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Health Risk Associated with Chronic Exposure to Cadmium: A Systematic Review

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ABSTRACT

Cadmium is a chemical element; it has symbol Cd and atomic number 48. This soft, silvery-white metal is chemically similar to the two other stable metals in group 12, zinc and mercury. Like zinc, it demonstrates oxidation state +2 in most of its compounds, and like mercury, it has a lower melting point than the transition metals in groups 3 through 11. Cadmium and its congeners in group 12 are often not considered transition metals, in that they do not have partly filled d or f electron shells in the elemental or common oxidation states. The average concentration of cadmium in Earth's crust is between 0.1 and 0.5 parts per million (ppm). It was discovered in 1817 simultaneously by Stromeyer and Hermann, both in Germany, as an impurity in zinc carbonate.

Cadmium occurs as a minor component in most zinc ores and is a byproduct of zinc production. Cadmium was used for a long time as a corrosion-resistant plating on steel, and cadmium compound are used as red, orange, and yellow pigments, to color glass, and to stabilize plastic. Cadmium use is generally decreasing because it is toxic (it is specifically listed in the European Restriction of Hazardous Substances Directive[5]) and nickel–cadmium batteries have been replaced with nickel–metal hydride and lithium-ion batteries. One of its few new uses is in cadmium telluride solar panels.

Although cadmium has no known biological function in higher organisms, a cadmium-dependent carbonic anhydrase has been found in marine diatoms.

KEYWORDS-cadmium, chronic, health, risk, humans, toxicity

INTRODUCTION

Characteristics

Physical properties

Cadmium is a soft, malleable, ductile, silvery-white divalent metal. It is similar in many respects to zinc but forms complex compounds.[6] Unlike most other metals, cadmium is resistant to corrosion and is used as a protective plate on other metals. As a bulk metal, cadmium is insoluble in water[7] and is not flammable; however, in its powdered form it may burn and release toxic fumes.[8]

Chemical properties

Although cadmium usually has an oxidation state of +2, it also exists in the +1 state. Cadmium and its congeners are not always considered transition metals, in that they do not have partly filled d or f electron shells in the elemental or common oxidation states.[9] Cadmium burns in air to form brown amorphous cadmium oxide (CdO); the crystalline form of this compound is a dark red which changes color when heated, similar to zinc oxide. Hydrochloric acid, sulfuric acid, and nitric acid dissolve cadmium by forming cadmium chloride ($CdCl_2$), cadmium sulfate ($CdSO_4$), or cadmium nitrate ($Cd(NO_3)_2$). The oxidation state +1 can be produced by dissolving cadmium in a mixture of cadmium chloride and aluminium chloride, forming the Cd_2^{2+} cation, which is similar to the Hg_2^{2+} cation in mercury(I) chloride.[6]

$$Cd + CdCl_2 + 2\ AlCl_3 \rightarrow Cd_2(AlCl_4)_2$$

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The structures of many cadmium complexes with nucleobases, amino acids, and vitamins have been determined.[10]

Isotopes

Naturally occurring cadmium is composed of eight isotopes. Two of them are radioactive, and three are expected to decay but have not measurably done so under laboratory conditions. The two natural radioactive isotopes are ^{113}Cd (beta decay, half-life is 7.7×10^{15} y) and ^{116}Cd (two-neutrino double beta decay, half-life is 2.9×10^{19} y). The other three are ^{106}Cd, ^{108}Cd (both double electron capture), and ^{114}Cd (double beta decay); only lower limits on these half-lives have been determined. At least three isotopes – ^{110}Cd, ^{111}Cd, and ^{112}Cd – are stable. Among the isotopes that do not occur naturally, the most long-lived are ^{109}Cd with a half-life of 462.6 days, and ^{115}Cd with a half-life of 53.46 hours. All of the remaining radioactive isotopes have half-lives of less than 2.5 hours, and the majority have half-lives of less than 5 minutes. Cadmium has 8 known meta states, with the most stable being ^{113m}Cd ($t_{1/2}$ = 14.1 years), ^{115m}Cd ($t_{1/2}$ = 44.6 days), and ^{117m}Cd ($t_{1/2}$ = 3.36 hours).[11]

The known isotopes of cadmium range in atomic mass from 94.950 u (^{95}Cd) to 131.946 u (^{132}Cd). For isotopes lighter than 112 u, the primary decay mode is electron capture and the dominant decay product is element 47 (silver). Heavier isotopes decay mostly through beta emission producing element 49 (indium).[11]

One isotope of cadmium, ^{113}Cd, absorbs neutrons with high selectivity: With very high probability, neutrons with energy below the cadmium cut-off will be absorbed; those higher than the cut-off will be transmitted. The cadmium cut-off is about 0.5 eV, and neutrons below that level are deemed slow neutrons, distinct from intermediate and fast neutrons.[12]

Cadmium is created via the s-process in low- to medium-mass stars with masses of 0.6 to 10 solar masses, over thousands of years. In that process, a silver atom captures a neutron and then undergoes beta decay.[13]

History

Cadmium (Latin cadmia, Greek καδμεία meaning "calamine", a cadmium-bearing mixture of minerals that was named after the Greek mythological character Κάδμος, Cadmus, the founder of Thebes) was discovered in contaminated zinc compounds sold in pharmacies in Germany[14] in 1817 by Friedrich Stromeyer.[15] Karl Samuel Leberecht Hermann simultaneously investigated the discoloration in zinc oxide and found an impurity, first suspected to be arsenic, because of the yellow precipitate with hydrogen sulfide. Additionally Stromeyer discovered that one supplier sold zinc carbonate instead of zinc oxide.[5] Stromeyer found the new element as an impurity in zinc carbonate (calamine), and, for 100 years, Germany remained the only important producer of the metal. The metal was named after the Latin word for calamine, because it was found in this zinc ore. Stromeyer noted that some impure samples of calamine changed color when heated but pure calamine did not. He was persistent in studying these results and eventually isolated cadmium metal by roasting and reducing the sulfide. The potential for cadmium yellow as pigment was recognized in the 1840s, but the lack of cadmium limited this application.[16][17][18]

Even though cadmium and its compounds are toxic in certain forms and concentrations, the British Pharmaceutical Codex from 1907 states that cadmium iodide was used as a medication to treat "enlarged joints, scrofulous glands, and chilblains".[19]

In 1907, the International Astronomical Union defined the international ångström in terms of a red cadmium spectral line (1 wavelength = 6438.46963 Å).[20][21] This was adopted by the 7th General Conference on Weights and Measures in 1927. In 1960, the definitions of both the metre and ångström were changed to use krypton.[22]

After the industrial scale production of cadmium started in the 1930s and 1940s, the major application of cadmium was the coating of iron and steel to prevent corrosion; in 1944, 62% and in 1956, 59% of the cadmium in the United States was used for plating.[5][23] In 1956, 24% of the cadmium in the United States was used for a second application in red, orange and yellow pigments from sulfides and selenides of cadmium.[23]

The stabilizing effect of cadmium chemicals like the carboxylates cadmium laurate and cadmium stearate on PVC led to an increased use of those compounds in the 1970s and 1980s. The demand for cadmium in pigments, coatings, stabilizers, and alloys declined as a result of environmental and health regulations in the 1980s and 1990s; in 2006, only

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7% of to total cadmium consumption was used for plating, and only 10% was used for pigments.[5] At the same time, these decreases in consumption were compensated by a growing demand for cadmium for nickel–cadmium batteries, which accounted for 81% of the cadmium consumption in the United States in 2006.[24]

Occurrence

Cadmium makes up about 0.1 ppm of Earth's crust. It is much rarer than zinc, which makes up about 65 ppm.[25] No significant deposits of cadmium-containing ores are known. The only cadmium mineral of importance, greenockite (CdS), is nearly always associated with sphalerite (ZnS). This association is caused by geochemical similarity between zinc and cadmium, with no geological process likely to separate them. Thus, cadmium is produced mainly as a byproduct of mining, smelting, and refining sulfidic ores of zinc, and, to a lesser degree, lead and copper. Small amounts of cadmium, about 10% of consumption, are produced from secondary sources, mainly from dust generated by recycling iron and steel scrap. Production in the United States began in 1907,[18] but wide use began after World War I.[26][27]

Metallic cadmium can be found in the Vilyuy River basin in Siberia.[28]

Rocks mined for phosphate fertilizers contain varying amounts of cadmium, resulting in a cadmium concentration of as much as 300 mg/kg in the fertilizers and a high cadmium content in agricultural soils.[29][30] Coal can contain significant amounts of cadmium, which ends up mostly in coal fly ash.[31]

Cadmium in soil can be absorbed by crops such as rice and cocoa. Chinese ministry of agriculture measured in 2002 that 28% of rice it sampled had excess lead and 10% had excess cadmium above limits defined by law. Consumer Reports tested 28 brands of dark chocolate sold in the United States in 2021, and found cadmium in all of them, with 13 exceeding the California Maximum Allowable Dose level.[32]

Some plants such as willow trees and poplars have been found to clean both lead and cadmium from soil.[33]

Typical background concentrations of cadmium do not exceed 5 ng/m^3 in the atmosphere; 2 mg/kg in soil; 1 µg/L in freshwater and 50 ng/L in seawater.[34] Concentrations of cadmium above 10 µg/L may be stable in water having low total solute concentrations and p H and can be difficult to remove by conventional water treatment processes.[35]

Production

Cadmium is a common impurity in zinc ores, and it is most often isolated during the production of zinc. Some zinc ores concentrates from zinc sulfate ores contain up to 1.4% of cadmium.[36] In the 1970s, the output of cadmium was 6.5 pounds (2.9 kg) per ton of zinc.[36] Zinc sulfide ores are roasted in the presence of oxygen, converting the zinc sulfide to the oxide. Zinc metal is produced either by smelting the oxide with carbon or by electrolysis in sulfuric acid. Cadmium is isolated from the zinc metal by vacuum distillation if the zinc is smelted, or cadmium sulfate is precipitated from the electrolysis solution.[27][37]

The British Geological Survey reports that in 2001, China was the top producer of cadmium with almost one-sixth of the world's production, closely followed by South Korea and Japan.[38]

Applications

Cadmium is a common component of electric batteries, pigments,[39] coatings,[40] and electroplating.[41]

Batteries

In 2009, 86% of cadmium was used in batteries, predominantly in rechargeable nickel–cadmium batteries. Nickel–cadmium cells have a nominal cell potential of 1.2 V. The cell consists of a positive nickel hydroxide electrode and a negative cadmium electrode plate separated by an alkaline electrolyte (potassium hydroxide).[42] The European Union put a limit on cadmium in electronics in 2004 of 0.01%,[43] with some exceptions, and in 2006 reduced the limit on cadmium content to 0.002%.[44] Another type of battery based on cadmium is the silver–cadmium battery.

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Electroplating

Cadmium electroplating, consuming 6% of the global production, is used in the aircraft industry to reduce corrosion of steel components.[41] This coating is passivated by chromate salts.[40] A limitation of cadmium plating is hydrogen embrittlement of high-strength steels from the electroplating process. Therefore, steel parts heat-treated to tensile strength above 1300 MPa (200 ksi) should be coated by an alternative method (such as special low-embrittlement cadmium electroplating processes or physical vapor deposition).

Titanium embrittlement from cadmium-plated tool residues resulted in banishment of those tools (and the implementation of routine tool testing to detect cadmium contamination) in the A-12/SR-71, U-2, and subsequent aircraft programs that use titanium.[45]

Nuclear fission

Cadmium is used in the control rods of nuclear reactors, acting as a very effective neutron poison to control neutron flux in nuclear fission.[41] When cadmium rods are inserted in the core of a nuclear reactor, cadmium absorbs neutrons, preventing them from creating additional fission events, thus controlling the amount of reactivity. The pressurized water reactor designed by Westinghouse Electric Company uses an alloy consisting of 80% silver, 15% indium, and 5% cadmium.[41]

Televisions

QLED TVs have been starting to include cadmium in construction. Some companies have been looking to reduce the environmental impact of human exposure and pollution of the material in televisions during production.[46]

Anticancer drugs

Complexes based on heavy metals have great potential for the treatment of a wide variety of cancers but their use is often limited due to toxic side effects. However, scientists are advancing in the field and new promising cadmium complex compounds with reduced toxicity have been discovered.[47]

Compounds

Cadmium oxide was used in black and white television phosphors and in the blue and green phosphors of color television cathode ray tubes.[48] Cadmium sulfide (CdS) is used as a photoconductive surface coating for photocopier drums.[49]

Various cadmium salts are used in paint pigments, with CdS as a yellow pigment being the most common. Cadmium selenide is a red pigment, commonly called cadmium red. To painters who work with the pigment, cadmium provides the most brilliant and durable yellows, oranges, and reds – so much so that during production, these colors are significantly toned down before they are ground with oils and binders or blended into watercolors, gouaches, acrylics, and other paint and pigment formulations. Because these pigments are potentially toxic, users should use a barrier cream on the hands to prevent absorption through the skin[39] even though the amount of cadmium absorbed into the body through the skin is reported to be less than 1%.[8]

In PVC, cadmium was used as heat, light, and weathering stabilizers.[41][50] Currently, cadmium stabilizers have been completely replaced with barium-zinc, calcium-zinc and organo-tin stabilizers. Cadmium is used in many kinds of solder and bearing alloys, because it has a low coefficient of friction and fatigue resistance.[41] It is also found in some of the lowest-melting alloys, such as Wood's metal.[51]

Semiconductors

Cadmium is an element in some semiconductor materials. Cadmium sulfide, cadmium selenide, and cadmium telluride are used in some photodetectors and solar cells. HgCdTe detectors are sensitive to mid-infrared light[41] and used in some motion detectors.

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Laboratory uses

Helium–cadmium lasers are a common source of blue or ultraviolet laser light. Lasers at wavelengths of 325, 354 and 442 nm are made using this gain medium; some models can switch between these wavelengths. They are notably used in fluorescence microscopy as well as various laboratory uses requiring laser light at these wavelengths.[52][53]

Cadmium selenide quantum dots emit bright luminescence under UV excitation (He–Cd laser, for example). The color of this luminescence can be green, yellow or red depending on the particle size. Colloidal solutions of those particles are used for imaging of biological tissues and solutions with a fluorescence microscope.[54]

In molecular biology, cadmium is used to block voltage-dependent calcium channels from fluxing calcium ions, as well as in hypoxia research to stimulate proteasome-dependent degradation of Hif-1α.[55]

Cadmium-selective sensors based on the fluorophore BODIPY have been developed for imaging and sensing of cadmium in cells.[56] One powerful method for monitoring cadmium in aqueous environments involves electrochemistry. By employing a self-assembled monolayer one can obtain a cadmium selective electrode with a ppt-level sensitivity.[57]

Biological role and research

Cadmium has no known function in higher organisms and is considered toxic.[58] Cadmium is considered an environmental pollutant that causes health hazard to living organisms.[59] Administration of cadmium to cells causes oxidative stress and increases the levels of antioxidants produced by cells to protect against macro molecular damage.[60]

However a cadmium-dependent carbonic anhydrase has been found in some marine diatoms.[61] The diatoms live in environments with very low zinc concentrations and cadmium performs the function normally carried out by zinc in other anhydrases. This was discovered with X-ray absorption near edge structure (XANES) spectroscopy.[61][62]

Cadmium is preferentially absorbed in the kidneys of humans. Up to about 30 mg of cadmium is commonly inhaled throughout human childhood and adolescence.[63] Cadmium is under research regarding its toxicity in humans, potentially elevating risks of cancer, cardiovascular disease, and osteoporosis.[64][65][66][67]

Environment

The biogeochemistry of cadmium and its release to the environment has been the subject of review, as has the speciation of cadmium in the environment.[68][69]

Safety

Cadmium	
Hazards	
GHS labelling:[70]	
Pictograms	
Signal word	Danger

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Hazard statements	H301, H330, H341, H350, H361fd, H372, H410
Precautionary statements	P201, P202, P260, P264, P273, P304+P340+P310
NFPA 704 (fire diamond)	4 0 0

Individuals and organizations have been reviewing cadmium's bioinorganic aspects for its toxicity.[71] The most dangerous form of occupational exposure to cadmium is inhalation of fine dust and fumes, or ingestion of highly soluble cadmium compounds.[5] Inhalation of cadmium fumes can result initially in metal fume fever, but may progress to chemical pneumonitis, pulmonary edema, and death.[72]

Cadmium is also an environmental hazard. Human exposure is primarily from fossil fuel combustion, phosphate fertilizers, natural sources, iron and steel production, cement production and related activities, nonferrous metals production, and municipal solid waste incineration.[5] Other sources of cadmium include bread, root crops, and vegetables.[73]

There have been a few instances of general population poisoning as the result of long-term exposure to cadmium in contaminated food and water. Research into an estrogen mimicry that may induce breast cancer is ongoing, as of 2012.[73] In the decades leading up to World War II, mining operations contaminated the Jinzū River in Japan with cadmium and traces of other toxic metals. As a consequence, cadmium accumulated in the rice crops along the riverbanks downstream of the mines. Some members of the local agricultural communities consumed the contaminated rice and developed itai-itai disease and renal abnormalities, including proteinuria and glucosuria.[74] The victims of this poisoning were almost exclusively post-menopausal women with low iron and low body stores of other minerals. Similar general population cadmium exposures in other parts of the world have not resulted in the same health problems because the populations maintained sufficient iron and other mineral levels. Thus, although cadmium is a major factor in the itai-itai disease in Japan, most researchers have concluded that it was one of several factors.[5]

Cadmium is one of six substances banned by the European Union's Restriction of Hazardous Substances (RoHS) directive, which regulates hazardous substances in electrical and electronic equipment, but allows for certain exemptions and exclusions from the scope of the law.[75]

The International Agency for Research on Cancer has classified cadmium and cadmium compounds as carcinogenic to humans.[76] Although occupational exposure to cadmium is linked to lung and prostate cancer, there is still uncertainty about the carcinogenicity of cadmium in low environmental exposure. Recent data from epidemiological studies suggest that intake of cadmium through diet is associated with a higher risk of endometrial, breast, and prostate cancer as well as with osteoporosis in humans.[77][78][79][80] A recent study has demonstrated that endometrial tissue is characterized by higher levels of cadmium in current and former smoking females.[81]

Cadmium exposure is associated with a large number of illnesses including kidney disease,[82] early atherosclerosis, hypertension, and cardiovascular diseases.[83] Although studies show a significant correlation between cadmium exposure and occurrence of disease in human populations, a molecular mechanism has not yet been identified. One hypothesis holds that cadmium is an endocrine disruptor and some experimental studies have shown that it can interact

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with different hormonal signaling pathways. For example, cadmium can bind to the estrogen receptor alpha,[84][85] and affect signal transduction along the estrogen and MAPK signaling pathways at low doses.[86][87][88]

The tobacco plant absorbs and accumulates heavy metals such as cadmium from the surrounding soil into its leaves. Following tobacco smoke inhalation, these are readily absorbed into the body of users.[89] Tobacco smoking is the most important single source of cadmium exposure in the general population. An estimated 10% of the cadmium content of a cigarette is inhaled through smoking. Absorption of cadmium through the lungs is more effective than through the gut. As much as 50% of the cadmium inhaled in cigarette smoke may be absorbed.[90] On average, cadmium concentrations in the blood of smokers is 4 to 5 times greater than non-smokers and in the kidney, 2–3 times greater than in non-smokers. Despite the high cadmium content in cigarette smoke, there seems to be little exposure to cadmium from passive smoking.[91]

In a non-smoking population, food is the greatest source of exposure. High quantities of cadmium can be found in crustaceans, mollusks, offal, frog legs, cocoa solids, bitter and semi-bitter chocolate, seaweed, fungi and algae products. However, grains, vegetables, and starchy roots and tubers are consumed in much greater quantity in the U.S., and are the source of the greatest dietary exposure there.[92] Most plants bio-accumulate metal toxins such as cadmium and when composted to form organic fertilizers, yield a product that often can contain high amounts (e.g., over 0.5 mg) of metal toxins for every kilogram of fertilizer. Fertilizers made from animal dung (e.g., cow dung) or urban waste can contain similar amounts of cadmium. The cadmium added to the soil from fertilizers (rock phosphates or organic fertilizers) become bio-available and toxic only if the soil pH is low (i.e., acidic soils).

Zinc, copper, calcium, and iron ions, and selenium with vitamin C are used to treat cadmium intoxication, though it is not easily reversed.[82]

Regulations

Because of the adverse effects of cadmium on the environment and human health, the supply and use of cadmium is restricted in Europe under the REACH Regulation.[93]

The EFSA Panel on Contaminants in the Food Chain specifies that 2.5 µg/kg body weight is a tolerable weekly intake for humans.[92] The Joint FAO/WHO Expert Committee on Food Additives has declared 7 µg/kg body weight to be the provisional tolerable weekly intake level.[94] The state of California requires a food label to carry a warning about potential exposure to cadmium on products such as cocoa powder.[95]

The U.S. Occupational Safety and Health Administration (OSHA) has set the permissible exposure limit (PEL) for cadmium at a time-weighted average (TWA) of 0.005 ppm. The National Institute for Occupational Safety and Health (NIOSH) has not set a recommended exposure limit (REL) and has designated cadmium as a known human carcinogen. The IDLH (immediately dangerous to life and health) level for cadmium is 9 mg/m^3.[96]

Lethal dose[97]	Organism	Route	Time
LD_{50}: 225 mg/kg	rat	oral	n/a
LD_{50}: 890 mg/kg	mouse	oral	n/a
LC_{50}: 25 mg/m^3	rat	n/a	30 min

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In addition to mercury, the presence of cadmium in some batteries has led to the requirement of proper disposal (or recycling) of batteries.

Product recalls

In May 2006, a sale of the seats from Arsenal F.C.'s old stadium, Highbury in London, England was cancelled when the seats were discovered to contain trace amounts of cadmium.[98] Reports of high levels of cadmium use in children's jewelry in 2010 led to a US Consumer Product Safety Commission investigation.[99] The U.S. CPSC issued specific recall notices for cadmium content in jewelry sold by Claire's[100] and Wal-Mart[101] stores.

In June 2010, McDonald's voluntarily recalled more than 12 million promotional Shrek Forever After 3D Collectible Drinking Glasses because of the cadmium levels in paint pigments on the glassware.[102] The glasses were manufactured by Arc International, of Millville, New Jersey, USA.[103]

II. DISCUSSION

Cadmium is a naturally occurring toxic metal with common exposure in industrial workplaces, plant soils, and from smoking. Due to its low permissible exposure in humans, overexposure may occur even in situations where trace quantities of cadmium are found. Cadmium is used extensively in electroplating, although the nature of the operation does not generally lead to overexposure. Cadmium is also found in some industrial paints and may represent a hazard when sprayed. Operations involving removal of cadmium paints by scraping or blasting may pose a significant hazard. The primary use of cadmium is in the manufacturing of NiCd rechargeable batteries. The primary source for cadmium is as a byproduct of refining zinc metal.[1] Exposures to cadmium are addressed in specific standards for the general industry, shipyard employment, the construction industry, and the agricultural industry.[2]

Signs and symptoms

Acute

Acute exposure to cadmium fumes may cause flu-like symptoms including chills, fever, and muscle ache sometimes referred to as "the cadmium blues." Symptoms may resolve after a week if there is no respiratory damage. More severe exposures can cause tracheobronchitis, pneumonitis, and pulmonary edema. Symptoms of inflammation may start hours after the exposure and include cough, dryness and irritation of the nose and throat, headache, dizziness, weakness, fever, chills, and chest pain.

Chronic

Complications of cadmium poisoning include cough, anemia, and kidney failure (possibly leading to death).[3] Cadmium exposure increases one's chances of developing cancer.[4] Similar to zinc, long-term exposure to cadmium fumes can cause lifelong anosmia.

Bone and joints

One of the main effects of cadmium poisoning is weak and brittle bones.[3] The bones become soft (osteomalacia), lose bone mineral density (osteoporosis), and become weaker. This results in joint and back pain, and increases the risk of fractures. Spinal and leg pain is common, and a waddling gait often develops due to bone deformities caused by the long-term cadmium exposure. The pain eventually becomes debilitating, with fractures becoming more common as the bone weakens. Permanent deformation in bones can occur.[3] In extreme cases of cadmium poisoning, mere body weight causes a fracture.

Renal

The kidney damage inflicted by cadmium poisoning is irreversible. The kidneys can shrink up to 30 percent. The kidneys lose their function to remove acids from the blood in proximal renal tubular dysfunction. The proximal renal tubular dysfunction causes hypophosphatemia, leading to muscle weakness and sometimes coma. Hyperchloremia also occurs. Kidney dysfunction also causes gout, a form of arthritis due to the accumulation of uric acid crystals in the joints because of high acidity of the blood (hyperuricemia). Cadmium exposure is also associated with the development of kidney stones.

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Sources of exposure

Smoking is a significant source of cadmium exposure. Even small amounts of cadmium from smoking are highly toxic to humans, as the lungs absorb cadmium more efficiently than the stomach.[5] Cadmium is emitted to the electronic cigarette (EC) aerosol but, on currently available data, the lifetime cancer risk (LCR) calculated doesn't exceed the acceptable risk limit.[6][7]

Environmental

Buildup of cadmium levels in the water, air, and soil has been occurring particularly in industrial areas. Environmental exposure to cadmium has been particularly problematic in Japan where many people have consumed rice that was grown in cadmium-contaminated irrigation water. This phenomenon is known as itai-itai disease.[8]

People who live near hazardous waste sites or factories that release cadmium into the air have the potential for exposure to cadmium in air. However, numerous state and federal regulations in the United States control the amount of cadmium that can be released to the air from waste sites and incinerators so that properly regulated sites are not hazardous. The general population and people living near hazardous waste sites may be exposed to cadmium in contaminated food, dust, or water from unregulated or accidental releases. Numerous regulations and use of pollution controls are enforced to prevent such releases.

Some sources of phosphate in fertilizers contain cadmium in amounts of up to 100 mg/kg,[9][10] which can lead to an increase in the concentration of cadmium in soil (for example in New Zealand).[11]

Food

Food is another source of cadmium. Plants may contain small or moderate amounts in non-industrial areas, but high levels may be found in the liver and kidneys of adult animals. The daily intake of cadmium through food varies by geographic region. Intake is reported to be approximately 8 to 30µg in Europe and the United States versus 59 to 113 µg in various areas of Japan.[12] A small study of premium dark chocolate samples found 48% had high levels of cadmium, the source commonly being the presence of cadmium in soil in which they were grown.[13]

Occupational exposure

In the 1950s and 1960s industrial exposure to cadmium was high, but as the toxic effects of cadmium became apparent, industrial limits on cadmium exposure have been reduced in most industrialized nations and many policy makers agree on the need to reduce exposure further. While working with cadmium it is important to do so under a fume hood to protect against dangerous fumes. Brazing fillers which contain cadmium should be handled with care. Serious toxicity problems have resulted from long-term exposure to cadmium plating baths.

Workers can be exposed to cadmium in air from the smelting and refining of metals, or from the air in plants that make cadmium products such as batteries, coatings, or plastics. Workers can also be exposed when soldering or welding metal that contains cadmium. Approximately 512,000 workers in the United States are in environments each year where cadmium exposure may occur. Regulations that set permissible levels of exposure, however, are enforced to protect workers and to make sure that levels of cadmium in the air are considerably below levels thought to result in harmful effects.

Artists who work with cadmium pigments, which are commonly used in strong oranges, reds, and yellows, can easily accidentally ingest dangerous amounts, particularly if they use the pigments in dry form, as with chalk pastels, or in mixing their own paints.

Consumer products

Cadmium is used in nickel-cadmium batteries; these are some of the most popular and most common cadmium-based products.

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In February 2010, cadmium was found in an entire line of Wal-Mart exclusive Miley Cyrus jewelry. The charms were tested at the behest of the Associated Press and were found to contain high levels of cadmium. Wal-Mart did not stop selling the jewelry until May 12 because "it would be too difficult to test products already on its shelves".[14]

On June 4, 2010, cadmium was detected in the paint used on promotional drinking glasses for the movie Shrek Forever After, sold by McDonald's Restaurants, triggering a recall of 12 million glasses.[15]

Toxicology

Cadmium is an extremely toxic industrial and environmental pollutant classified as a human carcinogen: Group 1, according to the International Agency for Research on Cancer;[4] Group 2a, according to Environmental Protection Agency (EPA); and a 1B carcinogen as classified by European Chemical Agency.[16][17]

Toxicodynamics

Inside cells, cadmium ions act as a catalytic hydrogen peroxide generator. This sudden surge of cytosolic hydrogen peroxide causes increased lipid peroxidation and additionally depletes ascorbate and glutathione stores. Hydrogen peroxide can also convert thiol groups on proteins into nonfunctional sulfonic acids and is also capable of directly attacking nuclear DNA. This oxidative stress causes the afflicted cell to manufacture large amounts of inflammatory cytokines.[18][19]

Toxicokinetics

Inhaling cadmium-laden dust quickly leads to respiratory tract and kidney problems which can be fatal (often from kidney failure). Ingestion of any significant amount of cadmium causes immediate poisoning and damage to the liver and the kidneys. Compounds containing cadmium are also carcinogenic.[20]

Diagnosis

Biomarkers of excessive exposure

Increased concentrations of urinary beta-2 microglobulin can be an early indicator of kidney dysfunction in persons chronically exposed to low but excessive levels of environmental cadmium. The urinary beta-2 microglobulin test is an indirect method of measuring cadmium exposure. Under some circumstances, the Occupational Health and Safety Administration requires screening for kidney damage in workers with long-term exposure to high levels of cadmium.[21] Blood or urine cadmium concentrations provide a better index of excessive exposure in industrial situations or following acute poisoning, whereas organ tissue (lung, liver, kidney) cadmium concentrations may be useful in fatalities resulting from either acute or chronic poisoning. Cadmium concentrations in healthy persons without excessive cadmium exposure are generally less than 1 μg/L in either blood or urine. The ACGIH biological exposure indices for blood and urine cadmium levels are 5 μg/L and 5 μg/g creatinine, respectively, in random specimens. Persons who have sustained kidney damage due to chronic cadmium exposure often have blood or urine cadmium levels in a range of 25-50 μg/L or 25-75 μg/g creatinine, respectively. These ranges are usually 1000-3000 μg/L and 100-400 μg/g, respectively, in survivors of acute poisoning and may be substantially higher in fatal cases.[22][23]

Treatment

A person with cadmium poisoning should seek immediate medical attention, both for treatment and supportive care.[24]

For a non-chronic ingestive exposure, emetics or gastric lavage shortly after exposure can beneficially decontaminate the gastrointestinal system. Activated charcoal remains unproven.[25] The US CDC does not recommend chelation therapy,[25] in part because chelation may accentuate kidney damage.[24]

For long-term exposure, considerable evidence indicates that the traditional chelator EDTA can reduce a body's overall cadmium load. Co-administered antioxidants, including nephroprotective glutathione, appear to improve efficacy. For patients with extremely fragile kidneys, limited evidence suggests that sauna sweat may differentially excrete the metal.[24]

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Epidemiology

In a mass cadmium poisoning in Japan, a marked prevalence for skeletal complications has been noted for older, postmenopausal women, however, the cause of the phenomenon is not fully understood, and is under investigation. Cadmium poisoning in postmenopausal women may result in an increased risk for osteoporosis. Current research has pointed to general malnourishment, as well as poor calcium metabolism relating to the women's age.[26] Studies are pointing to damage of the mitochondria of kidney cells by cadmium as a key factor of the disease.[27]

History

An experiment during the early 1960s involving the spraying of cadmium over Norwich was declassified in 2005 by the UK government, as documented in a BBC News article.[28]

III. RESULTS

Cadmium poisoning has been reported from many parts of the world. It is one of the global health problems that affect many organs and in some cases it can cause deaths annually. Long-term exposure to cadmium through air, water, soil, and food leads to cancer and organ system toxicity such as skeletal, urinary, reproductive, cardiovascular, central and peripheral nervous, and respiratory systems. Cadmium levels can be measured in the blood, urine, hair, nail and saliva samples. Patients with cadmium toxicity need gastrointestinal tract irrigation, supportive care, and chemical decontamination traditional-based chelation therapy with appropriate new chelating agents and nanoparticle-based antidotes. Furthermore it has been likewise recommended to determine the level of food contamination and suspicious areas, consider public education and awareness programs for the exposed people to prevent cadmium poisoning.

Over a few decades ago, to follow the abundant accessibility of various chemical materials, the rate of intoxication has amazingly increased (1, 2). People may use some drugs and chemicals in the wrong way, as a result they may be poisoned intentionally or accidentally (3, 4). Heavy metals similar to other poisonous chemicals, from natural or industrial sources, can pose serious threats to human life (5). Cadmium (Cd, atomic number 48, atomic mass number 112, melting point 321 °C, and boiling point 765°C) is an element with soft, ductile, silvery white with bluish color, lustrous, and electropositive properties. It does not have any odor or taste, and is very poisonous. Cd has eight stable isotopes: ^{106}Cd, ^{108}Cd, ^{110}Cd, ^{111}Cd, ^{112}Cd, ^{113}Cd, ^{114}Cd, and ^{116}Cd. The most common isotopes are ^{112}Cd and ^{114}Cd (6). Cadmium also forms a variety of complex organic amines, sulfur complex, chloro complexes, and chelates. Cd ions form soluble salts of carbonates, arsenates, phosphates, and ferrocyanide compounds. Accompanying zinc production, it can be produced in different commercial forms. It is used as alloys in electroplating (auto industries) and in production of pigments (cadmium sulfate, cadmium selenide), likewise as stabilizers for polyvinyl plastic, and in batteries (rechargeable Ni-Cd batteries) (6, 7).

Epidemiology: In spite of the dramatic worldwide production, consumption and release of Cd compounds in the environment show no efficient recycling way for them. Accordingly, human exposure to Cd compounds may create a serious health problem. Cadmium has been used in nickel-cadmium battery, as a pigment in paint production, likewise, in electroplating and producing polyvinyl chloride plastic. Furthermore, cadmium is present in most foodstuffs, and depending on dietary habits, its level varies greatly.

Cadmium considerably exists in environment, as a result of human activities, such as the use of fossil fuels, metal ore combustion and waste burning. Leaking sewage sludge to agricultural soil may cause the transfer of cadmium compounds adsorbed by plants that may play a significant role in food chain, and accumulate in various human organs. Also, the other great source of cadmium exposure is cigarette smoke. When cadmium was measured in smokers' blood samples, it showed that they had 4-5 times cd levels in blood higher than the non-smokers (8).

Exposure to cadmium in many different ways has been reported during the past century. Damage to the lungs in Cd-exposed workers was reported as early as the 1930s. Moreover, in the next decades, some bone and kidney toxicity cases of cadmium exposure were described. After World War II, in the 1960's and 1970's, Japanese people suffered from different levels of pollution. Itai-itai disease was one of these conditions caused by chronic cadmium

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contaminated rice fields. The number of patients affected by the disease was estimated around 400 patients from 1910 to 2007 (9).

Another international collaborative study in 16 European countries has reported that the amount of cadmium in mother-child couples exceeded the tolerable weekly intake. In that study, Poland had the highest urine-Cd in comparison between the16 countries while Denmark showed the lowest level (10). In the United States, approximately 600 tons of Cd compound are produced every year and 150 tons are imported from other countries (11).

While most parts of Iran, rice and wheat are the daily staple food. Iranian farmers in achieving high quality crops may have applied enormous amount of phosphate fertilizers and sludge waste, which consequently contains higher concentration of cadmium. This may increase Cd absorption via consumption of foods produced in crops.

Based on FAO/WHO rules the permitted level of cadmium in rice is 0.2 mg/kg (12). The result showed Iranian rice samples had higher level of Cd than the permitted concentration. In addition, the risk will increase consuming other sources such as farm products (vegetables) and sea foods (fish, etc), if cadmium contamination occurs (13).

Nowadays, cadmium exposure has decreased in many countries (14), but it has a very long biological half-life (10-30 years) (10) and human activities related to cadmium should be restricted to a minimal or no harmful level (10).

It is necessary to prepare the basic information of cadmium poisoning and design an educational and prophylactic plan to substantially reduce the incidence of its toxicity. The present review may be informative and helpful to achieve the purpose of managing all aspects of cadmium compound poisoning.

Mechanism of Toxicity: Cadmium affects cell proliferation, differentiation, and apoptosis. These activities interact with DNA repair mechanism, the generation of reaction oxygen species (ROS) and the induction of apoptosis (15). Cadmium binds to the mitochondria and can inhibit both cellular respiration and oxidative phosphorylation at low concentration (16).

It results in chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA- protein crosslinks in cell lines. Cadmium causes mutations and chromosomal deletions potentially (17). Its toxicity involves depletion of reduced glutathione (GSH), binds sulfhydryl groups with protein, and causes to enhance production of reactive oxygen species (ROS) such as superoxide ion, hydrogen peroxide, and hydroxyl radicals. Cadmium also inhibits the activity of antioxidant enzymes, such as catalase, manganese-superoxide dismutase, and copper/zinc-dismutase (18). Metallothionein is a zinc – concentrating protein that contains 33% cysteine. Metallothionein also can act as a free-radical scavenger. It scavenges hydroxyl and superoxide radicals (19). Generally, the cells that contain metallothioneins are resistant to cadmium toxicity. On the other hand, the cells that cannot synthesize metallothioneins are sensitive to cadmium intoxication (20). Cadmium can modulate the cellular level of Ca^{2+} and the activities of caspases and nitrogen-activated protein kinases (MRPKs) in the cells, in which these processes cause apoptosis indirectly (21).

While P_{53} causes cell death by directly binding to mitochondrial membrane proteins. Expression of B-cell lymphoma-extra-large (Bcl-xl), which is a transmembrane molecule in the mitochondria, suppresses mitochondrial-mediated apoptosis and enhances cancer cells. To address the challenge to the observation posed; binding of P_{53} to Bcl-xl can inhibit protein and apoptotic cell death (22).

Cadmium can induce ROS production and result in oxidative stress. This mechanism may express the role of cadmium in organ toxicity, carcinogenicity and apoptotic cell death .

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Clinical Manifestation: Different forms of cadmium compounds have different clinical manifestations and toxic effects that were explained in the details below.

Cadmium bone and Itai-itai disease: Several studies mentioned cadmium can affect the skeletal system. Exposure to cadmium caused skeletal demineralization, whereby it may directly interact with bone cells, diminish mineralization, also inhibit procollagen C-proteinases and collagen production (22). Clinical findings associated with osteoporosis include pain, physical impairment, and decreased quality of life. Besides, decreased bone density imparts increased risk for bone fractures. Osteoporotic fractures are most common in post-menopausal women that can result to disability. Pseudofractures following osteomalacia and severe skeletal decalcification may be observed as well (23).

When serum PTH levels decreased with higher cadmium exposure, this may induce the release of calcium from bone tissue (24). Cadmium may interact with metabolism of calcium, vitamin D_3 and collagen. Therefore osteomalacia or osteoporosis could be observed in delayed manifestations of severe cadmium poisoning (22).

Itai-itai disease is the most severe form of chronic cadmium intoxication. The first recognition occurred in Jinzu river, Toyama Prefecture, Japan (25). Two hypotheses have been proposed to explain bone lesion. Direct actions of cadmium on bone include; disappearance of metaphyseal trabeculas and shortened epiphyseal cartilage in which cadmium caused osteoporotic, but does not observe osteomalacic changes via radiographical controls. Indirect effects of cadmium on bone include; thinning bone cortex, trabecular bone loss, in addition there is a decrease in number of osteocytes and acid mucopolysaccharides in epiphyseal cartilage (25). Cadmium intoxicants cause femoral and low back pain in initial manifestation, the further pain spread to the other areas of the body. Moreover, skeletal deformities can cause bone fractures (26).

Renal damage in cadmium toxicity: Cadmium predominantly accumulates in kidney and liver, but it can be found in other tissues such as bone and placenta. It has been reported that occupational and environmental exposures to cadmium have implicated renal dysfunction (27). Cadmium exposure can show early signs of renal damage, proteinuria, calcium loss and tubular lesion. Urine analysis may help to prove early signs of renal damage (16). Generally, the glomerular filtration rate (GFR) and reserve filtration capacity will be diminished, and severe cadmium toxicity may induce nephrotoxicity with complications such as; glucosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, polyuria and decreased buffering capacity (28). Cellular damage and functional integrity in proximal tubules resulted in loss of calcium, amino acids, enzymes, and increase proteins in the urine. On the other hand, a decreased tubular reabsorption of a few molecular-weight proteins, lead to tubular proteinuria. The most common proteins in urine are beta 2-microglobulin, retinol- binding protein and alpha 1-microglobulin (29).

Cadmium and reproductive system: Several previous studies found that cadmium has the potential to affect reproduction and development in several mammalian species, and recent studies have also confirmed these findings (30). Compared to animal studies, it is claimed that cadmium decreases density, volume and number of sperms, and increases immature sperm forms (31). These problems are followed by a defect in spermatogenesis, sperm quality, and secretory functions of accessory glands. Besides, it decreases libido, fertility, and serum testosterone level (32). In female reproductive system, the function of ovary and development of oocytes may be inhibited. Steroidogenesis is reduced under Cd toxicity and ovarian hemorrhage and necrosis can co-occur (30). It has been reported that the rate of spontaneous abortion and time of pregnancy are increased and the rate of live births decreased (31).

Cadmium and cardiovascular system: In vitro studies have indicated the involvement of cadmium in endothelial dysfunction as well as carotid intima-media thickness (IMT). Moreover, the formation of atherosclerotic plaques were promoted in vivo (33). Following cadmium intoxication, endothelial dysfunction at starting of cardiovascular disease (CVD), loss of endothelial cell structure causing cell death, and thrombogenic events may occur. These results support the hypothesis cadmium involvement in cardiovascular disease and myocardial infarction (34). Epidemiologic studies had shown the association of cadmium exposure with risk of high blood pressure (systolic and diastolic blood pressures).

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Cadmium may inhibit endothelial nitric oxide synthase and suppresses acetylcholine induced vascular relaxation resulting in hypertension (35). It may stimulate production of cytokines and induce endothelial damage. These mechanisms cause atherogenesis and long- term exposure may increase the incidence of peripheral arterial disease (36). Cadmium toxic exposure may increase cardiovascular mortality (37).

Cadmium and other systems: The acute central and peripheral neurotoxicity of cadmium has been recently reported (38). Cadmium may also induce cellular damage and lipid peroxidation in brain. Its effect on monoaminoxidase (MAO) is responsible for oxidative deamination of monoamine neurotransmitters (38). Cadmium increases production of free radicals in CNS and decreases cellular defense against oxidation (39) . In general, the outcomes of this mechanism are olfactory dysfunction, neurobehavioral defects in attention, disorder in psychomotor activity, and memory (40). Poisoning may lead to neurodegenerative disorders, such as Parkinson, Alzheimer, and Huntington's diseases accompanying with loss of memory and behavioral changes.

Recent study has shown a possible involvement of cadmium in pulmonary diseases such as chronic obstructive disease and emphysema (41). Animal studies showed that cadmium chloride can decrease lung vital capacity and increase alveolar wall thickness. Inhalation of cadmium as vapor in the absence of antioxidants, and condition of oxidative stress, may result in pulmonary inflammation and emphysema (41). According to the Agency for Toxic Substances and Disease Registry (ATSDR) suggestion; cadmium is a possible lung carcinogen in humans (41).

Cadmium is absorbed through the gastrointestinal tract (GIT). Its solubility and absorption are affected by gastric and/ or intestinal pH. In fact, cadmium reacts with HCl and forms of cadmium chloride. It can induce the inflammation of GIT. The H_2 blockers can raise gastric pH, causing to decrease the solubility and inhibit the absorption of cadmium (42). Several studies had shown cadmium can induce liver damage in acute stage. Prolonged oral cadmium ingestion can cause Itai-itai disease in chronic phase (43).

Limited research studies in cadmium poisoning with skin manifestations showed hyperkeratosis and acanthosis, accompanied with occasional ulcerative change, and an increase of the mitotic index of the skin cells (44).

Cadmium and carcinogenicity: Cadmium compounds were categorized as carcinogenic in humans by International Agency for Research on Cancer (IARC) (45). It may be considered as lung carcinogen, also inducer of prostatic or renal cancers .The important point is that cadmium can disorder testosterone production and induce testicular interstitial cells hyperplasia (46). Some reports suggested that cadmium may be involved malignancies of liver, hemotopoitic system, bladder and stomach (47). Furthermore, cadmium may be a potential risk factor for breast cancer. Another study suggested that cadmium exposure may be involved in pancreas cancer because of inducing increased risk for neoplasia (47).

The cellular and molecular mechanisms implicating cadmium carcinogenicity include the activation of proto-oncogenes, inactivation of tumor suppressor genes, disruption of cell adhesion, and inhibition of DNA repair (48). In fact, DNA strand damage or DNA-protein crosslinks disorder may completely cause to inhibit cell growth. In summary, it is suggested that cadmium exposure can affect cell proliferation, differentiation, apoptosis, cell signaling and other cellular activities. These activities could bear on carcinogenesis directly or indirectly (47).

Diagnostic evaluation: Cadmium levels in blood, urine, hair and nails samples are often determined in paraclinic lab tests.

Urine: Kidneys are the main organ to be affected by cadmium in long term exposure (49). Crinnion suggested; urinary cadmium concentration equal or greater than 0.5 µg/g creatinine is associated with renal damage, also the concentrations more than 2.0 µg/g of creatinine may be translated into extensive damage (50).

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Tubular dysfunction followed by cadmium nephrotoxicity increases urinary excretion of low molecular weight proteins such as $ß_2$-microglobulin, α_1 microglobulin, retinol binding protein, enzymes such as N - acetyl - ß – glucosaminidase, and calcium (51). In this situation, sensitive tests (low molecular weight proteinuria) may be positive and mixed proteinuria (low and high molecular weight proteins excretion in urine) is seen (28).

Blood: Long cadmium half-life (30 years) may be due to long term accumulation of cadmium in the body but the short half-life of cadmium in blood (three to four months) could have result in a recent exposure. The limit of detection for blood cadmium concentration is 0.3 µg/L (52). Blood Cadmium was measured by two techniques; either electrothermal atomic- absorption spectrophotometry or the inductively coupled plasma mass spectrometry. Based on the research studies done in the National Health and Nutrition Examination Surveys (NHANES), the values at or below the limit of detection of cadmium in all of participants are follows: 1999-200: 0.3µg/l; 2003-2004: 0.14µg/l; 2005-2010: 0.2µg/l; (53).

Hair–nail and saliva: Determination of the trace element levels in hair and nails is the subject of interest in biomedical sciences (54). Trace elements accumulate in the body in a long time may affect biomedical and metabolic processes over time (55). Additionally, the sampling, transport and storage of hair and nails samples are easy and feasible and analysis of trace elements in the samples is cheap and fast (55).

Cadmium accumulates in body for a long time and its concentration can gradually increase several years after exposure .The levels of cadmium in the hair have different reference values of various countries e.g., in Italy is 0.03 mg/kg, England 0.11 mg/kg, and in Japan 0.05 mg/kg(55). Further, it is reported that the amount of cadmium in hair is 0.61 ± 1.13 µg g^{-1} and the nails 1.11 ± 0.83 µg g^{-1} elsewhere (56). Saliva analysis can be an excellent method for long term detection of heavy metal contamination. The mean level of cadmium in saliva with tolerable standard limit in human body is less than 0.55 µg/l (57).

Application of nanomaterial in the diagnosis of cadmium poisoning: Nanomaterials have different applications such as tissue and organ engineering, medical instruments, drug delivery, diagnosis evaluation, prevention and management (58). Utilizing nanotechnology for diagnosing and eliminating toxic metals such as cadmium can help to manage cadmium intoxication and increase environment safety (59).

Several nanoparticles have been used for diagnostics. One of the nanoparticles is quantum dots (QDs). QDs are made of fluorescent labels of cadmium selenide or zinc sulfide. When cadmium poisoning occurs, it is released and entered into cells containing zinc ions. Capping QDs with ZnO effectively prevents cadmium formation, and achieving better to cover material is done. A gene expression test helped to determine this coating (60).

Treatment of cadmium poisoning

Immediate considerations: After evaluation of the airways, breathing and circulation, protection and care is necessary. The GIT should be irrigated to remove cadmium containing solutions. Acute or chronic ingesting of cadmium salts is rare, but it may lead to death. The lowest lethal dose of Cd is 5 gr in a 70 kg man. If emesis has not occurred, gastric lavage is performed soon. A small nasogastric tube tube must be used (61). Activated charcoal cannot effectively absorb the metal.

Hospitalization may help the patients exposed to cadmium for evaluating the extent of liver damage, gastrointestinal, urinary and respiratory tracts thus, we suggest supportive therapy (61).

Natural and chemical decontamination: Industrial and mining activities may release cadmium ions in waste water. Natural decontamination can be introduced using some medicinal plants. The seeds of Moringa oleifera, peanuts

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(Arachis hypogaea), cowpeas (Vigna unguiculata), urad (Vigna mungo) and corn (Zea mays) were used for water purification. These seeds can absorb and neutralize colloidal positive charges. This action causes to absorb the negative charged impurities and metals in waste water (62).

Some plants are used for phytomediation to extract and detoxify some pollutants. They have ability to accumulate heavy metals such as; Cd, Cr, Pb, Co, Ag, Se and Hg in their tissues. For example, Cleome Gynandra has been used as a phytoorigin detoxifier (63). Phytochelating activity has an important role in metal detoxification by the sequestration of Zn and Cd (64).

The removal of heavy metals from contaminated soil includes; 1) washing, leaching, flushing with chemical agents, 2) adding some non- toxic materials to reduce solubility of heavy metal 3) electromigration, 4) covering the original pollutants with clean materials, 5) mixing polluted materials with clean materials in surface and subsurface to reduce the concentration of heavy metals, and 6) phytoremediation by plants (65). The absorption yield depends on different factors such as; pH of environment, ionic power, and metal concentration in solution or biomass. These factors can affect biological storage, biogeochemical migration and toxic properties of heavy metals (66).

Chelating agents

Ethylenediaminetetraacetic acid (EDTA): EDTA significantly increased urinary elimination of cadmium. One important point is that EDTA may increase Cd content in the kidneys and may increase the risk of renal dysfunction (67). Normal dose of EDTA is 500 mg of Ca^{2+} EDTA in combination with 50 mg/kg of glutathione (GSH) via IV infusion over the next 24 hours and repeated over 12 consecutive days (68). Renal dysfunction could be reversed if its initial urine cadmium concentration is <10 µg/gr of creatinine. Urine cadmium concentration more than 10 µg/gr of creatinine may induce irreversible renal damage (67).

Penicillamine (DPA): Penicillamine used to reduce toxic concentrations of mercury and lead exposure, is not efficient in cadmium overdose (69).

Dimercaprol: Dimercaprol [British anti- Lewisite (BAL)] is efficient antidote in heavy metal poisoning (70). BAL and their analogues meso-2, 3-dimercaptosuccinic acid DMSA and 2, 3-dimercapto-1-propanesulfonic acid DMPS are used as antidote course of therapy for heavy metal poisoning.

BAL must be administered in the first 4 hours of poisoning. Deep intramuscular injection of a dose 3-4 mg/kg in gluteal muscle is recommended. It is given every 4 hours for the first two days, and twice daily for the next 10 days (71). It has been reported that cadmium-BAL complex has more nephrotoxic effects than cadmium alone (28) and previously mentioned that the combination is not helpful (72) and it is recommended to treat or manage actual poison exposure with other treatments. Possibly, BAL therapy may increase the risk of nephrotoxicity (73). In addition, BAL increases kidney and liver cadmium burdens, may decrease survival and enhances nephrotoxicity. For these reasons, it is not given in cadmium intoxication.

Dithiocarbamates: Dithiocarbamate derivatives have been used in many fields such as; agriculture, manufacturing, and medicine (74). N- tetramethylene dithiocarbamate (ATC) is one of derivatives of dithiocarbamates with chelating action. It enhances the urinary and biliary excretion of cadmium, also reduces the side effects and general symptoms of poisoning. It may be useful for primary diagnostic evaluation of the efficacy of chelating agents (75). The efficacy of dithiocarbamates has been confirmed in reducing cadmium toxicity in animal studies (61). There is a necessity for the administration of these chelating agents in humans to be documented.

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Meso 2, 3-dimercaptosuccinic acid (Succimer, DMSA): It is a water-soluble analogue of BAL, with chemical formula $C_4H_6O_4S_2$ (76). Tolerable dose of DMSA is10 mg/kg, three times a day (61) but it is not an intracellular chelator. Cadmium binds tightly to metallothionein and stores in liver and kidneys. In consequence, it seems that DMSA cannot be a drug of choice in cadmium poisoning (16).

2, 3- dimercapto-1-propane sulfonic acid (Unithiol, DMPS): It is a water soluble analogue of BAL with chemical formula $C_3H_7O_3S_3Na$. It is available in different dosage forms as oral, intravenous, rectal, or topical (76). DMPS is transported into intracellular space. It has not shown major adverse effects (77). DMPS is oxidized to disulfide form. At least 80% of DMPS is oxidized within the first 30 min and 84% of total DMPS is excreted by the kidneys within 96 hours (78). Dose: 5 mg/kg intravenously 4 hourly for 24 hours, and may be increased to 100 mg twice a day, if needed.

New DMSA analogues: DMSA mono and diesters are more effective and safe antidotes for heavy metal poisoning compared to DMSA alone (79). Among these monoesters, monoisoamyl DMSA (MiADMSA), a C_5 branched alkyl monoester was shown to be effective for lead, cadmium, mercury and gallium arsenide overdose (80). MiADMSA is a water- soluble, lipophilic chelating agent. It can enter intracellularly and access to different endogenous ligands. Consequently MiADMSA is more preferred than its parent compound (80).

MiADMSA can enter into cell and bind to intracellular cadmium. Because of the effects of antioxidants, cadmium-induced oxidative stress is delayed due to the presence of MiADMSA (79).

Monomethyl DMSA (MmDMSA) and Monocyclohexyl DMSA (MchDMSA) are the other DMSA analogues .They are lipophilic compounds and can penetrate into cells. They are efficient after oral administration and may reduce the whole body cadmium levels following its overdose (79).

Combination therapy with chelating agents and other substances: Combination therapy is an effective route in the management of heavy metal toxicity (3). Optimal effects of chelating agent therapy may be achieved when combination of DMSA and MiADMSA is administered (77). A combination of DMSA and calcium trisodium diethylene triaminepentaacetate (CaDTPA) has been effectively used in acute oral cadmium. These two agents reduce cadmium concentration and toxic effect in the body (81). It has been found that N-acetyl cysteine (NAC) and DMPS reduced cadmium – induced hepatic and renal metallothionein Also, NAC may increase the efficacy of DMPS (82).

Some reports have shown that antioxidants like vitamin C and vitamin E have protective effect against cadmium induced toxicity in different experimental animals (83). Combination of ascorbic acid, alpha-tocopherol, and selenium can be effective against cadmium toxicity in rat. As a result, lipid peroxidation increased and glutathione levels decreased in the intestine of rats. This combination showed a protective effect of the combination against cadmium toxicity in intestine (84). Indeed, vitamins A, C, E, and selenium can prevent or reduce many toxic effects of cadmium on some organs and tissues such as liver, kidney, skeleton, and blood. The other elements are zinc and magnesium with many clinical applications. It has been suggested that zinc facilitates immune function and prevent free radicals. Magnesium is an essential cofactor to activate many enzyme systems in humans. Zn and Mg can reverse Cd- induced renal toxicity. Cadmium toxicity causes to decrease antioxidant enzymes, produces reactive oxygen species, and lipid peroxidation. In fact, Zn and Mg can confront reactive oxygen species and lipid peroxidation(85). Chelating agents for cadmium poisoning are ongoing, and may produce a new agent that is accessible, safe and effective, without aggravating end-organ. Overall, there is no evidence to justify the use of any chelator regarding treatment of cadmium toxicity.

Application of nanoparticle in the treatment of cadmium poisoning: Cadmium can be adsorbed by Al_2O_3 nanoparticles. Generally, Al_2O_3 nanoparticles are appropriate for removing Zn and Cd from solution/sorbent systems. Al_2O_3 nanoparticles with low citrate concentrations are used to remove Cd and Zn from contaminated solutions (86). Carbon nanotubes (CNTs) remove metal ions from aqueous solutions (87). Cadmium can be removed from wastewater by nanosized TiO_2 particles (88).

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Plasma exchange-hemodialysis-plasmapheresis: Plasma exchange may have started 24-36 hours after the appearance of clinical signs and symptoms, when life-threatening toxicity happened and the health team could not choose any alternative treatment. Plasma exchange must only be used in emergency situations. Hence, it can potentially be helpful in heavy-metal toxicity (89).

Hemoperfusion and hemodialysis are not useful in the treatment of cadmium poisonings. Furthermore, cadmium is eliminated very differently, it has very low residual renal function and inefficient cadmium removal via dialysis. In severe renal damage, hemodialysis has benefits in replacing kidney function (90). Some of the toxic substances can strongly bind to plasma proteins and cannot be removed through hemodialysis. Plasmapheresis is practical and sensible to remove protein- bound heavy metals in plasma. Nonetheless, there are no controlled studies on plasmapheresis in any specific intoxication (91).

IV. CONCLUSION

In Conclusion, Cadmium compound poisoning leads to harmful effects on various organs and systems. It is considered as a potential worldwide threat to environment and human being. It transports via air, water, soil, and food chain, etc. There are risks for human health from exposure to cadmium compounds. Cadmium intoxications need decontamination via GIT irrigation, supportive care, and chemical decontamination, the use of nanoparticles, traditional and new chelating agents and combination therapy.

It is recommended to identify the individual's highly sensitive people to cadmium exposure, and ensure any contamination of agricultural soils, drinking water and food chain. It is necessary to pay attention to the handling of cadmium compounds and it is then suggested to detect the contaminated sites and design education and awareness programs for the potential at risk population to minimize cadmium toxicity.

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