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Sara Bashir Ali EL-Hengary *

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Research Article

Cadmium Toxicity: Insight into Sources, Toxicokinetics, and Effect on Vital Organs and Embryos

Sara Bashir Ali EL-Hengary [1], Fikry Ali Abushofa [2], and, Azab Elsayed Azab [3]

[1,2] Department of Zoology, Faculty of Science, Zawia University, Libya

[3] Department of Physiology, Faculty of Medicine, Sabratha University, Libya

***Corresponding Author:** Sara Bashir Ali EL-Hengary, Professor of the Faculty of Psychology/University of Havana (San Rafael No. 1168 between Mazón and Basarrate Vedado).

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Abstract

Background: Elemental cadmium, cadmium oxide, sulfide, and chloride are resurrected to the atmosphere from both natural and anthropogenic sources. cadmium concentrations in the blood, urine and kidney cortex are substantially higher in smokers compared to never smokers. Absorbed cadmium accumulates primly in the renal cortex and liver. The pancreas, thyroid, gall-bladder and testes can also include comparatively high concentrations.

Objectives: The current review aimed to highlight on the effect of cadmium chloride on vital organs and embryos. Absorption of cadmium from the lungs is a major source of exposure between smokers and the occupationally exposed. Cadmium accumulates with age even a maximum level is arrived at about age 50. Metallothionein has been identified in the liver, kidneys, duodenum, urine and blood of animals. It has been postulated that metallothionein passes through the red cell membrane and is transformed to the kidney. Cadmium being a divalent cation is accumulated by transfers mechanisms developed for necessary metals. Cadmium may interact with zinc, iron, magnesium, manganese, calcium and selenium and cause their secondary disability and so break down metabolism, resulting in the final morphological and functional changes in many organs. Toxicity could result from cadmium (Cd^{2+}) interacting with cellular ingredients until without get into the cell, but by interaction with receptors on their surface. Cadmium forms covalent and ionic bonds with atoms of sulfur, oxygen, and hydrogen present in the sulfhydryl groups, disulfide, carboxyl, imidazole or severally amino compounds present in the cells, causing significant disruption of their homeostasis. The principle target organelle of cadmium is the mitochondria. Symptoms of acute cadmium intoxicating usually appear after 24 hours are shortness of breath, general weakness, fever. It can also cause pulmonary edema, pneumonia and in acute cases, respiratory failure and death. Cadmium accumulates in the renal cortex and induces tubular damage. It may cause nephrotoxicity by procreating free radicals and/or by inducing necrosis, apoptosis and creatinine increase in plasma and urea increase in the serum. Exposure to cadmium can cause skeletal damage. Cadmium is attached to low bone mineralization, a high rate of fractures, increased osteoporosis and intense bone pain. It accumulates in the proximal tubular cells, it compresses cellular functions, which may result in reduced transformation among two forms of vitamin D3. This is probably to causes a decrease in calcium absorption and bone mineralization, which in turn may produce osteomalacia. The skeletal effects observed in young rats exposed to cadmium during the period of rapid skeletal growth and teratogenesis or skeletal effects recorded include sirenomelia (fused lower limbs), Amelia (absence of one or more limbs) and retard ossification of the sternum and ribs, dysplasia of facial bones and rear limbs and edema. Cadmium has been shown to be both embryotoxic and teratogenic in a different of animal species. It accumulates in human placenta and its concentration in cord blood increase with maternal exposure. Cadmium may be responsible for decreasing the volume of fetal capillaries in the terminal villi of the placenta. Furthermore, increasing the connective tissue about the fetal vessels changed synthesis of serum and amniotic fluid proteins and decreased expression of growth factors also may key a role in cadmium teratogenicity. Cadmium induces oxidative stress in many organisms at the cellular level, which may outcomes in physiological damage to various organs such as kidneys, liver, lung, pancreas, testes, placenta and bones Cadmium induces oxidative stress in many organisms at the cellular level, which may outcomes in physiological damage to various organs such as kidneys, liver, lung, pancreas, testes, placenta and bones. Reactive oxygen species reacting with polyunsaturated fatty acids of cell membranes initiate lipid

peroxidation process that results in modulation of proteins, alteration in membrane components and this reason the loss of their impartiality and irrevocable damage.

Conclusion: It can be concluded that symptoms of acute cadmium intoxicating are shortness of breath, general weakness, fever. pulmonary edema, and pneumonia. Cadmium accumulates with age in the different organs in the body and induces oxidative stress at the cellular level, which may outcomes in physiological damage to various organs such as kidneys, liver, lung, pancreas, testes, placenta and bones. Reactive oxygen species reacting with polyunsaturated fatty acids of cell membranes initiate lipid peroxidation process that results in modulation of proteins, alteration in membrane components and this reason the loss of their impartiality and irrevocable damage. Cadmium has been shown to be both embryotoxic and teratogenic in a different of animal species.

Keywords: cadmium chloride toxicity; vital organs; hepatorenal toxicity; embryos; animals teratogenic

Introduction

Cadmium is a soft, silver - white, blue-tinged, lustrous metal (Tellez-Plaza *et al.*, 2012). It is a naturally occurring element of comparatively poor abundance in the earth's crust (0.1-0.5 ppm). While it takes place in air, water, soil as well as in tissues of plants and animals, it is not found in free state. The centers for disease control and prevention (CDC) lists cadmium as number seven on its list of the 275 most venturous substances (Satarug *et al.*, 2010). The air, diet, smoking and occupational exposure are the major sources of cadmium exposure thus exposure to cadmium (Tellez-Plaza *et al.*, 2012).

Cadmium is a very toxic heavy metal and an important environmental pollutant is found naturally in very limited quantities (Djurasevic *et al.*, 2017). It causes toxicity in respiratory, digestive, reproductive, and skeletal systems and some sensitive organs including kidney and liver. In addition, It has been shown to target multiple organs and systems following intoxication causing nephrotoxicity, osteotoxicity immunotoxicity, and leads to adverse cardiovascular effects and some diabetic complications (Tourabi *et al.*, 2013; Gil-Velázquez *et al.*, 2013). It is a well characterized teratogens inducing embryo-toxicity, including growth effects, mortality and a range of congenital malformations in multiple species comprised exencephaly, microphthalmia, club foot, gastroschisis and umbilical hernia which depend upon the stage of organogenesis during which cadmium exposure occurs (El-Sayed *et al.*, 2013). Cadmium does not generate ROS directly, but can alter GSH levels and influence cell thiol status, inducing the expression of metallothionein in the liver (Ronco *et al.*, 2011).

1. Sources of cadmium exposure

Elemental cadmium, cadmium oxide, sulfide, and chloride are resurrected to the atmosphere from both natural and anthropogenic sources. Atmospheric cadmium compounds are transposed usually for long distances and deposited onto surface soils and water with minimal transduction in the atmosphere. Measurement data from northern Europe for the period 1980–88 were reported as being about 0.1 μg/m in distant areas, 0.1–0.5 μg /m^3 in countryside areas, 1–10 μg/m^3 in metropolitan areas and 1–20 μg/m^3 in industrial areas with levels of up to 100 μg/m^3 being remarked akin emission sources cognate differences were remarked in the USA (Pakkanen *et al.*, 2001).

Natural and anthropogenic sources (e.g. mine/smelter wastes, commercial fertilizers derivative from phosphate ores or sewage sludge, municipal waste landfills) involvement to the levels of cadmium found in soil and sediments. Wet or dry deposition of atmospheric cadmium on plants and soil can conduces cadmium get into the food-chain through foliar absorption or root uptake (Gao *et al.*, 2010).

Cadmium is existed in food in its inorganic form either as salts or linked to proteins such as metallothionein. Cadmium concentrations in food are periodically observation by organizations such as the National Food and agriculture organization (FAO) and the world health organization (WHO) has determined a provisional tolerable weekly intake (PWTI) of 7μg/kg body weight (Tsadilas *et al.*, 2005) (Figure 1). Data from these surveys observation that the highest concentrations are found in foods like offal, shellfish, and certain seeds. These food classes tend to form only a small ratio of the diet and as a outcomes, foods such as grains and vegetables exampled the most of dietary cadmium exposure (Committee, 201; Liu *et al.*, 2018)

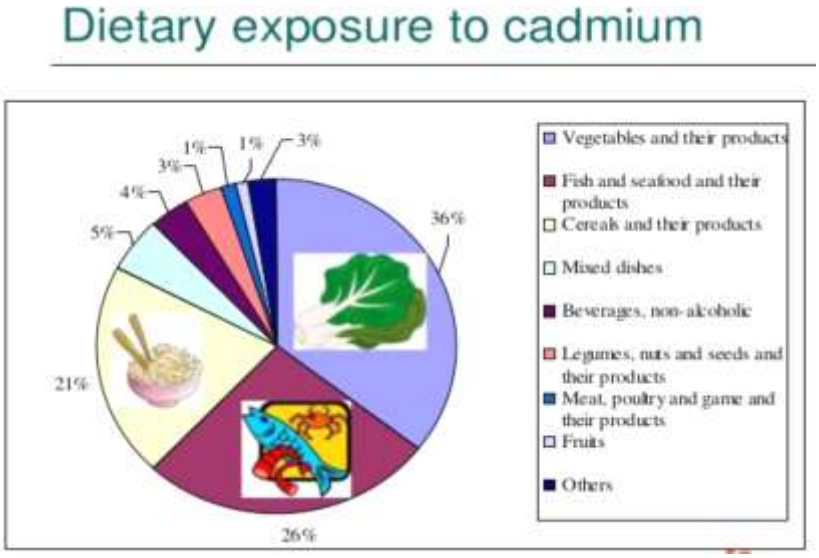


Figure 1: Dietary exposure of cadmium (EFSA, 2012).

Tobacco is a main source of cadmium exposure between smokers. The cadmium content of tobacco leaves is comparatively high with each cigarette containing around 1-2 µg of cadmium, depending on the origin of the tobacco. It is determined that about 10% of this cadmium is inhaled and between 10-50% of inhaled cadmium is absorbed (Salehi *et al.*, 2019).

As an outcomes cadmium concentrations in the blood, urine and kidney cortex are substantially higher in smokers compared to never smokers. Generally, maternal smoking has been also interlinked with lower rate birth weight an increase in teratogenesis in some studies increased the occurrence of involuntary abortions and ectopic pregnancy (Hyland *et al.*, 2015).

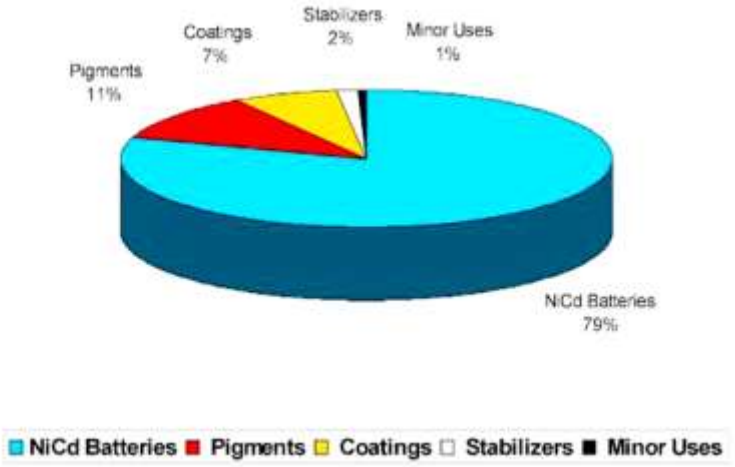
2. Production and uses of cadmium:

Cadmium metal has certain characteristics that make it favorable for an extensive diversity of industrial applications. These contain: excellent erosion resistance, decrease melting temperature, high mellowing, high thermal and electrical conductivity It is utilized and traded universally as a metal and as an ingredient in six categories of products, where it gives adjunctive performance traits According to the US Geological Survey (Lalor, 2008).

The key employs of cadmium in 2007 were: nickel– cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and other (includes non-ferrous alloys, semiconductors and photovoltaic devices) 0.8% (Rudnik and Nikiel, 2007) (USGS, 2008). The initial use of cadmium in the form of cadmium hydroxide is in electrodes for Ni–Cd batteries. Because of their performance distinct (e.g. high cycle lives, excellent low- and high-temperature performance) (Matta *et al.*, 2022).

Cadmium is also present as an impurity in non-ferrous metals (zinc, lead and copper), iron and steel, fossil fuels (coal, oil, gas, peat, and wood), cement and phosphate fertilizers. Cadmium sulfide compounds (e.g. cadmium sulfide, cadmium sulfoselenide, and cadmium lithopone) are utilized as pigments in a wide diversity of applications, involving engineering plastics, glass, glazes, ceramics, rubber, enamels, artists' colors, and fireworks. Ranging in color from yellow to deep-red maroon (Deore *et al.*, 2019).

Cadmium salts of organic acids (commonly cadmium laurate or cadmium stearate, utilized in clumps with barium sulfate) were widely used in the past as heat and light stabilizers for stretchable polyvinyl chloride and other plastics (Mhammad *et al.*, 2015) (Figure 2).



3. Toxickinetics:

3. 1. Absorption of cadmium from the gastrointestinal tract:

In human, the gastrointestinal cadmium absorption after ingestion is 3-5% whereas cadmium absorption from inhalation is 10-50% gastrointestinal absorption of cadmium in adults is an about 5%. Absorption occurs basically in the small intestine through active uptake by the divalent-metal transformer (DTM1) (Satarug *et al.*, 2010).

In animal studies, females have been found to absorb more dietary cadmium than males. The presence of other divalent or trivalent cations in the diet may compete for absorption with cadmium and as a consequence, dietary levels of trace elements and minerals, including calcium, manganese and zinc may affect the rate of cadmium absorption. Dietary factors, like fiber content, may also influence the rate of cadmium absorption from the gastrointestinal tract (Bishak *et al.*, 2015).

3.2. Absorption of cadmium from the lungs:

Absorption of cadmium from the lungs is a major source of exposure between smokers and the occupationally exposed. Absorption of cadmium from the lungs is estimated at among 10-50%. A number of factors appraises the absorption of inhaled cadmium these include, particle size, deposition, mucociliary and alveolar extricate, chemical sorts and solubility. Data on the respiratory absorption of cadmium in humans comes mainly from studies contrast smokers and non-smokers. Based on organ cadmium burden, accounted that approximately 50% of cadmium inhaled via cigarette smoke is absorbed (Satarug *et al.*, 2010).

3.3. Distribution:

Absorbed cadmium accumulates primly in the renal cortex and liver. The pancreas, thyroid, gall-bladder and testes can also include comparatively high concentrations. Several studies propose that accumulation of cadmium in the human body is a function of age; one author allegations that there is a 200-fold excess in the cadmium content of the body in the first 3 years of life, and that in this early period humans accumulate although one-third of their total body burden (Bishak *et al.*, 2015).

The human placenta is an effective barrier to cadmium and the body burden of the newborn is evaluated to be less than 0.001 mg compared with 15 to 30 mg in an adult. Cadmium accumulates with age even a maximum level is arrived at about age 50; the total body burden of a person of 50 years of age ranges from 5 to 40 mg. About half the body burden is found in the kidneys and liver (Osman *et al.*, 2000; Flora and Pachauri, 2010).

Metallothionein has been identified in the liver, kidneys, duodenum, urine and blood of animals. It has been postulated that metallothionein passes through the red cell membrane and is transformed to the kidney. Cadmium in the red blood cells is also released into the plasma when haemolysis take place (Martelli *et al.*, 2006)**.**

Metallothionein may play mainly role in the detoxification of cadmium; toxic effects likely result when the quantity of metallothionein present in the liver is insufficient to bind with absorbed cadmium. An *in vitro* study has shown that human serum alpha-2 macroglobulin is also a cadmium-binding protein.

3.4. Cadmium excretion:

The major route of excretion is via urine, the average daily excretion for humans being approximately 2-3 µg, about 0.01 % of total body burden. Its amount in the urine may be a pointer of the amount of the metal in the body. Small amounts of cadmium usually conjugated with glutathione, cysteine or metallothionein are excreted in the feces. The daily excretion of cadmium from the body (principally by the kidneys) does not exceed 0.01% of the amount of this element consumed in the diet (Sarkar, Ravindran and Krishnamurthy, 2013)(Figure3).

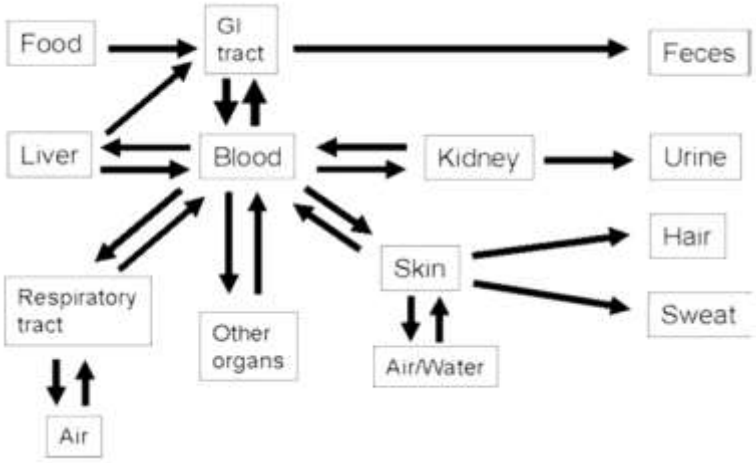


Figure 3: Absorption and distribution of cadmium in animals (Świergosz-Kowalewska, 2001).

4. Mechanisms of cadmium toxicity:

4.1. Interference with Essential Metals:

In all likelihood, cadmium being a divalent cation is accumulated by transfers mechanisms developed for necessary metals. From physical and chemical characteristics, those metals are most probably to be zinc, iron, magnesium, manganese, calcium and selenium (Genchi *et al.*, 2020)**.**

Cadmium may interact with these elements and cause their secondary disability and so break down metabolism, resulting in the final morphological and functional changes in many organs. Interaction of cadmium with iron, copper and zinc are fairly well conception and branded. Zinc also inhibit cell apoptosis induced by cadmium ions (Moulis, 2010) (Figure. 4).

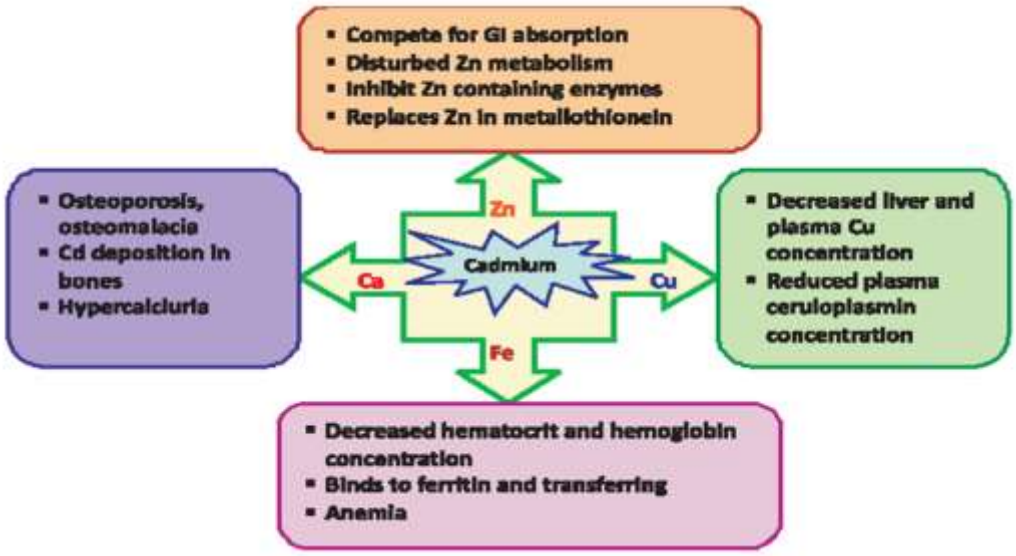


Figure 4 : Interaction of cadmium with essential nutrients by which it causes its toxic effects (Flora *et al.*, 2008)**.**

4.2. Disruption of signaling and Biomolecules:

Toxicity could result from cadmium (Cd^{2+}) interacting with cellular ingredients nonetheless without get into the cell, but by interaction with receptors on their surface. Cadmium forms covalent and ionic bonds with atoms of sulfur, oxygen and hydrogen present in the sulfhydryl groups, disulfide, carboxyl, imidazole or severally amino compounds present in the cells, causing significant disruption of their homeostasis (Bridges and Zalups, 2005).

There are many data which refers the adverse effect of cadmium on cellular signaling pathways. This interferes with the reception and processing in the cells where the external signals reach and prevent their proper functioning. Cadmium may interfere with cell signaling at each stage of signal transformation and can act on receptors, second messengers, transcription factors(Sarkar *et al.*, 2013).

The principle target organelle of cadmium is the mitochondria. Cadmium introduce the mitochondria through calcium channels and induces conformational changes in proteins situated in the membrane by binding to thiol groups therefore, interfere with oxidative phosphorylation and alter its membrane permeability conduce reduction in membrane potential, lower in cellular ATP levels, disturbances in homeostasis of calcium, sodium, potassium and ultimately leakage of cytochromes, Fe (II) ions conduce increased ROS and different of effects consequences contain excess producing of reactive oxygen species and differences in the expression of some genes which trigger cell cycle arrest, differentiation, immortalization or apoptosis. Ubiquitin attached to protein substrates is often signaled by post-translational alterability (Cuypers *et al.*, 2010) (Figure 5).

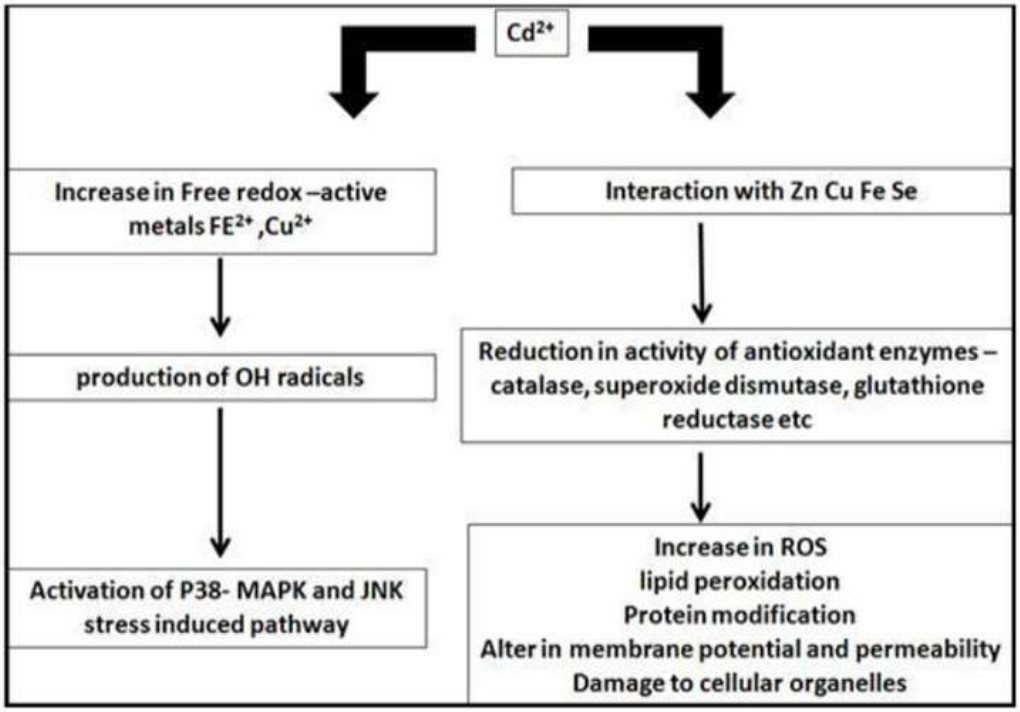


Figure 5: Schematic representation of intracellular effects of cadmium (Sarkar *et al.*, 2013)**.**

5. Adverse health effects:

Cadmium poses a great health hazard to humans until at very low concentrations in the body and because the body has limited ability to respond to cadmium exposure as the metal cannot undergo metabolic degradation to less toxic species and is poorly excreted. The objective organs for cadmium toxicity in animals include the liver, kidney, lungs, testes, prostate, heart, skeletal system, nervous system and immune system. Thus, prolonged human exposure to Cd results in its aggregation in the body and conduce diseases mainly affecting lungs and kidneys (Salvatori *et al.*, 2004).

Symptoms of acute cadmium intoxicating usually appear after 24 hours are shortness of breath, general weakness, fever. It can also cause pulmonary edema, pneumonia and in acute cases, respiratory failure and death. Women have above cadmium body burden than men, reversed as higher concentrations of cadmium in blood, urine and kidney cortex (Vahter *et al.*, 2007).

The main reason for the higher body burden in women is excess intestinal uptake of dietary cadmium. Blood cadmium is significant the most valid marker of last exposure and is usually evaluated in all blood (Sarkar *et al.*, 2013).

5.1. Effect of cadmium on kidney:

Kidney is an important target organ following chronic cadmium exposure. Cadmium accumulates in the renal cortex and induces tubular damage, which affects the ability to reabsorb substances from the initial urine following chronic cadmium exposure a large ratio of cadmium in plasma is bound to metallothionein (MT). Since the MT-cadmium complex has a small molecular size it is efficiently filtered through the glomerulus and reabsorbed by the tubular cells (National Food Institute Denmark *et al.*, 2019) (Nordberg and Nordberg, 2022).

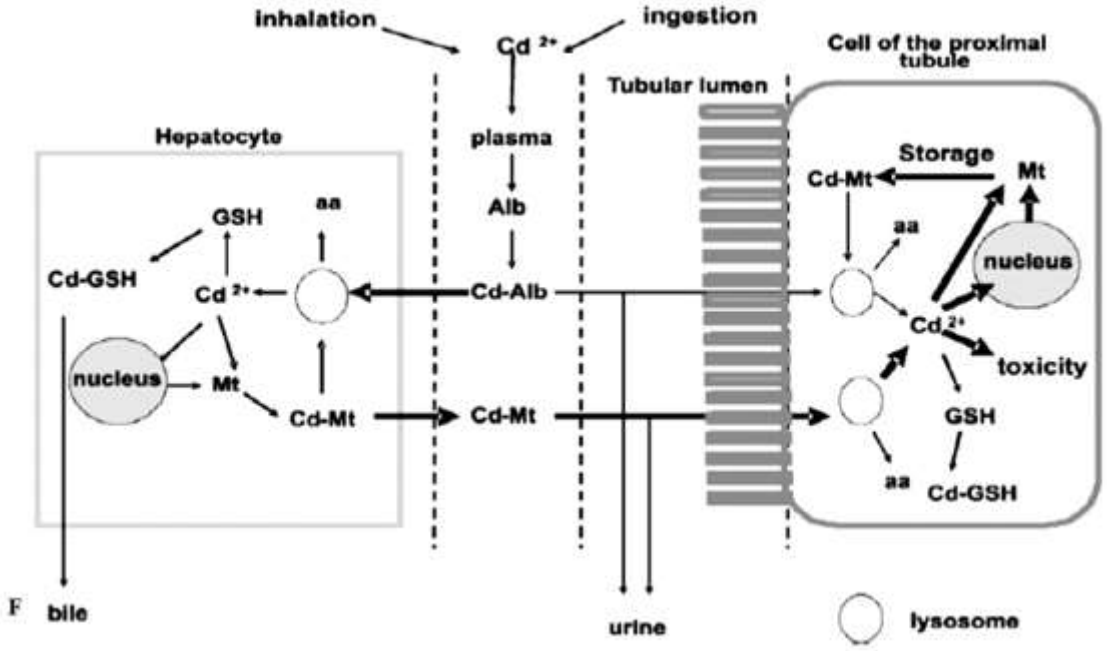
In the tubular cells, the MT-cadmium complex is ultimately reduced by lysosomes and cadmium is released into the cytoplasm where it may be re-linked to MT outputted by the tubular cells or bound to functional groups in the cell. The first early sign of cadmium – induced tubular damage is proteninuria, which is characterized by excess urinary excretion of low-molecular weight proteins and tubular enzymes (Johri *et al.*, 2010).

Numerous mechanisms have been reported to clear-up the toxic effect of cadmium on renal cells. Cadmium may cause nephrotoxicity by procreating free radicals and/or by inducing necrosis, apoptosis and creatinine increase in plasma and urea increase in the serum (Al-

Hashem *et al.*, 2009) (Figure 6).

5.2. Effect of cadmium on liver:

Cadmium accumulate in the liver following inhalation or oral exposure in humans, but there is little evidence for liver damage in humans exposed to Cd^{2+}. So that up to 75% of the total body burden is presence in these organs reported that cadmium lead to liver damage and an excess in activities of serum hepatic marker enzymes. Furthermore, cadmium hepatotoxicity is likely affected in two paths; on one hand, by the occurrence of inflammatory state, and on the other hand by direct toxic action of cadmium on liver cells (Renugadevi and Prabu, 2010) (Figure 6).



5.3. Effect of cadmium on hematological parameters:

Cadmium is one of many factors signaled to result in a spectrum of pathophysiological conditions that directly or indirectly alter red blood cell (RBC) producing. The production of RBC is dependent on the formation of hemoglobin (Hb); an important rate-limiting step during erythropoiesis enzyme delta-aminolevulinic acid dehydratase (ALAD) plays a major role in Hb constituting and its activity is an indicator of the rate of Hb synthesis (Tiwari *et al.*, 2012).

5.4. Effect of cadmium on skeletal system:

Studies in humans and animals have referred to that exposure to cadmium can cause skeletal damage (Rahimzadeh *et al.*, 2017). Cadmium is attached to low bone mineralization, a high rate of fractures, increased osteoporosis and intense bone pain. These were traits of *itai-itai* disease, first shown in Japan in the 1940's between people who had eaten rice grown on fields irrigated with cadmium - polluted water classic *itai-itai* disease resulted from a collection of low calcium diet and high cadmium exposure, which caused kidney disease and afterwards bone disease (Aoshima, 2016).

The main pact of epidemiological data has been produced from studies in polluted regions of Japan, most of the patients were postmenopausal women and exposing osteoporosis possibly enhanced by cadmium poisoning was proposed to be the actual reason for the noticed symptoms (Nogawa *et al.*, 2004).

Cadmium accumulates in the proximal tubular cells, it compresses cellular functions, which may result in reduced transformation among two forms of vitamin D3. This is probably to causes a decrease in calcium absorption and bone mineralization, which in turn may produce osteomalacia. Rather than cadmium may act directly on bone cells promoting bone resorption and decreasing bone transposition mechanisms of action is not clear (Bhattacharyya, 2009).

The skeletal effects observed in young rats exposed to cadmium during the period of rapid skeletal growth and teratogenesis or skeletal effects recorded include sirenomelia (fused lower limbs), Amelia (absence of one or more limbs) and retard ossification of the sternum and ribs, dysplasia of facial bones and rear limbs and edema (Brzóska and Moniuszko-Jakoniuk, 2005).

5.5. Effect of cadmium on placenta:

Any drugs or chemical given to the mother will cross the placenta to some extent unless it is break down or changed during placental passage or its molecular size or lipid solubility limits transplacental transfer. For drug or chemicals with low molecular weight, the transmission from placenta to fetus is crossed on the concentration gradient (Briggs, Freeman and Yaffe, 2012).

The placenta can act as a selective barer to cadmium transformed Cadmium concentration has been found to be about half as high in cord blood as in maternal blood in numerous studies including both smoking and nonsmoking women the mechanism residue elusive. Placental (MT) has previously been suggested as the main cadmium binding protein but its role in inhibiting transfer of certain metals residue inconclusive. The metal binding characteristics, localization and inducibility of placental MT suggests that MT may play a role in preventing transform of cadmium from mother to fetus (Salvatori *et al.*, 2004).

The correlations of maternal, placental and fetal blood levels of cadmium reference to that cadmium combines in the placenta have reported that cadmium salts given in small amounts to pregnant rats evoked speedily progressive alteration in the placenta, resulting in destruction of the pars fetalis which could cause embryonic death and uterine hemorrhage as shown by combines of cadmium in the

placenta at levels around 10 times higher than maternal blood cadmium concentration has been found in studies of women in Belgium and the United States (Sakamoto *et al.*, 2012).

However, it is not known why zinc and copper, which also attached to MT are able to be transformed to the fetus whereas cadmium transfer is restricted. One likely may be the changes in binding affinities of metals to MT. Since MT binds cadmium with a higher affinity than zinc. Zinc could be released from MT and readily transformed. Whereas cadmium would remain tightly bound to MT. Additionally, cadmium-MT is more resistant to degradation than zinc-MT *in vivo* and so, the higher susceptibility of zinc-MT would allow zinc to pass into the fetus. Copper is also tightly linked to MT but other copper binding proteins like ceruloplasmin, transcuprein and albumin may be more important in its transmit (Kippler *et al.*, 2010).

Localized metallothionein in full-term human placenta and in fetal cells in human placenta. Metallothionein was found in trophoblasts (which facilitate transport of substances get into the placenta from the maternal blood). However, cells (moved macrophages capable of phagocytosis and protein ingestion), amniotic epithelial cells (fetal derivatives) and decidual cells (endometrial stromal cells that have been transmitted below hormonal impact into large pale cells rich in glycogen) (Klaassen *et al.*, 2009; Furukawa *et al.*, 2019).

However, the mechanism of cadmium accumulation in the placenta is unknown. Because of its high affinity for cadmium and its localization in placenta, MT was suspected to be the major protein responsible for sequestering cadmium in the placenta and thus reducing fetal exposure. By administering cadmium late in gestation to rats with different basal MT levels and measuring the fetal accumulation (Ronco *et al.*, 2011).

6. Teratogenesis:

Teratology is the study of abnormal development in embryos and lead to congenital malformation or birth abnormalities. These anatomical or structural abnormalities are found at birth although they may not be diagnosed even later in life. They may be visible on the surface of the body or inward to the viscera (Allen *et al.*, 2007).

The term teratogen is derived from the Greek language and means "monster-former". The important brands of teratogens contain drugs, environmental chemicals and radiation for an agent to be categorized as a teratogen it must cause some developmental abnormalities in one or more kinds. Teratogens can act in numerous paths. They may directly be impacting the production of gametes and indirectly or directly weakening fetal growth/development (O'rahilly and Müller, 2010).

Teratogens commonly work only during sensitive stage of embryonic development. The interval of time the embryo is exposed to the teratogen will also impacting the morphological abnormalities. There is significant research that makes it evident that the period of organogenesis is an especially weakly time. There is diversity of causes of congenital malformations including: genetic factors (chromosomal abnormalities as well as single gene defects), environmental factors (drugs, toxins, infectious etiologies, mechanical forces) and multifactorial etiologies including a combination of environmental and genetic factors (Schumacher, 2004).

Birth defects in mammals have many potential etiologies. Though estimates vary between studies. the relative frequency of different etiologies can be broken down as follows: 20- 25% genetic based, 10% intrauterine assault (materna1 infection or disease), 1 % drug/chemical and 65-70% identified causes. It is believed that most noticed malformations with an unknown etiology are the result of interactions among drugs/chemicals and genetic structure but the interaction has not been proven (Van Gelder *et al.*, 2010).

6.1. Cadmium as animals teratogenic:

Cadmium has been shown to be both embryotoxic and teratogenic in a different of animal species. It accumulates in human placenta and its concentration in cord blood increase with maternal exposure. Although some evidence suggests that cadmium may be involved in human teratogenesis, it is very difficult to get direct data to confirm this because few exponents can be conducted on human embryos (Kippler *et al.*, 2010).

Teratogenic effects of cadmium have been described in a number of in vivo and in vitro experiments also can determined by dose and route of administration, age of gestation, sorts and strain of the animals. For example, organogenesis is the phase that developing embryos are most sensitive to cadmium (Schaefer *et al.*, 2020).

Cadmium cross through the placenta into the fetus has been rather limited after closure of the vitiline duct. A factor that may be of critical importance or an involvement to the development of the embryotoxicity and teratogenicity of cadmium is the interaction with zinc. Maternal zinc deficiency excess fetus capability effect to maternal cadmium treated and prevent the transfer of zinc from the mother to the fetus and inhibits zinc-dependent enzymes in the fetus (Ronco *et al.*, 2011). Cadmium may be responsible for decreasing the volume of fetal capillaries in the terminal villi of the placenta. Furthermore, increasing the connective tissue about the fetal vessels changed synthesis of serum and amniotic fluid proteins and decreased expression of growth factors also may key a role in cadmium teratogenicity. Maternal to fetal transmit of cadmium is very stropped late in gestation (Ji *et al.*, 2011).

7. Oxidative stress:

Oxidative stress is a commonly term utilized to describe operation of tissue damage caused by reactive oxygen species. It is often known as an imbalance in benefit of the oxidants and in disfavor of the antioxidants, potentially leading to cellular damage. Antioxidants are which substances that when found even at low concentrations contrast to those of the oxidizable substrate significantly retard or prevent oxidation of that substrate (Milatovic, Montine and Aschner, 2011).

The damage caused by this imbalance can affect a specific molecule, cell or organ system adverting of this damage are often indicated as damage products and they include changes to DNA bases, protein oxidation products and products of lipid peroxidation. Oxidative stress has been associated with alteration in protein phosphorylation in mammalian cell and excess expression of stress proteins. Oxidative stress is also known lead to changes in cell viability and to induce tissue damage. Thus, oxidative stress may be involved in membrane damage, cell cycle alters, mutagenicity and carcinogenicity which ultimately perform abnormal cellular function and disease in the organism (Gutteridge and Halliwell 2010; Birben et al. 2012).

The developing embryo is particularly susceptible to high levels of ROS because of its weak antioxidants defense; specially in the early stages of organogenesis a lot of neonatal diseases are interlinked with oxidative stress consequently the quantity that access the embryo. Moreover, maternal production of factors that meddle with embryonic. ROS -mediated signal transferring or alter embryonic determinants of oxidative stress may also involve in the risk of teratogenicity whenever ROS are increased in embryos, it is the outcomes of embryonic metabolic changes instead of exposure to ROS of maternal edified (Wells *et al.*, 2005) (Figure 7).

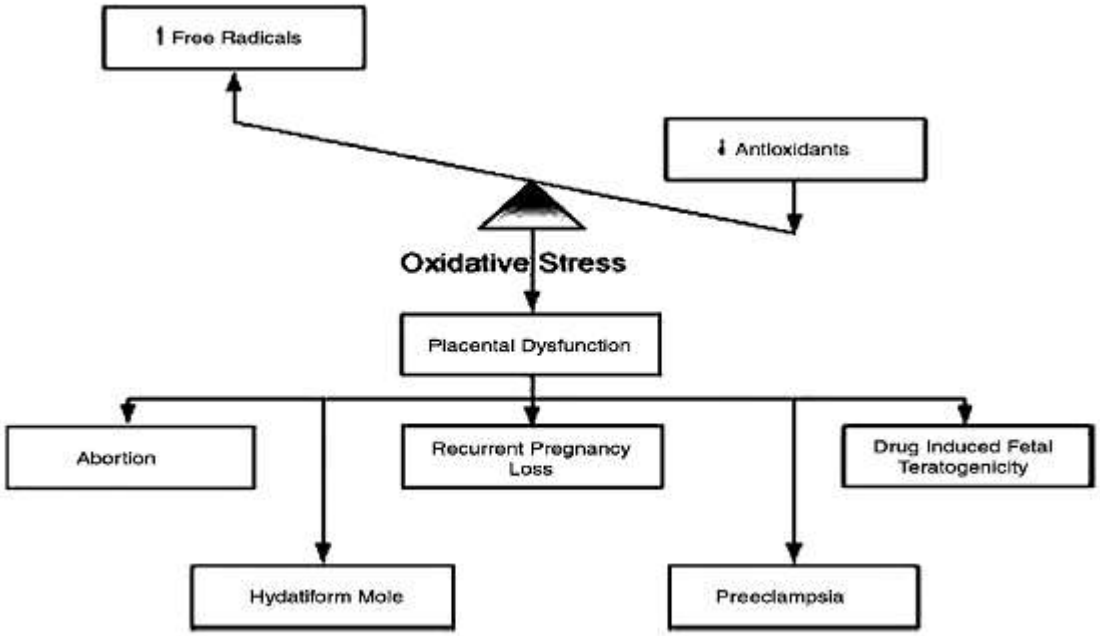


Figure 7: Role of oxidative stress in recurrent pregnancy loss (Gupta *et al.*, 2007)**.**

7.1. Cadmium and oxidative stress:

Cadmium induces oxidative stress in many organisms at the cellular level, which may outcomes in physiological damage to various organs such as kidneys, liver, lung, pancreas, testes, placenta and bones (Mladenović *et al.*, 2010).

Cadmium is a bivalent cation and is incapable to create free radicals directly yet the production of reactive oxygen species (ROS) after cadmium exposure has been marked in severally studies. The effects of cadmium-stimulates oxidative stress in the cells and tissues of animals and plants are summarized in reviews. Cadmium is unable to catalyze redox reactions in biological systems below physiological terms. It has been displayed, anyhow that cadmium excess the concentration of free redox-active metals like Fe (II), Cu (II) probable by their alternative in different proteins, alteration in mitochondrial membrane possibility and preventing the flow of electrons from reduced ubiquinone to cytochrome c (Wätjen and Beyersmann, 2004).

The precisely role of ROS in the activation of signal transformation pathways involved in defense mechanisms during cadmium stress, still wants to be explained. The oxidative stress that appears in cells subjected to cadmium impairs their antioxidant defense mechanisms, outcomes in lowering of glutathione - SH-related proteins and alteration antioxidant enzyme activity, activates proto-oncogenes, which caused increasing production of protein products that stimulate cell proliferation (Valko *et al.*, 2005).

Low efficiency of antioxidant mechanisms in cells exposed to cadmium may result from the interaction of cadmium with zinc, copper, iron and selenium outcomes in a reduce in activity of antioxidant enzymes: superoxide dismutase, catalase, glutathione peroxidase. Regardless of the mechanism of enhancing of oxidative stress in cells by cadmium, excess in ROS take place which cause the damage and alteration in their structure and metabolism. Their increases stimulate mitochondrial membrane lipid peroxidation, which can perform damage to these organelles. ROS reacting with polyunsaturated fatty acids of cell membranes initiate lipid peroxidation process that results in modulation of proteins, alteration in membrane components and this reasons the loss of their impartiality and irrevocable damage (Genchi *et al.*, 2020).

8. Conclusion

It can be concluded that symptoms of acute cadmium intoxicating are shortness of breath, general weakness, fever. pulmonary edema, and pneumonia**.** Cadmium accumulates with age in the different organs in the body and induces oxidative stress at the cellular level, which may outcomes in physiological damage to various organs such as kidneys, liver, lung, pancreas, testes, placenta and bones. Reactive oxygen species reacting with polyunsaturated fatty acids of cell membranes initiate lipid peroxidation process that results in modulation of proteins, alteration in membrane components and this reason the loss of their impartiality and irrevocable damage. Cadmium has been shown to be both embryotoxic and teratogenic in a different of animal species.

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