ISSN 2350-1030

International Journal of Recent Research in Physics and Chemical Sciences (IJRRPCS)
Vol. 6, Issue 2, pp: (30-43), Month: October 2019 – March 2020, Available at: www.paperpublications.org

TOXICITY OF HEAVY METALS, A SUBJECT IN REVIEW

Stephen Juma Mulware

Department of mathematical sciences, Charleston Southern University, Charleston, South Carolina, USA.

Author email id: smulware@csuniv.edu

Abstract: **Metals are categorized in three main ways according to their impact on human health- nutritionally essential, nonessential with a possible beneficial effect, or nonessential with toxic effects. For both nutritionally essential and toxic metals, the amount of exposure from the environment most often, through ingestion, can determine either the level of benefit or toxicity derived from such exposure. Nutritionally essential metals may cause adverse health effects at some levels below or beyond the level required for optimum nutrition. Similarly, the degree of toxicity from nonessential metals depends on the level of exposure among other factors. Heavy metal toxicity, just like chemical toxicity, has become one of the most pressing health hazards of modern times. In this article, we review the main toxicity of heavy metals and their compounds on human health.**

Keywords: **Bioavailability, Carcinogenicity, Exposure, Heavy metals, Human health, Metal toxicity.**

1. INTRODUCTION

Heavy metals are naturally occurring elements that are found throughout the earth's crust and have potential human and environmental toxicity [1, 5]. However, most environmental contamination and human exposure result from anthropogenic activities such as mining and smelting operations, industrial production and use, and domestic and agricultural use of metals and their compounds [2]. Other sources of environmental contamination are through metal corrosion, atmospheric deposition, soil erosion of metal ions and leaching of heavy metals, sediment re-suspension and metal evaporation from water resources to soil and ground water, as well as natural phenomena like weathering and volcanic eruptions. Industrial activities including metal processing in refineries, coal burning in power plants, petroleum combustion, nuclear power stations and high tension lines, plastics, textiles, microelectronics, wood preservation and paper processing plants also play a major role as heavy metal source in environmental contamination [3].

Heavy metals 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. The heavy metals can enter the body from a wide variety of sources including foods, drinks, contaminated air, and contact with the skin, vaccines, injections and implants within the body. Some heavy metals such as copper, iron, manganese, and zinc have important physiological functions in the body when present in small amounts. [3,4] For example, zinc is an important cofactor for several enzymatic reactions; cobalt atom forms the core of vitamin B while iron plays a major role in formation of hemoglobin in the red blood cells. Copper also serves as an essential co-factor for several oxidative stress-related enzymes including catalase, superoxide dismutase, peroxidase, cytochrome c oxidases, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase [2, 3]. In addition, copper has the ability to cycle between an oxidized state, Cu (II), and reduced state, Cu (I), a property used by cuproenzymes involved in redox reactions [3]. This property can also result in generation of superoxide and hydroxyl radicals, which have been associated with cellular damage leading to Wilson disease in humans.

Most of the heavy metals are known to be xenobiotic that is to say that they have no useful role in human physiology [2]. Such metals have tendency to accumulate in certain tissues since they cannot be metabolized by living systems and can be very toxic even in trace concentrations. Such metals and their compounds interfere with functions of various organs and

systems like the central nervous system (CNS), the hematopoietic system, liver, and kidneys [6]. Table 1 shows some common symptoms and diseases associated by heavy metals exposure.

Table 1: Symptoms/ Diseases Related to Heavy Metals

Allergies/overburdened immune system	Toxic metals like mercury ill beneficial gut bacteria exposing it to toxins/allergens that can compromise the immune system
Autoimmune Disease	When metals binds with body proteins, they are attacked by body immune system causing autoimmune disorders.
High-cholesterol/Cardiovascular disease	A rise in cholesterol, which leads to cardiovascular problems protect the nerve and brain against exposure to toxins and heavy metals.
Low immune systems/ Cancers	Heavy metals increase the production of free radicals and oxidative stress leading to tissue acidification, and environment conducive for growth of all Cancer cells.
Neurological diseases/Chronic fatigue	Alzheimer, MS, ALS, Autistic Spectrum Disorder, and Parkinson's disease, can all be linked to heavy metal neurotoxic effects.
Low Libido, PMS, Impotence, Prostate Problems	Heavy metals lower zinc levels, which are necessary for the proper levels of progesterone and testosterone.
Diabetes	Heavy metals, mainly mercury, can cause overgrowth of yeast and fungus (candida) that releases metabolic waste called mycotoxins, which inhibits the absorption of insulin, thus creating diabetes.
Neurotransmitter inhibition	Heavy metals inhibit certain important neurotransmitters including, dopamine, serotonin, adrenalin, and melatonin.

When exposed at young age, children can develop lifelong physical, intellectual, and behavioral impairments [7]. Metal ions can interact with cell components such as DNA and nuclear proteins, causing DNA damage and conformational changes that may lead to cell cycle modulation, carcinogenesis or apoptosis. Because of their high degree of toxicity, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals that are of public health concern and have been categorized as"known" or "probable" human carcinogens based on epidemiological and experimental studies as listed by United States Environmental Protection Agency (U.S. EPA), and the International Agency for Research on Cancer (IARC). Several studies have shown that reactive oxygen species (ROS) production and oxidative stress play a key role in the toxicity and carcinogenicity of these heavy metals [8, 9, and 10]. Other metals of concern to EPA include aluminum, antimony, barium, beryllium, silver, strontium, and thallium especially due to their numerous industrial uses, which increases the probability of human exposure.

Most heavy metals are also considered trace elements due to their presence in trace concentrations (parts per billion range) in various environmental matrices. As trace metals, their

bioavailability is determined by physical factors such as temperature, phase association,

adsorption and sequestration. In addition, this determination is also affected by chemical factors that influence speciation at thermodynamic equilibrium, complexation kinetics, lipid solubility and octanol/water partition coefficients [4]. Biological factors such as species characteristics, trophic interactions, and biochemical/physiological adaptation, also play an important role in determining their adverse effects in cell biology [4]. This review provides an analysis of the environmental occurrence, production and use, potential for human exposure, and mechanisms of toxicity, genotoxicity, and carcinogenicity of heavy metals.

2. HEAVY METAL TOXICITY

2.1 Arsenic and arsenic compounds

Apart from naturally present in the environment, arsenic can also be released in larger quantities through volcanic activity, erosion of rocks, forest fires, and human activity. Wood preservative contains about 90% of the industrial arsenic in addition to other products like paints, pesticides, dyes, metals, drugs, soaps, semi-conductors and even some animal feeds. Similarly other industrial practices such as copper or lead smelting, mining, and coal burning also release Arsenic in the environment [11]. In the environment, arsenic is usually found combined with other elements as inorganic and organic

forms. Inorganic arsenic is known to be more toxic than organic one. Arsenic trioxide (As2O3) is the most common inorganic arsenical in air, while (AsO43-) or arsenites (AsO2) occur in water, soil, or food. In fishes arsenic ranged between 5 to 100 µg/g and reach to 100 to 250 µg/g in species at the top of the food chain. Nearly 80-95 % of total arsenic is present, as organic compounds thus do not cause any damage to health (arsenosugar, arsenolipids, etc). Different studies have reported varying Arsenic levels in different samples, for instance from 1.5 to 2.5 µg/L in blood; from 0.25 to 0.88 µg/L in hair; and an average concentrations between 20 and 50 µg/L in urine [12, 13].

The health effects of arsenic exposure depends on the level of exposure. Lower level exposure can cause nausea and vomiting, decreased production of red and white blood cells, abnormal heart rhythm, damage This review provides an analysis of the environmental occurrence, production and use, potential for human exposure, and molecular mechanisms of toxicity, genotoxicity, and carcinogenicity of arsenic, cadmium, chromium, lead, and mercuryto blood vessels. Long term and high-level exposures are associated with hypertension and serious impacts on the cardiovascular system, and even hepatic damage and death. High inorganic arsenic ingestion may also lead to various dermal effects like hyperkeratosis, hyperpigmentation and hypopigmentation; periorbital swelling; the occurrence of spontaneous abortion and damage of the nervous system. Some studies have shown a suppressive effect on spermatogenesis and gonadotrophin and testosterone release in rats [14]. Arsenic and its compounds are highly carcinogenic to humans. Lung cancer and skin cancer were in patients treated with inorganic trivalent arsenic compounds, as well as those drinking water with high levels of arsenic and those with occupational exposures to inorganic arsenic compounds in mining and copper smelting industries, respectively [15]. Other cancers liked to arsenic toxicity include kidney and bladder [16]. The toxicity of arsenic and its inorganic compounds has been classified as acute toxicity, sub-chronic toxicity, genetic toxicity, developmental and reproductive toxicity [17]; immunotoxicity [18]; biochemical and cellular toxicity [19]. The inorganic arsenic toxicity can also induce oxidative stress leading to the inhabitation of DNA repair. It has been reported that arsenic induced oxidative stress also causes DNA strand breaks, alkali-labile sites, which eventually results into DNA adducts [20]. Other studies determined that arsenic mediation have altered methylation status of oncogenes and tumor suppressor genes and in the processes enhancing carcinogenesis [21].

A systematic assessment of cofactors associated with increased arsenic-induced cancers established that arsenical skin lesions (melanosis, leucomelanosis and keratosis) are a hallmark of chronic arsenic toxicity. The skin lesions have a short time latency and may appear within a few years of exposure unlike other arsenic-induced cancers, which have a longer latency, which can take decades. These studies show that the risk of arsenic-induced skin lesions and cancers is greater among men than in women. The higher risk of arsenic-related skin lesions in men have been compounded by other variables identified as independent risk factors of non-melanoma skin cancer, including cigarette smoking and ultraviolet radiation exposure. Other variable that influence the arsenic exposure effects on skin lesions and cancer includes occupational exposures, nutritional habits, socioeconomic status, and genetic factors, have also been shown to influence [22, 23].

2.2 Barium and Barium compounds

Barium is a naturally occurring, silvery-white earth metal. Ii is highly reactive with air forming various compounds. When barium is combined with other elements to form barium compounds, it has many applications. Barium carbonate is used as a rat poison, barium-nickel alloys are used for spark-plug electrodes and in vacuum tubes as a drying and oxygen-removing agent. Barium sulfide is used in fluorescent lamps while barium sulfate is used in diagnostic medicine where it is ingested prior to receiving an x-ray to provide better imaging. Barium nitrate and chlorate give fireworks a green color. Barium compounds are also used in drilling muds, paint, bricks, ceramics, glass, and rubber.

Barium exposure can happen through a number of channels including occupational exposure, groundwater contamination, environmental pollution, cigarette smoke, and even certain medical procedures. Health effects barium is not known to cause cancer. Barium exposure, however, can cause serious health problems. Classic signs of barium toxicity include low blood potassium, cardiac arrhythmias, respiratory failure, gastrointestinal dysfunction, paralysis, muscle twitching, and elevated blood pressure [24]. Severe barium toxicity can lead to kidney damage, respiratory failure, and death [25]. Continuous and regular barium exposure has been identified as a potential contributor in the development of neurodegenerative diseases, including multiple sclerosis [26]. Short-term exposure can cause vomiting, abdominal cramps, diarrhea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness. Large amounts of barium intake can cause, high blood pressure, changes in heart rhythm or paralysis and

possibly death. Regulatory limits described by EPA are: 2.0 parts per million (ppm) in drinking water while OSHA has recommended a limit of 0.5 milligrams of soluble barium compounds per cubic meter of workplace air for 8 hour shifts and 40 hour work week. Beryllium and beryllium compounds

2.3 Beryllium and Beryllium compounds

Beryllium (Be) occurs naturally in the form of beryllium aluminum silicate (beryl), $3BeO.Al_2O_3.6SiO_2$. It is naturally present in rocks, coal and oil, soil and volcanic dust. Out of the over 40 known beryllium-bearing minerals, only beryl and bertrandite ($4BeO.2SiO_2.H_2O$) are commercially vital, with beryl containing ca. 11 % beryllium oxide while Bertrandite containing less than 1 % beryllium, which can be processed into beryllium hydroxide. Beryllium alloys with many metals are very strong with high electrical and thermal conductivity as well as high resistance to corrosion and fatigue. These properties make beryllium an important component of wide range of industrial applications including electronics and weaponry among others. Health effects to Beryllium exposure vary from the amount and duration of exposure or even the individual exposed. Beryllium sensitization is the activation of the body's immune response to beryllium. Beryllium sensitization can result from inhalation or skin exposure to beryllium dust, fume, mist, or solutions [27]. While no clinical symptoms are associated with sensitization, a sensitized individual is at risk of developing Chronic Beryllium Disease (CBD) when inhalation exposure to beryllium has occurred [28]. The BeLPT - Beryllium sensitization may be detected with the beryllium lymphocyte proliferation test (BeLPT), a blood test for measuring the immune response to beryllium. The observation of beryllium-specific lymphocyte proliferation in an individual peripheral blood sample indicates an abnormal response and may indicate beryllium sensitization. There is some concern about the accuracy of the BeLPT. A single BeLPT has been reported to have a false-positive rate of about 1% [29]. Many programs therefore rely on a second test to confirm a positive result, which has been reported to reduce the false-positive rate to about 0.02% [29].

CBD is a chronic granulomatous lung disease caused by inhaling airborne beryllium after becoming sensitized to beryllium. The common symptoms of CBD are shortness of breath, unexplained coughing, fatigue, weight loss, fever, and night sweats. CBD can result from inhalation exposure to beryllium at levels below the current OSHA PEL (0.2 µg/m3). Progression of CBD can vary among individuals. For instance, after initial exposure to beryllium, some victims may quickly develop mild and severe symptoms of CBD. CBD can progress to a chronic obstructive lung disorder, resulting in loss of quality of life and the potential for decreased life expectancy [30]. CBD shares many signs and symptom. The immunological behavior of T-lymphocytes (T-cells, which play a central role in cell-mediated immunity) following beryllium exposure has been explained in terms of toxic kinetic and toxic dynamic effects. About 70 % of the total beryllium, ranging between 10–100 ng/g serums was detected in pre-albumin and clinical studies of acute beryllium disease, respectively [31, 32]. The programmed death pathway (PD1) is active in beryllium-induced disease and significantly control beryllium-induced T cell proliferation. According to some studies, beryllium exposure in the cell mediates a thiol imbalance that leads to oxidative stress, which in turn may transform the proliferation and clonal expansion of CD4+ T-cells [33]. Beryllium-induced proliferation of T-lymphocytes from the lungs of a CBD patients are associated with human leukocyte antigens (HLA-DP) alleles that have been found to possess a glutamic acid in the 69th position of the B1 chain of this molecule [34, 35]. It has been found that exposure to beryllium-ferritin result in the production of persistent antigen, linked to the chronicity of CBD and its development even years after one had been exposed [32]. Since the presence of circulating beryllium-specific CD4+ T-cells directly correlates with the severity of lymphocytic alveolitis, studies have shown that there is a great increase in antigen-specific effecter memory CD4+ T-cells in the lungs of CBD patients [34].

Industrial and occupational exposure are linked to beryllium induced respiratory distress, which are linked to upward trend and reported deaths from lung cancer according to OSHA determinations. The binding of ionic beryllium to nucleic acids cause genetic transformation in mammalian cells that can result into infidelity of DNA replication [36]. This genetic transformation is likely to cause lung cancer to the exposed individuals. A high relative risk of up to 2.3 would likely cause acute beryllium pneumonitis, which is linked to higher lung cancer rates [37]. The same study has shown that the probability of contracting lung cancer is increased among those with acute beryllium disease (standard mortality ratio, SMR = 2.32) than in those with chronic beryllium disease (CBD) (SMR = 1.57) [37]. A report on carcinogens indicated that the exposure to beryllium and its compounds caused the growth of lung tumors in rats that were exposed through a single intra-tracheal instillation or a 1-h inhalation [38]. Liver cancer and pancreatic cancer is also linked to beryllium exposure [39]. According to IARC reports, beryllium inhalation by experimental animals, intra-tracheal studies on rats, intra-bronchial studies on monkeys and intravenous or intramedullary administration to rabbits showed sufficient evidence

of carcinogenicity to beryllium and its compounds [15]. The International Agency for Research on Cancer (IARC) classifies beryllium as a Group 1 carcinogen (carcinogenic to humans), and the National Toxicology Program (NTP) lists beryllium as a known human carcinogen. Acute beryllium disease (ABD) is a rapid onset form of chemical pneumonia that results from breathing high airborne concentrations of beryllium of levels at or above 100 μg/m^3 and may be fatal in 10 percent of cases. ABD is extremely rare in the workplace today due to more stringent exposure controls implemented following occupational and environmental standards set in the 1970s.

2.4 Cadmium and cadmium compounds

Cadmium is naturally present in almost all soils and rocks, including coal and mineral fertilizers, and even air and unpolluted seawater. Cadmium is a wide spread environmental pollutant that is emitted in the air by mines, metal smelters and industries, which use cadmium compounds for alloys, batteries, pigments, metal electro-plating and plastics [40]. Health effects Cadmium and cadmium compounds are known human carcinogens as declared by International Agency for Cancer Research [41]. All forms of tobacco contains a significant exposure to cadmium making tobacco smoking, both active and passive, the largest single source of human exposure to cadmium and in effect its carcinogenic effect. The effects of tobacco smoking are exuberated by the fact that the absorption of cadmium from the lungs into the body cells is much greater than the gastrointestinal tract absorption [42, 43]. Cadmium ions are readily absorbed by plants and stored in the stem, leaves and fruits, on which herbivorous animals feed on. This makes the affected animal and plant food products, also sources of cadmium inorganic salt exposure to humans through the food chain. Several studies have established the presence of cadmium in food items like milk and animal fatty tissues [42] and sea foods such as mollusks and crustaceans [44, 45, 46]. Studies have shown that cadmium have no essential functions in human body and can produce toxic effects even at very low doses [47]. This toxicity results from both extracellular and intracellular interaction between cadmium and the biological system. Cadmium acts as an inhibitor of sulfydryl enzymes and also has affinity for Cadmium acts as an inhibitor of sulfydryl enzymes and also has affinity for other cell ligands like hydroxyl, carboxyl, phosphatyl, cysteinyl and hystidyl side chains of protein, and therefore can disrupt pathways of oxidative phosphorylation [48]. Because there is no homeostatic control of cadmium in the human body, it is highly toxic metal.

The kidney, which is the target organ, stores more than a third of all absorbed cadmium in the body. When high amounts of Cd^{2+} are introduced into the body, it replaces Zn^{2+} at the key enzyme sites causing metabolic disorders. Other toxic effects include respiratory disorders, damage to the kidney and development of kidney stones. The carcinogenic effects of cadmium varies in different studies. While some in vitro studies have shown that cadmium induces DNA strand breaks, DNA–protein crosslinks, oxidative DNA damage and chromosomal aberrations, mostly at high cytotoxic concentrations [49], other studies show that it modulate the expression of pro-oncogenes [50], and inhibit the function or expression of the DNA repair systems [51]. Other studies have shown that cadmium indirectly generates ROS and consequently DNA, lipid and protein oxidation in various cell lines, which lead to DNA damage and hence tumor growth. Long-term exposure to lower levels leads to a buildup in the kidneys and possible kidney disease, lung damage, and fragile bones. Regulatory limits established by EPA is 5 parts per billion (ppb) or 0.005 parts per million (ppm) of cadmium in drinking water. Food and Drug Administration (FDA) has recommended that concentration in bottled drinking water should not exceed 0.005 ppm (5 ppb). Whereas OSHA has recommended an average of 5 micrograms per cubic meter of workplace air for an 8-hour workday, 40-hour workweek limit of exposure.

2.5 Chromium and chromium compounds

Chromium is found in rocks, animals, plants, soil and volcanic dust and gasses, and can be a liquid, solid, or gas. Chromium compounds bind to soil and are not likely to migrate to ground water but they are very persistent in sediments in water. Chromium predominantly exists in the environment in one of two valence states: trivalent chromium (Cr III), which occurs naturally and is an essential dietary nutrient needed for normal glucose, protein and fat metabolism, and hexavalent chromium (Cr VI), which, along with the less common metallic chromium (Cr 0), is a product of industrial processes [11]. Ferrochrome production industries including ore refining, chemical and refractory processing, cement-producing plants, automobile brake lining and catalytic converters for automobiles and leather tanneries. These industrial chrome pigments are mostly linked to the atmospheric burden of chromium [53]. Humans are exposed to chromium (generally chromium [III]) by eating food, drinking water and inhaling air that contains the chemical with the average daily intake from air, water and food estimated to be less than 0.2–0.4, 2.0 and 60 μg respectively [11]. Dermal exposure

to chromium may occur during the use of consumer products that contain chromium, such as wood treated with copper dichromate or leather tanned with chromic sulfate.

There is little evidence for the carcinogenicity of metallic chromium and trivalent chromium compounds in humans. Cr (III) is actually an essential human nutrient required to promote the insulin action for utilization of sugars, proteins and fats. Sufficient evidence have established that hexavalent chromium compounds calcium chromate, zinc chromate, strontium chromate and lead chromate are carcinogenetic. The first epidemiological study of carcinogenic effect on chromate production workers in the United States that demonstrated an association with lung cancer in which, the percentage death due to cancer of the respiratory system was 21.8%; the percentage expected was 1.4% [54]. Studies of workers in the chromium pigment, chrome plating, and ferrochromium industries showed a statistically vital association between exposure to Cr (VI) and lung cancer [11, 55, and 56]. Other epidemiological studies of workers in chromate industries also showed significantly increased risk for nasal and sinus cancers [11].

Based on these and other studies, the U.S. Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) have classified inhaled Cr (VI) as a known human carcinogen [57, 58]. The World Health Organization (WHO) has determined that Cr (VI) is a human carcinogen. The Department of Health and Human Services (DHHS) has determined that Cr (VI) compounds are known to cause cancer in humans [11]. Potential excess risk of death from lung cancer have been clearly established by analysis of those exposed to the previous permissible exposure limit (PEL) for Cr (VI) of 52 µg/m³ [59, 60, and 61]. Carcinogenicity is mainly to be associated with the inhalation exposure to the less soluble/insoluble Cr (VI) compounds. The toxicology of Cr (VI) does not reside with the elemental form but rather, varies greatly among a wide variety of very different Cr (VI) compounds [62].

Chromium ions is most carcinogenic in the form of CrO_4^{+2} which enters the body cell by sulfate uptake pathway and is ultimately reduced to Cr (III) through a Cr (IV) glutathione intermediate species. The hexavalent latter complex then binds with the DNA to produce a kinetically inert and potentially damaging lesion and can cause abnormal phenotype due to the formation of ROS [63]. Chromium represses a suppressor protein p53, whose inactivation through mutations is associated with many types of human cancers. The p53 protein is essential for many biological processes including regulation of genes involved in cell cycle, cell growth arrest after DNA damage and apoptosis [64]. The reactive chromium intermediates like Cr (V) and Cr (IV) also generate OH^- -radicals which cause DNA strand breaks, base modification, lipid peroxidation and nuclear transcription factor NF-kB activation, a process which also inactivates p53 hence enhancing cancer development [65]. The unstable intermediate Cr (V) and Cr (IV) ions also activates oxygen agents and thiyl and organic radicals (RS^- and R^-), which are responsible for the DNA and other observed cellular damage. Cr (IV) has been reported to cause severe liver effect including derangement of the liver cells, necrosis, lymphocytic and histiocytic infiltration, and increase in Kupffer cells [66]. Cases of hepatic effects after oral exposure to Cr (VI) compounds have also been reported. Elevated liver enzyme levels were reported flowing ingestion of 150 mL solution containing 22.5 g potassium dichrome [67]. Hepatomegaly [67, 68] and hepatic failure [70] have also been noted in the cases of acute poisoning. Regulatory limits established by EPA is 0.1 ppm (parts per million) in drinking water. The FDA determined that Chromium concertation should not exceed 1 milligram per liter (1 ppm) in bottled water. OSHA regulations includes an average of between 0.0005 and 1.0 milligram per cubic meter of workplace air for an 8-hour workday, 40-hour workweek, depending on the compound.

2.6 Lead and lead compounds

Lead exists both as a free metal and in various compounds. Unique properties of lead, like softness, high malleability, ductility, low melting point and resistance to corrosion, have resulted in its widespread applications in different industries like automobiles, paint, ceramics, and plastics, among others. This in turn has led to a manifold rise in the occurrence of free lead in biological systems and the inert environment. Because of human activities, such as fossil fuel burning, mining, and manufacturing, lead and lead compounds can be found in all parts of our environment including plants, animals, air, water, dust and soil. Inorganic lead compounds, such as tetraethyl lead and tetra methyl lead, are combined with carbon groups while lead oxide and lead chloride, are combinations of lead with other elements. Human exposure is mainly by inhalation from dust or fumes and by ingestion. Due to its widespread uses, more environmental exposures are from man-made rather than natural sources. Inorganic lead salts, with ionic bonds like lead acetate, have different chemical properties and toxicological effects compared to organo-lead compounds, with covalent bonds like tetraethyl lead. Lead toxicity is a particularly insidious hazard with the potential of causing irreversible health effects in humans.

Lead is known to interfere with a number of body functions including the central nervous, hematopoietic, hepatic and renal system producing serious disorders [71]. Even though acute toxicity related to occupational exposure is quite uncommon, chronic toxicity is much more common and occurs at blood lead levels of about 40–60 ug/dL. Chronic toxicity can be much more severe if not treated in time and is characterized by persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma [72].

Several epidemiological and animal experimental studies suggest that inorganic lead compounds are associated with increased risks of tumorigenesis. Lead acetate, lead sub-acetate and lead phosphate have been found to cause tumors in the kidneys of rats and mice [73]. In rats, the carcinogenic risks of lead compounds can be induced at doses that are not associated with organ toxicity and in mice that do not produce a-2 urinary globulin in the kidney. The kidney, particularly the tubule epithelium of the renal cortex, is the principal target organ for the carcinogenicity of lead salts in animals irrespective of the means of exposure. Since renal epithelial tumors are very rare in untreated rats and mice of both sexes, even low incidences of these neoplasms in lead treated animals are good indicators of a carcinogenic effect [38]. Most observed mechanisms of lead carcinogenicity include direct DNA damage, clastogenicity, or inhibition of DNA synthesis or repair [74, 75]. Lead can also cause the generation of ROS and cause oxidative damage to DNA. It has been reported as a main mechanism of lead induced toxicity. The onset of oxidative stress, under lead influence, occurs on account of two different pathways operative simultaneously; first comes the generation of ROS, like hydro peroxides ($HO_2^{\bullet}$), singlet oxygen and hydrogen peroxide (H_2O_2), and second, the antioxidant reserves become depleted [76]. According to some studies, lead can substitute for zinc in several important proteins that function as transcriptional regulators, including protamine. This reduces the binding of these proteins to the recognition elements in genomic DNA, a process that suggests an epigenetic involvement of lead in altered gene expression [77].These events may be of particular relevance in trans placental exposures and later cancer. Lead–zinc interactions in proteins can also cause post-translational changes in protein structure. The tumor suppressor protein p53 is a zinc-binding protein and thus if zinc is displaced by lead in p53, may result in a structurally altered form of the protein with functional consequences not different from mutation or deletion of the p53 gene expressed by cadmium [78]. Occupational exposures to lead is linked to increase risk of lung stomach, kidney and bladder cancers in humans.

Lead exposure affects the hematopoietic system directly through restraining the synthesis of hemoglobin by inhibiting various key enzymes involved in the heme synthesis pathway. In addition, by reducing the life span of circulating erythrocytes by increasing the fragility of cell membranes results in anemia [79, 80]. Acute high-level lead exposure of lead poisoning produces *hemolytic anemia***,** while prolonged high blood level exposure produces *frank anemia* [81]. Lead affects the heme synthesis pathway in a dose dependent way by downregulating three key enzymes involved in the synthesis of heme. These enzymes includes *δ-aminolevulinic acid dehydratase (ALAD)***,** a cytosolic enzyme which catalyzes the formation of porphobilinogen from δ-aminolevulinic acid (ALA), *aminolevulinic acid synthetase (ALAS)***,** a mitochondrial enzyme which catalyzes the formation of aminolevulinic acid (ALA), and finally, the mitochondrial enzyme *ferrochelatase* which catalyzes the insertion of iron into protoporphyrin to form heme [82]. Lead exposure can also cause renal dysfunction especially at high levels (>60 µg/dL), however, damage at lower levels has also been reported (~10 µg/dL) [83]. Renal functional abnormality can be of two types: acute nephropathy and chronic nephropathy. Lead exposure also have significant negative effects on the reproductive system in both men and women. For men, the effects includes reduced libido, abnormal spermatogenesis, chromosomal damage, infertility, abnormal prostatic function and changes in serum testosterone. Women on the other hand, are more susceptible to infertility, miscarriage, premature membrane rupture, pre-eclampsia, pregnancy hypertension and premature delivery [84]. Regulatory limits established by EPA is 15 parts per billion (ppb) in drinking water, and 0.15 micrograms per cubic meter in air.

2.7 Mercury and mercury compounds

Mercury occurs naturally in the earth's crust. It is released into the environment from volcanic activity, weathering of rocks and through human activity including coal-fired power stations, residential coal burning for heating and cooking, industrial processes, waste incinerators and because of mining for mercury, gold and other metals. Metallic mercury is used to produce chlorine gas and caustic soda, and is used in thermometers, dental fillings, switches, light bulbs, and batteries. Once in the environment, bacteria mercury can transform mercury into methylmercury which bio-accumulates in fish and shellfish. Methylmercury also biomagnifies for instance, a large predatory fish are more likely to have high levels of mercury because of eating many smaller fish that have acquired mercury through ingestion of plankton.

Elemental and methylmercury are toxic to the central and peripheral nervous systems. The inhalation of mercury vapor have significant adverse effects on the nervous, digestive and immune systems, lungs and kidneys, and may be fatal [85, 86]. The inorganic salts of mercury are corrosive to the skin, eyes and gastrointestinal tract, and may induce kidney toxicity if ingested. Neurological and behavioral disorders was observed after inhalation, ingestion or dermal exposure of different mercury compounds [87]. Symptoms include tremors, insomnia, memory loss, neuromuscular effects, headaches and cognitive and motor dysfunction. Mild, subclinical signs of central nervous system toxicity was on individuals exposed to an elemental mercury level in the air of 20 $\mu g/m^3$ or more for several years. Kidney effects has been reported, ranging from increased protein in the urine to kidney failure. Heavy or prolonged exposure can do irreversible damage especially in fetuses, infants, and young children. Young's syndrome disease is caused by long-term consequence of early childhood mercury poisoning [88]. Mercury chloride is cancer causative agent as it has caused increases in several types of tumors in rats and mice, while methyl mercury has caused kidney tumors in male rats. The EPA has classified mercuric chloride and methyl mercury as possible human carcinogens [85]. Regulatory limits established by EPA includes 2 parts per billion parts (ppb) in drinking water while FDA has set a limit of 1 part of methylmercury in a million parts of seafood. OSHA also established regulatory limit of 0.1 milligram of organic mercury per cubic meter of workplace air and 0.05 milligrams per cubic meter of metallic mercury vapor for 8-hour shifts and 40-hour workweek.

2.8 Silver and silver compounds

Silver is a rare but naturally occurring element. It is slightly harder than gold and is very ductile and malleable. It is widely distributed in the earth's crust and is found in soil, fresh and seawater, and the air. It is readily absorbed into the human body with food and drink and through inhalation. Silver is not an acknowledged trace element in the human body and fulfils no physiological or biochemical role in any tissue even though it interacts with several essential elements including zinc and calcium. Physiologically, it exists as an ion in the body. Silver is becoming more pervasive in human food, in dental and medical devices, in implants and even the clothes. Silver forms silver-protein complexes when absorbed into the circulatory system through which it is deposited in key soft tissues, including the skin, liver, kidney, spleen, lungs, and brain. Silver has many applications including to making jewelry, silverware, electronic equipment, and dental fillings. Silver metal is also used in electrical contacts and conductors, in brazing alloys and solders, and in mirrors. Silver compounds are used in photographic film. Dilute solutions of silver nitrate and other silver compounds are used as disinfectants and as an antibacterial agents. Silver iodide has been used in studies to seed clouds to produce rain. Having high silver levels in blood or urine is often the result of occupational exposure. However, high silver levels in hair can result from consistent, yet potentially harmful, low level exposure. Principle routes of gastrointestinal absorption of silver includes; contaminated food, occupational exposures to metallic silver dust, silver oxide, and silver nitrate aerosols; drinking water; silver nitrate or colloidal silver therapies in oral hygiene and gastrointestinal infection. Other routes includes; colloidal silver preparations labelled as "food supplements" or "alternative medicines", silver acetate antismoking therapies, silver amalgams used in dentistry, and accidental consumption of silver nitrate or other colourless silver compounds.

The most common health effect associated with prolonged exposure to silver are the development of an irreversible pigmentation of the skin (known as argyria) and/or the eyes (known as argyrosis). The affected area becomes bluish-gray or ash gray and is most prominent in areas of the body exposed to sunlight [89, 90]. Once in the body, silver is absorbed, carried by the bloodstream and deposited in various tissues throughout the body. Areas of the body most likely to be pigmented are the eyes, internal organs, and sun-exposed areas such as the face, ears, forearms, hands, and nails [91]. Inhalation of soluble silver compounds has been reported to cause both upper (nose and throat) and lower (chest) respiratory tract irritation [92]. Bronchitis, emphysema and a reduction in pulmonary volume have been observed when silver polishers were exposed to metallic silver, as well as to other metals. Silver ion accumulation possess a high affinity for the thiol groups in the liver leading to reduced glutathione thus depleting the amount of reduced glutathione available for biochemical pathways. Reduced glutathione plays an important role in maintaining proper structure and function of red blood cells, as well as eliminating organic peroxides [93]. Exposure to high levels of silver in the air has resulted in breathing problems, lung and throat irritation, and stomach pains. Skin contact with silver can cause mild allergic reactions such as rash, swelling, and inflammation in some people. Silver is not considered a human carcinogen. The Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) currently enforce a Permissible Exposure Limit (PEL) of 0.01 mg/m^3 for metallic and soluble silver compounds [94, 95]. The National Institute for Occupational Safety and Health (NIOSH) established a Recommended Exposure Limit (REL)

of 0.01 mg/m^3 for both soluble silver compounds and silver metal dust, which does not differ from the OSHA PEL [95]. EPA recommends concentration in drinking water not to exceed 0.10 parts per billion (ppb) and requires that spills or accidental releases of 1,000 pounds or more be reported.

3. ROLE OF BIOACCUMULATION

The bioaccumulation of heavy metals in living organisms and bio-magnifications describes the processes and path- ways of pollutants including heavy metals from one trophic level to another. Plants known as hyper-accumulators have the ability to absorb high levels of metals from the soils and accumulate them in their roots, stems, leaves and fruits [97]. Harvesting such plants for human consumption exposes the humans to harmful levels of metals some of which have high levels of toxicity. This is a major concern especially if plants are collected from areas with high concentrations of metals in the soil. Metals uptake by plants is dependent on soil acidity (pH) and plant types. The higher the acidity, the more soluble and mobile the metals and metal compounds become, and the more likely they are to be taken up and accumulated in plants. Root crops like potatoes and carrots, leafy vegetables and parts of plants that grow near the soil like strawberries are a higher risk for exposure to metal contamination than the higher portions of plants, like fruits or berries. Visual symptoms of bioaccumulation in plants may include coloring changes on plants among other stressful conditions.

When animals are exposed to these metals, through feeding on affected plants, drinking contaminated water, and other pathways, they can also bio-accumulate heavy metals in different parts of the body which can then exposed humans who use such animal products for food. Heavy metal accumulations have been reported on animal products like milk and other meat. Aquatic fishes and seafood have been determined to be the greatest bio-accumulators. The concentrations of heavy metals in organs of fish and other aquatic life depicts the level of pollution both past and present, in the aquatic environment [98]. Various metals are accumulated in fish body in different amounts. These differences result from different affinity of metals to fish tissues, different up- take, deposition and excretion rates of various species [99]. All these contaminated fish and seafood can find their way into the human food chain exposing people to heavy metal contamination.

4. CONCLUSION

This review discussed the main exposure routes and major health hazards related to heavy metals. Heavy metals such as arsenic, cadmium, chromium, lead, mercury and silver occur naturally in the environment. However, human activities contribute significantly to their environmental contamination. These metals are systemic toxicants whose exposure have been known to cause adverse health effects in humans, including cardiovascular diseases, developmental abnormalities, neurologic and neurobehavioral disorders, diabetes, hearing

loss, hematologic and immunologic disorders, as well as being carcinogenic in nature. The type of heavy metal and its chemical form, the time and amount of dose determines the severity of the adverse health effect, with some lingering long after exposure, and thus can have life-long effects on human health if not treated on time. Speciation in addition to other factors mostly influences metal toxicokinetics and toxicodynamics, and is highly impacted by valence state, particle size, solubility, biotransformation, and chemical form of the metals involved. Even though most studies have been focused on the effects of individual metal exposures, very little is known about the effects of exposure to a mixture of these metals. More studies are needed in this area. Finally, there is need for regulatory agencies to strictly monitor and control exposure due to anthropogenic activities and to provide support to developing countries whose residence are more at risk for exposure due to contaminated water and food substances given the inadequate availability of medical supply.

REFERENCES

[1] P.B. Tchounwou, G.C. Yedjou., K.A. Patlolla, J.D. Sutton. “Heavy Metal Toxicity and the Environment. In: Luch A. (eds)” *Molecular, Clinical and Environmental Toxicology*. Experientia Supplementum, vol 101, 2012 Springer, Basel. https://doi.org/10.1007/978-3-7643-8340-4_6

[2] H. Howard, *Human health and heavy metals exposure. In: McCally M(ed) Life support: the environment and human health*, Cambridge MIT press, Cambridge, pp 1–13

[3] N.C. Amadi, J.S Offor, C. Frazzoli, *et al*. “Natural antidotes and management of Metal toxicity” Environ *Sci Pollut Res*, 26: 18032, 2019. https://doi.org/10.1007/s11356-019-05104-2

[4] P.B. Tchounwou, G. C. Yedjou, K. A. Patlolla, J. D. Sutton, "Heavy Metal Toxicity and the Environment. In: Luch A. (eds)", Molecular, *Clinical and Environmental Toxicology.* Experientia Supplementum, vol. 101: 133-64, 2012. doi:10.1007/978-3-7643-8340-4_6

[5] J. E. Saunders, B. G. Jastrzembski, J. C. Buckey, D. Enriquez, T.A. MacKenzie, M. R. Karagas, "Hearing Loss and Heavy Metal Toxicity in a Nicaraguan Mining Community: Audiological Results and Case Reports", *Audiol Neurotol*, 18:101-113, 2013. doi: 10.1159/000345470

[6] Flora SJ, Pachauri V., "Chelation in metal intoxication", *Int J Environ Res Public Health*. 7(7):2745–2788, 2010. doi:10.3390/ijerph7072745

[7] S. E. Margaret, "Chelation: Harnessing and Enhancing Heavy Metal Detoxification—A Review," The Scientific World Journal, vol. 2013, Article ID 219840, 13 pages, 2013. https://doi.org/10.1155/2013/219840.

[8] O. Hyder, M. Chung, D. Cosgrove, et al. "Cadmium exposure and liver disease among US adults". J Gastrointest Surg. 17: 1265– 1273, 2013 https://doi.org/10.1007/s11605-013-2210-9

[9] V. Mudgal, N. Madaan, A. Mudgal, R. Singh, S. Mishra, "Effect of toxic metals on human health", *Open Nutraceut J.* 2010; 3: 94– 99. DOI: 10.2174/1876396001003010094.

[10] A.J. Baig, T. G. Kazi, A. Q. Shah, *et al*. "Arsenic speciation and other parameters of surface and ground water samples of Jamshoro, Pakistan", *Int J Environ Anal Chem.*, 92: 28– 42, 2012. https://doi.org/10.1080/03067319.2010.496053

[11] Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological profile for arsenic.* Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, 2000.

[12] P. Apostoli, "The role of element speciation in environmental and occupational medicine," *Fresenius J Anal Chem*. 363: 499504, 1999. https://doi.org/10.1007/s002160051233

[13] N. Yamato, "Concentration and chemical species of As in human urine and hair", Bull *Environ Contamin Toxicol.* 40: 633-40.1998. https://doi.org/10.1007/BF01697507

[14] M. Sarkar, G. R. Chaudhuri, A. Chattopadhyay and N. M. Biswas, "Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats," *Asian J Androl.* 5: 27-31, 2003.

[15] P. Boffetta, "Carcinogenicity of trace elements with reference to evaluations made by the International Agency Research on cancer," *Scand J Work Environ Health*. 19 (Suppl 1):67–70, 1993. https://www.jstor.org/stable/40966378

[16] Agency for Toxic Substance and Disease registry (ATSDR), *Toxicological profile for arsenic. U.S. Department of Health and Human Services, Public Health Humans Services, Center for Disease Control*, Atlanta, 2003.

[17] Agency for Toxic Substances and Disease Registry (ATSDR), *Toxicological Profile for Chromium*, 1998.

[18] T. Sakurai, C. Kojima, T. Ohta, and K. Fujiwara, "Evaluation of in vivo acute immunotoxicity of a major organic arsenic compound arsenobetaine in seafood, International Immunopharmacology, Volume 4, Issue 2, 2004, Pages 179-184, ISSN 1567-5769, https://doi.org/10.1016/j.intimp.2003.11.004.

[19] A. Mudhoo, S. K. Sharma, V. K. Garg, and T. H. Tseng, "Arsenic: an overview of applications, health and environmental concerns and removal process," *Crit Rev Environ Sci Technol.* 41:435–519, 200. https://doi.org/10.1080/10643380902945771

[20] Y. S. Pu, K. Y. Jan, T. C. Wang, et al. "8-Oxoguanine DNA glycosylase and MutY homolog are involved in the incision of arsenite-induced DNA adducts," *Toxicol Sci.* 95:376–382, 2007. doi:10.1093/toxsci/kfl166

[21] J. F. Reichard, A. Puga, "Effects of arsenic exposure on DNA methylation and epigenetic gene regulation," *Epigenomics.* 2:87–104, 2010. https://doi.org/10.2217/epi.09.45

[22] H. Ahsan, Y. Chen, and Q. Wa, "DNA repair gene XPD and susceptibility to arsenic-induced hyperkeratosis," *Toxicol Lett.* 2003; 143:123–13, 2003. https://doi.org/10.1016/S0378-4274(03)00117-6

[23] Y. Chen, J. H. Graziano and F. Parvez, "Modification of risk of arsenic-induced skin lesions by sunlight exposure, smoking, and occupational exposures in Bangladesh," *Epidemiology.* 17:459–467, 2008. www.jstor.org/stable/20486249.

[24] I. A. Jacobs, J. Taddeo, K. Kelly and C. Valenziano, "Poisoning as a result of barium styphnate explosion," *Am J Ind Med.* 41(4):285-8, 2002. https://doi.org/10.1002/ajim.10056

[25] C. H. Johnson, V. J. Van Tassell, "Acute barium poisoning with respiratory failure and rhabdomyolysis," *Ann Emerg Med*. 20(10):1138-42, 1991. https://doi.org/10.1016/S0196-0644(05)81393-9

[26] M. Purdey, "Chronic barium intoxication disrupts sulphated proteoglycan synthesis: a hypothesis for the origins of multiple sclerosis," *Med Hypothesis*. 62(5):746-54, 2004. https://doi.org/10.1016/j.mehy.2003.12.034

[27] D. Middleton, and P. Kowalski, "Advances in identifying beryllium sensitization and disease,"Int J Environ Res Public Health. 7(1):115-24, 2010. https://doi.org/10.3390/ijerph7010115

[28] A. Seidler, U. Euler, J. Müller-Quernheim, K. I. Gaede, U. Latza, D. Groneberg and S. Letzel, "Systematic review: Progression of beryllium sensitization to chronic beryllium disease," *Occup Med (Lond).* 62(7):506-13, 2012. https://doi.org/10.1093/occmed/kqs069

[29] D. C. Middleton, J. Fink, P. J. Kowalski, M. D. Lewin, T. Sinks, "Optimizing the BeLPT criteria for beryllium sensitization," *Am. J. Ind. Med*. 51:166–172, 2008. https://doi.org/10.1002/ajim.20548

[30] D. C. Middleton, "Chronic Beryllium Disease: Uncommon Disease, Less Common Diagnosis," *Environmental Health Perspectives.* 106 (12):765-767, 1998. https://doi.org/10.1289/ehp.98106765

[31] T. K. Stiefel, K. Schultz, H. Zorn, and G. Tolg, "Toxicodynamic studies of beryllium," *Arch Toxicol* 45(2):81–92, 1980. https://doi.org/10.1007/BF01270905

[32] G. R. Cooper, and P. A. Harrison, "The uses and adverse effects of beryllium on health," *Indian J Occup Environ Med*. 13(2):65–76, 2009. doi: 10.4103/0019-5278.55122

[33] D. R. Dobis, R. T. Sawyer, M. M. Gillespie, J. Huang, L. S. Newman, L. A. Maier, et al. "Modulation of lymphocyte proliferation by antioxidants in chronic beryllium disease," *Am J Respir Crit Care Med*. 77:1002–1011, 2008. https://doi.org/10.1164/rccm.200707-1021OC

[34] A. P. Fontenot, M. T. Falta, B. M. Freed, L. S. Newman and B. L. Kotzin, "Identification of pathogenic T cells in patients with beryllium-induced lung disease," *J Immunol.* 163:1019–1026, 1999. http://www.jimmunol.org/content/163/2/1019 1999; 163:1019-1026;

[35] Z. Wang, G. M. Farris, L. S. Newman, Y. Shou, L. A. Maier, H. N, "Smith, et al. Beryllium sensitivity is linked to HLA-DP genotype," *Toxicology*. 165:27–38, 2001. https://doi.org/10.1016/S0300-483X(01)00410-3

[36] A. Leonard, and R. Lauwerys, "Mutagenicity, carcinogenicity and tetragenicity of beryllium," *Mutat Res*. 186:35–42, 1987. https://doi.org/10.1016/0165-1110(87)90013-3

[37] K. Steenland, and E. Ward, "Lung cancer incidence among patients with beryllium disease: a cohort mortality study," *J Natl Can Ist*. 83:1380–1385, 1991. https://doi.org/10.1093/jnci/83.19.1380

[38] International Agency for Research on Cancer (IARC), *IARC monographs on the evaluation of carcinogenic risks to humans.* Arsenic and arsenic compounds, vol 23, pp 39, 1980.

[39] J. D. Stoeckle, and T. Mancuso, "Beryllium disease," *Science*. 183:449, 1974. DOI: 10.1126/science.183.4123.449

[40] N. Harrison, *Inorganic contaminants in food. In: Watson DH (ed) Food chemical safety contaminants,* 1st edn. Woodhead Publishing Ltd, Cambridge, pp 148–168. ISBN 1-85573-462-1, 2001.

[41] International Agency for Research on Cancer (IARC), *IARC monographs on the evaluation of carcinogenic risks to humans;* vols 1–58. Lyon: IARC pp. 1972–1993.

[42] E. Figueroa, "Are more restrictive food cadmium standards justifiable health safety measures or opportunistic barriers to trade? An answer from economics and public health," *Sci Total Environ*. 389:1–9, 2008. https://doi.org/10.1016/j.scitotenv.2007.08.015

[43] Y. Ming-Ho, *Environmental toxicology: biological and health effects of pollutants*, chap 12, 2nd edn. CRC Press LLC, Boca Raton, USA, ISBN 1-56670-670-2, 2005.

[44] M. I. Castro-González, and M. Méndez-Armenta, "Heavy metals: implications associated to fish consumption," *Environ Toxicol Pharmacol*. 26:263–271, 2008. https://doi.org/10.1016/j.etap.2008.06.001

[45] WHO, "Evaluation of certain food contaminants. Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives," *WHO Technical Report Series, No*. 930 (2006).

[46] WHO, "Evaluation of certain food additives contaminants. Sixty-first report of the joint FAO/WHO Expert Committee on Food Additives," *WHO Technical Report Series, No*. 922, (2004).

[47] W. F. Binner, W. J. Bridges and J. Rose J (eds), *Trace elements in health.* Butterworth, p 1, 1983.

[48] S. S. Dara, *Text book of environmental chemistry and its pollution control*. 2. New Delhi: S. Chand & Co. Ltd; 1997.

[49] S. A. Mouron, C. D. Golijow, F. N. Dulout, "DNA damage by cadmium and arsenic salts assessed by the single cell gel electrophoresis assay," *Mutat Res.* 498:47–55, 2001. https://doi.org/10.1016/S0378-4274(02)00039-5

[50] M. Waisberg, P. Joseph, B. Hale and D. Beyersmann, "Molecular and cellular mechanisms of cadmium carcinogenesis," *Toxicology*. 192:95–117, 2003. https://doi.org/10.1016/S0300-483X(03)00305-6

[51] C. Giaginis, E. Gatzidou, and S. Theocharis, "DNA repair systems as targets of cadmium toxicity," *Toxicol Appl Pharmacol*. 213:282–290, 2006. doi: 10.18632/aging.100226

[52] Y. Wang, J. Fang, S. S. Leonard, and K. M. Rao, "Cadmium inhibits the electron transfer chain and induces reactive oxygen species," *Free Radic Biol Med*. 36:1434–1443, 2004. https://doi.org/10.1016/j.freeradbiomed.2004.03.010

[53] U.S. Environmental Protection Agency, "Toxicological Review of Trivalent Chromium" *Toxicol Lett;* 41: 261–8, 1998.

[54] W. Machle, and F. Gregorius, "Cancer of the respiratory system in the United States chromate-producing industry." *Public Health Rep* 63: 114-127, 1948. DOI: 10.2307/4586677

[55] S. Langard, T. Vigander. "Occurrence of lung cancer in workers producing chromium pigments," *British Journal of Industrial Medicine* 40(1): 71-4, 1983. http://dx.doi.org/10.1136/oem.40.1.71

[56] A. Sheffet, I. Thind *et al*. "Cancer mortality in a pigment plant utilizing lead and zinc chromates," *Archives of Environmental Health*. 37(1): 44-52, 1982. https://doi.org/10.1080/00039896.1982.10667532

[57] International Agency for Research on Cancer, *Chromium, Nickel and Welding*. IARC Monograph on the Evaluation of Carcinogenic Risks to Huma, Vol 49, Lyon, 1990.

[58] EPA, *Toxicological Review of Trivalent Chromium. CAS No. 16065-83-1. In support of Summary Information on the Integrated Risk Information System (IRIS).* U.S. Environmental Protection Agency, Washington, D.C., 1998

[59] E. R. Braver, P. Infante *et al*., "An analysis of lung cancer risk from exposure to hexavalent chromium," Teratogenesis, *Carcinogenesis, & Mutagenesis* 5(5): 365-78, 1985. https://doi.org/10.1002/tcm.1770050507

[60] H. J. Gibb, P. S. Lees, *et al*., "Lung cancer among workers in chromium chemical production," *American Journal of Industrial Medicine* 38(2): 115-26, 2000. https://doi.org/10.1002/1097-0274(200008)38:2<115::AID-AJIM1>3.0.CO;2-Y

[61] R. M. Park, J. F. Bena, *et al*., "Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment," *Risk Analysis* 24(5): 1099-108, 2004. https://doi.org/10.1111/j.0272-4332.2004.00512.x

[62] S. A. Katz, H. Salem, "The toxicology of chromium with respect to its chemical speciation: a review," *Journal of Applied Toxicology* 13(3): 217-24, 1993. https://doi.org/10.1002/jat.2550130314

[63] I. Bertini, B. H. Gray, V. J. S. Lippard, *In Bioinorganic chemistry.* Viva Books Private Ltd., p 513, 1998.

[64] M. Hollstein, K. Rice, S. M. Greenblatt, T. Soussi, R. Fuchs, T. Sorlie, E. Hovig, B. Smith-Sorensen, R. Montesano, C. C. Harris, "Database of p53 gene somatic mutations in human tumors and cell lines," *Nucleic Acids Res* 22:3551–3555, 1994. PMCID: PMC308317

[65] S. Wang, S. S. Leonard, J. Ye, M. Ding, X. Shi, "The role of hydroxyl radical as a messenger in Cr(VI)-induced p53 activation," *Am J Physiol Cell Physiol* 279(3):C868–C875, 2000. https://doi.org/10.1152/ajpcell.2000.279.3.C868

[66] S. Hong, B. Jason, C. Max, "Oral Chromium exposure and toxicity" *Curr Environ Health Rep.* 2015 Sep; 2(3): 295–303. doi: 10.1007/s40572-015-0054-z

[67] Z. Kolaciski, P. Kostrzewski, et al. "Acute potassium dichromate poisoning: a toxicokinetic case study," *Journal of Toxicology, Clinical Toxicology* 37(6): 785-91, 1999. https://doi.org/10.1081/CLT-100102458

[68] K. L. Meert, J. Ellis, et al., "Acute ammonium dichromate poisoning," *Annals of Emergency Medicine* 24(4): 748-50, 1994. https://doi.org/10.1016/S0196-0644(94)70288-8

[69] C. A. Michie, M. Hayhurst, et al., "Poisoning with a traditional remedy containing potassium dichromate," *Human & Experimental Toxicology* 10(2): 129-31, 1991. https://doi.org/10.1177/096032719101000207

[70] Y. Loubieres, A. de Lassence, et al., "Acute, fatal, oral chromic acid poisoning," *Journal of Toxicology - Clinical Toxicology* 37(3): 333-6, 1999. https://doi.org/10.1081/CLT-100102431

[71] S. J. S Flora, "Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure," *Oxid Med Cell Longev*. 2:191–206, 2009. http://dx.doi.org/10.4161/oxim.2.4.9112

[72] S. J. S. Flora, G. Flora, and G. Saxena, "Environmental occurrence, health effects and management of lead poisoning," In: José S. C, José S, editors. Lead. Amsterdam: *Elsevier Science* B.V. pp. 158–228, 2006. https://doi.org/10.1016/B978-044452945-9/50004-X

[73] International Agency for Research on Cancer (IARC), *IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluation of carcinogenicity, an updating of IARC monographs: lead and lead compounds*, vol 1–42 (suppl 7), pp 230, 1998.

[74] J. Landolph,, "Molecular mechanisms of transformation of CH3/10T1/2 C1 8 mouse embryo cells and diploid human fibroblasts by carcinogenic metal compounds," *Environ Health Perspect*. 102:119–125, 1994. https://doi.org/10.1289/ehp.94102s3119

[75] A. Hartwig, R. D. Snyder, R. Schlepegrell, et al., "Modulation by Co (II) of UV-induced DNA repairs, mutagenesis and sister chromatid exchanges in mammalian cells," *Mutat Res.* 248:177–185, 1990. https://doi.org/10.1016/0027-5107(91)90099-A

[76] S. J. S. Flora, Nutritional components modify metal absorption, toxic response and chelation therapy," *J Nut Environ Med*. 12:53–67, 2002. https://doi.org/10.1080/13590840220123361

[77] B. Quintanilla-Vega, D. J. Hoover, E. K. Silbergeld, M. Waalkes, and L. D. Anderson, *Interaction between lead and protamine 2 from human spermatozoa*. International symposia on environment, lifestyle, and fertility, Aarhus, Denmark, 1997.

[78] Y. Xin, K. Samuel, C. Ying et al., "Zinc Metallochaperones Reactivate Mutant p53 Using an ON/OFF Switch Mechanism: A New Paradigm in Cancer Therapeutics", volume 24(18):4505-4517, 2018. Doi:0.1158/1078-0432.CCR-18-0822P.

[79] T. L. Guidotti, J. McNamara, and M. S. Moses, "The interpretation of trace element analysis in body fluids," *Indian J Med Res.* 128:524–532, 2008. Doi:10.1.1.623.6489 R. Cornelis, *Handbook of elemental speciation II: species in the environment, food, medicine & occupational health*. Wiley, 2005.

[80] A. G. Vij, "Hemopoietic, hemostatic and mutagenic effects of lead and possible prevention by zinc and vitamin C," *Al Ameen J Med Sci*. 2:27–36, 2009.

[81] S. Piomelli, "Childhood lead poisoning," *Pediatr Clin North Am*. 49:1285–1304, 2002. DOI: 10.1016/S0031-3955(02)00097-4

[82] L. D. Grant, *Environmental Toxicants.* John Wiley & Sons, Inc. Lead and compounds; pp. 757–809, 2008.

[83] S. J. S. Flora, "Arsenic induced oxidative stress and its reversibility" *Free Rad Biol Med.* 51:257–281, 2011. https://doi.org/10.1016/j.freeradbiomed.2011.04.008

[84] ATSDR, Mercury ToxFAQ, ToxFAQs: Mercury, Agency for Toxic Substances and Disease Registry, 1999.

[85] M. G. Cherian, J. G. Hursh, and T.W. Clarkson, "Radioactive mercury distribution in biological fluids and excretion in human subjects after inhalation of mercury vapor," *Archives of Environmental Health.* 33 (3): 190–214, 1978. https://doi.org/10.1080/00039896.1978.10667318

[86] C. H. Ngim, S. C. Foo, K. W. Boey, and J. Keyaratnam, "Chronic neurobehavioral effects of elemental mercury in dentists," *British Journal of Industrial Medicine*. 49 (11): 782–790, 1992. http://dx.doi.org/10.1136/oem.49.11.782

[87] W. F. Hendry, R. P. A'Hern and P. J. Cole, "Was Young's syndrome caused by exposure to mercury in childhood," *BMJ.* 307 (6919): 1579–82, 1993. doi: https://doi.org/10.1136/bmj.307.6919.1579

[88] ATSDR, "Toxicological Profile for Silver. TP-90-24. Atlanta, GA: Agency for Toxic Substances and Disease Registry, 1990.

[89] V. Toth, M. Marschalko, J. Harsing,S. Karpati, "Grayish discoloration of the face – argyria", *Orv Hetil,* 9;150(32):1503-7, 2009. doi: 10.1556/OH.2009.28682.

[90] D. R. Juberg, F. T. Hearne, *Silver and gold.* In Bingham E, Cohrssen B, Powell CH, editors. Patty's toxicology, 5th edn. New York: John Wiley, 2001.

[91] B. Nathan, Z. Jonathan, J. David, "Argyria caused by chronic ingestion of silver," CMAJ *Canadian Medical Association Journal*. 190(5):E139, 2018. DOI: 10.1503/cmaj.171374

[92] C. Baldi, C. Minoia, A. Di Nucci *et al*., "Effects of silver in isolated rat hepatocytes," *Toxicol Lett;* 41: 261–8, 1998. https://doi.org/10.1016/0378-4274(88)90063-X

[93] OSHA, *United States Code of Federal Regulations, 29CFR Part 1910.1000, Air contaminants,* final rule. Vol. 54. Washington, DC: Occupational Safety and Health Administration. p. 2702, 1989.

[94] NIOSH, *Reports and Memoranda. NIOSH publication no. 92-100 U.S. Department of Health*, Education, and Welfare, 1992.

[95] NIOSH. *Registry of toxic effects of chemical substances (RTECS): silver,* VW3500000 (last updated August 2003) Cincinnati, OH: National Institute for Occupational Safety and Health, 2003.

[96] Z. Svobodova, O. Celechovska, J. Kolara, T. Randak and V. Zlabek, "Assessment of Metal Contamination in the Upper Reaches of the Ticha Orlice River," Czech Journal of *Animal Science.* Vol. 49; (4):458-641, 2004. https://doi.org/10.17221/4332-CJAS.

[97] A. J. Farkas, J. Salanki and I. Varanka, "Heavy Metal Con- centrations in Fish of Lake Balaton, Lakes and Reser-voirs," *Research and Management,* Vol. 5 (4): 271-279, 2000. https://doi.org/10.1046/j.1440-1770.2000.00127.x

[98] R. C. Ravera, G. M. Beone, M. Dantas and P. Lodigiani, "Trace Element Concentrations in Freshwater Mussels and Macrophytes as Related to Those in Their Environment," *Journal of Limnology*, Vol. 62 (1): 61-70, 2003. DOI: 10.4081/jlimnol.2003.61