

A REVIEW ARTICLE ON TOXIC MECHANISM OF HEAVY METALS

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ABSTRACT

Heavy metals are naturally occurring elements that have a high atomic weight and a density at least 5 times greater than that of water. Their multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment; raising concerns over their potential effects on human health and the environment. Their toxicity depends on several factors including the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals. Because of their high degree of toxicity, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals that are of public health significance. These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, even at lower levels of exposure. They are also classified as human carcinogens (known or probable) according to the U.S. Environmental Protection Agency, and the International Agency for Research on Cancer. This review provides an analysis of their environmental occurrence, production and use, potential for human exposure, and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity.

Keywords: Acute poisoning, Chronic poisoning, Heavy metals, Mechanistic action, Oxidative stress

1. INTRODUCTION

Heavy metals have harmful effects on human health, and exposure to these metals has been increased by industrial and anthropogenic activities and modern industrialization. Contamination of water and air by toxic metals is an environmental concern and hundreds of millions of people are being affected around the world. Food contamination with heavy metals is another concern for human and animal health. Concentration of heavy metals in water resources, air, and food is assessed with this regard. Metals among the other environmental pollutants may also occur naturally and remain in the environment. Hence, human exposure to metals is inevitable, and some studies have reported gender differences in the toxicity of metals. They may frequently react with biological systems by losing one or more electrons and forming metal cations which have affinity to the nucleophilic sites of vital macromolecules. Several acute and chronic toxic effects of heavy metals affect different body organs. Gastrointestinal and kidney dysfunction, nervous system disorders, skin lesions, vascular damage, immune system dysfunction, birth defects, and cancer are examples of the complications of heavy metals toxic effects. Simultaneous exposure to two or more metals may have cumulative effects. High-dose heavy metals exposure, particularly mercury and lead, may induce severe complications such as abdominal colic pain, bloody diarrhoea, and kidney failure.

MERCURY (Hg)

Mercury (Hg) is found in air, water, and soil and exists in three forms: elemental or metallic mercury (Hg⁰), inorganic mercury (Hg⁺, Hg²⁺), and organic mercury. Elemental mercury is liquid at room temperature and can be readily evaporated to produce vapour. Mercury vapour is more hazardous than the liquid form. Container breakage causes Hg⁰ spills and inhaling large amounts of Hg vapour can be fatal. Organic mercury compounds such as methyl mercury (Me-Hg) or ethyl mercury (Et-Hg) are more toxic than the inorganic compounds. The order of increasing toxicity related to different forms of mercury is defined as Hg⁰ < Hg²⁺, Hg⁺ < CH₃-Hg. Mercury compounds have many applications in mining for example extraction of gold and some industrial processes. In lamp producing factories, Hg is used in the production of fluorescent light bulbs. Me Hg and Et-Hg have been used as fungicides to protect plants against infections. Moreover, mercury has had medicinal uses in the past, but such drugs have been replaced by safer pharmaceutical medicines. Animal Studies In an animal model of acute toxicity, exposure to Hg vapor (550 µg/m³) resulted in mercury deposits in different parts of the brain and also in the spinal cord. Vapor exposure can cause a 70% increase in brain metallothionein, a metal binding protein, in the mice demonstrated cognitive impairment and hippocampal damage in rats with oral chronic administration of HgCl₂. They also found that mercury levels in the hippocampus increased to 0.04 µg/g while the control group had Hg concentrations less than 0.01%. Another study indicated methylmercury chloride induced CNS injury in rats receiving different doses of 0.05, 0.5, and 5 mg/kg Hg against normal saline group. CNS damage was showed via the increased expression of c-fos protein in cortex and hippocampus as an important signal transduction pathway. Hg accumulation in the brain was also observed in treated rats Human Studies Microorganisms in marine environments perform natural bio methylation reactions to produce Me-Hg. Me-Hg enters the food chain of

aquatic animals and eventually enters the human body through the consumption of fish. Cooking fish does not diminish its Hg content. An incident of exposure to organic Hg via the consumption of contaminated fish occurred in Minamata Bay, Japan, in the middle of 1950s. Soon afterward, the illness came to be known as Minamata disease. Chronic Hg toxicity caused neurological damage including ataxia, muscle weakness, numb limbs, disturbance in speech, chewing, and swallowing, and brisk and increased tendon reflex.

Target Organs and Health Effects

1. Brain and Nervous System: Mercury is highly neurotoxic, with methylmercury posing the greatest threat. In adults, exposure can lead to tremors, memory loss, mood swings, and cognitive decline. Chronic exposure in children can result in developmental delays, cognitive deficits, and motor impairments due to mercury's ability to interfere with brain development. Prenatal exposure is especially dangerous, as methylmercury readily crosses the placenta, affecting fetal brain development and increasing the risk of cognitive impairments, learning disabilities, and attention deficits.

2. Kidneys: The kidneys are highly sensitive to inorganic mercury, which accumulates in renal tissues and causes nephrotoxicity. Prolonged exposure can lead to kidney inflammation, proteinuria (protein in the urine), and kidney failure in severe cases. Mercury exposure may disrupt the kidneys' ability to filter blood effectively, impacting overall renal health and potentially leading to chronic kidney disease over time.

3. Cardiovascular System: Studies have linked methylmercury exposure to cardiovascular issues, such as hypertension (high blood pressure), atherosclerosis (hardening of the arteries), and increased risk of heart attacks. This effect is particularly concerning in populations that consume large amounts of fish, which may contain high levels of methylmercury. Mercury's impact on cardiovascular health is believed to result from oxidative stress and inflammatory processes that damage blood vessels and impair heart function.

4. Immune System: Mercury exposure can weaken the immune system by altering immune cell function and increasing susceptibility to infections. It promotes inflammation and autoimmune reactions, where the immune system attacks the body's own cells. Mercury exposure has been associated with various autoimmune diseases, such as lupus and multiple sclerosis, in people exposed to high levels of mercury.

Regulatory Standards and Prevention

Regulatory agencies, such as the Environmental Protection Agency (EPA) and the World Health Organization (WHO), have set guidelines to limit mercury emissions and reduce human exposure. For example, the EPA regulates mercury emissions from coal-fired power plants and sets safety standards for mercury in drinking water and seafood. The WHO has set limits for mercury exposure, especially in sensitive populations such as pregnant women and children, to protect fetal

LEAD (Pb)

Lead is a harmful environmental pollutant which has high toxic effects to many body organs. Even though Pb can be absorbed from the skin, it is mostly absorbed from respiratory and digestive systems. Pb exposure can induce neurological, respiratory, urinary, and cardiovascular disorders due to immune-modulation, oxidative, and inflammatory mechanisms. Furthermore, Pb could disturb the balance of the oxidant-antioxidant system and induce inflammatory responses in various organs. Exposure to Pb can produce alteration in physiological functions of the body and is associated with many diseases. Pb is highly toxic which has adverse effects on the neurological, biological, and cognitive functions in the bodies. The international level-of-concern for Pb poisoning is 10 µg/dl in the blood. Adulteration of opium with Pb has been considered as a threat to human health in recent years

Target Organs and Health Effects

1. Brain and Nervous System: Lead is a potent neurotoxin, particularly harmful to children, as it can disrupt the development of the central nervous system. Even low levels of lead exposure in children can cause irreversible cognitive impairment, lower IQ, behavioural issues, learning disabilities, and attention deficits. In adults, chronic exposure is linked to neurological symptoms like memory loss, mood changes, headaches, and in severe cases, encephalopathy (brain damage).

2. Cardiovascular System: Lead exposure is associated with hypertension (high blood pressure) and an increased risk of cardiovascular disease. Studies suggest that lead interferes with the smooth muscle cells in blood vessels, contributing to hardening of the arteries (atherosclerosis) and increasing the risk of heart attacks and strokes. This cardiovascular impact is seen even at relatively low levels of chronic exposure.

3. Kidneys: Lead accumulates in the kidneys over time and can cause nephrotoxicity, leading to kidney damage and impaired kidney function. Chronic exposure can lead to reduced glomerular filtration rate, proteinuria (protein in the urine), and eventually, kidney failure if exposure persists. The kidneys' ability to filter waste is further compromised in those exposed to lead over a long period.

4. Reproductive System: Lead toxicity has been linked to reproductive issues in both men and women. In men, lead exposure can reduce sperm count, affect sperm quality, and lead to infertility. In women, lead can disrupt hormone balance, contribute to menstrual irregularities, and increase the risk of miscarriage, premature birth, and developmental issues in the fetus. Lead exposure during pregnancy is particularly dangerous, as it can cross the placental barrier, affecting fetal development and potentially causing low birth weight, cognitive deficits, and physical malformations.

Regulatory Standards and Prevention

To reduce the public health risks of lead, regulatory agencies like the Environmental Protection Agency (EPA), the Centres for Disease Control and Prevention (CDC), and the World Health Organization (WHO) have established strict standards for acceptable lead levels in air, water, soil, and consumer products. For example, the CDC recommends intervention for children with blood lead levels at or above 5 micrograms per decilitre ($\mu\text{g/dL}$), and the EPA has set the maximum contaminant level for lead in drinking water at 15 parts per billion (ppb)

CHROMIUM (Cr)

Chromium (Cr) is found in the earth's crust and seawater and is a naturally occurring heavy metal in industrial processes. Cr has multiple oxidation states ranging from -2 to $+6$, in which the trivalent and hexavalent forms are the most common stable forms, Cr (VI) is related to a series of diseases and pathologies while Cr (III) is required in trace amounts for natural lipid and protein metabolism and also as a cofactor for insulin action. Based on the International Agency for Research on Cancer (IARC) report (2018), hexavalent chromium has been classified as a group I occupational carcinogen. In this context, a meta-analysis of 973,697 workers involving 17 standardized incidence ratios (SIRs) from seven countries and four kinds of occupations found that 11,564 of them had cancer. The primary route of exposure for non-occupational human populations occurs via ingestion of chromium containing food and water or dermal contact with products containing chromium. Furthermore, metallurgical, refractory, and chemical industries release a large amount of Cr into soil, ground water, and air which causes health issues in humans, animals, and marine life. Cr can cause a variety of diseases through bioaccumulation in human body. This ranges from dermal, renal, neurological, and GI diseases to the development of several cancers including lungs, larynx, bladder, kidneys, testicles, bone, and thyroid.

Target Organs and Health Effects

1. Respiratory System: Inhalation is a common exposure route in occupational settings where hexavalent chromium dust or fumes are present. Chronic exposure can lead to nasal septum perforations, nosebleeds, asthma, and lung irritation. Hexavalent chromium is a known carcinogen, strongly linked to lung cancer, especially among workers in industries like metalworking and welding. Long-term exposure damages lung tissues, increasing the risk of respiratory diseases and lung cancer.

2. Skin and Eyes: Direct skin contact with hexavalent chromium causes dermatitis, a painful and itchy skin inflammation, and can lead to the formation of ulcers, also known as "chrome holes." Prolonged exposure can cause skin sensitization, making individuals more susceptible to allergic reactions upon subsequent exposure. Contact with eyes may result in severe irritation, burns, and, in extreme cases, loss of vision.

3. Kidneys and Liver: Hexavalent chromium can be absorbed through the digestive tract or lungs and accumulate in the kidneys and liver, where it causes oxidative damage, leading to organ dysfunction. Over time, chronic exposure can lead to nephrotoxicity (kidney toxicity) and hepatotoxicity (liver toxicity), impairing the body's ability to detoxify and filter out waste, which can ultimately result in organ failure in severe cases.

Regulatory Standards and Prevention

Regulatory agencies, such as the Environmental Protection Agency (EPA) and the World Health Organization (WHO), have set guidelines to limit mercury emissions and reduce human exposure. For example, the EPA regulates mercury emissions from coal-fired power plants and sets safety standards for mercury in drinking water and seafood. The WHO has set limits for mercury exposure, especially in sensitive populations such as pregnant women and children, to protect fetal development and early childhood health.

ARSENIC (As)

Arsenic as a harmful heavy metal is one of the main risk factors for the public health. Sources of As exposure are occupational or via the contaminated food and water. As has a long history of use, either as a metalloid substance or as a medicinal product. It is notoriously known as the king of poisons and poison of kings. As is present as a contaminant in food, water, and environment. Arsenic exists in the forms of metalloid (As_0), inorganic (As^{3+} and As^{5+}), organic, and arsine (AsH_3). The order of increasing toxicity of As compounds is defined as organic arsenicals $< \text{As}_0 < \text{inorganic species} (\text{As}^{5+} < \text{As}^{3+}) < \text{arsine}$.

Target Organs and Health Effects

1. Skin: Chronic arsenic exposure is strongly associated with skin disorders. These include hyperpigmentation (dark patches on the skin) and keratosis (thickening of the skin), particularly on the palms and soles. In some cases, arsenic exposure causes skin cancer, especially squamous cell carcinoma, which can be highly invasive if untreated.

2. Liver and Kidneys: Arsenic accumulates in the liver and kidneys, causing toxicity that can lead to organ dysfunction and failure over time. In the kidneys, it can impair filtration processes, leading to proteinuria and potentially kidney failure in cases of prolonged exposure. In the liver, arsenic causes oxidative damage, increasing the risk of liver disease, including cirrhosis and liver cancer.

3. Lungs: Exposure to arsenic through inhalation, often in occupational settings like mining and smelting, increases the risk of lung diseases. Long-term exposure is associated with respiratory symptoms, such as chronic cough and shortness of breath, and a significantly increased risk of lung cancer, especially for workers exposed to arsenic dust

2. CONCLUSION

The heavy metals enter the body from different ways including drinking water, air, food, or occasionally dermal exposure. Following absorption, heavy metals are retained, and they accumulate in the human body. Bioaccumulation of toxic metals leads to a diversity of toxic effects on a variety of body tissues and organs. Metal toxicity can have acute or chronic manifestations. Heavy metals disrupt cellular events including growth, proliferation, differentiation, damage repairing processes, and apoptosis. Toxic metals can also promote epigenetic alterations which can influence gene expression. Comparison of the mechanisms of action reveals similar pathways for these metals to induce toxicity including ROS generation, weakening of the antioxidant defence, enzyme inactivation, and oxidative stress.

On the other hand, some researches have shown that the metals selectively bind to specific macromolecules. The interaction of Pb with ALAD and

ferrochelatase is within this context. Reactions of other heavy metals with certain proteins were discussed as well. Some toxic metals including Cr, Cd, and As cause genomic instability. Defects in DNA repair following the induction of oxidative stress and DNA damage by these metals is considered as the cause of their carcinogenicity.

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