ENVIRONMENTAL CONTAMINATION AND TOXICITY OF HEAVY METALS (A REVIEW)

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ABSTRACT: *Heavier metals are naturally occurring elements with densities at least five times greater than water's and huge atomic weights. Their many uses in industry, agriculture, home goods, medicine, and technology have led to their extensive release into the environment, which has raised concerns about their potential impact on human health and the environment. The chemical species, amount, and method of exposure are only a few of the factors that determine how dangerous they are. Other factors include the exposed person's age, gender, heredity, and nutritional status. Because of their extreme toxicity, mercury, lead, chromium, cadmium, and arsenic are deemed priority metals that are relevant to public health. As systemic toxicants, these metals are known to harm a wide variety of organs even at low concentrations of exposure. They are deemed carcinogenic to humans by both the prestigious International Agency for Research on Cancer and the United States Environmental Protection Agency. This research delves into the production and use of the substance, its possible effects on humans, and the molecular processes of carcinogenicity, genotoxicity, and toxicity.*

Keywords: Carcinogenicity, Genotoxicity, Toxicity, Human exposure, Production and use, Heavy metals

INTRODUCTION

Metals with a density higher than water are called heavy metals [1]. Heavy metals are another name for metalloids like arsenic that may be dangerous even at low exposure levels, on the assumption that they are poisonous and heavy [2]. In recent years, these metals' contamination of the environment has become an increasingly pressing issue for human health and the environment on a global scale. Furthermore, human exposure has grown substantially as a result of the exponential development in the number of these chemicals' industrial, agricultural, household, and technological usage [3]. In the environment, several metal sources are found which include atmospheric, household effluent, pharmaceutical, agricultural, industrial, and geogenic sources [4]. Environmental contamination is mostly caused by point sources, which include metal-based industrial operations such as foundries, smelters, mining, and others [1, 3, 4].

While heavy metals are present in all of Earth's crust, human activities such as metal mining and smelting, industrial production and use, and the use of metals and compounds containing metals in agriculture and household settings are the primary causes of environmental contamination and human exposure [4–7]. Additional pathways for environmental contamination include metal corrosion, air deposition, soil erosion, heavy metal leaching, sediment re-suspension, and metal evaporation from water resources into soil and groundwater [8]. Reportedly, weathering and volcanic eruptions are also significant contributors to metal contamination. Industrial sources include, but are not limited to, enterprises that process paper, plastic, textiles, microelectronics, wood, metal, coal, petroleum, nuclear power, and high-tension lines [9–11].

Many physiological and biological processes need metals including magnesium, selenium, nickel, molybdenum, magnesium, manganese, iron, chromium, copper, cobalt, and zinc [12]. As a result of not getting enough of particular micronutrients, several deficiency diseases and syndromes manifest [12]. The fact that heavy metals are present in several environmental matrices at very low quantities (between 0.1 and 0.01%) [13] further qualifies them as trace elements. Physical variables like temperature, phase association, adsorption, and sequestration all have an impact on their bioavailability. Furthermore, octanol/water partition coefficients, complexation kinetics, lipid solubility, and chemical variables affecting speciation at thermodynamic equilibrium are also relevant [14]. Trophic interactions, species characteristics, and the capacity to adapt physiologically and biochemically are also important biological factors [15]. The vital heavy metals contribute to the physiological and metabolic processes in all living things. Involved in a wide variety of oxidation-reduction reactions, they are integral parts of many key enzymes [12]. Several enzymes associated with oxidative stress need copper as a co-factor. These enzymes include dopamine β-monooxygenase, monoamine oxidase, cytochrome c oxidases, peroxidase, superoxide dismutase, catalase, and ferroxidases [16–18]. So, it's an essential nutrient that's part of a lot of metalloenzymes that do things like make hemoglobin, break down carbs, make catecholamines, and cross-link keratin, collagen, and elastin. Because copper may cycle between an oxidized and a reduced state, cuproenzymes that participate in redox reactions make use of this property [16–18]. The fact that copper may undergo transitions from Cu(II) to Cu(I) would make it potentially dangerous because of the radicals superoxide and hydroxyl that might be created [16–19]. Furthermore, cellular damage produced by elevated copper exposure has been linked to Wilson disease in humans [18, 19]. While copper and many other elements are essential for bodily function, too much of any one metal may harm cells and tissues, leading to a cascade of unsavory side effects and diseases. Copper and chromium are two examples of metals with a narrow concentration range between beneficial and detrimental effects [19, 20]. Due to their lack of established biological roles, the following metals are also considered non-essential: metals such as aluminum, antimony, arsenic, barium, bismuth, cadmium, gallium, germanium, gold, indium, lead, lithium, mercury, nickel, platinum, silver, strontium, tellurium, thallium, tin, titanium, vanadium, and uranium [20].

There is evidence that heavy metals may damage many cellular organelles and biological system components. Enzymes that play a role in metabolism, detoxification, and

damage repair are among them, along with the cell membrane, mitochondria, lysosome, endoplasmic reticulum, and nuclei [21]. Researchers have shown that metal ions may cause DNA damage and alter its structure, which in turn can cause apoptosis, cancer, or alterations to the cell cycle [20-22]. We found that some metals, including mercury, lead, chromium, cadmium, and arsenic, are hazardous and carcinogenic due to reactive oxygen species (ROS) and oxidative stress [23-32], respectively.

Some of the mechanisms that contribute to the carcinogenicity and toxicity caused by heavy metals remain unclear. However, it is well acknowledged that each metal has unique traits and physicochemical properties, which in turn cause specific toxicological effects. This research examines the environmental occurrence, production, and consumption of arsenic, cadmium, chromium, lead, and mercury, as well as their potential exposure to humans and the molecular processes by which they are toxic, genotoxic, and carcinogenic.

Arsenic

Industrial use and production, environmental occurrence

The element arsenic is present in almost all environmental matrices, although in trace amounts [33]. Inorganic arsenic is mostly found in two forms: trivalent arsenite and pentavalent arsenate. Organic forms include trimethylarsine oxide, dimethylarsinic acid, and monomethylarsonic acid, all of which are methylated metabolites. Soil erosion and volcanic eruptions are two examples of natural processes that may pollute the environment with arsenic [33]. Human activity is another major contributor. Herbicides, insecticides, fungicides, algicides, sheep dips, wood preservatives, and dyes are only a few of the agricultural items made from arsenic-containing compounds obtained via industrial manufacture. Also, veterinarians have used them to get rid of tapeworms in cattle and sheep [34]. Compounds containing arsenic have been used to treat trypanosomiasis, syphilis, yaws, and amoebic dysentery for at least a hundred years [34, 35]. Some tropical diseases, such as amoebic dysentery and African sleeping sickness, and parasitic disorders, like filariasis in dogs and blackheads in chickens and turkeys, are still treated with arsenic-based drugs in veterinary medicine [35]. Arsenic trioxide is now a valid anticancer medication for acute promyelocytic leukemia, according to a recent FDA approval [36]. One mechanism by which it exerts its therapeutic effects is by causing leukemia cells to commit programmed cell death, more often known as apoptosis [24,25].

Exposure

In countries like Bangladesh, India, Chile, Uruguay, Mexico, and Taiwan, where groundwater is highly contaminated with arsenic, millions of people are supposedly exposed to the metal daily. Oral (by swallowing), inhalation, skin contact, and parenteral routes are all potential ways that arsenic might be exposed to the body [33, 34, 37]. Arsenic air concentrations may range from 20 to 100 ng/m^3 in urban areas, but only 1 to 3 ng/m3 in rural regions unaffected by human activity. Usually, its water content is below 10µg/L, however, you could find higher concentrations close to places where minerals are mined or naturally occurring [38].

The bulk of people's exposure comes mostly from their food, with an average daily consumption of around 50 µg. In areas where arsenic poisoning is prevalent, exposure via the air, water, and soil may become substantial, even though it is usually much lower. Worker exposure to arsenic levels may be much higher in companies that produce or use arsenic compounds i.e. wood preservation processes, semiconductor manufacturing, pesticide production and application, refining of metallic ores, smelting, glass-making, ceramics, winemaking [39]. The United States Environmental Protection Agency has identified arsenic at 781 out of 1,300 hazardous waste sites [33, 39]. Animals, contaminated soil, water, or even airborne dust particles are just a few of the many ways that people might come into contact with these places [40].

Significant levels of arsenic pollution are cause for concern because arsenic may have many detrimental effects. The epidemiological survey demonstrated a strong inter-relationship between exposure to arsenic and increased health outcomes regarding systemic and carcinogenic [41]. Attention has been drawn to the toxicity of arsenic due to recent reports of huge populations exposed to high quantities in their drinking water in countries such as West Bengal, Bangladesh, Thailand, Inner Mongolia, Taiwan, China, Mexico, Argentina, Chile, Finland, and Hungary. Developmental abnormalities, cancer, diabetes (eosinophilia) peripheral vascular disease, and cardiovascular disease are among the clinicopathological problems shown by these populations. Arsenic exposure affects almost every system in the body, including the nervous, gastrointestinal, pulmonary, skin, and cardiovascular systems [41]. There is a relationship between arsenic's molecular shape and the time- and dosage-dependent negative health effects [42, 43]. The precise process by which arsenic induces tumors in humans is still unknown, despite the seemingly strong evidence connecting the two [44].

Mechanisms of Toxicity and Carcinogenicity

It is difficult to analyze the harmful effects of arsenic since its toxicity is considerably affected by its oxidation state, and solubility [45]. Research has shown that the toxicity of arsenic depends on several factors, including gender, age, genetic predisposition, exposure frequency, length, and dose [46]. Inorganic arsenic has been associated with most cases of arsenic poisoning in humans. Inorganic trivalent arsenite (AsIII) is as much as two to ten times more dangerous than pentavalent arsenate (AsV) [5]. This is probably the process by which arsenic affects so many different bodily systems [5, 47].

Arsenic hinders cellular respiration by inhibiting many enzymes in the mitochondria. One mechanism by which arsenic is harmful is because it uncouples oxidative phosphorylation [48]. Arsenic inhibits pyruvate oxidation and fatty acid betaoxidation in vitro [49]. Inorganic arsenic is mostly broken down in humans by methylation [40, 47]. People used to think that methylation was a way to detoxify arsenic, but new studies suggest that certain methylated metabolites with trivalent arsenic may be even more dangerous than arsenite [41].

Genotoxicity studies in humans and rodents have demonstrated that arsenic compounds hinder DNA repair in

exposed cells [53], and induce sister-chromatid exchanges, micronuclei formation, and chromosomal abnormalities in cultured cells [50–52]. Reversion testing for Salmonella typhimurium cannot detect mutations brought about by arsenic compounds. Although arsenic compounds are considered to be minor mutagens in bacterial and mammalian cells, they exhibit clastogenic properties in many different kinds of cells when tested in vitro and in vivo [54]. Research into the carcinogenic mechanisms behind arsenic toxicity using in vitro cell transformation experiments can be useful in situations when animal models are unavailable. Cytotoxic effects of arsenic and arsenical compounds on Syrian hamster embryo (SHE) cells have been documented [55, 56], in addition to morphological alterations in mouse C3H10T1/2 and BALB/3T3 cells.

Arsenic trioxide is known to damage human (DNA) lymphocytes [57] and mice leukocytes [58] according to the found test. In addition, research has shown that arsenic compounds may amplify genes, and stop cell division [58, 59]. As mutagens and promoters, they have been linked to many harmful chemicals [60, 61].

According to Zhao et al. [62], arsenic may induce aberrant gene expression by producing DNA hypomethylation, which in turn functions as a carcinogen. In addition to its significant stimulation of AP-1 transactivational activity and extracellular signal-regulated protein kinase Erk1 [63, 64]. But how exactly arsenite's activation of JNK causes tumor development or cell transformation remains a mystery.

In a separate study, Trouba et al. [65] found that cells might be more vulnerable to mitogenic activation after long-term exposure to high arsenic concentrations. To review, several research conducted in the last few years have shown that arsenic may interfere with cell signaling pathways. One such system is the p53 signaling pathway, which has been associated with various kinds of tumors in both animal models and human cases [66, 68]. Cancers in humans may develop after long-term exposure to arsenic.

A variety of different cancers are being studied for potential treatment success with arsenic trioxide, which has recently shown promise in treating acute promyelocytic leukemia [69, 70]. Acute promyelocytic leukemia's critical molecular pathway for cancer cell formation has been identified. A study conducted by Puccetti et al. [71] found that human lymphoblast cells were more susceptible to arsenic-induced cell death when they were pushed to overexpress the BCR-ABL gene. Arsenic trioxide may induce selective apoptosis in acute promyelocytic leukemia cells, according to their findings. This compound is tumor-specific. Several investigations conducted recently suggest that arsenic may induce cell death by influencing other signaling pathways [72, 73]. Some research suggests that arsenic may be useful in treating myeloma and acute promyelocytic leukemia [74]. In conclusion, several cancer therapy studies have shown that arsenic trioxide injections may halt cell cycle progression and kill cancer cells in vitro.

Mutations and p53 gene expression in tumors obtained from arsenic-intoxicated individuals have also been the subject of prior studies. Programmed cell death, genomic plasticity, cell cycle control, DNA repair, and differentiation are just a few of the many biological activities that p53 facilitates. There is mounting evidence from several studies that arsenic may affect gene expression [75-78] as well as cells from colon cancer [79], lung cancer [80], human leukemia [81], Jurkat-T lymphocytes [82], while cells from liver carcinoma [83] are also affected. Our in vitro experiments have shown that arsenic inhibits these activities in a variety of cell types. In addition, we have shown that n-acetyl cysteine and ascorbic acid, which are both antioxidants, may impact the oxidative stress-mediated arsenic-induced cytotoxicity pathway [84–86].

The carcinogenic effects of inorganic arsenic have been the subject of several hypotheses. The molecular processes by which arsenical promotes cancer, however, remain mostly unknown at this time. As an alternative to its more common genotoxic and mutagenic effects, inorganic arsenic may enhance tumor development by changing signal transduction pathways associated with cell proliferation and growth [68]. No scientific consensus has been reached about the mechanism(s) by which arsenic causes cancer, despite recent substantial progress in this area. Arsenic carcinogenesis has nine proposed mechanisms of action, according to a recent review [87].

Cadmium

Industrial use and production, environmental occurrence

The environmental and occupational impacts of cadmium, a heavy metal, are very worrisome. Its typical concentration in Earth's crust is 0.1 mg/kg, yet there are enormous amounts of it there. The environmental concentration of cadmium compounds is highest in sedimentary rocks, with a concentration of around 15 mg/kg in marine phosphates [88].

Cadmium is often used in a variety of industrial operations. Alloys, pigments, and batteries are the three main products that primarily use cadmium [89]. Although cadmium's use in batteries has increased significantly in recent years, environmental concerns have caused a decline in its commercial utilization in industrialized countries. Take the United States as an example; the average daily intake of cadmium is around 0.4µg/kg, which is less than half of the oral reference dose suggested by the U.S. EPA [90].

Exposure

The two most common ways to absorb cadmium are via food and secondhand smoke from cigarettes. Skin absorbs very seldom. People may be exposed to cadmium in a variety of ways; smoking is one of the most common, but other methods include working with primary metals, consuming tainted food, smoking cigarettes, and being in cadmium-contaminated workplaces [91, 92, 93, 94]. In addition, cadmium levels in the body may be substantially increased by eating cadmium-rich foods. Some examples include dried seaweed, cocoa powder, prawns, mussels, mushrooms, and liver [95, 96]. Osteoporosis and reduced bone mineral density as possible outcomes of long-term low-level cadmium exposure [97-99].

Many people choose to find out how much cadmium they've been exposed to by testing their blood or urine. High blood cadmium levels indicate recent exposure to cadmium, as may be seen in cigarette smoke. When cadmium is detected in urine, it may be used to determine renal load or cadmium accumulation. To account for dilution, the cadmium/creatinine ratio is often used [100-103]. Because of

cadmium's persistent usage in industrial applications, human exposure to metal and environmental contamination have both increased dramatically during the last century [104].

Carcinogenicity and toxicity (Molecular Mechanisms)

It is believed that reactive oxygen species (ROS) are the principal mechanism by which cadmium harms cells [105-111]. ROS damages single-strand DNA and impedes protein and nucleic acid synthesis [112]. It is not well understood how cadmium poisoning occurs. Studies reveal that cadmium exposure triggers the expression of many stress response pathways, such as those associated with heat shock, oxidative stress, stringent response, cold shock, and SOS [113-115]. In vitro studies have shown that cadmium, at concentrations between 0.1 and 10 mM, may induce DNA damage via cytotoxic effects and free radicals [116, 117]. Research in living organisms has shown that cadmium, at a dosage of 1 mg/kg body weight, controls male fertility in a mouse model [118]. Cadmium, on the other hand, is a moderate mutagen rather than a carcinogen [119]. The generation of inositol polyphosphate, a rise in cytosolic free calcium in several cell types [120], and the blocking of calcium channels [121, 122] are all signal transduction pathways that have been associated with cadmium.

Cadmium compounds have been classified as human carcinogens by many regulatory agencies. According to the International Agency for Research on Cancer and the United States National Toxicology Programme, there is enough evidence to suggest that cadmium causes cancer in humans [91]. Consistent findings linking cadmium exposure in the workplace to lung cancer and strong evidence from animal studies showing the pulmonary system as a target site are the main reasons for classifying cadmium as a human carcinogen [91]. So far, cadmium-induced lung cancer in humans has been most definitively shown to occur in the lung. In addition to the adrenal glands, testes, injection sites, and hemopoietic system, cadmium carcinogenesis in animals may affect other tissues [91, 108, 109]. Additionally, exposure to cadmium in the workplace or environment has been associated with the development of malignancies in the stomach, hematological system, kidney, liver, and prostate, according to studies [108, 109, 126-128].

Chromium

Industrial use and production, environmental occurrence

Chromium (Cr) is an element that exists naturally on Earth and has valence states ranging from II to VI, which correspond to different amounts of oxidation [129]. Iron chromite and other ores include trivalent chromium compounds, also known as Cr(III) compounds, which are inert. In terms of stability, the hexavalent [Cr(VI)] form is second to none [28]. Elements chromium [Cr(0)] are very uncommon to find in nature. The majority of the chromium that seeps into our air, water, and soil comes from industrial operations, but there are numerous other natural and human-made sources as well. The primary sectors that release chromium into the atmosphere include those dealing with metals, tanneries, chromate production, stainless steel welding, ferrochrome, and chrome pigments. Air and wastewater chromium emissions, mostly from the chemical, refractory, and metallurgical industries, have been linked to elevated environmental chromium concentrations. Hexavalent chromium, or Cr(VI)[130], is the most common form of chromium that humans emit into the environment. Several groups, both government and non-government, have classified the toxic industrial byproduct hexavalent chromium [Cr(VI)] as a carcinogen for humans [130-132]. Exposure toxicity is proportional to chromium's degree of oxidation; metal chromium is quite harmless, while hexavalent chromium is very harmful. Soil, water, air, and biological components naturally contain Cr(III), but all things containing Cr(VI) were thought to be man-made at one point. Despite this, levels of naturally occurring Cr(VI) in both surface and groundwaters are above the 50 µg/liter drinking water guideline set by the World Health Organisation (133). Chromium pollutes many ecosystems since it is used so extensively in many industrial processes [134-136].

Exposure

To maintain healthy glucose, lipid, and protein metabolism, animals and humans alike need the mineral [Cr(III)]. It does this by making insulin work better [5]. Industrial workers exposed to Cr(VI) have a considerable risk of Cr-induced diseases, which has raised severe concerns about occupational exposure [137]. Some species and the human race as a whole may also be in danger. It is projected that 33 tonnes of total Cr are released into the environment annually [130]. The "safe" limit of 5µg/m3 for an 8-hour time-weighted average has been established by the U.S. Occupational Safety and Health Administration (OSHA), even though this reduced amount might still provide a carcinogenic risk [138]. While the typical human air value ranges from 1 to 100 ng/cm3 [139], these levels may be higher in areas close to Cr industries.

Chromium exposure in the workplace occurs via inhalation [140]. Chromium concentrations in the river and lake water range from 26 µg/L to 5.2 mg/L, in seawater from 5 to 800 µg/L, and in soil from 1 to 3000 mg/kg [129]. Chromate concentrations in food are greatly affected by processing and cooking methods. [141, 142, 143]. It is believed that the prevalent dermatitis cases observed in construction workers are caused by exposure to chromium present in cement, for example [143]. Occupational and environmental exposure to chemicals containing Cr(VI) may cause a variety of harmful consequences, including cancer of the respiratory tract, allergies, asthma episodes, and damage to the kidneys [5, 144].

Air pollution with high concentrations of chromium (VI) may irritate the nasal mucosa and lead to ulcers. Anaemia, sperm destruction, ulcers and inflammation in the small intestine and stomach, and damage to the male reproductive system are the most typical health difficulties that animals encounter when they eat chromium (VI) compounds. It doesn't seem that similar problems are caused by compounds containing chromium (III), which are far less dangerous. Some individuals have severe reactions to chromium (VI) or chromium (III), including severe skin redness and swelling. Chromium(VI) in drinking water increases the risk of stomach cancer in both humans and animals. Serious neurological, hematological, liver, pulmonary, cardiovascular, and gastrointestinal adverse effects, including death, have been reported in humans who have inadvertently

or intentionally taken extraordinarily high quantities of chromium (VI) compounds [141,145].

Mechanisms of Toxicity and Carcinogenicity

Chromium compounds' toxicity is dependent on their oxidation state and solubility. For the same amount of water and concentration, Cr(VI) compounds seem to be much more systemically dangerous than Cr(III) compounds due to their status as powerful oxidizing agents, potential causticity, and irritation [146, 147]. When Cr(VI) reduction takes place distant from the site of toxic or genotoxic activity, it is considered a detoxifying process; nevertheless, when it occurs in or near the cell nucleus of target organs, it may activate chromium toxicity [148]. Since cells are not good at absorbing Cr(III) form of the metal, toxicity will not be shown if Cr(VI) is transformed to this form outside of cells. The equilibrium between external Cr(VI) and intracellular Cr(III) determines the amount and rate of Cr(VI) entry into cells and toxicity [134].

Ascorbic acid, glutathione reductase, hydrogen peroxide (H2O2), and GSH may normally decrease Cr(VI), which can enter many cell types. Reactive intermediates including Cr(III), Cr(V), thiol radicals, and hydroxyl radicals are formed during this reduction. Proteins, DNA, and membrane lipids may all be damaged by any of these species, which can compromise the functioning and integrity of cells [149-151].

Gumbleton and Nicholls [152] and others found that rats' kidneys were injured after receiving a single subcutaneous injection of Cr (VI). According to research by Bagchi et al. [153, 154], liver mitochondrial and microsomal lipid peroxidation, and a rise in the excretion of urine lipid metabolites such as malondialdehyde were seen in rats that were administered Cr (VI) orally in water.

Cr (VI) has reportedly had negative effects on human health. Epidemiological studies have shown a link between occupational exposure to Cr (VI) compounds and the development of lung cancer in workers [142, 148, 155, 156]. It is believed that oxidative damage is the culprit responsible for these genotoxic outcomes, which include DNA strand breaks and chromosomal abnormalities [157, 158]. On the other hand, recent studies have shown that Cr(VI) carcinogenesis is influenced by non-oxidative mechanisms [160].

One possible carcinogenic connection is inhalation of the less soluble or insoluble Cr(VI) molecules. The toxicity of Cr(VI) is not proportional to its elemental form. In a wide variety of chemically unique Cr(VI) complexes, it varies greatly [161, 162]. According to a mountain of epidemiological evidence, Cr(VI) is the main culprit behind cancer. Size, crystal modification, surface charge, phagocytization capability, and chromium solubility are some of the additional characteristics that may play a key role in determining cancer risk [135]. According to current research on goldfish (Carassius auratus) kidneys and livers, chromium (VI) causes biochemical, genotoxic, and histopathologic effects [163].

Many hypotheses have been advanced to account for the carcinogenic effects of chromium and its salts; nevertheless, discussing metal carcinogenesis is not without its difficulties. A metal cannot be claimed to be intrinsically carcinogenic because the potencies of its several components might fluctuate. Due to the wide variety of chemical exposures in industrial settings, it is difficult to identify a single agent responsible for the carcinogenic effects. Consequently, the mechanism of action or group of metal compounds is often connected to the carcinogenic risk, rather than a specific substance. Many factors, including the metal's chemical form, the size of the aerosolized particle, and the particle's physical characteristics (such as crystal modification and surface charge), influence the metal's carcinogenic potential [164].

Lead

Industrial use and production, environmental occurrence

Lead, a bluish-gray metal that occurs naturally, is present in trace amounts in Earth's crust. The majority of the lead in the air comes from human activities, such as mining, burning fossil fuels, and manufacturing, even though lead is present in nature. Lead has several applications in manufacturing, farming, and household products. The majority of that amount, 83%, went into making lead-acid batteries. The rest, 1.7%, went into other items such as sheet lead, 2.6% into oxides for paint, glass, pigments, and chemicals, and 3.5% into weaponry [165, 166].

Caulking, pipe solder, paints, and ceramic products containing lead have seen a significant decline in their industrial use as of late [167]. Despite this, statistics indicate that 25% of the 16.4 million US households with several children under the age of six still had high amounts of lead-contaminated decaying paint, dust, or adjacent bare dirt [168]. Children whose playtimes include bare, polluted soil are at increased risk for elevated lead levels in blood and lead in dust and dirt may recontaminate cleansed homes [169-172].

Exposure

The most common routes of lead exposure are the consumption of lead-contaminated foods, drinks, or paints and the breathing in of lead-contaminated dust or aerosols [173, 174]. Adults may take up to 35–50% of lead via water, while children can absorb even more. The rate of lead absorption is affected by factors such as physiological conditions and age. Although the bulk of lead is stored in the skeleton, the organs that absorb the most lead are the kidneys, liver, and other soft tissues such as the brain and heart [175]. The nervous system is particularly vulnerable to lead toxicity. The central nervous system might experience headaches, irritability, short attention span, memory loss, and dullness as early indications of lead exposure [170, 173].

Over the last several decades, lead exposure has been significantly decreased as a result of many efforts [173, 174]. Not only has the federal government outlawed lead in paint, petrol, and soldered cans, but many state and municipal health department programs have also supported lead abatement in housing and screening programs for child lead poisoning [167]. Even with these efforts' successes, lead exposure is still a big problem for human health [176, 177]. Lead, the most pervasive toxicant, affects many different bodily systems, including the kidneys, liver, and central nervous system [173].

The use of lead in hobbies, certain traditional medicines and cosmetics, deteriorating house paints, working with lead, and exposure to lead from these sources are common causes of lead exposure [167, 174]. Several studies analyzed blood lead levels in American populations [176]. Even though these

surveys have typically shown a decrease in blood lead levels during the 1970s, a large number of youngsters still have high levels (> 10µg/dL). Therefore, lead poisoning is still one of the most common childhood health problems in the United States [167, 173, 174, 176-179]. Pregnant women are more vulnerable to the harmful effects of lead exposure. Fetuses are particularly vulnerable to lead exposure during pregnancy because the metal is readily absorbed by the mother [180]. Animal studies have shown that lead exposure during pregnancy is associated with low birth weight, preterm delivery, and neurological abnormalities in the offspring [182, 183], and human data corroborate these findings [181].

Carcinogenicity and toxicity (Molecular Mechanisms)

Multiple studies have shown lead's negative impacts on human health. Studies have shown that children with blood level poisoning have a lower IQ [178, 179, 184, 185]. Reduced sperm count in men and spontaneous miscarriages in women are among the adult reproductive effects associated with high lead exposure [186, 187]. Brain damage, kidney damage, and gastrointestinal issues are the results of acute lead exposure, while chronic lead exposure may negatively impact blood pressure, and kidneys [173, 174, 178, 179, 184-187].

One of the primary metabolic mechanisms via which lead causes damage is its ability to bind with proteins and mimic or hinder the activities of calcium [173]. In the skeleton, lead has supplanted calcium as a mineral component. Lead binds to molecules in living organisms and, via a cascade of mechanisms, hampers their functional capacity. Lead alters the structure and function of enzymes by binding to their sulfhydryl and amide groups. Reduced enzyme activity may result from lead's ability to obstruct the passage of essential cations like calcium or to compete with significant metallic cations for binding sites [188, 189]. Moreover, there was a strong association between lead blood content and malondialdehyde (MDA) levels in exposed workers, as shown by Jiun and Hseien [190]. Glutathione peroxidase and superoxide dismutase (SOD) levels were significantly higher in the red blood cells of lead-exposed workers compared to non-exposed persons, according to subsequent studies [191]. In our lab, we have recently discovered that lead-induced toxicity and apoptosis in human cancer cells involve various cellular and molecular processes. These processes include oxidative stress, cell death induction, DNA damage, phosphatidylserine externalization, caspase-3 activation, transcriptional activation of stress genes, and damage to the cell membrane.

Lead, according to a plethora of research, blocks neuronal signaling and intracellular signal transduction by blocking calcium-dependent pathways. Organelle storage, such as the endoplasmic reticulum and mitochondria, may be affected by lead because it interferes with intracellular calcium cycling [194, 195]. Lead may sometimes impede calcium-dependent activities, such as the release of glutamatergic neurons' receptor-coupled ionophores and several neurotransmitters [196]. Lead seems to improve calcium-dependent activities in some cases, including calmodulin and protein kinase C [194, 197].

Experimental investigations have shown that lead may cause kidney tumors in rats and mice [198, 199, 200]. More than only morphological defects in cultured rat cells, lead exposure has also been associated with sister chromatid swaps, and gene mutations [204-206].

Mercury

Industrial use and production, environmental occurrence

Mercury, a heavy metal, is in the series of transition elements on the periodic table. The fact that it occurs in nature in three separate forms—organic, inorganic, and elemental—each with its unique toxicity profile [207] is what sets it apart. At room temperature, the elemental liquid mercury is a very vapor-pressured liquid that is also discharged into the air as vapor. Mercury may also exist as a cation with an oxidation state of +2 (mercuric) or +1 (mercurous) [208]. Bacteria in water and soil methylate inorganic (mercuric) mercury forms to produce methylmercury, the most common organic form of mercury in nature [209].

The ubiquitous environmental pollutant mercury causes profound alterations in bodily tissues and a cascade of detrimental health effects [210]. Various chemical forms of mercury are found in the environment and may have an impact on both animals and humans. Mercuric, elemental mercury vapor, organic mercury compounds, and inorganic mercury are all part of this class. Mercury is a ubiquitous element in the environment, meaning it is exposed to all living things, including plants and animals [212].

For example, caustic soda production, nuclear reactors, antifungal agents in wood processing, solvents for reactive and precious metals, pharmaceutical product preservatives, electrical industry (switches, thermostats, batteries), and dental amalgams are just a few of the many industrial uses for mercury [213, 214].

Exposure

Dental work, preventive medical treatments, agricultural and industrial operations, food contamination, accidents, and work-related activities are all potential sources of mercury exposure to people [215]. Dietary consumption of fish and amalgam fillings in teeth are the leading sources of chronic, low-level mercury exposure [216, 217].

The two most absorbent forms of mercury are methyl mercury (MeHg) and elemental mercury (Hg0). According to [218], dental amalgams contain almost half of the elemental mercury. The lining of the airways in the lungs and mouth are excellent receptors for the elemental vapour because of its high lipophilicity. Before entering the bloodstream, Hg0 swiftly traverses several cell membranes, including those of the placenta and the blood-brain barrier [219]. Upon entering the cell, Hg0 is oxidized, changing into the highly reactive Hg^{2+}. Because it is soluble in lipids and absorbed quickly in the gastrointestinal tract, methyl mercury may readily penetrate the placental and blood-brain barriers after consuming fish. After consumption, the excretion rate of mercury is negligible. The renal, hepatic, and cerebral tissues store a considerable quantity of the ingested substance. Nephrotoxicity, neurotoxicity, and gastrointestinal toxicity are some of the negative effects of mercury [213].

Carcinogenicity and toxicity (Molecular Mechanisms)

The molecular mechanisms of mercury's toxicity point to oxidative stress as a contributing factor, by its chemical activity and biological features [220, 221]. The mitochondria

are the primary sites of reactive oxygen species (ROS) production in eukaryotic organisms as a result of normal metabolism [222-224].

An increase in reactive oxygen species is caused by an increase in arachidonic acid synthesis, which is in turn increased by activation of phospholipase A2. Arachidonic acid is also attacked by reactive oxygen species [225]. There are several mechanisms by which inorganic and organic mercury affect calcium homeostasis [226]. Furthermore, it has been shown that rats treated with HgCl2 had elevated levels of MDA in their testes, livers, kidneys, and lungs due to mercury compounds [227]. Research has shown a correlation between the level of hepatotoxicity and nephrotoxicity and this increase in concentration [228]. Pretreatment with selenium, an antioxidant, significantly lowers lipid peroxidation caused by HgCl2. Both direct binding to mercury and cofactoring with glutathione peroxidase to scavenge reactive oxygen species (ROS) are examples of selenium's biological activities [229]. Vitamin E shields the liver against mercury chloride-induced lipid peroxidation, according to other observations [230].

The public health community has placed a high priority on studies investigating metal-induced carcinogenicity. The three known steps of carcinogenesis are promotion, progression, and metastasis [231, 232], in addition to DNA mutations, which were previously thought to be key players because they could either activate oncogenesis or inhibit tumor suppression. Mercury and other toxic metals alter the biological activity of cellular organelles, according to studies [231, 233]. In addition, there is mounting evidence that reactive oxygen species (ROS) play a significant role in mediating cellular responses to metals [234-236].

The hypothesis that mercury exposure might cause cancer is a hotly contested one. Although several studies have shown that mercury has genotoxic potential, no study has found a correlation between exposure to the metal and genotoxic harm [237]. Based on their findings, researchers have pinpointed oxidative stress as the chemical mechanism by which mercury causes genotoxicity. Consequently, research has shown that mercury may cause cells to produce reactive oxygen species (ROS), which can damage DNA and potentially initiate carcinogenic processes [238, 239]. When these free radicals come into contact with nucleic acids, it might cause changes to the DNA. Despite the fact that compounds containing mercury do not produce mutagenesis in bacterial testing, eukaryotic cell lines have been shown to undergo mutational events when exposed to inorganic mercury at concentrations as low as 0.5 µM [240, 241, 242].

People who ingest methylmercury-contaminated fish have glutathione levels that are greater than usual, according to research [243]. Researchers also found a favourable correlation between glutathione levels and mercury in the blood. Mercury exposure was also confirmed by their findings of polyploidal aberrations and an increased mitotic index [243]. Studies on population health have shown that genotoxic alterations caused by variations in enzyme activity occurred in communities exposed to mercury. These results suggest that even modest amounts of mercury exposure over time could impair enzyme activity and induce cellular oxidative stress [244]. The link between mercury exposure and cancer is, without question, a hotly contested topic. Mercury exposure in cells may make them more susceptible to DNA damage, according to in vitro study. These studies add to the growing body of evidence that mercury's carcinogenicity and toxicity may differ across different types of cells, organs, and animals.

CONCLUSION

Heavy metals such as arsenic, mercury, cadmium, chromium, and lead are present in nature, according to a comprehensive review of the available evidence. Still, pollution is mostly the result of human actions. All sorts of human diseases have been associated with these metals, which are known as systemic toxicants. These include diabetes, hearing loss, developmental abnormalities, neurological and behavioural disorders, cardiovascular illnesses, various forms of cancer, and hematologic and immunologic disorders. Skin contact, inhalation, and oral consumption are the three most common entry points. Negative health effects may range from mild to severe, depending on factors such as the kind of heavy metal, its chemical form, exposure duration, and dose. Many factors, including as valence, particle size, solubility, chemical form, and biotransformation, govern speciation, which in turn affects metal toxicokinetics and toxicodynamics. Even though specific metals have proven acute and long-term effects, the health repercussions of mixtures of hazardous elements are unclear. New evidence suggests that these dangerous compounds may interfere with the metabolic processes of minerals that are vital to human health, such as zinc, iron, calcium, and copper [245, 246]. The cumulative harmful effects of heavy metals have received very little attention from scientists. The negative consequences of heavy metal exposure might be cumulative, synergistic, or antagonistic depending on the metals in question.

A recent meta-analysis of several studies that dealt with metal interactions found that biomarker-specific exposure to metal/metalloid combinations including arsenic, lead, and cadmium had more severe effects at comparatively high dosage and low dose levels [247]. Results showed that these effects were due to genetic factors, exposure duration, and dose. In addition, compared to those exposed to inorganic arsenic or cadmium alone, those exposed to both elements together caused more severe kidney injury [248]. Many areas that are contaminated with metals pose a significant threat to human health due to chronic low-dose exposure to many elements. To manage chemical mixtures and evaluate health hazards, it is essential to understand the molecular basis of interactions between heavy metals. The molecular mechanisms and public health impacts of human exposure to harmful metal combinations remain unclear, necessitating more research.

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