Chapter 5

Effect of Some Heavy Metals (Cobalt and Cadmium) on Biochemical Events

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Abstract

Heavy metals have been spreading into the atmosphere and soil through human activities and natural means since ancient times. Earthquakes, volcanic eruptions, floods, etc. Heavy metals entering surface and subsurface waters for various reasons spread throughout the ecosystem. But natural spread also has its limits. Water and air pollutants from industrial activities are more likely to be chemically released into the environment. Industrialization has led to heavy metal pollution, which has increased over time. We are exposed to more than 35 metals in our external environment, 23 of which are heavy metals. The definition of heavy metal is used for metals with a density above 5 g/cm^3. Lead (Pb), cadmium (Cd), chromium (Cr), iron (Fe), cobalt (Co), copper (Cu), nickel (Ni), mercury (Hg) and zinc (Zn) are frequently encountered. Heavy metals are released into the atmosphere from a variety of sources and through various process steps. Heavy metals entering the atmosphere from various sources can affect the ecological balance by mixing with the soil, surface waters, and even groundwater through dry and wet accumulation.

1. INTRODUCTION

Toxic metals can be defined as heavy metals regardless of their atomic weight or density (Singh et al., 2011). Density is often considered the determining factor, and metals with a density above 5 g/cm^3 are defined as heavy metals (Järup, 2003). Heavy metals are a group of environmental chemicals that are ubiquitous and non-biodegradable (Wu et al., 2016).

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Pollution of the biosphere with heavy metals is a serious problem for the world. The release of these metals into the environment has increased significantly, mainly due to human activities related to fossil fuel use, ore mining and processing, municipal waste, fertilizers, pesticides and urban wastewater (Basile et al., 2012).

Assessment of the risks of chemicals to humans is based on the assumption that these chemicals are genotoxic or non-genotoxic. Genotoxic carcinogens and their metabolites are thought to act through a mechanism of action that involves direct and possibly irreversible covalent binding to DNA, whereas non-genotoxic carcinogens or their metabolites are thought to act through a mechanism of action that involves covalent binding to DNA. As noted in the risk and hazard definitions above, for risk assessment purposes, lifetime exposure to genotoxic carcinogens at threshold or no-potential-effect doses is a linear "low-dose response." The threshold below which no significant evoked effects are observed. It is considered a non-genotoxic carcinogen. This suggests that homeostatic mechanisms can compensate for biological perturbations caused by low intake levels, and that structural or functional changes that could lead to adverse effects, including cancer, are observed only at higher intake levels (Dorne et al., 2011).

Heavy metals affect the human body by causing the production of reactive oxygen species (ROS) and contributing to oxidative stress toxicity. This may affect some enzymes, organelles and components involved in metabolism, detoxification and damage repair, leading to DNA damage, carcinogenesis or apoptosis (Tchounwou et al., 2012). This damage, which occurs during intracellular metabolic processes, affects organs and systems, causing kidney, cardiovascular, developmental and neurological diseases, reproductive disorders and various types of cancer (Goyer and Clarkson, 1996).

1.1 Heavy Metals

"Heavy metals" are metals with a density of 5 g/cm^3 or more, which have been used since ancient times when humans began to process metals. This allows 53 out of 90 naturally occurring elements to be identified as heavy metals (Abernathy et al., 1999; Holleman, 2019). Metals are elements that readily donate electrons to form bright cations with characteristic colors. 84 of the 118 elements in the periodic table have metallic properties. Most metals are used in industry due to their good electrical and thermal conductivity and good machinability. Heavy metals are generally defined as metals with a density above 5 g/cm^3, but in medicine, this definition is expressed as metals that have toxic effects on biological systems, regardless of the atomic weight of the element. There are more than 60 metals in this group, including lead, cadmium, chromium, iron, cobalt, selenium, copper, nickel, mercury and zinc (Öztoprak, 2018).

All soils contain almost every metal on the periodic table, but the proportions of metals in soil vary greatly. Heavy metals in soil;

1) It binds to the crystal structure of primary and secondary minerals,

2) It binds to the surface of secondary minerals such as clay, oxide, carbonate,

3) It binds to organic matter in the soil and

4) They occur free and as ions and are water-soluble organic and inorganic compounds (Peters, 1987; Alloway, 2013; Davidson, 2013; Young, 2013).

However, heavy metals are generally found stable on Earth as compounds containing carbonates, phosphates, silicates and sulphides (Rose et al., 1979; Kahvecioğlu et al., 2003; Young, 2013). However, thanks to human interventions such as pH, temperature, soil biology, agricultural methods used, products grown, new chemicals added to the soil and irrigation, heavy metals that are tightly bound to soil minerals can be converted into soil minerals. It can transform into forms that can be absorbed by minerals (Brümmer and Helms, 1983; Jorgensen, 1993; McLaughlin et al., 1994; Cieśliński et al., 1996; Weggler et al., 2004. Jiang et al., 2008).

Naturally occurring heavy metals on Earth are released from local areas to various environmental regions through natural events such as volcanic eruptions, atmospheric precipitation, rock collapse, sea salt dispersion, forest fires, erosion and wind (Ali et al., 2021). Anthropogenic releases of heavy metals date back to ancient times, when they were used for various purposes such as jewelry, hookahs, and weapons, and have been used for centuries without any known biological effects on humans. Their increasing use with the age of industrialization has led to a rapid increase in their distribution and increased contact with living organisms. Compared to natural processes, anthropogenic activities release three times more chromium and arsenic, six times more lead and mercury, eight times more cadmium and 19 times more selenium into the soil (Kahvecioğlu et al., 2003). The industrial sectors that most effectively emit heavy metals into the environment include the steel industry, waste incineration and power plants, fertilizer industry, chlor-alkali industry and glass manufacturing (Kahvecioğlu et al., 2003).

A significant portion of heavy metals in industrial wastewater is found in sewage sludge, and the dissolved portion ultimately flows into surface waters and oceans. From there, heavy metals mix with drinking water, air and soil and enter the food chain. Since heavy metals, which accumulate from the first step of the food chain to the top, have very long half-lives and cannot be easily metabolized, they tend to accumulate in the tissues after entering the human body through breath, skin and mouth (Kahvecioğlu et al., 2003; Bakar and Baba, 2009). Heavy metals show their effects by binding to the sulfhydryl groups of enzymes and proteins and forming reactive oxygen species (ROS). Active oxygen species that reduce the functionality of important macromolecules also cause oxidative stress. Oxidative stress can be followed by disruption of cell membrane structures, inhibition of enzymes and proteins, structural changes, DNA damage, apoptosis and carcinogenesis (Babali-mood et al., 2021).

While heavy metals accumulate and affect target organs in the body, they also affect many metal-sensitive organs and systems. These effects include organ dysfunctions, metabolic disorders, changes in hormonal effects, congenital diseases, immune system dysfunctions, cancer, etc. (Öztoprak, 2018; Babali-mood et al., 2021). Heavy metals are found in very low concentrations in the body and are therefore considered trace elements. Trace elements are divided into physiological and toxic elements according to their presence in the body. Various physiological trace elements such as copper (Cu), selenium (Se), zinc (Zn), molybdenum (Mo), manganese (Mn) and cobalt (Co) play important roles as cofactors in some enzymes, vitamins and hormones. These physiological trace elements must be present in the body at a certain concentration (1 to 10 ppm (mg/L)), and their deficiency not only causes various diseases but, if necessary, can also cause toxic substances such as heavy metals to remain in the body. Toxic heavy metals such as cadmium (Cd), lead (Pb), mercury (Hg), arsenic (As) and chromium (Cr) have no important function in the body and can harm humans even at very low concentrations. Toxic (1-10 ppb (μg/L)). These are metals that have toxic effects on the body (Tchounwou et al., 2012; Öztoprak, 2018).

1.2 Heavy Metal Sources and Ways of Distribution in Nature

Sources of heavy metals occur naturally and are not due to human influence. These metals have always entered our world through meteorites from the formation of the Earth to the present day, and they continue to enter our world in the same way, albeit to a lesser extent. While the Earth was still a mass of lava, due to its density, these metals turned into liquid magma and a significant portion of it accumulated in the center of the Earth. Some of it remained in the magma and mantle layers. The accumulation of heavy metals in the Earth's crust continued as meteor showers continued to impact the Earth even after cooling began (Photos, 1989; Kabata-Pendias and Pendias, 2000). In addition, heavy metals from magma and mantle layers still reach the earth's surface, especially through volcanic eruptions, earthquakes and rock fractures, and are dispersed by precipitation (Lahd Geagea et al., 2008; Pirrone and Mason, 2009).

Another important source is industrial facilities that use heavy metals or products containing heavy metals in their operating processes. Various heavy metals found in such products used in industrial facilities spread to the environment, especially through water, precipitation, air and leakage from the storage areas used by the company (Nriagu and Pacyna, 1988; Lehndorff and Schwark, 2008). For this reason, heavy metal pollution can be seen mainly in developed countries. Many studies have shown that heavy metals accumulate more in the air, soil and water of developed countries in the Northern Hemisphere than in countries in the Southern Hemisphere (Birke and Rauch, 1999; Ikem et al., 2008). Moreover, in the Southern Hemisphere, a significant portion of atmospheric heavy metals are natural, whereas in some places in the Northern Hemisphere, up to 80% are man-made (Buat-Ménard, 1984).

Highways are another important source of heavy metal emissions into the environment. An accumulation occurred for approximately 100 years, until the use of unleaded gasoline was phased out in countries around the world in recent years by Blay-Miguel and colleagues (Puxbaum and Limbeck, 2004). In addition, cadmium released from vehicle tires is an important pollutant that causes problems on highways and roads and in crowded urban areas due to vehicle use (Jankiewicz and Adamczyk, 2007; Rao et al., 2016).

Another source that releases heavy metals into the environment, especially agricultural lands, is the agricultural sector. Chemical fertilizers, pesticides and agricultural machinery commonly used in agricultural production processes around the world are also important sources of heavy metals (Goodroad and Caldwell, 1979). Many heavy metals, especially cadmium, found in phosphate fertilizers, are polluted in agricultural lands by the farmers themselves. Phosphate fertilizers produced worldwide contain high amounts of cadmium, depending on the source, and ongoing agricultural activities lead to continued cadmium accumulation in agricultural soils (Dahl et al., 2008).

In addition, many pesticides used against diseases, pests and weeds in agriculture contain heavy metal active substances and/or additives (Hoch, 2001). Even if the excessive use of such substances is ignored, the heavy metals contained in these substances can be mixed directly into the soil with rain and the soil of some parts of the plant, even when used in large quantities or applied to the plant surface. It then accumulates in the soil. Moreover, in many countries, especially in developed countries where agriculture is intensive, a significant number of farmers use unnecessary and excessive amounts of pesticides (Matschullat, 2000). For this reason, many researchers continue to work on some methods to reduce the use of agricultural pesticides, such as critical thresholds, the use of alternative methods, natural control agents and the use of natural medicines (Alengebawy et al., 2021).

1.2.1 Some Heavy Metal and Its Effects

1.2.1.1 Cobalt

Cobalt is hard, shiny silver and has a brittle structure. It is a ferromagnetic metal and its behavior is similar to nickel and iron. Magnetic permeability is about two-thirds that of iron. Pure cobalt is obtained by reducing the resulting compound with aluminium, carbon or hydrogen, and in its pure form, it has the highest known Curie temperature (1121 °C). For this reason, it is used in the production of materials that require magnetic properties at high temperatures (Fang et al., 2017). Cobalt (Co) is one of the transition elements in group IX B of the periodic table, with an atomic number of 27 and a density of 8.90 g/cm^3. Cobalt is found at 0.001% in the Earth's crust and occurs as a byproduct of other metals, especially copper. The main cobalt ores are cobaltite (CoAsS) and erythrite ($Co_3(AsO_4)_2$) (Anonima, 2023). Although it is found everywhere in nature, it constitutes only 0.001% of the earth's crust. It is found in small amounts in rocks, soil, plants, animals and nodules on the seabed. Metamorphic rock formations are based on cobalt concentrates. Therefore, the cobalt content in metamorphic rocks depends mainly on the amount of the element in the volcanic or sedimentary rock source. Cobalt is obtained as a by-product of mining, particularly from ores of copper, nickel, silver, gold, lead and zinc. Cobalt is one of the most basic elements in the world. Although pure cobalt has little use, its use as an alloying element and chemical resource makes it strategically important. It has important application areas in industrial and military applications. Cobalt is most commonly used in superalloys and special steels used in the rocket industry, as well as in rechargeable batteries for portable electronic devices such as cell phones and laptops. Its compounds are used as catalysts in the petroleum and ceramic industries, as pigments in paints, and as drying agents in inks and varnishes.

Cobalt, in the form of cobalamin, is an important component of vitamin B12, which is essential for red blood cell production and preventing pernicious anemia. This means that it belongs to the group of trace elements necessary for humans. Cobalt is abundant in organ meats such as liver and molluscs such as oysters and mussels, which contain vitamin B12 (Goyer and Clarkson, 1996). Human cobalt intake varies greatly from person to person and is generally between 5 and 50 μg/day. Most of the cobalt consumed by humans is inorganic and represents only a small fraction of vitamin B12. Cobalt compounds other than cobalamin can cause toxic effects on living organisms (Aitio, 2015).

Exposure of the general population to cobalt occurs primarily through the consumption of food and drinking water. However, because cobalt is used in a variety of applications, you may come into contact with cobalt in consumer products. Sources of exposure include leather products (shoes, jewelry, clothing), jewelry, mobile phones, chemicals, cutting oils, cement, laptops, etc. takes place. Cobalt is the most common source of exposure that causes dermatitis when used outside of work. You may also be exposed to cobalt in cosmetics. Studies have shown that eye shadows, especially those produced in China, contain cobalt concentrations above 10 μg/g. Cobalt concentrations of up to 1.30 μg/g in lipstick and 2.2 μg/g in skin creams have been measured (Anonimb, 2023).

Cobalt salts are used in paint dryers, as catalysts and in the production of many pigments. It has been used for centuries to color porcelain, glass, ceramics, tiles and enamel (Goyer and Clarkson, 1996).

Cobalt is beneficial for humans because it is part of vitamin B12, which is essential for human health. Cobalt stimulates the production of red blood cells and is therefore used to treat anemia in pregnant women. However, excessive cobalt intake causes erythropoietic effects. Chronic oral administration of large amounts of cobalt to treat anemia can lead to the development of goiter. Epidemiological studies have shown that the incidence of goiter is higher in regions with high cobalt concentrations in water and soil. This goitrogenic effect has been demonstrated when administered orally to children at a dose of 3-4 mg/kg during the treatment of sickle cell anemia (Goyer and Clarkson, 1996).

Cobalt (+2) ions are genotoxic, and some types of cobalt have been shown to have carcinogenic effects in laboratory animals. The main target organ of cobalt in humans is the respiratory system. In the workplace, workers are exposed to inorganic cobalt compounds primarily through inhalation of dust. Observed health effects include decreased lung function, asthma, interstitial lung disease, wheezing, and shortness of breath (Aitio, 2015). Other target organs include the hematopoietic system, cardiac muscle, thyroid, and nervous system. Patients with cobalt alloy implants, especially metal hip prostheses, may experience endogenous cobalt exposure, which may be associated with local or systemic toxicity (Aitio, 2015). Cobalt added to beer to increase foam has also been reported to cause symptoms similar to cardiomyopathy and heart failure (Goyer and Clarkson, 1996).

Cobalt does not accumulate in the body and is mostly rapidly excreted in the urine. Cobalt concentrations in urine or blood can be used as biomarkers of recent exposure to soluble cobalt species (Aitio, 2015). At relatively high exposures, there is a rapid and sustained decrease in excretion for approximately 24 hours, followed by a more gradual phase of elimination. At low exposure levels, urinary cobalt excretion is relatively constant but may be 4 to 10 times higher than in unexposed individuals. Slow elimination may continue for at least 4 weeks after exposure. Changes in blood cobalt concentrations are smaller but do occur post-exposure (Alexandersson, 1998). In healthy people, the average blood cobalt concentration is 0.6 μg/L and the urine cobalt concentration is 0.42 μg/g creatinine (Anonimb, 2023).

1.1.1.2 Cadmium

Cadmium is a silvery-white, soft, electropositive and malleable metal with many properties similar to zinc. Cadmium and its compounds are highly toxic substances. Cadmium does not occur naturally as a single mineral. It is found in very small amounts in zinc minerals as $CdCO_3$ or CdS. Cadmium is found in less than 1 mg/kg in the earth's crust (EFSA, 2009). Cadmium (Cd) is a toxic heavy metal with atomic number 48 and density 8.65 g/cm3, located in the transition metals section of group II B of the periodic table. It is found in the earth's crust at concentrations of 0.1-0.5 ppm and is generally obtained as a byproduct of zinc, lead and copper production (Faroon et al., 2013). Cadmium forms compounds in the +2 oxidation state and is not found in pure form in nature. Compared to other heavy metals, cadmium has the highest water solubility. In terms of its chemical properties, it is between zinc and mercury and is close to zinc. When it reacts with acids, it forms salts such as cadmium nitrate, cadmium chloride and cadmium sulfate, which are easily soluble in water. Cadmium does not dissolve in alkaline environments such as alcohol (Öztoprak, 2018; Anonim, 2023). The amount of cadmium released into nature is 25,000 to 30,000 tons per year, of which 4,000 to 13,000 tons come from human activities. The main source of cadmium that affects human life. Tobacco smoke, refined foods, hookah, coffee, tea, coal combustion, shellfish, fertilizers used during the seeding stage, and smoke generated during industrial production. Cadmium is especially used in rechargeable batteries and alloys (EFSA, 2009).

Cadmium has very soft physical properties, so it can be easily processed into wire rod, plate, etc. can be processed into . Cadmium is often used as an electrode component in the production of Ni-Cd batteries. Cadmium compounds are used as pigments in engineering plastics, ceramics, glasses, enamels and toners. Cadmium has excellent corrosion resistance, so it is widely used as a coating material for metals such as steel and iron. Cadmium is also used as a plastic stabilizer, heat and light stabilizer in polyvinyl chloride (PVC) production, and lawn fungicide (Faroon et al., 2013; Aitio, 2015). Cadmium ions exert their effects on oxidative stress by binding to antioxidants containing sulfhydryl groups such as: B. Glutathione. It also binds to metalloenzymes that bind to cadmium, zinc, magnesium, selenium, calcium and iron metals and destroys their functionality. This inhibition of the enzymes glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) increases free radicals. Oxidative stress is necessary for cadmium toxicity. It promotes tumor development through effects on mutagenesis and cell cycle. The main carcinogenic mechanisms caused by cadmium include induction of inflammatory processes, oxidative stress, delayed apoptosis, DNA damage, decreased DNA repair capacity, altered gene expression, cell proliferation, and abnormal DNA methylation (Genchi, 2020).

Because cadmium is chemically similar to zinc, it binds to the zinc site in the active site of histone demethylases and to the zinc finger motifs of steroid hormone receptors and other DNA-binding molecules, causing changes in academic functions. There are epidemiological studies showing an association between occupational (inhalation) exposure to cadmium and lung cancer. For this reason, IARC classifies cadmium and its compounds as "Group I substances" that are carcinogenic to humans. There is insufficient evidence that it is carcinogenic when ingested (Sheikh et al., 2023). The more soluble cadmium chloride, cadmium oxide fumes and cadmium carbonate are the most toxic cadmium compounds. Exposure to cadmium oxide fume causes metal fume fever, characterized by fatigue, headache, chills, dry throat and nose, irritability, and fever. Inhalation of cadmium vapor or other heated cadmium-containing substances may cause acute chemical pneumonia and pulmonary edema. Inhalation of high doses can be fatal (Goyer and Clarkson, 1996; Anonymous, 2020).

Cadmium, carried in the blood by binding to albumin, is mostly taken up by the liver, where it induces metallotia (MT) synthesis. Cadmium metallothiene complexes do not readily cross the placental barrier or the blood-brain barrier and therefore have very low toxicity to the fetus and central nervous system. Cadmium accumulates in the body, especially in the liver and kidneys, but also in the bones, pancreas and muscles. The kidney is considered a critical organ after long-term exposure (Aitio, 2015).

Long-term exposure to cadmium causes lower respiratory tract fibrosis, alveolar damage leading to emphysema, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). Destruction of alveolar macrophages is responsible for the lesions occurring in the lungs. The released enzymes cause irreversible damage to the alveolar basement membrane, including septal rupture and interstitial fibrosis. Cadmium has been found to increase pulmonary toxicity by reducing alpha-1-antitrypsin activity (Goyer and Clarkson, 1996; Anonymous, 2020).

People with severe cadmium nephropathy may experience excessive calcium excretion associated with kidney stones and increased urine output. Skeletal changes are likely related to calcium loss and include bone pain, osteomalacia, and osteoporosis. Itai-Itai disease is the first disease described to be caused by cadmium poisoning, including severe bone deformities and symptoms of chronic kidney disease (Goyer and Clarkson, 1996; Anonymous, 2020).

Epidemiological studies have shown an association between occupational (inhalation) exposure to cadmium and lung cancer. Results from an epidemiological study of 20,459 participants in Belgium and the United States showed consistent evidence that lifelong environmental cadmium exposure causes lung cancer through creatinine and urine cadmium measurements (Nawrot et al., 2020). Another cohort study reported that the mean blood cadmium concentration of breast cancer patients was more than 3 μg/L, i.e., 2.35 times higher than that of controls. The same group of researchers investigated the relationship between the presence of cadmium in the blood and nasopharyngeal cancer and reported that the average cadmium concentration in the blood was significantly higher in cases than in controls (Peng et al., 2015). Other studies have also been reported showing that environmental exposure to this toxic metal may be associated with prostate, bladder, pancreatic, and kidney cancers (Genchi, 2020).

Conclusion

Heavy metals have significant effects on human health, even in trace amounts. Heavy metals are widely used in our daily life and industry. Contact with heavy metals has increased, especially with the increase in industrial activities. The release of heavy metals into the atmosphere, soil and water, whether natural or human-made, poses a great danger to humanity. This risk increases depending on the dose and duration of exposure, and may even lead to the development of tumors and cancer. Serious health problems occur especially after exposure during childhood and accumulation in the body for many years. Studies on arsenic, cadmium, nickel and chromium have shown that these metals are highly carcinogenic to humans. Depending on the degree of exposure, they can affect biochemical processes in the body and cause disorders.

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