Chapter

Toxicity of Heavy Metals

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Abstract

Heavy metals are elements who exist naturally in the environment, but rapid urbanization and industrialization led to increased levels of these metals. These metals can reach the human body through food, water or air, where they have the property to accumulate in various tissues and organs for long periods of time and to produce serious effects on certain organs and the proper functioning of the body. Studies have also shown that heavy metals can have important effects, including on plants or animals. Their toxicity is dependent on factors such as dose, route of exposure, time of exposure, level of concentration, as well as age, gender, genetics, and nutritional status of exposed individuals. There is a growing interest from researchers to detect various physical, physical-chemical or microbiological methods to reduce or eliminate the presence of these metals, especially from surface or wastewater, which are mainly responsible for food contamination. This chapter present the main characteristics of heavy metals, the sources of contamination of exposure, as well as their toxicity on some environmental segments and especially on living organisms.

Keywords: contamination, heavy metals, human health, sources of exposure, toxicity

1. Introduction

Heavy metals (HM) represent a group of metallic elements and metalloids characterized by a relatively density higher than 5 g/cm^3, an atomic number greater than 20 and with properties like conductance of heat, current and luster surface [1–3].

Pollution or contamination of the environment with heavy metals is a major concern, due to their capacity to bioaccumulate and persistence in the environment, non-biodegradable nature, contaminate the food chains and their toxicity on the environment and living organisms (humans, animals and plants) [1–3]. Heavy metal toxicity is a concern of ecological, nutritional, evolutionary and environmental reasons [1].

Heavy metals are among the most investigated pollutants and received a higher attention by researchers, because of their toxicity [2, 4]. These elements are naturally present in the environment, but on which modern industrialization and urbanization, anthropogenic activities and use of fertilizers, led to increased levels of these metals in the environment and implicitly to a high exposure of living things to them [2, 5]. Among the heavy metals and the most toxic metalloids are chromium, mercury, arsenic, cadmium, lead, nickel, copper, zinc, but the most common heavy metals in the environment are chromium, manganese, nickel, lead, cadmium, copper and zinc [2].

Regarding their functions in biological systems, heavy metals can be essential and nonessential. The nonessential heavy metals do not possess biological functions in living organisms, being non-essential to metabolic system, both for plants and animals. Their category includes lead, cadmium, mercury, aluminum and arsenic [2, 6, 7], being able to exert toxic effects even at low concentrations [8]. The essential heavy metals are elements, which are indispensable for plant and animals, which play a vital role in biological processes and entire metabolism and may be required in living organism in different concentrations [2, 8]. These heavy metals are considered as trace elements because of their presence in trace concentrations (less than 10 ppm) in different environmental matrices [9]. The essentiality and toxicity of the trace metals depending on the dose of exposure [10]. This category includes 19 elements, among which the most important are manganese, iron, copper, zinc, nickel and chromium [2].

Trace elements or trace minerals are minerals necessary for the body, but in amounts between 1 and 100 mg/day for adults and represents less than 0.01–0.02% of the total body weight [10–12]. When they exceed these threshold concentrations, they become dangerous to the health of living organisms [1].

According to WHO classification, trace elements can be divided into three groups, such as essential elements (zinc, iodine, molybdenum, copper, selenium, chromium), probably essential elements (manganese, silicon, boron, vanadium, nickel) and potentially toxic elements (lead, cadmium, fluorine, mercury, aluminum, arsenic, barium, lithium, tin [13, 14].

Another classification of the trace elements was made by Frieden in 1981, based on their levels in biological tissues, being divided into 3 groups, namely essential trace elements (boron, cobalt, copper, iodine, manganese, molybdenum, zinc), probably essential trace elements (chromium, fluorine, nickel, selenium, vanadium) and physically promotive trace elements (bromine, lithium, silicone, tin) [13, 15].

The present chapter presents the characteristics of heavy metals, the main sources of heavy metal contamination of the environment, as well as human exposure sources. The impact of their toxicity on various environmental segments, such as water, air, soil, as well as on living organisms, animals, but especially humans, has also been described.

2. Sources of environmental contamination

Heavy metals contamination of environment can come both from natural sources and from anthropogenic processes. Natural emissions of heavy metals include volcanic eruptions, rock weathering, sea-salt sprays, forest fires, biogenic sources, windborne soil particles and can be found in the nature as oxides, hydroxides, silicates, sulphates, sulphides, phosphates, organic compounds [4].

Anthropogenic processes which can release heavy metals in different environmental compartments, are industries, agriculture (insecticides, pesticides which can release As), fossil fuels combustion (Ni, V, Hg, Se, Sn), wastewater, mining, smelting (As, Cu, Zn), corrosion, metallurgical processes, residual organic matter, transportation (Pb) [4, 7, 16].

3. Toxicity

Heavy metals can produce side effects on soil, on water, on air, but also on plants, animals and humans [3, 4, 17]. In soil, high levels of heavy metals can produce

alteration of soil quality through modification of pH, color, porosity and natural composition [4, 18], but also low crop production, loss of many types of normal flora and habitat [19]. Their accumulation into the water imposes serious problems on humans and ecosystems [4], due to decreasing of drinking water quality and purity, decreasing water supplies for all living organisms [19]. High levels of heavy metals in air can lead to harmful health problems, including respiratory infections, cardiovascular disease, premature mortality, eyes and skin irritation, but also can cause infrastructure deterioration, acid rain increasing, corrosion, eutrophication and haze [4], low yields of the crop, not enough oxygen [19]. In plants, they can produce damage of roots or leaves, interfere in important biochemical process, such as photosynthesis, alteration of minerals absorption, damage of chlorophyll, reduce the growth and development of the roots, which leading to reduction pf overall growth of the plant [3, 20, 21].

The toxicity of heavy metals in animal is manifested through decreased body weight, kidney damage, liver affections, shortened life span, increased oxidative stress, modifications of cells composition, DNA damage [17]. In humans they can produce kidney damage, liver affections, pulmonary effects, several types of cancer [3].

Heavy metals became toxic when are not metabolized by the body and accumulates in organs and soft tissues [4]. They reach the human body by ingesting contaminated water or food, inhalation of absorption through the skin. Among the pathways, ingestion in the common route that helps the heavy metals to enter to the animal bodies [3, 4]. The effect of this metals can be inhibitory, stimulatory and toxic for some biochemical processes [3], being able to produce various health problems on nervous system (Alzheimer, Parkinsoma, depression, dementia), on bone system (bone mineralization) an on reproductive system. Also, can produce DNA damage, RNA affection, or cancer of lungs, skin, bladder, due to production of ROS [3]. Their toxicity depends the dose of exposure, time of exposure, pollutant concentration, organism which are exposed to it, nature and oxidation state of the metal [3, 4].

3.1 Toxicity of lead (Pb)

Lead is the most important toxic heavy metal in the environment because can cause serious environmental contamination and health problems [1, 10]. The main sources of environmental contamination including industrial processes, such as fossil fuel burning, mining, smelting, manufacturing, recycling activities. It is also used for leaded pipes, lead-glazed or lead-soldered containers, leaded paint, leaded gasoline, leaded aviation fuel [10, 22].

The inorganic lead can enter into the human body by inhalation (pulmonary absorption) of contaminated air or by smoking (15%), or by ingestion (gastrointestinal absorption) of food (65%) and water (20%) [1, 3, 22, 23]. Although organic compounds are absorbed through skin, inorganic compounds cannot be absorbed [10].

According to the WHO guidelines, the international level of concern of poisoning with lead is 25 μg/dl of blood for adults and for children, it must be less than 5 μg/dl of blood [23]. Their absorption is influenced by the age and physiological status of the exposed person [22].

However, the nervous system is most affected by exposure to high concentrations of lead, in both children and adults. Because children absorb 4–5 times more ingested lead, it can cause impaired neurobehavioral development, learning disabilities, speech and language handicaps, poor attention span, lower IQ, diminished

intelligence, anti-social behavior [10, 22]. At high concentration, lead can produce coma, convulsions and even death on children and may be left with mental retardation and behavioral disorders [10]. In adults it can be manifested headache, poor attention, irritability, loss of memory, dullness [9, 22]. Increased absorption rate was observed when other nutrients such as calcium or iron are lacking. Even at lower concentrations, known as safe levels, children face learning or behavioral problems, decreased intelligence in children [10]. Although it mainly affects the nervous system, the largest amount of lead is found in the kidneys [9, 22].

Research has shown that this heavy metal can cross the placental barrier in pregnant women who have high levels of it in the blood, causing fetal abnormalities such as low IQ level, encephalopathy, neurological disorders, disruption of calcium levels in nerve cells [3]. Pregnant women exposed to lead, can manifest miscarriage, premature birth, reduced birth weight, stillbirth [10, 22].

After absorption, 99% of lead is bound to the hemoglobin, being circulated through the vascular system to soft tissues, bones, liver, kidneys (organs of lead excretion), hair [3, 10, 19], being stored especially in teeth and bones (where in incorporated into the mineral in place of calcium) [10, 22]. The stored Pb can be reintroduced into the bloodstream, especially during pregnancy, exposing the fetus [10].

Lead can produce lungs disorders, reduced pulmonary function, anemia, liver damage, cardiovascular dysfunction, renal impairment, immunotoxicity, disturbance of the balance free radicals-antioxidant system, cognitive impairments [1, 5, 10, 17]. Anemia occurs as a result of the interaction that this metal has with the important enzymes involved in the synthesis of hemoglobin, enzymes that are responsible and transport oxygen. Thus, by retardation of these enzymes, the hemoglobin concentration is reduced [3]. At high concentration, it can produce high risk of hypertension, gastrointestinal disorders, Alzheimer's disease, kidneys damage, interfere in vitamin D metabolism and thyrotoxicity, by affecting the normal function of thyroid gland, [3, 19, 22].

In people with high levels of lead in the blood, there was an impairment of sexual function, manifested by decreased libido, decreased sperm count and their mobility, changes in sperm composition [3, 22].

Also, this metal can cause changes at cellular level, such as decreased cell viability, cell distortion, reduced cohesion, lipid peroxidation, damage of protein folding, stop structural protein synthesis, intra- and inter-cellular signaling, apoptosis, ionic transportation, especially of calcium, cell adhesion, release of neurotransmitters, inhibiting enzymes activity, inhibits mineral absorption, affecting the activities of mitochondria and endoplasmic reticulum, decreases level of glutathione, generation of reactive oxygen species or reducing antioxidants [1, 3, 17, 22]. Lead has ability to inhibit or mimic the activity of calcium and perturbs their intracellular cycling, may interfere with proteins, can be bound to biological molecules and interfering with their function by various mechanisms [22].

Studies demonstrated that lead can produce genetic damage by mechanisms which include inhibition of DNA synthesis and repair, oxidative damage, being considered by the International Agency for Research on Cancer (IARC) as a probable human carcinogen [22].

Studies performed on animal models have shown altered homeostasis, induced kidney damage, decreases of antioxidant levels, decreased body weight, shortened life span, increases of total protein, albumin, histamine, creatinine, decreased red blood cells count [5, 17].

3.2 Toxicity of cadmium (Cd)

Cadmium is an industrial compound, used in plastic industry, for obtaining plastic stabilizer, but also for production of color pigments, alloys (being a by-product of zinc production), glass production, electroplating industries, welders, rechargeable batteries (about three-fourths of cadmium production). Others important sources include emissions from industrial activities, such as mining or smelting [1, 5, 9, 19, 22, 24].

Exposure to cadmium is achieved by ingestion of food or water, inhalation of contaminated dust, especially for employers which work in primary metal industries or in cadmium-contaminated places, or by smoking cigarettes [3, 5, 10, 19, 22]. Because this metal could not penetrate the skin barrier, dermal exposure not represent a health concern [10].

The main way of exposure for smokers is the smoking, while, for non-smokers, the primary source of exposure is food, such as peanuts, crustaceans and mollusks, leafy vegetables, sunflower seeds, cocoa powder, rice, grains, soybeans, mushrooms, potatoes [3, 10, 22, 25]. Biomonitoring studies have shown that in the case of cigarette smokers, blood and urine levels were generally high, moderate in former smokers and in non-smokers they were reduced [22]. This is related the capacity of this metal to accumulate in high concentrations in tabaco leaves [5, 26]. Their toxicity depends both, the dose of exposure and the exposure time [3]. The percentage of cadmium, absorbed after ingestion is 5–10%, but in diets with a low intake of iron, calcium or protein, the percentage absorbed is higher [10].

In case of occupational workers, in industries which uses this metal, inhalation is the primary way of exposure, so that a percentage of 5–35% of inhaled cadmium is absorbed into the blood, depending the form, particle size, or site of deposition. If this metal reaches the level of the alveoli, its absorption into the blood could be 100% [10]. Their chronic exposure has been associated with changes in pulmonary function, emphysema, decreases in olfactory function [22].

The most toxic form is divalent cadmium ion (Cd^{2+}), which is the most common form and may disturb the basic cellular functions and can cause various side effects [3, 22]. This element can cause side effects even at low concentrations, due to its low excretion rate [17, 27].

Also, it has the capability to replace iron and copper in different cytoplasmic and membrane proteins, and these unbounded substituted metals participate in oxidative stress processes, due to their increased levels [17].

When it binds to cysteine-rich proteins, its concentration inside the body increases 3000 times, forming compounds, such as metallothionein, which can produce hepatotoxicity, nephrotoxicity [1, 3]. If attached to compounds such as histidine, glutamate or cysteine, it can cause iron deficiencies. As a result of exposure, the immune system and endocrine system is affected, even at a young age [3].

Studies have shown that women have higher levels of cadmium than men, and pregnant women have more levels than non-pregnant women. Cadmium does not cross the placental barrier, and remains trapped in it, preventing it from affecting the prenatal exposure of the fetus [3].

The target organs for cadmium are the liver, bones, vascular system, nerve tissues, but especially the kidneys, leading to their damage or malfunction [3, 17, 19, 28]. As their concentration inside the kidneys increases, the rate of calcium excretion from the body is high, which means an increased risk of kidney stones [3, 17, 29]. Also, its

renal excretion causes damage to the renal tubules and tubular disfunction by promoting oxidative stress in proximal tubular cells [3, 17].

In case of acute ingestion, symptoms such as vomiting, vertigo, abdominal pain, burning sensation, muscle cramps, shock, loss of consciousness, nausea, convulsions appear in 15–30 min. Because this heavy metal is a severe pulmonary and gastrointestinal irritant, erosion of the intestinal tract, diseases of pulmonary, hepatic or renal or coma could appear, depending the route of poisoning [22].

The exposure to low levels, may affect the prostatic lipid metabolism and the increasing of the fatty acids used to synthesis of phospholipids, with effects on the composition and functions of the plasma membrane [3].

High levels of cadmium in the blood cause a decrease in bone density, especially in pregnant women. Also, it can produce Itai-itai bone disease, which is characterized by painful degenerative bone disease (such as osteomalacia and osteoporosis), renal tubular abnormalities, calcium and phosphate excretion, lung cancer [5, 10, 30].

Chronic exposure can cause effects such as anemia, emphysema, osteoporosis, renal disorders, anosmia, chronic rhinitis, but also have a depressant effect, by changing the levels of serotonin, norepinephrine or acetylcholine [3, 22].

By accumulating in the pancreas and blood, the both exocrine and endocrine function of the pancreas is affected, resulting in a reduction in serum insulin. It may also affect the pancreas to resisting the secretion of insulin, and producing diabetes type 2. Research has shown that it can affect adipose tissue and can lead to obesity. Research has shown that exposure to this element can alter the balance of pituitary hormones. On reproductive system, Cd can affect the synthesis of testosterone and progesterone, spontaneous abortion, low birth weight, changes and apoptosis of germ cells, reducing of semen quality, damage of DNA of sperm cells, apoptosis of Sertoli cells [3].

Long term exposure to cell, it could transform normal cell into malignant cells. Because it contributes to the development of certain types of cancer, such as lung, prostate, pancreatic or kidney cancer, especially in case of occupational exposure, it has been classified as no. 1 human carcinogen by the International Agency for Research on Cancer USA [3, 5, 17, 22, 31]. Rodent studies have demonstrated the capacity of this metal to causes pulmonary adenocarcinomas or prostatic proliferative lesions, leading to adenocarcinomas [22].

At the cellular level, Cd disrupts the respiratory chain of the mitochondria, involved in transport across cell membranes and cell damage through production of reactive oxygen species (ROS), blocking calcium channels, hinders sulfhydryl enzymes, interacts with some cell ligands, promote lipid peroxidation and protein carbonylation. It also affects oxidative phosphorylation pathways, mitochondrial genes involved in cell apoptosis, reducing the ATP level and the energy production. This heavy metal affects the activity of some antioxidant enzymes, such as glutathione reductase, catalase, glutathione peroxidase. Also, cadmium could interact with DNA and may reduce its binding capacity or repair, DNA damage or disruption of synthesis of nucleic acid or proteins [3, 17, 22, 24].

Animal studies have shown that it can produce disorders in the metabolism of zinc, copper and calcium, being able to decrease their absorption and resulting in low dietary intake [5, 32, 33]. The hepatotoxicity and nephrotoxicity of Cd was also observed, after administration of certain doses of cadmium [5, 33]. At cellular level, changes in cell-cell adhesion, autophagic response, changes in cellular signaling pathways, cell death [5], mitochondrial swelling, decrease in antioxidant levels, increases in urinary proteins, more vacuoles and lysosomes in proximal tubule cells were observed [17].

3.3 Toxicity of arsenic (As)

Arsenic is one of the most important heavy metals, with property of a semi metallic, is found in nature in the form of metalloid (As^0) inorganic and organic form, and arsine (AsH_3) [1, 17, 22, 34]. The main inorganic forms include the trivalent form, arsenite (As^{3+}), and the pentavalent form, arsenate (As^{5+}). Among the organic compounds of arsenic are the methylated metabolites, such as monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and trimethylarsine oxide [9, 22]. Inorganic arsenic compounds, found in water is more toxic than organic compounds, found in seafood, which is less harmful [1, 10, 17, 23, 35]. Studies demonstrated thar trivalent arsenite is 2–10 times more toxic than pentavalent arsenate [22]. The order of increasing toxicity of arsenic compounds is the following, organic arsenicals < metalloid (As^0) < inorganic forms (As^{5+} < As^{3+}) < arsine [5, 36, 37].

Arsenite, which is prevalent and more mobile, has the capability to bind to thiol or sulfhydryl groups of proteins and inactivate more than 200 enzymes, with effects on different organ systems, but also to inhibits the uptake of glucose into cells, fatty acid oxidation, production of acetyl coenzyme A, gluconeogenesis, synthesis of glutathione reductase and thioredoxin reductase. Arsenate can replace phosphate, involved in biological processes, including the transport system [3, 17, 22, 23, 38]. Environmental pollution with this heavy metal, occur as a result of volcanic eruptions, soil erosion or some anthropogenic activities [9, 22]. It is used to obtain industrially products, such as, insecticides, herbicides, fungicides, algicides, smelting, mining, sheep dips, ceramics and glass making, wood preservatives, refining of metallic ores, paints, dye stuffs or for some medicinal treatments for syphilis, yaws, amoebic dysentery, trypanosomiasis [1, 22].

The exposure to elevated levels of inorganic arsenic occurs through ingestion (oral route) of food and water contaminated, inhalation of smoking tobacco, dust or burning smoke from arsenic-treated wood, working in a place where this metal is made or used, dermal contact and parenteral route [5, 10, 22]. Diet, and especially water, is the most important source of exposure, with an intake of about 12–50 μg/day, but the dietary requirement has been suggested to be between 12 and 25 12–50 μg/day [22, 23, 39]. Food sources of arsenic are seafood, poultry, grains (especially rice), bread, cereal products, mushrooms, dairy products [23, 40].

Exposure from air and soil is much smaller, but in areas with a high contamination, the intake through these ways may become significant [22]. Inorganic and organic compounds leave the body through renal excretion. Most of inorganic compounds are eliminated within several days, but some will remain stored for several months or even longer. Organic compounds are eliminated by the body much faster than inorganic arsenic, so most of them will leave the body in a few days [10]. After the absorption in the body, the target organs are lungs, spleen, kidneys, liver, but also, hair, skin and nails, but the last three for long-term accumulation [5].

Researcher showed a strong association between arsenic exposure and increased risks of carcinogenic and systemic health effects, including cardiovascular, dermatologic, nervous, hepatobiliary, renal, gastrointestinal and respiratory diseases [3, 9, 22]. So, in the case of poisoning, the symptoms manifested are abdominal pain, hemolysis, keratosis and hyperkeratosis, edema, gangrene and finally skin cancer [3, 23, 35]. The severity of symptoms varies depending upon the oxidation state and chemical species of arsenic, the solubility, frequency and exposure time, exposure dose, individual susceptibilities, age, gender, genetic and nutritional factors of exposed person [3, 9, 22].

It has been observed that in the case of persons exposed to high concentrations, symptoms such as developmental abnormalities, diabetes, cardiovascular and peripheral vascular disease, pulmonary disease, hearing loss, liver fibrosis, cirrhosis, melanosis, hematologic disorders (anemia, leukopenia, eosinophilia), neurologic and neurobehavioral disorders and different carcinoma have occurred [1, 9, 17, 22, 41, 42].

Long term exposure influences the promotion of carcinogenesis in various tissues or organs, so in areas with higher pollution, was observed a higher mortality rate for different types of cancers, such as kidney, skin, liver, lungs and bladder [3, 9, 10, 22]. For this reason, arsenic and arsenic compounds has been classified as carcinogenic to humans by International Agency for Research on Cancer (IARC) [3, 10]. Also, symptoms like, pigmentation changes, skin lesions, hyperkeratosis, was observed, which may be a precursor to skin cancer. Even at low concentration for a long time, it could change the color of the skin [1, 10]. Chronic arsenic toxicity is termed arsenicosis [1].

At lower concentration, for shorter exposure, arsenic and its compounds may cause nausea and vomiting, reduced production of erythrocytes and leukocytes, abnormal heart beat, damage of blood vessels [1].

This heavy metal could cross the placenta, particularly during early gestation, and affect the fetus, leading to adverse pregnancy outcomes, such as spontaneous abortion, stillbirth, preterm birth, low birth weight), higher infant mortality [5, 10, 43]. Numerous studies demonstrated that in utero or in childhood exposure to this metal, can lead to increases mortality in young adults due to multiple cancers, cardiovascular diseases, kidney failure, lung damage [10, 44], but also negative impact on cognitive developments, intelligence and memory [10, 45].

Their genotoxicity was demonstrated through its capacity to inhibit DNA repair, induce some chromosomal anomalies and DNA damage, sister-chromatid exchanges, arrest cells in mitosis, induce expression of some genes and gene amplification, interfere with formation of micronuclei in different cells, promote oxidative stress, altered growth factors, interfere with cell signaling pathways, inhibition of cell proliferation, promote apoptotic mechanism in various cell (monocytes, T-cells, cancer cells, melanocytes, dermal cells, keratinocytes), mitochondrial disfunctions [5, 17, 22, 46].

In addition to the ability to bind certain structures or to replace some compounds, at cellular level, arsenic compounds could inhibit the mitochondrial enzymes involved in cellular respiration, inactivate some enzymes, such as thiolase and dihydrolipoyl dehydrogenase and affects the oxidative phosphorylation [22].

Animal studies released that arsenic could produce deficits of growth, altered liver and breast milk triglyceride levels [17, 47], decrease of cell viability, induced apoptosis in some cells, increased oxidative stress, increased phosphorylation [17, 48], lower levels of corticosterone receptor, reduced learning and memory [17, 49].

3.4 Toxicity of mercury (Hg)

Mercury or hydrargyrum is a heavy metal which belong to the transition elements series of periodic table [9, 22] and exist in the nature in three chemical forms, such as elemental or metallic or elementary mercury (Hg^0), inorganic mercurous (Hg^{+1}) and mercuric (Hg^{+2}) and organic mercury compound, methylmercury (MeHg or CH3-Hg) and ethylmercury (EtHg or CH3CH2-Hg), the last two being obtained through methylation of inorganic mercuric form by microorganisms found in water and soil [5, 9, 17, 22, 50, 51]. Each chemical form has its own toxicity and chemical properties [9, 22]. Organic Hg compounds are more harmful than inorganic Hg, the

order of increasing toxicity being following: metallic mercury (Hg^0) < inorganic mercuric (Hg^{2+}) < inorganic mercurous (Hg^{1+}) < organic compounds [5]. At room temperature, elementary mercury is a liquid with high vapor pressure and released into nature as Hg vapor, which are more hazardous than liquid form [5, 9, 23].

It is used in numerous industrial processes, including mining (for extraction of gold), electrical industry (switches, thermostats, batteries), in lamp production factories (for fluorescent light bulbs), caustic soda production, measurement instruments (thermometers, manometers, barometers, mercury switches), nuclear reactors, paint industries, antifungal agents for wood processing, fungicides in agriculture (methylmercury and ethylmercury), soaps and some skin lightening creams (as mercury chloride) [1, 5, 22, 23, 52].

This metal can reach into the body through inhalation and ingestion of food contamination, especially of fish and seafood, but also by dental amalgams (which contain over 50% elemental mercury), preventive medical practices, industrial and agricultural operations, occupational operations [17, 22].

The most absorbed chemical species are elementary and methyl mercury (Me-Hg) [5, 22]. Metallic mercury, which is highly lipophilic, is absorbed by lungs (80%) and tissues lining the mouth and then passed into the cell through cell membranes when in oxidized and became inorganic mercuric (Hg^{2+}), highly reactive. The elementary mercury has the capacity to cross the blood-brain barrier and the placental barrier [5, 22], having a higher neurotoxicity compared to inorganic mercury, which passes the cell membrane in a slower rate, but cannot cross the blood brain barrier and placenta [5]. Metallic mercury is slightly absorbed in the gastrointestinal tract, the toxicity in this case being reduced [5].

Methyl mercury is easily absorbed in gastrointestinal tract (95%) and circulated in the body, where bound to thiol groups, such as cysteine, with which it can form compounds able to pass the blood brain barrier [5, 17, 53]. Toxicokinetic of ethylmercury is similar with that of methylmercury [5, 53].

Methyl mercury entered in organism through the consumption of fish [5, 54], is absorbed in the gastrointestinal tract and due to its lipophilicity can pass the blood-brain barrier and placental barrier [22]. Cooking of fish does not diminish or eliminate mercury content [5]. Exposure to methyl mercury can produce mental retardation, cerebral palsy, deafness, blindness, dysarthria (especially at children exposed in utero) [17]. Instead, at higher concentration for short time, this could produce lung damage, nausea, vomiting, skin rashes, increased heart rate and blood pressure. Symptoms of organic mercury poisoning are depression, fatigue, memory problems, headache, tremors, hair loss [1].

Mercury and its compounds excretion rate depends on its oxidation state [10]. Elemental and inorganic mercury is eliminated by the kidney (urine) and minimally through gastrointestinal tract (feces), having a half-life of 30–60 days [10, 55, 56]. Organic compounds are excreted by feces, but are recirculated enterohepatic, in this case the half-life being 70 days.

Major of absorbed mercury accumulates into kidneys (where produce adverse effects on proximal tubules), hair, neurological tissues and liver [5, 22]. Because it accumulates in hair, it represents an index of exposure to methylmercury [5].

Elemental mercury exposure is associated with cough, dyspnea, fever, tremors, polyneuropathy of axonal sensor motor, malaise, gingivitis, delusions, hallucinations, mercurial erythrism, while exposure to inorganic mercury produce insomnia, renal tubular damage, wight loss, erythema, pruritus, hypersalivation, excessive perspiration [17].

Chronic mercury exposure produces neurological disorders, such as ataxia, shyness, tremors, numb limbs, memory problems, inability to speak, irritability, chewing, swallowing, muscle weakness, but also renal system disorders [1, 5, 23, 57]. Patients exposed to higher levels of methylmercury present increased tendon reflex [5, 57]. Low dose mercury can produce effects on neuronal systems, both on developing fetus and adolescent stage [17, 58], but also cell cytotoxicity, oxidative stress, which are associated with neurodegenerative disorders like Alzheimer and Parkinson [17, 51, 59]. At low concentration, it can affect the human endocrine system, through reduced production of thyroid gland hormone, affecting physiological functions of endocrine glands, reduced binding capacity of hormone to receptor, the most affected hormones being adrenaline, estrogen, testosterone and insulin [3].

On reproductive system, studied demonstrated their capacity to produce infertility in both, men and women. In male the spermatogenesis is affected, while in women could affect the levels of progesterone and estrogens, which produce disfunctions in ovaries, irregular menstruation and sloped uterus [5].

Because mercury can pass the placenta during pregnancy, it can affect fetus and can cause various abnormalities of the baby, such as developmental disabilities, dysplasia of the cerebral and cerebral cortexes and neuronal ectopia, especially after exposure to methylmercury [3, 5, 17, 57].

Into the cell, inorganic compounds and methylmercury interact with cysteine residues of proteins, product oxidative stress through generation of reactive oxygen species (ROS), which can produce enzymes, nucleic acid and lipids damage and may proceed to cell death [17]. They can affect the calcium homeostasis, by increasing intracellular calcium through acceleration the influx from extracellular medium and mobilizing intracellular stores [22]. Methylmercury also interact with sulfhydryl (–SH) and selenohydryl (–SeH) groups of the proteins and could produce damage of nucleophilic groups involved in catalytic, binding and transport functions [17]. Inorganic mercury also produces reactive oxygen species (ROS) through affecting oxidative phosphorylation and electron transport [22].

A number of compounds, such as vitamin C, vitamin E, selenium, melatonin and enzymes, including, glutathione reductase, glutathione peroxidase, catalase, superoxide dismutase, can have a protective effect on the body through antioxidant mechanisms to reduce or avoid the formation of reactive oxygen species. Mercury genotoxicity was associated with DNA damage, conformational changes in proteins responsible for DNA repair, genetic mutations, mitotic spindle, chromosomal segregation, action on nucleic acids [22].

3.5 Toxicity of aluminum (Al)

Aluminum, the third most common metal of the earth crust, exist in the environment in only one oxidation state (Al^{3+}). It is naturally present in food, but also in the environment, as silicates, oxides and hydroxides. Aluminum and its compounds are poorly absorbed through ingestion and inhalation, but the rates of absorption are not yet known [1, 10].

The ways in which this metal can reach the body are ingestion, inhalation, dermal contact or drugs [3, 10, 60]. Human exposure takes place through the consumption of drinking water, food and beverages that are high in aluminum content, working in environment with high levels of this metal, hemodialysis, long term intravenous nutrition, cosmetic products, utensils and medicines which contains it, dusty environments [1, 3, 10]. Patients with kidney dialysis are more exposed to this metal,

through contaminated dialysates and phosphate binders [1]. The bioavailability of aluminum from diet is influenced by its form, as well as the presence of other food constituents which help him to form complexes [10].

The primary way of excretion is through urine. Due to the its natural presence and intake from food, all people have some levels in the body, and also in the urine [10]. People suffering from kidney disease has a low rate of elimination from the body, which involves its accumulation in the body, affecting the bones and brain [1, 3]. Also, their accumulation in the body, leading to changes in proximal tubules, such as increases in number and size of lysosomes, damage of mitochondria [3].

After entry to body, aluminum accumulates in soft tissues where interact with proteins and lipids and may produce changes in their structure [3].

In case of poisoning, the principal symptoms are nausea, ulcer of mouth and skin, skin rashes pain, vomiting, diarrhea and arthritic pain [1, 3].

On nervous system, aluminum may produce loss of memory and coordination, problems with balance, neurodegenerative disorders, such as Alzheimer, dementia, Parkinson, sclerosis. The studies demonstrated that higher concentration of aluminum found in different parts of brain could initiate the development of Alzheimer disease in humans [1, 3]. This metal could form a complex with adenosine triphosphate (ATP) from neuronal cells, which can affect their signaling and cause excitotoxicity [3].

Dialysis patients treated with dialysis fluids which contain aluminum, showed neurotoxic effects, while humans exposed to high aluminum dust in the workplace, manifested aluminosis [10, 61].

Humans exposed to higher levels could manifest changes of secondary hyperparathyroidism, adynamic bone disease, osteomalacia, the last two being characterized by low bone remodeling. Their toxicity is associated with lung disorders, anemia, nervous system problems, impaired iron absorption [1]. The accumulation of aluminum in bones impaired the bone formation process, known as osteodystrophy and put antiproliferative effects on osteoblasts [3]. Workers chronically exposed to aluminum, developed contact dermatitis and irritant dermatitis [1].

At cellular level, studies conducted demonstrated that it can disturbs the homeostasis of magnesium, calcium and iron, lower cholinergic elevations, apoptotic death of neuronal cells, inhibition of enzymes involved in DNA repair, inhibition of activity of antioxidant enzymes, cross linking of DNA, affecting cell viability, plasma membrane, microvilli and cell function in cells kidney [3, 62]. This increases the peroxidation of lipids from plasma membrane, by enhancement of lipid hydroperoxides, which can reduce the molecular arrangement of lipoprotein at the surface of membrane, but, also physical and chemical properties change in high density lipid (HDL). Also, aluminum is involved in high production of reactive oxygen species (ROS), which may obstruct normal process of mitochondria, initiation of inflammatory events and accumulation of iron, which induces genotoxicity in neuronal cells and death cells, affects the gene expression through interaction between aluminum and nucleic acid and monophosphate nucleotides [3].

3.6 Toxicity of chromium (Cr)

Chromium exists in environment in oxidation states and from Cr^{+2} to Cr^{+6} [1, 3, 5, 22, 63]. It does not exist in elementary state (Cr^{0}) [3, 22]. Trivalent oxidation state of Cr is considered more stable, followed by Cr^{+4}. The most commonly forms are Cr^{+3} and Cr^{+6}, both oxidation states being toxic to animals, humans and plants [5, 63]. Cr^{+3}

is immobile and insoluble in water, while Cr^{+6} is mobile and highly soluble in water [1, 13]. The solubility of chromium depends on its pH, Cr^{+3} is soluble only in acidic pH, while in neutral and alkaline pH, Cr^{+3} gets precipitated [23].

Environmental contamination with it, occurs by oil burning, catalyst, pigments production, chromium steel, tannery facilities, but also fertilizers and sewage, because is extensively used in several industries, like metallurgy, refractory, tannins, production of paints and pigments, pulp and paper production, wood preservation [1, 9, 22]. Chromium released by the anthropogenic activities in the environment occurs mainly in the hexavalent form [22].

Human exposure occurs through ingestion of food and water which contain, inhalation, especially in case of occupational workers or by dermal contact [5, 64]. Through their bioaccumulation in the body, a variety of affections can appear, such as, dermal, renal, neurological and gastrointestinal diseases, but also development of several types of cancer, on lung, larynx, kidney, testicles, bones, bladder, thyroid [5, 65]. Chromium can affect the reproductive function in men, due to sperm count decline [19]. Ingestion of drinking water containing high level of chromium may cause tumor in stomach [3]. The target organs are lungs, but significant chromium exposure can take place through skin [3, 22].

Occupational exposure to chromium increases the risk of cancer of lung, liver, gastrointestinal tract and central nervous system, while in female workers cause abortion [3, 13, 38]. Excess of chromium can produce thyroid cancer through reduction of requirement level of thyroid hormone in the body, disrupting hormones synthesis and secretion, interfering in its metabolism or interaction with their receptors [3, 66].

Some humans are sensitive to Cr^{3+} and after exposure allergic reactions, including redness and swelling of the skin, can appear. This oxidation state is poorly absorbed by any way, the toxicity being attributable to Cr^{+6} oxidation form [22].

Ingestion of Cr^{+4} can cause irritation and ulcer of stomach and small intestine, anemia, disfunctions of male reproductive system and at high dose produces sever problems on nervous, respiratory and cardiovascular systems, digestive organs, excretory function [3]. Researcher studies demonstrated that high levels in water were associated with cancers of liver, lung and genitourinary system [5, 67].

Cr^{+6} can produce adverse effects on excretory system, reproductive system, asthma, allergy, irritation and ulcers in the stomach and small intestine, anemia, increased mortality due the development of cancer of lung, larynx, kidney, testicular, thyroid, bones [3, 5, 22, 68], and in case of excess inhalation appear irritation and ulcer of nose [3, 22]. Also, it can reduce the DNA replication, damage DNA transcription, chromosome aberrations and affection of RNA [3, 5, 69]. Inside the cell, Cr^{+6} is converted into Cr^{+5}, as intermediate, and then in Cr^{+3}, which can form complexes with proteins and DNA [1, 3]. Cr^{+5} and other intermediate compounds, including reactive species of carbon and oxygen, that form during the reduction of Cr^{+6} to Cr^{+3}, can react with DNA [3]. When hexavalent cation reacts with cellular reductants, Cr^{+4} and Cr^{+3} can also be obtained. Cr^{+6} was classified as group I occupational carcinogen [5, 70].

In cell, mechanism of chromium toxicity generates reactive oxygen species (ROS), which bring cell apoptosis, damage of DNA, genomic instability [3, 5, 71], suppression of DNA synthesis and genes expression [3], but also induces hyperexpression of some antioxidant enzymes, such as, peroxidase, catalase, superoxide dismutase [23].

Their carcinogenicity and toxicity depend of concentration, time of exposure, tissue and cell type [5, 72], route of exposure (ingestion, inhalation or dermal) [10], generation of free radicals [5, 73], oxidation state and its reactivity [5, 10, 22],

3.7 Toxicity of copper (Cu)

Copper is a trace element, component of many enzymes, including ceruloplasmin and cytochrome C oxidase, tyrosinase and dopamine beta-hydrolase, zinc-copper superoxide dismutase (antioxidant defense) and others, having function in transport functions, detoxification, antioxidant defense, immune function, pigmentation and melanin production [10, 74]. When it is present in high levels in the body, it may become toxic [3].

Human exposure take place through its release from water carrying pipes, fungicides, cooking utensils, birth control tablets, food. Copper has the highest redox activity, which lead to production of reactive oxygen species. Also, it binds to thiol groups of proteins and cause changes in liver enzymes involved in biotransformation processes [3].

At cell level, it can change the activity of natrium (Na^+)/potassium (K^+) ATP-ase and change of plasma membrane permeability, due the affection of the natrium/potassium pumps and increases of level of natrium in cytoplasm [3]. Large amounts of copper are stored in the liver [74], while the target organs are nervous system organs, including ganglia, neurons, cerebellum and hippocampus [3].

Excess of copper in the body or hypercupremia, occurs naturally during pregnancy, but also by chronic exposure to it, being associated with a number of diseases including Wilson's disease, hepatic disorders (cirrhosis, hepatitis, gastroenteritis), neurodisorders, hyperceruplasmin [3, 10, 74]. Neurodisorders produced by chronic exposure to copper include neurodegenerative disorders, like Alzheimer and Parkinson, but also Huntington disease, amyotrophic lateral sclerosis [3], cognitive impairment, personality and behavioral changes [74].

Cells studies demonstrated that copper is accumulated in some cancer cell, such as colon cancer cell, ovarian cancer cells, breast cancer cell, more than in normal cells. Also, at cellular level, it can cause oxidative damage of DNA, their reduction can be made by use of Cu specific chelating agents [3].

Hypocupremia or copper deficiency are represented by serum level less than normal value of 0.64–1.56 μg/mL. Extreme hypocupremia could produce Menkes disease, known as Menkes kinky hair syndrome, a genetic disorder, characterized by steely hair, due to a mutation of the transport protein mediating the copper uptake from the intestine, but also by progressive neurological deterioration and early childhood death [10].

3.8 Toxicity of zinc (Zn)

Another trace element, zinc, is involved in over 200 enzymes, with action in immune system, catalytic and structural structures, but also, in processes like synthesis and degradation of some components, including lipids, proteins, carbohydrates, nucleic acids, transcription and translation of polynucleotide, genetic expression, cell proliferation and differentiation, normal growth and development during pregnancy, childhood, adolescence, reduced growth rate and impaired resistance to infection [10].

Exposure to zinc of human is made by inhalation of zinc vapors and ingestion of a large overdose of zinc supplements, which contain zinc sulfate, overusing denture cream, but also by consumption of contaminated food and water [75, 76].

Zinc poisoning, at intakes higher than 100 mg/day, has been associated with abdominal pain, vomiting, diarrhea, nausea.

Long term exposure can cause malabsorption of copper and in case of diabetics, it can affect immune function associated with diabetes mellitus [10]. Severe toxicity

present symptoms like kidney injury, pancreatic function damage, liver failure, dehydration and acute gastrointestinal bleed, septic shock, lethargy, sideroblastic anemia and dizziness [74, 76]. Zinc inhalation could produce dyspnea, airway inflammation and acute respiratory distress symptom, especially in case of occupational exposure [76].

Because this metal could interfere in copper absorption in the gastrointestinal tract, leading to copper deficiency [10], chronic exposure can cause polyneuropathy and can affect bone marrow [76].

3.9 Toxicity of nickel (Ni)

Nickel is an essential trace element for plant, animals and human, but also a chemical pollutant which exist in several oxidation states, but most common is Ni^{2+}. In the body, it is involved in activation of some enzymes, in protein structure and function, in prolactin production [3, 10].

Environmental contamination with nickel comes from natural sources, like volcanic emissions, weathering of soils, but also from industry, being used in catalysts for automobile, electroplating, electroforming, jewelry production, medical prostheses, production of nickel-cadmium batteries, cast coins [19].

This metal can reach the body through ingestion of contaminated water and food, inhalation of dust or smoking cigarettes and dermal contact, leading to increases level of Ni in blood, urine and body tissues. However, less than 10% of ingested nickel is absorbed by gastrointestinal tract [3, 10].

It can pass through plasma membrane through diffusion, calcium transport channels and phagocytosis, is circulated to various tissues, where bind with albumin, histidine and macroglobulin. In case of nickel, the target organs are kidneys, bons, lungs, liver, brain and glands of endocrine system, but it is not accumulated in those, being excreted outside [3].

Nickel exposure can produce disorders of liver, kidney, spleen, brain and tissues, but also vesicular eczema, nasal and lung cancer. Also, it interferes in iron resorption, which lead to anemia, disturb the incorporation of calcium into skeleton, causing parakeratosis damage [10]. On reproductive system, this metal affects the quality of semen and cause abnormalities in it, including the tail of sperms [3].

Occupational exposure can cause allergic dermatitis, known as “nickel allergy”. In case of dermal contact, skin rash or allergic dermatitis appear, due to wearing of nickel-plated jewelry. Women are more sensible to nickel than men, especially in pregnant women which work in metallurgic industry and their babies hence structure abnormalities [3, 10].

At cellular level, it can produce breaking of DNA strands, cross linking of DNA protection, DNA oxidation, nucleotides removal, genes mutations, modifications of chromatids, binding to enzymes involved in DNA repair and degradation of protein, generation of ROS, enhances lipid peroxidation, affecting calcium and sulfhydryl homeostasis, degradation of glutathione [3].

4. Conclusions

Heavy metal pollution is global treat and increasing day by day, due to many natural and anthropogenic activities, which disturb natural composition of soil, water and air, but also of living organisms [3, 23].

These metals can enter the body from sources of contamination by ingestion, inhalation or dermal contact, where they are absorbed, then bioaccumulated in various organs or target tissues, for different periods of time [5, 22]. The most important is the occupational exposure for those working in industries where these metals are produced or used, which can be reduced by various engineering solutions [1].

Heavy metals can affect organs and their functions, causing adverse effects in humans like, cardiovascular, neurologic, gastrointestinal, immunologic, endocrine, reproductively disorders, but also various types of cancer, including lungs, bladder, skin. But, the severity of those side effects depends on chemical state, time and dose of exposure, solubility [22].

In order to prevent exposure to these metals, as well as the occurrence of health problems, it is important to establish safety limits for different matrices [19].

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References

[1] Jaishankar M, Tseten T, Anbalagan N, Mathew BB, Beeregowda K. Toxicity, mechanism and health effects of some heavy metals. Interdisciplinary Toxicology. 2014;**7**(2):60-72. DOI: 10.2478/intox-2014-0009

[2] Ali H, Khan E, Ilahi I. Environmental chemistry and ecotoxicology of hazardous heavy metals: Environmental persistence, toxicity and bioaccumulation. Journal of Chemistry. 2019;**2019**:6730305. DOI: 10.1155/2019/6730305

[3] Rehman AU, Nazir S, Irshad R, Tahir K, Ur Rehman K, Ul Islam R, et al. Toxicity of heavy metals in plants and animals and their uptake by magnetic iron oxide nanoparticles. Journal of Molecular Liquids. 2021;**321**:114455. DOI: 10.1016/j.molliq.2020.114455

[4] Masindi V, Muedi KL. Environmental contamination by heavy metals. In: Saleh HEDM, Aglan RF, editors. Heavy Metals. Chichester: IntechOpen; 2018. pp. 115-133. DOI: 10.5772/intechopen.76082

[5] Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic mechanisms of five heavy metals: Mercury, lead, chromium, cadmium and arsenic. Frontiers in Pharmacology. 2021;**12**:643972. DOI: 10.3389/fphar.2021.643972

[6] Rai PK, Lee SS, Zhang M, Tsang YF, Kim KH. Heavy metals in food crops: Health risks, fate, mechanisms and management. Environment International. 2019;**125**:365-385. DOI: 10.1016/j.envint.2019.01.067

[7] Edelstein M, Ben-Hur M. Heavy metals and metalloids: Sources, risks and strategies to reduce their accumulation in horticultural crops. Scientia Horticulturae. 2018;**234**:431-444. DOI: 10.1016/j.scienta.2017.12.039

[8] Koller M, Saleh HM. Introductory chapter: Introducing heavy metals. In: Saleh HEDM, Aglan RF, editors. Heavy Metals. Vol. 2018. Chichester: IntechOpen; 2018. pp. 3-11. DOI: 10.5772/intechopen.74783

[9] Kaur R, Sharma S, Kaur N. Heavy metals toxicity and the environment. Journal of Pharmacognosy and Phytochemistry. 2019;**SP1**:247-249

[10] Aliasgharpour M. Trace elements in human nutrition (II)—An update. International Journal of Preventive Medicine. 2020;**11**(2):1-17. DOI: 10.4103/ijpvm.IJPVM_48_19

[11] Frieden E. New perspective on the essential trace element. Journal of Chemical Education. 1985;**62**(11):917-923

[12] Kulkarni N, Kalele K, Kulkarni M, Kathariya R. Trace elements in oral health and disease: An updated review. JDRR. 2014;**1**(2):100-104. DOI: 10.4103/2348-2915.133959

[13] Bhattacharya PT, Misra SR, Hussain M. Nutritional aspects of essential trace elements in oral health and disease: An extensive review. Scientifica. 2016;**2016**:5464373. DOI: 10.1155/2016/5464373

[14] Aliasgharpour M, Marjan RF. Trace elements in human nutrition: A review. The Journal of Medical Investigation. 2013;**2**(3):115-128. DOI: 10.4103/ijpvm.IJPVM_48_19

[15] Prashanth L, Kattapagari KK, Chitturi RT, Baddam VRR, Prasad LK. A review on role of essential trace elements in health and disease. Journal Dr.NTR University of Health Sciences. 2015;**4**(2):75-85. DOI: 10.4103/2277-8632.158577

[16] He Z, Shentu J, Yang X, Baligar VV, Zhang T, Stoffella PJ. Heavy metal contamination of soils: Sources, indicators, and assessment. Journal of Environmental Indicators. 2015;**9**:17-18

[17] Wu X, Cobbina SJ, Mao G, Xu H, Zhang Z, Yang L. A review of toxicity and mechanism of individual and mixtures of heavy metals in the environment. Environmental Science and Pollution Research. 2016;**23**:8244-8259. DOI: 0.1007/s11356-016-6333-x

[18] Musilova J, Arvay J, Vollmannova A, Toth T, Tomas J. Environmental contamination by heavy metals in region with previous mining activity. Bulletin of Environmental Contamination and Toxicology. 2016;**97**:569-575. DOI: 0.1007/s00128-016-1907-3

[19] Al-Lami AMA, Khudhaier SR, Aswad OA. Effects of heavy metals pollution on human health. Annals of Tropical Medicine and Public Health. 2020;**23**:1-4. DOI: 10.36295/ASRO.2020.231125

[20] Zeng F, Qiu B, Wu X, Niu S, Wu F, Zhang G. Glutathione-mediated alleviation of chromium toxicity in rice plants. Biological Trace Element Research. 2012;**148**:255-263. DOI: 10.1007/s12011-012-9362-4

[21] Najeeb U, Ahmad W, Zia MH, Malik Z, Zhou W. Enhancing the lead phytostabilization in wetland plant *Juncus effusus* L. through somaclonal manipulation and EDTA enrichment. Arabian Journal of Chemistry. 2014;**14**(2):3310-3317. DOI: 10.1016/j.arabjc.2014.01.009

[22] Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metals toxicity and the environment. EXS. 2012;**101**:133-164. DOI: 10.1007/978-3-7643-8340-4_6

[23] Pratush A, Kumar A, Hu Z. Adverse effect of heavy metals (As, Pb, Hg, and Cr) on health and their bioremediation strategies: A review. International Microbiology. 2018;**21**:97-106. DOI: 10.1007/s10123-018-0012-3

[24] Rashid K, Sinha K, Sil PC. An uppdate on oxidative stress-mediated organ pathophysiology. Food and Chemical Toxicology. 2013;**62**:584-600. DOI: 10.1016/j.fct.2013.09.026

[25] Chunhabundit R. Cadmium exposure and potential health risk from foods in contaminated area, Thailand. Toxicology Research. 2016;**32**(1):65-72. DOI: 10.5487/tr.2016.32.1.065

[26] Proshad R, Zang D, Uddin M, Wu Y. Presence of cadmium and lead in tobacco and soil with ecological and human health risks in Sichuan province China. Environmental Science and Pollution Research. 2020;**27**:18355-18370. DOI: 10.1007/s11356-020-08160-1

[27] Pretto A, Loro VL, Morsch VM, Moraes BS, Menezes C, Santi A, et al. Alterations in carbohydrate and protein metabolism in silver catfish (*Rhamdia quelen*) exposed to cadmium. Ecotoxicology and Environmental Safety. 2014;**100**:188-192. DOI: 10.1016/j.ecoenv.2013.11.004

[28] Tsutsumi T, Ishihara A, Yamamoto A, Asaji H, Yamakawa S, Tokumura A. The potential protective role of lysophospholipid mediators in nephrotoxicity induced by chronically

exposed cadmium. Food and Chemical Toxicology. 2014;**65**:52-62. DOI: 10.1016/j.fct.2013.12.019

[29] Hambach R, Lison D, D'Haese PC, Weyler J, De Graef E, De Schryver A, et al. Co-exposure to lead increases the renal response to low levels of cadmium in metallurgy workers. Toxicology Letters. 2013;**222**:213-218. DOI: 10.1016/j.toxlet.2013.06.218

[30] Nishijo M, Nakagawa H, Suwazono Y, Nogawa K, Kido T. Causes of death in patients with Itai-itai diseases suffering from severe chronic cadmium poisoning: A nested case-control analysis of follow-up study in Japan. BMJ Open. 2017;**7**(7):e015694. DOI: 10.1136/bmjopen-2016-015694

[31] Kim TH, Kim JH, Le Kim MD, Suh WD, Kim JE, Yeon HJ. Exposure assessment and safe intake guidelines for heavy metals in consumed fishery products in the Republic of Korea. Environmental Science and Pollution Research International. 2020;**27**:33042-33051. DOI: 10.1007/s11356-020-09624-0

[32] Borowska S, Brzóska M, Galażyn-Sidorczuk M, Rogalska J. Effect of an extract from *Aronia melanocarpa* L. berries on boy status of zinc and cooper under chronic exposure to cadmium: An in vivo experimental study. Nutrients. 2017;**9**(12):1374. DOI: 10.3390/nu9121374

[33] Fay MJ, Alt LAC, Ryba D, Salamah R, Peach R, Papaeliou A. Cadmium nephrotoxicity is associated with altered microRNA expression in the rat renal cortex. Toxics. 2018;**6**(1):16

[34] Mulware SJ. Trace elements and carcinogenicity: A subject in review. 3 Biotech. 2013;**3**(2):85-96. DOI: 10.1007/s13205-012-0072-6

[35] Parmar M, Thakur LS. Heavy metal Cu, Ni and Zn: Toxicity, health hazard and their removal techniques. International Journal of Plant, Animal and Environmental Sciences. 2013;**3**(3):143-157

[36] Sattar A, Xie S, Hafeez MA, Wang X, Hussain HI, Iqbal Z. Metabolism and toxicity of arsenical in mammals. Environmental Toxicology and Pharmacology. 2016;**48**:214-224. DOI: 10.1016/j.etap.2016.10.020

[37] Kuivenhoven M, Mason K. Arsenic (Arsine) Toxicity. Treasure Island. FL: StatPearls Publishing;

[38] Yang L, Li X, Chu Z, Ren Y, Zhang J. Distribution and genetic diversity of the microorganisms in the biofilter for the simultaneous removal of arsenic, iron and manganese from simulated groundwater. Bioresource Technology. 2014;**156**:384-388. DOI: 10.1016/j.biortech.2014.01.067

[39] Mahmood A, Malik RN. Human health risk assessment of heavy metals via consumption of contaminated vegetables collected from different irrigation sources in Lahore, Pakistan. Arabian Journal of Chemistry. 2014;**7**(1):91-99. DOI: 10.1016/j.arabjc.2013.07.002

[40] Cheyns K, Waegeneers N, De Wiele TV, Ruttens A. Arsenic relies from foodstuff upon food preparation. Journal of Agricultural and Food Chemistry. 2017;**65**(11):2443-2453. DOI: 10.1021/acs.jafc.6b05721

[41] Ahmed MK, Habibullah-Al-Mamun M, Parvin E, Akter MS, Khan MS. Arsenic induced toxicity and histopathological changes in gill and liver tissue of freshwater fish, tilapia (*Oreochromis mossambicus*). Experimental and Toxicologic Pathology. 2013;**65**:903-909. DOI: 10.1016/j.etp.2013.01.003

[42] He J, Wang M, Jiang Y, Chen Q, Xu S, Xu Q, et al. Chronic arsenic exposure and angiogenesis in human bronchial epithelial cells via the ROS/miR-199a-5p/HIF-1α/COCS-2 pathway. EHP. 2014;**122**(3):255-261. DOI: 10.1289/ehp.1307545

[43] Quansah R, Armah FA, Essumang DK, Luginaah I, Clarke E, Marfoh K, et al. Association of arsenic with adverse pregnancy outcomes/infant mortality: A systematic review and meta-analysis. Environmental Health Perspectives. 2015;**123**:412-421. DOI: 10.1289/ehp.1307894

[44] Farzan SF, Karagas MR, Chen Y. In utero and early life arsenic exposure in relation to long-term health and disease. Toxicology and Applied Pharmacology. 2013;**272**:384-390. DOI: 10.1016/j.taap.2013.06.030

[45] Tolins M, Ruchirawat M, Landrigan P. The developmental neurotoxicity of arsenic: Cognitive and behavioral consequences of early life exposure. Annals of Global Health. 2014;**80**:303-314. DOI: 10.1016/j.aogh.2014.09.005

[46] Mochizuki H. Arsenic neurotoxicity in humans. International Journal of Molecular Sciences. 2019;**20**(14):3418. DOI: 10.3390/ijms20143418

[47] Rahman MK, Choudhary MI, Arif M, Morshed MM. Dopamine-β-hydroxylase activity and levels of its cofactors and other biochemical parameters in the serum of arsenicosis patients of Bangladesh. International Journal of Biomedical Sciences. 2014;**10**:52-60

[48] Rai NK, Ashok A, Rai A, Tripathi S, Nagar GK, Mitra K, et al. Exposure to As, Cd and Pb-mixture impairs myelin and axon development in rat brain, optic nerve and retina. Toxicology and Applied Pharmacology. 2013;**273**:424-258. DOI: 10.1016/J.TAAP.2013.05.003

[49] Ramsey KA, Foong RE, Sly PD, Larcombe AN, Zosky GR. Early life arsenic exposure and acute and long-term responses to influenza A infection in mice. Environmental Health Perspectives. 2013;**121**:1187-1193. DOI: 10.1289/ehp.1306748

[50] Li R, Wu H, Ding J, Fu W, Gan L, Li Y. Mercury pollution in vegetables, grains and soils from areas surrounding coal-fired power plants. Scientific Reports. 2017;**7**:1-9. DOI: 10.1038/srep46545

[51] Carocci A, Rovito N, Sinicropi MS, Genchi G. Mercury toxicity and neurodegenerative effects. In: Whitacre DM, editor. Reviews of Environmental Contamination and Toxicology. 1st ed. Vol. 229. Switzerland: Springer; 2014. 1-18 p. DOI: 10.1007/978-3-319-03777-6_1

[52] Morais S, Costa FG, Pereira ML. Heavy metals and human health. In: Oosthuisen J, editor. Environmental Health—Emergencies Issues and Practice. Chichester: IntechOpen; 2012. pp. 227-246

[53] Bridges CC, Zalups RK. Mechanisms involved in the transport of mercuric ions in target tissues. Archives of Toxicology. 2017;**91**(1):63-81. DOI: 10.1007/s00204-016-1803-y

[54] Moriarity RJ, Liberda EN, Tsuji LJS. Subsistence fishing in the Eeyou Istchee (James Bay, Quebec, Canada): A regional investigation of fish consumption as a route of exposure to methylmercury. Chemosphere. 2020;**258**:127413. DOI: 10.1016/j.chemosphere.2020.127413

[55] Caito SW, Jackson BP, Punshon T, Scrimale T, Grier A, Gill SR. Variation

in methylmercury metabolism and elimination status in humans following fish consumption. Toxicological Sciences. 2018;**161**:443-453. DOI: 10.1093/toxsci/kfx226

[56] Bjørklund G, Dadar M, Mutter J, Aaseth J. The toxicology of mercury: Current research and emerging trends. Environmental Research. 2017;**159**:545-554. DOI: 10.1016/j.envres.2017.08.051

[57] Dos Santos AA, Chang LW, Liejun Guo G, Aschner M. Chapter 35—Fetal Minamata disease: A human episode of congenital methylmercury poisoining. In: Slikker W, Paule MG, Whang C, editors. Handbook of Developmental Neurotoxicology. 2nd ed. Cambridge, MA: Academic Press; 2018. pp. 399-406

[58] Kovacic P, Somanathan R. Recent developments in the mechanism of teratogenesis-electron transfer, reactive oxygen species, and antioxidants. In: Laher I, editor. Systems Biology of Free Radicals and Antioxidants. 1th ed. Chichester: Springer; 2014. pp. 567-580. DOI: 10.1007/978-3-642-30018-9_39

[59] Goldman SM. Environmental toxins and Parkinson's disease. Annual Review of Pharmacology and Toxicology. 2014;**54**:141-164. DOI: 10.1146/annurev-pharmtox-011613-135937

[60] Nampoothiri M, John J, Kumar N, Mudgal J, Nampurath GK, Chamallamudi MR. Modulatory role of simvastatin against aluminum chloride-induced behavioral and biochemical changes in rats. Behavioural Neurology. 2015;**2015**:210169. DOI: 10.1155/2015/210169

[61] Klotz K, Weistenhöfer W, Neff F, Hartwig A, Thriel CA, Drexler H. The health effects of aluminum exposure. Deutsches Ärzteblatt International. 2017;**114**:653-659. DOI: 10.3238/arztebl.2017.0653

[62] Maya S, Prakash T, Madhu KD. Multifaced effects of aluminum in neurodegenerative diseases: A review. Biomedicine & Pharmacotherapy. 2016;**83**:746-754

[63] Shekhawat K, Chatterjee S, Joshi B. Chromium toxicity and its health hazard. International Journal of Advanced Research. 2015;**3**(7):167-172

[64] Nickens KP, Patierno SR, Ceryak S. Chromium genotoxicity: A double-edged sword. Chemico-Biological Interactions. 2010;**188**(2):276-288. DOI: 10.1016/j.cbi.2010.04.018

[65] Fang Z, Zhao M, Zhen H, Chen L, Shi P, Huang Z. Genotoxicity of tri-and hexavalent chromium compounds in vivo and their modes of action an DNA damage in vitro. PLoS One. 2014;**9**(8):e103194. DOI: 10.1371/journal.pone.0103194

[66] Vigneri R, Malandrino P, Giani F. Heavy metals in the volcanic environment and thyroid cancer. Molecular and Cellular Endocrinology. 2017;**457**:73-80

[67] Linos A, Petralias A, Christophi CA, Christoforidou E, Kouroutou P, Stoltidis M. Oral ingestion of hexavalent chromium through drinking water and cancer mortality in an industrial area of Greece—An ecological study. Environmental Health. 2011;**10**(1):50. DOI: 10.1186/1476-069x-10-50

[68] Deng Y, Wang M, Tian T, Lin S, Xu P, Zhou L. The effect of hexavalent chromium on the incidence and mortality of human cancers: A meta-analysis based on published epidemiological cohort studies. Frontiers in Oncology. 2019;**9**:24. DOI: 10.3389/fonc.2019.00024

[69] Wise SS, Wise JP. Chromium and genomic stability. Mutation Research. 2012;**733**(1-2):78-82. DOI: 10.1016/j.mrfmmm.2011.12.002

[70] Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: An update from the IARC monographs. Occupational and Environmental Medicine. 2018;**75**(8):593-603. DOI: 10.1136/oemed-2017-104944

[71] Pavesi T, Moreira JC. Mechanisms and individuality in chromium toxicity in humans. Journal of Applied Toxicology. 2020;**40**:1183-1197. DOI: 10.1002/jat.3965

[72] Ferreiera LMR, Cunha-Oliviera T, Sobral MC, Abreu PL, Alpoim MC, Urbano AM. Impact of carcinogenic chromium on the cellular response to proteotoxic stress. International Journal of Molecular Sciences. 2019;**20**(19):4901. DOI: 10.339/ijms20194901

[73] De Loughery Z, Luczak MW, Zhitkovich A. Monitoring Cr intermediates and reactive oxygen species with fluorescent probes during chromate reduction. Chemical Research in Toxicology. 2014;**27**(5):843-851. DOI: 10.1021/tx500028x

[74] Strachan S. Trace elements. Current Anaesthesia & Critical Care. 2010;**21**:44-48

[75] Rahimzadeh MR, Kazemi S, Moghadadamnia AA. Zinc poisoning—Symptoms, causes, treatments. Medicinal Chemistry. 2020;**20**(15):1489-1498. DOI: 10.2174/1389557520666200414161944

[76] Agnew UM, Slesinger TL. Zinc Toxicity. Florida, USA: StatPearls Publishing; 2021