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Review article

Cadmium in plants, humans and the environment

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Abstract

Heavy metals are the most persistent and complex pollutants in nature. They not only reduce the quality of the atmosphere, water bodies and food crops, but also pose a threat to the health and well-being of animals and people. Metals are accumulated in the tissues of living organisms since contrary to most organic compounds; they are not subject to metabolic degradation. Cadmium (Cd) is one of the heavy metals as well as one of the most important pollutants that easily transported in plants, then distributed to all plant organs, and thus easily transferred to the food chain. So far, studies have not shown any positive effects of Cd on living organisms. Cd can be harmful on human health even in low concentrations, which can cause many serious illnesses and even deaths. In this article, a literature review has been made under the topics of the general properties of Cd, its distribution in nature, its sources and usage areas, the entryways of Cd into plants, its transportation as well as importance in plant metabolism; effects on plants as a heavy metal, the antagonistic-synergistic relationship of Cd with other elements, remediation methods can be applied in soils exposed to Cd contamination, the passageways of Cd to nutrients, its entry into the body and its transportation, and finally the effects of Cd on humans and animals.

Keywords: *Heavy metal; metal accumulation; metal uptake; pollution; toxicity*

1. Introduction

Unplanned urbanization and industrialization depending on the rapid increase in the human population, increase the pollution by heavy metals and cause deterioration of ecological balance (Ozturk et al., 2017). As a result of environmental pollution soil, water and air are also polluted and the level of pollution is becoming more dangerous on living things day by day (Akguc et al., 2010). Heavy metals are, one of the most critical factors causing environmental pollution (Yang et al., 2018; Karahan et al., 2020).

The sustainability of human beings has always been dependent on plant life as a source of food, raw materials and energy. Plants can easily uptake the nutrients they need to grow and complete their physiological periods from the soil throughout their roots. These nutrients can be found in the soil in the form in which they are found in plants (Carfagna et al., 2013; Meena et al., 2020). The role of each nutrient in plant nutrition is different and thus, in agricultural practices they must be applied to the plants in a balanced way (Okcu et al., 2009; Elemike et al., 2019).

The elements necessary for the growth and survival of plants are called "plant nutrients". It is possible to find almost all elements that exist in nature in the analysis of plant tissue and organs (Hawkesford et al., 2016). However, 16 of these elements (C, H, O, N, P, S, K, B, Ca, Cl, Cu, Fe, Mg, Mn, Mo and Zn) are "essential nutrients" for all plants. Six of these elements (Al, Co, Na, Ni, Si and V) are "beneficial elements" that are considered necessary only in some plants or metabolic pathways (Ozyigit et al., 2018; Karahan et al., 2020).

Metals such as Cd, Co, Cr, Cu, Fe, Hg, Mn, Ni, Pb, Se and Zn, which have relatively large atomic mass, exhibit their own

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physical structure and have atomic weights are greater than 5 g cm^{-3} are called as "heavy metals". More than sixty elements are considered as heavy metals, and these metals are located in a large part of the periodic table called "transition elements" (Salzer, 1999; Duffus, 2002; Yalcin et al., 2020).

Some of the heavy metals are involved in metabolism by participating in the structure of vitamins, enzymes and hormones, while others take part in absorption and digestion (Azevedo and Lea, 2005; Pohl et al., 2011). Heavy metals such as Cu, Fe, Mn, Mo, Ni and Zn are needed for living things up to a certain dose; these elements are called "micro or trace elements". Contrarily, heavy metals such as As, Cd, Cr, Hg and Pb are not essential for living things and even small amounts of them can show toxic effects (Altay et al., 2013; Ozyigit et al., 2018; Karahan et al., 2020). Heavy metals pose a great threat to plants, animals and humans when they are released in the environment as they accumulate in organisms through the food chain, causing serious diseases and even death (Kumar et al., 2019; Sevik et al., 2019; Karahan et al., 2020). Heavy metals can easily spread around, and affect the environment negatively even in Antarctica, where the life, as well as human habitat is limited (Corsolini, 2009). Therefore, the negative effects of heavy metals on living things should not be ignored (Baryla et al., 2001; Aissa and Kéloufi, 2012). The main factors that cause heavy metals to spread to the environment are industrial activities, motor vehicle exhausts, paints, use of metals as catalysts, mineral deposits and enterprises, volcanic activities, fertilizers and pesticides used in agriculture and urban wastes (Akguc et al., 2008; Osma et al., 2012; Ozyigit et al., 2016).

Cd, which belongs to the 2B group of the periodic table, is one of the most toxic and dangerous heavy metals for living things. The importance of Cd as an industrial and environmental pollutant has become more evident in recent years (Mishra et al., 2019). Cd can be found naturally (mobilizations of cadmium from the earth's crust are volcanoes and weathering of rocks) or spread to the environment due to anthropogenic activities like agricultural and food wastes, animal wastes and manure, logging and other wood wastes, urban refuse, municipal sewage sludge, miscellaneous organic wastes, solid wastes, fertilizer metal manufacturing, coal fly and bottom fly ash, wastage of commercial products and atmospheric fall-out (WHO, 2003; Akguc et al., 2008; Sabiha-Javied et al., 2009; Osma et al., 2012; Ozyigit et al., 2016). These factors increase the importance of Cd as a pollutant.

2. Cadmium element

The chemical symbol of cadmium is "Cd" with atomic number 48, atomic weight 112.41 g mol^{-1}, density 8.7 g cm^{-3}, boiling point 766.8°C and melting point 321°C as well as a silver-colored, soft, machinable heavy metal that cannot be found alone in nature. Among Cd salts, CdS, $CdCl_2$ and $CdSO_2$ are the best known. The chemical properties of Cd are similar to Zn in terms of plant uptake and metabolic functions. However, unlike Zn, an element has a toxic effect on plants, animals and humans (Garbisu and Alkorta, 2001). One of the ways it reaches the soil is synthetic fertilizers and pesticides. It can spread easily in nature due to its water solubility feature. It is taken into biological systems by plants and sea creatures in the form of Cd^{+2} and has the property of accumulation (Kayhan, 2006; Tripathi et al., 2020).

Cd, which is frequently used for the benefit of humanity today, unfortunately, is an important contaminant for the environment and humans. Since their compounds are mostly in powder and aerosol form, they are commonly taken by inhalation. International cancer research authorities divided chemicals into five groups according to their carcinogenic effects. Cd belongs to "Group 1" among "Carcinogenic Effective Substances in Human" due to its relationship with lung cancer. Since tin (Sn) metal was not found during the First and Second World War years, Cd was used as a substitute for Sn in food and canned containers. However, it has been noticed that Cd, which passes to acidic foods, causes poisoning, and therefore, it has been discontinued in a short time (WHO, 2019; Xu et al., 2019; Aslan, 2020). Living things are often exposed to Cd directly through the respiratory tract or food chain. Depending on the route of exposure, concentration a duration, Cd can cause damage to the lung, liver, kidney, bone, testicle and placenta (Paustenbach et al., 2003; Prozialeck et al., 2006; Meravi and Prajapati, 2013).

In plants exposed to toxic amounts of Cd, shrinkage of leaf surface area, yellowing (chlorosis), necrotic spot formation, leaf growth inhibition and leaf rolling are observed. However, the lack of Cd-based Fe and/or P deficiency or inhibition of Mn transport may be the reason for the chlorosis of the leaves (Koleli et al., 2004; Benavides et al., 2005; Lombardi and Sebastiani, 2005). Cd causes a decrease in yield and quality in plant production due to its inhibitory effects on plant photosynthesis rate, enzyme activity and ion uptake (Hassan et al., 2005; Siatka et al., 2012).

3. Distribution of cadmium

Cd is on the list of priority hazardous substances of many environmental non-governmental organizations and the United States Environmental Protection Commission. Living things are often exposed to Cd directly through the respiratory tract or food chain. The World Health Organization limited the weekly tolerable amount of Cd exposure to 50 μg and recommended it as 0.007 mg kg^{-1} body weight (WHO, 2000). Industrial activities, sewage wastes, the addition of fertilizers to agricultural soils and atmospheric deposits cause Cd to pass into the soil. In addition, diesel-powered machinery, long-term purification sludge and garbage manure applications to agricultural areas and the use of pesticides cause entry of Cd into the soil (Sabiha-Javied et al., 2009; Ozyigit et al., 2016; Tabelin et al., 2018).

4. Cadmium applications, uses and resources

It is thought that the annual exposure amount of Cd is 25-30 thousand tons. Human plays a role in 13 thousand tons of this amount (Zalups and Ahmad, 2003; Sui et al., 2018). The industries where Cd is frequently used can be listed as follows: Production of Ni-Cd batteries, refining of Cu, Pb and Zn ores, electroplating and galvanizing applications in order to prevent corrosion, adding to the composition as a preservative during the preparation of metal alloys, use as a stabilizer in plastic production, glass industry, ceramic making and dye production (Jovanovic et al., 2011; Akguc et al., 2008; Osma et al., 2012). Apart from these industrial areas given above, Cd is widely used in the production of household items, automobile and truck tires, photography, agricultural tools, aircraft parts, some industrial and hand tools, bolts, screws, screw nuts and nails (Awual et al., 2018; Ishchenko, 2018; Akguc et al., 2008; Osma et al., 2012). Additionally, in many industries, Cd is released as a by-product of Cu, Pb and Zn extraction. The uptake of Cd by humans and animals is mostly through foods. All food ingredients contain

Cd, even in small amounts. Some of the foods which have high levels of Cd are liver and offal, shellfish, mussels, seaweed, mushrooms, cocoa powder. Smoking also causes a high amount of chronic Cd exposure. Hazardous waste zones, factories that release Cd through air, and the metal refining industry are also important areas of Cd exposure (Chiocchetti et al., 2017; Vizuete et al., 2018; Aslan, 2020).

5. Entry of Cd element to plants, transport and storage

Metal transport from soil to plant roots occurs through diffusion and convection. With the dissolution of metals in the soil, metal concentration increases and as a result, complex structures are formed. Even if these complex structures are not taken into the cell by plant roots, it has been determined that they increase the transports carried out by diffusion towards the plant root in an effective amount. There are many factors that affect metal accumulation in plants. Among these factors, the mobility of the elements in the soil, their absorption by the roots, their storage in the root cells, the transport of the structures through xylem to above-ground parts, and the spread of metals in these parts are the most prominent factors (Clemens et al., 2002; Song et al., 2017).

The metals taken from the soil are initially stored in the plant roots. These metals are then passed from the roots to the xylem sap and transported to the aboveground parts of the plant with the effect of respiration power (Ismael et al., 2019). Metals reaching to the leaf are spread to leaf cells through apoplast and symplast. The distribution of the elements transported to the leaf by the apoplast and symplast is due to the binding of the metals to the chelators in the tissues. Phytochelatin (PC) and metallothioneins (MT) are the main chelators involved in the retention of metals (Filiz et al., 2019a). These chelators contain large amounts of cysteine sulfhydryl groups, which can bind to heavy metal ions and store them to form stable complexes (Prasad, 2013; Dvorak et al., 2020).

The process of heavy metal uptake and transport by plants includes the retention of metal ions by the roots, their entry to the roots and subsequent translocation to the aboveground organs through mass flow and diffusion (Jabeen et al., 2009). Plants also have molecules that can eliminate or tolerate the negative effects of metals. Some of the well-known of these molecules are phytochelatins, metallothioneins, organic acids, amino acids and metal chelators (Dučić and Polle, 2005; Ahmad et al., 2019; Filiz et al., 2019a). The strongest metal binders in plants are phytochelatins, which eliminates the negative effects of heavy metals. It has been proven in many researches that phytochelatin has a peptide structure and that Cd^{+2} is the strongest metal activator of phytochelatin synthase (Balzano et al., 2020). Metallothioneins are compounds with low molecular weight, heavy metal binding capacity, high content of cysteine groups and no aromatic amino acids (Ziller et al., 2017; Filiz et al., 2019b). In addition, the amino and carboxyl groups of amino acids have the ability to bind metal ions. Organic acids such as malate, oxalate and citrate are involved in the reaction against the negative effects of metals (Tamás et al., 2018).

Plants must initially transform the metals into a mobile form in order to absorb them from the soil. They reach this mobile form by using many methods. For instance, plants can secrete into the rhizosphere to dissolve and chelate the metal present in the soil through metal-chelating molecules. The heavy metal uptake of plants can be divided into three groups (Ayhan et al., 2006; Liang et al., 2019).

1. Metal-chelating molecules can perform the siderophores function in plants via phytochelatins and metallothioneins (Navarrete et al., 2019).

2. They can reduce the ionic metals by using metal reductases present in the structure of the plasma membrane (Shou et al., 2019; Terrón-Camero et al., 2019; Huang et al., 2020).

3. They can acidify and dissolve heavy metals by throwing protons from the roots to the soil (Zandonadi et al., 2016).

These three mechanisms can also be applied by mycorrhiza or root colonized bacteria. A plant can manage the negative effects of heavy metals by preventing the entry of them into the cell, and if it cannot prevent it, by detoxifying it in the cell. Studies have shown that cadmium is stored in vacuoles together with phytochelatins (Ashraf et al., 2019; Ahmad et al., 2019; Yamaguchi et al., 2020).

6. Effects of Cd on plants, its role in metabolism

Compared to animals, plants can take higher amounts of Cd without harm. Plants are negatively affected if excessive amounts of Cd is taken (Gill et al., 2012). It causes many physiological changes in the plant by changing nitrogen and carbohydrate metabolisms.

Cd prevents photosynthesis, disrupts chlorophyll synthesis and causes stomatal closure. The most important reason why excessive Cd concentrations disrupt chlorophyll biosynthesis is the inhibition of the synthesis of protochlorophyll reductase, which is involved in chlorophyll biosynthesis and aminolevulinic acid (Per et al., 2017). In addition, like other heavy metals, Cd causes free radical formation, which is responsible for oxidative destruction of thylakoid membrane lipids (Rai et al., 2016).

Many researches showing the effects of Cd in different organisms are exist. In a study investigating Cd toxicity in tomato plants reported that there was a linear relationship between the Cd concentration in the nutrient solution and the Cd in the root and shoots of the plants. Also, it was seen that the amount of Cd accumulated in roots of tomato is approximately 15 times more than its shoots as roots (Khan et al., 2019). In another study conducted using *Picea abies*, the amount of Cd accumulation in the roots induced parallel with the increased Cd concentration in the growing medium (Ozcan and Baycu, 2005).

A study conducted on bean seedlings (*Phaseolus vulgaris* L. cv. Strike), the effects of Cd, Cu, Hg and Pb on the quantities of total protein and abscisic acid (ABA) were investigated. Obtained results demonstrated that higher heavy metal exposures of the seedlings increased ABA production. Additionally, the total protein contents ($p<0.05$ or $p<0.01$) decreased with heavy metals' concentrations (Zengin and Munzuroglu, 2006).

Recent studies have revealed that Ca has important protective effects against Cd stress in plants. Ca mediates to Cd uptake rate and physiological changes due to Cd uptake in plants. Hayakawa et al. (2011) showed the negative effects of Ca application on Cd levels in *Gamblea innovans* leaves. The application of Ca at a low concentration caused a significant decrease in Cd uptake in the roots of rice (Kim et al., 2002). Similar reductions in Cd uptake were seen in soybean and wheat roots with the application of 1-10 mM Ca (Yang and Juang, 2015).

Reports on the effects of Cd toxicity in plants have shown changes in the uptake, transport and use of various elements and water in plants (Qin et al., 2020). The absorption of nitrate was reduced by the uptake of Cd, and relatedly the transport of nitrate from the roots to the stems was limited through the inhibition of nitrate reductase activity in the stems (Singh et al., 2019). Cd, which induces an increase in lipid peroxidation, also causes some changes in the functions of membranes (Zahra et al., 2018) and by suppressing chlorophyll biosynthesis and effecting the activities of enzymes involved in CO_2 fixation (Asati et al., 2016; Sadeghipour, 2018).

Some studies with Cd have shown that stress-dependent genomic changes cause variations in RAPD band profiles. For instance, Ozyigit et al. (2016) exposed *Kalanchoe daigremontiana* clones to Cd in different concentrations and observed new band formations in RAPD band profiles in 50, 200 and 400 µM applications. In addition, a decrease in band intensities in RAPD band profiles at concentrations of 100 µM, and an increase in band intensities at concentrations of 50, 200 and 400 µM were observed.

In another study, polymorphisms were observed in DNA profiles of *Arabidopsis* plant samples exposed to 4.0 and 5.0 mg L^{-1} Cd whereas polymorphisms were not obtained in DNA profiles 0.25 and 1.0 mg L^{-1} Cd (Wang et al., 2016).

Aslam et al. (2014) used 10 RAPD primers in *Capsicum annuum* samples exposed to 5 different Cd concentrations (20, 40, 60, 80 and 100 ppm) and a total of 184 (62 polymorphic and 122 monomorphic) bands in DNA profiles were obtained.

Recently, the highest levels of changes in RAPD profiles (lost and/or formed bands) after Cd application at different concentrations in heavy metal sensitive barley (*Hordeum vulgare* L.) genotypes were obtained in 225 µM Cd application by Cenkci and Dogan, 2015.

7. Antagonistic-synergistic relationship of Cd with other elements

Due to its chemical similarities, there is an antagonism between Ca^{2+} and Cd^{2+} cations; therefore, when they co-exist, they compete with each other in the uptake process in plants. Perfus-Barbeoch et al. (2002) stated that Cd can also enter plant cells through Ca channels. Ca has a protective function on the plasma membrane, and plays a significant role in controlling Cd accumulation in plants. Ca regulates the negative membrane potential, ensuring the stability and integrity of the cell membrane. Thus, the application of Ca reduces the total negative charge on the plant cell membrane and causes a decrease in Cd accumulation (Kinraide et al., 1998).

Cd, which has a very high transition rate from soil to plant and is very mobile in the soil, can be uptaken by plants in very low concentrations, especially in Zn deficiency. The possibility of accumulation in the edible parts of the plant indicates that this metal has a great danger potential for the environment (Koleli and Kantar, 2006).

Bioaccumulation of Cd strongly depends on the chemical properties of aquatic environments. Moreover, Cd accumulation occurs in a concentration-dependent manner, and some ions such as Mg^{2+} and Ca^{2+} have protective effects on aquatic organisms against Cd toxicity (Deleebeeck et al., 2008; 2009). These ions compete with Cd ions and suppress their toxicity (Deleebeeck et al., 2009; Schlekat et al., 2010).

In addition, it has shown that Zn and Hg reduce the teratogenic effect of Cd (McCarty, 2012). In the studies conducted on frogs, it has been determined that Zn prevents the toxic effects of Cd when they are used together (Othman et al., 2012).

8. Remediation methods of Cd-contaminated soils

Cd can be removed from soils by high-cost purification technologies or by a lower cost as well as an easily applicable method of phytoextraction (remediation of soils with plants, plants uptake heavy metals from the soil (Ozyigit and Dogan, 2014; Li et al., 2017).

In this technology, natural hyperaccumulator plant species are generally used. Some genera such as *Thlaspi, Urtica, Chenopodium*, *Polygonum* and *Allyssim* are capable of accumulating Cd, Cu, Pb, Ni and Zn and therefore, the cultivation of the members of these genera is considered an indirect method for the treatment of contaminated soils. Moreover, chelating agents can be added to increase the solubility of metals with low solubility in the soil solution. It includes the uptake of pollutants by plant roots followed by accumulation in above-ground organs and the destruction of plants by harvesting (Ozyigit and Dogan, 2014). This technique can be used to remove actively taken micronutrient elements like Cu and Zn and non-nutrient elements such as Cd, Ni and Pb. Phytoextraction technology can only be applied for areas where metal pollution is low or moderate since plant growth cannot be maintained in areas that are heavily contaminated (Padmavathiamma and Li, 2007; Goyal et al., 2020).

The rhizofiltration method includes the uptake and retention of large amounts of nutrients or metal pollutants from liquid growth media by plant roots. Roots of many plant species grown in hydroponic environment such as *Brassica juncea*, *Helianthus annuus* and *Phaseolus vulgaris* can be used to remove toxic metals such as Cu, Cd, Cr, Ni, Pb, Zn and U from liquid solutions (Ozyigit and Dogan, 2014; Shakoor et al., 2017).

9. Cd in foods

Cd and its compounds are widely used in the production of dye (dyestuff and ink production), glass, textile, electricity, battery, fungicide, insecticide and synthetic polymers with metal alloys (Akguc et al., 2008; Osma et al., 2012; Ozyigit et al., 2016). It has determined that the use of Cd in various industries causes an increased risk of food contamination of this toxic metal through soil, air and water and high levels of contamination in some foods was observed (Hezbullah et al., 2016). It has demonstrated that cereals, potatoes, leafy and rooted vegetables, fruits, liquid-solid oils, meat and dairy products can be contaminated with Cd. The use of Cd in galvanized zinc-coated packaging together with Zn has shown that such packaging materials cause poisoning in foods with high acidity. It has been thought that organic acids in foods increase the solubility of Cd in the structure of the packaging wall (Filippini et al., 2018). In addition, Cd that passes to acidic foods can also cause poisoning (Mohammad et al., 2018; Aslan, 2020).

10. Transport of Cd in human body

Cd usually enters the body via oral, respiratory and skin routes. With the absorption of Cd entering the body, it binds to blood cells and albumin, and then it is carried in the blood. It is initially transported to the liver through blood and then transported from the liver to the kidneys by binding to globulins for detoxification (Zhang et al., 2019a). The Cd accumulated in the kidneys negatively affects the filtration process in the Bowman capsule. This causes many essential proteins and the necessary glucose to be excreted with urine (Bobillier et al., 2006). It is taken into the cell via carrier proteins in the membrane. While it is taken into the cell, it binds to the carrier proteins similar to essential metals such as Ca, Cu, Fe and Zn. As a result, there is a race between them in binding to receptors on the membrane.

Cd absorption has been reported to increase when people and animals are fed diets lacking in elements such as Ca, Cr, Fe and Zn are inadequate in terms of protein (Vahter et al., 2002; Bergeron and Jumarge, 2006). Cd, which is absorbed through alveoli, intestinal lumen and skin and passed into the bloodstream, are transported by binding to the proteins containing metallothionein, albumin and thiol groups. They transport Cd to the cells through receptor-mediated endocytosis (Zalups and Ahmad, 2003). Animal studies and *in vitro* researches reported that metallothionein also protects cells against the toxicity of Cd (Bobillier et al., 2006; Othman et al., 2012).

11. Effects of Cd on animals and humans

It is calculated that the atmosphere in the residential areas is polluted with an average of 0.001 g m^{-3} level of Cd. As a compulsory consequence of this, it has been determined that people take 0.02 mg of Cd daily. It has been demonstrated that high inhalation of cadmium oxide (CdO) in the form of smoke causes lung edema and eventually has lethal effects. In cases of long-term exposure to Cd, it is determined that some cancer types such as prostate cancer and especially lung cancer, can be seen (Person et al., 2013).

Cd metal or its compounds have been shown to cause sarcoma disease when they are injected intramuscularly or subcutaneously (Yongming et al., 2011). Some of the negative effects of Cd are on Ca metabolism and causes hypercalcemia (higher than normal Ca level in the blood). In experiments on the effects of Cd on bone and Ca metabolism, it was reported that the sodium-glucose transport system in cortical cells of kidneys was inhibited (Dongre et al., 2013). In addition, among the skincare products frequently used by women such as eyeliner, blush, lipstick contain Cd and can cause skin cancer (Duruibe et al., 2007; Pratinidhi et al., 2018).

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Cd quickly converts to CdO in the air. Inorganic salts such as $Cd(NO_3)_2$, $CdSO_4$ and $CdCl_2$ are water-soluble. Acute effects in respiration are observed when the Cd concentration in the air exceeds the limit of 1 mg m^{-3}. Due to the low excretion of Cd from the body and accumulation, its negative effects on health can be observed over time. Industrially, Cd poisoning occurs with alloy compounds used during welding, electrochemical coatings, dyes containing Cd and batteries with Cd (Aslan, 2020).

The earliest finding of Cd nephrotoxicity, which is common in workers exposed to Cd, is tubular dysfunction in the form of low molecular weight proteinuria. However, the degree of proteinuria varies over time. It has been suggested that Cd-induced tubular proteinuria is irreversible in many workers for at least a couple of years (Fay et al., 2018; Chen et al., 2020).

Cd can cause DNA breaks and lipid peroxidation. Studies have shown that Cd toxicity causes apoptosis in proximal tubule cells (Wang et al., 2017). One of the important nephrotoxic effects of Cd is that it causes interstitial fibrosis as a result of tubular cell necrosis and inflammation (Fujiki et al., 2019). Since Cd shows the highest concentration of liver after the kidneys, thus determination of its hepatotoxic effects is also very important (Cao et al., 2017).

It was reported that no Cd-related liver enzyme elevation or low serum albumin was detected in the case of environmental Cd exposure (Lavryshyn and Gutyj, 2019; Yaseen, 2019). One of the early signs of Cd toxicity in the liver is impaired mitochondrial function (Okoye et al., 2019). The toxic effect of Cd on mitochondria is related to the increased glutathione and decreased glutathione peroxidase activity by Cd in liver cells rather than increased permeability of mitochondrial inner membrane (Abarikwu et al., 2017).

Cd is accumulated within the cell lysosomes, disrupting the integrity of the lysosomal membrane. The release of lysosomal proteases and phospholipases initiates a series of events that cause hepatocyte cytotoxicity (Wang et al., 2019). Acute exposure to gas mixtures containing high concentrations of Cd can cause fatal acute chemical pneumonia. However, the effects of chronic Cd exposure on the respiratory system seem to be more important. Smoking in the community is the most important reason for continuous and low-dose Cd exposure (Oztoprak et al., 2020; Tao et al., 2020).

Chronically uptake of Cd with either smoking or by respiratory tract in occupational risk group workers causes harmful effects on the respiratory system. The severity and time of occurrence of this damage depend on the concentration and duration of Cd exposure and it is usually seen over the years. It has been reported that chronic inflammation in the nose, pharynx and larynx can be developed in workers of Cd industry (Hassanin et al., 2017; Prokopowicz et al., 2019). Chronic obstructive pulmonary disease (COPD) is common in workers exposed to Cd and smokers. In these patients, the presence of emphysema has been demonstrated both clinically and radiologically (Sundblad et al., 2016).

It has been suggested that Cd-mediated apoptosis is sensitive to Clara cells and type II cells, and this apoptotic effect is associated with the increase in the *p53* and *Bax* genes (Lee et al., 2016). Ca metabolism disorders and bone diseases caused by Cd exposure are seen in the Japanese community, where there is a regular environmental exposure. The main features of Itai-itai disease are osteomalacia, which tend to painful bone fractures, osteoporosis and kidney tubular dysfunction. Cd can be effective on bones by disrupting calcium phosphate and vitamin D metabolism. Bone metabolism disorders have been reported in workers exposed to Cd. Osteomalacia due to Cd can be seen in these individuals. Chronic Cd exposure has been shown to reduce bone mass and increase the incidence of bone fractures (Nishijo et al., 2017a; Browar et al., 2018; Reyes-Hinojosa et al., 2019).

In histological studies, it was found that the application of chronic Cd caused dilatation in the Havers canals in the bones, the expansion of the pericellular area and the hyperplastic bone marrow into the metaphyseal cortical bone. Studies have shown that chronic exposure to Cd causes an increased risk of osteoporosis and osteoporosis-related bone fractures in both sexes, especially in older women (Ohta et al., 2000; Nishijo et al., 2017b; Huang et al., 2019).

In addition to the kidney and liver, Cd is also stored in the heart. However, compared to kidney and liver, the Cd concentration in the heart tissue is relatively lower. It has been shown in studies that Cd, causes metabolic and structural disorders in the heart and plays a role in the etiology of hypertension even in low concentrations (Asagba ve Obi, 2004; Bobillier et al., 2006). This model of hypertension is created by applying cadmium chloride ($CdCl_2$) (1 mg kg^{-1} per day, i.p.) regularly for 2 weeks. The mechanism of the development of hypertension with the application of $CdCl_2$ is explained by the fact that Cd metal mimics the effect of Ca ion with partial agonist effect and its direct contractionary effect on the vascular smooth muscle (Rathod et al., 1997; Resitoglu et al., 2016).

As a result of many experimental studies, it has been shown that the application of Cd salts in late pregnancy causes placental damage as Cd has teratogenic effects such as exencephaly and hydrocephalus in early pregnancy. In animal embryo cultures, Cd has been reported to cause reopening of the closed neural tube (Santoyo-Sánchez et al., 2018; Geng and Wang, 2019; Kmecick et al., 2019). The human placenta is also sensitive to toxic Cd activity (Erboga and Kanter, 2016; Zhang et al., 2016; Geng and Wang, 2019).

Cd can damage the fetus by affecting the metabolism of other elements such as Cu, Fe, Se and Zn. Smoking is also responsible for Cd toxicity during pregnancy. The incidence of low birth weight has increased in infants of smoker mothers, and there is an increase in placental mass. However, Cd was not found in breast milk in smoking mothers (Bobillier et al., 2006; Moynihan et al., 2017; Ali et al., 2018).

As a result of exposure to Cd for a long time, structural and functional disorders occur, especially in the male and female reproductive system (Zhang et al., 2019b). Mammal testicles are very sensitive to Cd as it causes a decrease in sperm motility and spermatogenesis index (Acosta et al., 2016; Nna et al., 2017). Testicular necrosis caused by Cd can cause permanent infertility. Although the molecular effects of Cd on male infertility are controversial, it has been suggested that chronic Cd application causes a decrease in fertility by joining sperm chromatin (Imafidon et al., 2016; Habib et al., 2019). In recent experimental studies on female rats, the application of Cd to ovulation has been shown to inhibit ovulation (Gautam and Chaube, 2018; Yang et al., 2019). In addition, Cd has been reported to prevent the accumulation of follicle-stimulating hormone (FSH) and cAMP-induced progesterone in ovarian granulosa cells (Massanyi et al., 2005; Li et al., 2019).

12. Conclusion

Currently, the use of synthetic fertilizers in agriculture, the consumption of agricultural products grown in areas contaminated with Cd, the use of contaminated drinking water and the inclusion of fishery products in the diet have made our contact with Cd inevitable. In addition, the consumption of organs such as liver and kidneys of grazing animals in contaminated areas and the consumption of contaminated plant foods, being in environments with high Cd concentrations for a long time and smoking are the leading factors in the contamination with Cd. As mentioned above, prolonged exposure to Cd causes oxidative damage in blood and liver tissues as well as histopathological changes, especially in kidney, brain and testicular tissues. As can be seen from the literature, Cd-related diseases are recently discovered and not well-known before. Thus, it is important to create Cd awareness. Conscious choices are crucial in protecting mental and physical health as well as the health of relationships and communication between individuals. One of the measures is to monitor and reduce the Cd level existed in airborne dust particles in residential areas; creating habitats with minimal dust particles and combating dust is also a serious measure against Cd exposure. Important Cd sources that can contaminate soil and water should be determined and measures should be taken in order to prevent contamination. Furthermore, it is necessary to measure the amount of Cd in food and water regularly and avoid consuming contaminated foods. To sum up, information and awareness-raising studies about the toxic effects of Cd and other heavy metals should be made a part of education at every level. The government should inform the public in cooperation with local governments for this.

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