel, can harm DNA.

Research on animals reveals teratogenic and reproductive impacts [41].

Chromium

Chromium Occurrences in the Environment, Industrial Production and Use

The element chromium occurs naturally in oxidation states II through VI. It is present in ores such as ferrochromite and is stable in trivalent form. There are several ways that chromium is released into the environment, but industrial facilities are the main source. One hazardous industrial contaminant that is known to cause cancer in humans is hexavalent chromium. The oxidation state determines the health risks; the metal form is low toxicity while the hexavalent form is highly noxious [42]. Due to its widespread use in a variety of industrial processes, chromium contaminates a large number of environmental systems. Commercial applications for chromium compounds include wood preservation, leather tanning, dyes and pigments, industrial welding, and chrome plating. Boilers and cookery systems also use chromium as an anticorrosive [43].

Chromium Potential for Human Exposure

The occupational exposure of over 300,000 workers to chromium and compounds containing chromium increases their chance of developing diseases related to Cr. For industrial workers, the U.S. Occupational Safety and Health Administration established 5µg/m^3 as a safe threshold, however there may still be a risk of cancer from this. The atmospheric concentrations of the general human population range from 1 to 100 ng/cm3 [44]. Exposure to chromium can happen through eating or inhalation; concentrations in soil range from 1 to 3000 mg/kg, in sea water from 5 to 800 µg/L, and in rivers and lakes from 26 µg/L to 5.2 mg/L. Chromium content in fresh foods range from less than 10 to 1,300 µg/kg. Higher amounts may be encountered by employees in industries connected to chromium. Exposure to environmental and occupational factors can lead to multiorgan toxicity, which can include respiratory cancer, allergies, asthma, and renal impairment [45]. Elevated chromium (VI) levels in animals have been linked to sperm destruction, anemia, ulcers, and irritation of the nose and male reproductive system. Compounds containing chromium (III) are not harmful and do not result in these issues. Some people have chromium sensitivity, which can lead to allergic responses and stomach cancers. Ingesting something by accident or on purpose might have serious health consequences, such as death or hospitalization.

Molecular mechanisms of Chromium Carcinogenicity and Toxicity

The solubility and oxidation state of chromium affect its toxicity. Because of their facile transit through cell membranes and corrosive character, Cr(VI) compounds are more hazardous than Cr(III) compounds. The main cause of chromium's toxicity is its Cr(VI) form, which the skin, gastrointestinal system, and lungs can all absorb. The amount and rate at which chromium can enter cells and have harmful effects depends on the balance between extracellular and intracellular Cr(VI) [46]. Under normal conditions, hydrogen peroxide, glutathione reductase, glutathione, andascorbic acid, can reduce Cr(VI), which enters many different types of cells. This reduction produces reactive intermediates, such as Cr(V), Cr(IV), thiylradicals, hydroxyl radicals, and finally Cr(III). Studies on animal models have shown harmful effects of Cr (VI) on mammals, including progressive proteinuria, urea nitrogen, creatinine, and renal damage. In humans, Cr (VI)-containing compounds have been linked to respiratory cancers, DNA strand breaks, and lipid peroxidation products in urine [47]. Oxidative damage is considered the underlying cause, but recent studies suggest non-oxidative mechanisms may also play a role in Cr(VI) carcinogenesis [48].

Lead

Occurrences in the Environment, Industrial Production and Use

Lead, a naturally occurring bluish-gray metal, is a substantial contributor to lead pollution due to human activities such fossil fuel burning, mining, and manufacture. It is utilized in many different businesses, such as those that produce lead-acid batteries, metal goods, ammunition, and X-ray shielding equipment [49]. Lead's industrial use in caulking, pipe solder, paints, and ceramic items has drastically decreased recently [50]. Nevertheless, in 16.4 million US houses with more than one kid under the age of six, significant amounts of lead-contaminated deteriorating paint, dust, or nearby bare soil were still present in 25% of the homes, according to reports [51]. Lead in dirt and dust frequently recontaminates dwellings that have been cleaned [52], and it raises blood lead levels in kids who play in bare, contaminated dirt [53]. As lead paint deteriorates on interior surfaces, dust and chips are now the main cause of lead poisoning in children [54]. Lead poisoning in children can occur in homes with decaying lead paint.

Lead Potential for Human Exposure

Ingestion of lead-contaminated food, water, or paints, as well as inhalation of lead-contaminated dust particles or aerosols, are the main ways that people are exposed to lead [55]. Through their drinking water, adults absorb 35 to 50% of lead, and children may absorb more than 50%. Age and physiological state are two factors that affect lead absorption. The kidneys absorb the largest amount of lead in the human body, followed by the liver and other soft tissues including the heart and brain; nonetheless, the majority of the lead in the body is found in the skeleton. The most susceptible organ system to lead poisoning is the neurological system. The initial signs of headache, poor focus, irritation, memory loss, and dullness are caused by lead exposure on the central nervous system [53]. The most widespread toxicant is lead, which has an impact on the kidneys, liver, central nervous system, hematopoietic system, endocrine system, and reproductive system, among other organs [55]. Lead exposure typically comes from using lead in hobbies, some traditional medicines and cosmetics, decaying household paints, working with lead, lead in crystals and ceramic vessels that leak into water and food, and lead exposure from these sources [50]. Lead exposure is especially dangerous for women, especially while they are pregnant. Pregnant women easily absorb lead, which is therefore easily passed to the growing fetus. Human data supports animal research, which links lead exposure during pregnancy to low birth weight and premature delivery, as well as to neurodevelopmental defects in the offspring [56].

Molecular Basis of Lead Carcinogenicity and Toxicity

Research indicates that exposure to lead can have negative consequences on both children and adults. These impacts include reduced cognitive function, delayed neurobehavioral development, impaired hearing, speech and language impairments, delayed growth, insufficient attention span, and antisocial conduct. In addition, gastrointestinal disorders, renal damage, brain damage, and reproductive problems can result from high lead exposure [55, 57]. The main mechanism by which lead causes toxicity is by its inhibition of calcium's activities and interactions with proteins. It attaches itself to biological molecules and changes their functioning [55]. It is found in minerals such as calcium. Reactive oxygen species (ROS) from lead intoxication cause cellular damage, and blood levels of malondialdehyde are correlated with lead concentrations [58]. Research indicates that exposed workers' erythrocytes had higher levels of antioxidant enzymes than those of non-exposed individuals [59]. Numerous cellular and molecular mechanisms, such as oxidative stress, transcriptional activation, DNA damage, phosphatidylserine externalization, and caspase-3 activation, are involved in lead-

induced toxicity and death in human cancer cells [60]. Abundant studies have shown that lead works by interfering with calcium-dependent mechanisms involved in intracellular signal transduction and neuronal signaling. Lead alters the releasability of organelle storage, including the endoplasmic reticulum and mitochondria, by disrupting the intracellular calcium cycling [61]. Certain calcium-dependent processes, such as the discharge of some neurotransmitters and receptor-coupled ionophores in glutamatergic neurons, are occasionally inhibited by lead [62]. In certain instances, lead seems to enhance calcium-dependent processes, like calmodulin and protein kinase C [63]. Lead is regarded as likely carcinogenic to humans [64] since experimental research has shown that it may cause kidney cancers in rats and mice [65]. Gene mutations and sister chromatid exchanges have also been linked to lead exposure [66].

Mercury

Mercury Occurrences in the Environment, Industrial Production and Use

Mercury is a heavy metal found in three forms: elemental, inorganic, and organic. It exists as a liquid with high vapor pressure and cation with +1 or +2 oxidation states. Methylmercury, the most common organic compound, is formed by microorganisms methylating inorganic mercury in soil and water [67, 68]. Several industrial operations, including the production of caustic soda, nuclear reactors, wood processing, pharmaceutical, electrical, and dentistry industries, all involve the use of mercury [69]. Federal prohibitions on the use of mercury compounds in paints and pesticides, as well as the decrease in its usage in batteries, caused the industrial demand for mercury to peak in 1964 and then begin a fast decline between 1980 and 1994 [70].

Potential of Human Exposure to Mercury

All forms of mercury exposure to humans occur from dental treatment, medical procedures, occupational activities, food contamination, and accidents, industrial and agricultural operations [71]. The main causes of long-term, low-level mercury exposure are fish eating and dental amalgams. Both naturally occurring off-gassing from the earth's crust and industrial contamination cause mercury to enter water. Mercury that enters streams is methylated by bacteria and algae. After then, methyl mercury enters fish and shellfish and finally finds its way into people via the food chain [72].

Molecular Basis of Mercury Carcinogenicity and Toxicity

Mercury toxicity is linked to three processes: covalent bond formation with protein cysteine residues, oxidative stress, and sulfhydryl reactivity. As a result, the amount of antioxidant enzymes in cells is reduced, which stops reactive oxygen species (ROS) from being produced [73]. The regulation of calcium homeostasis is impacted by oxidative stress and is essential for the activation of phospholipases, endonucleases, and proteases. Arachidonic acid is produced when phospholipase A_2 is activated, which raises reactive oxygen species. By raising intracellular calcium reserves and raising MDA levels in the liver, kidneys, lungs, and testes, among other ways, organic and inorganic mercury can disrupt calcium homeostasis [74]. Vitamin E and selenium can guard against lipid peroxidation brought on by $HgCl_2$ [75]. Polyploidal abnormalities, elevated mitotic index, and elevated glutathione levels in human populations have all been associated with mercury toxicity from contaminated seafood. Changes in enzymatic activity have been observed in epidemiological investigations, which may lead to oxidative stress and the inhibition of enzyme activity [76]. While there is debate over the link between mercury exposure and the development of cancer, in vitro research points to possible toxicity specific to specific cells, organs, and species as well as damage to DNA.

CONCLUSION

This paper explores the environmental impact of heavy metals such as cadmium, chromium, lead, mercury, and arsenic their toxicity and carcinogenicity. These metals are found in various sources, including food, work, and pollution. Long-term exposure can cause organ damage and cancer. The toxicity mechanisms include oxidative stress, signal transduction disruption, DNA damage, and gene expression changes. The paper calls for interdisciplinary research to understand these metals' interactions and develop effective policies to minimize environmental contamination and mitigate health risks.

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