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CADMIUM: TOXICITY AND CARCINOGENICITY IN HUMAN BEING

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Abstract: Cadmium is a natural element found in tiny amounts in air, water, soil, and food. All soils and rocks, including coal and mineral fertilizers, contain some cadmium. Most cadmium used in the United States is extracted during the production of other metals such as zinc, lead, and copper. Cadmium is used in many industries. It's used in the manufacturing of some batteries and solar cells, electroplating, and silver soldering. Construction workers involved in demolition can be exposed to dust containing cadmium.

Cadmium causes mutations and chromosomal deletions potentially. 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. The food groups that contribute most of the dietary cadmium exposure are cereals and cereal products, vegetables, nuts and pulses, starchy roots or potatoes, and meat and meat products. Due to their high consumption of cereals, nuts, oilseeds and pulses, vegetarians have a higher dietary exposure. EPA has classified cadmium as a Group B1 or "probable" human carcinogen. American Conference of Governmental Industrial Hygienists (ACGIH) considers cadmium a suspected human

Cadmium is a heavy metal of considerable toxicity with destructive impact on most organ systems. It is widely distributed in humans, the chief sources of contamination being cigarette smoke, welding, and contaminated food and beverages.

Keyword: Cadmium, mutations, chromosomal, toxicity, carcinogen.

Introduction: Cadmium is a chemical element with the symbol **Cd** and atomic number 48. Cadmium is a soft, malleable, ductile, silvery-white divalent metal. It is similar in many respects to zinc but forms complex compounds. 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 and is not flammable; however, in its powdered form it may burn and release toxic fumes. 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. 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 aluminum chloride, forming the Cd_2^{2+} cation, which is similar to the Hg_2^{2+} cation in mercury(I) chloride.[5]

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

The structures of many cadmium complexes with nucleobases, amino acids, and vitamins have been determined. Naturally occurring cadmium is composed of eight isotopes. Two of them are radioactive, and three are expected to decay but have not done so under laboratory conditions.

Cadmium makes up about 0.1 ppm of Earth's crust. It is much rarer than zinc, which makes up about 65 ppm. 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, but wide use began after World War I. Metallic cadmium can be found in the Vilyuy River basin in Siberia. 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. Coal can contain significant amounts of cadmium, which ends up mostly in coal fly ash. Cadmium in soil can be absorbed by crops such as rice. 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. Some plants such as willow trees and poplars have been found to clean both lead and cadmium from soil.

Typical background concentrations of cadmium do not exceed 5 ng/m3 in the atmosphere; 2 mg/kg in soil; 1 µg/L in freshwater and 50 ng/L in seawater. 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. Although cadmium has no known biological function in higher organisms, a cadmium-dependent carbonic anhydrase has been found in marine diatoms.

Biological Role

Cadmium has no known function in higher organisms and is considered toxic. Cadmium is considered an environmental pollutant that causes health hazard to living organisms. Administration of cadmium to cells causes oxidative stress and increases the levels of antioxidants produced by cells to protect against macro molecular damage. However a cadmium-dependent carbonic anhydrase has been found in some marine diatoms. 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.

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

The Biological Fate of Cadmium in the Body

Absorption of Cadmium

The principal factor determining how much cadmium is absorbed is the route of exposure. Once exposed, how much cadmium is absorbed depends on many factors: age, gender, smoking, and nutritional status. As a cumulative toxin, cadmium body burden increases with age. Women have been shown to have higher blood levels of cadmium than men. Typically, women, with lower iron status, are believed to be at risk for greater absorption of cadmium after oral exposure.

Inhalation

Once in the lungs, from 10% to 50% of an inhaled dose is absorbed, depending on particle size, solubility of the specific cadmium compound inhaled, and duration of exposure. Absorption is least for large (greater than 10 micrometers [µm]) and water-insoluble particles, and greatest for particles that are small (less than 0.1 µm) and water soluble. A high proportion of cadmium in cigarette smoke is absorbed because the cadmium particles found in that type of smoke are very small.

Ingestion

Most orally ingested cadmium passes through the gastrointestinal tract unchanged as normal individuals absorb only about 6% of ingested cadmium, but up to 9% may be absorbed in those with iron deficiency (ATSDR 1999). Also, cadmium in water is more easily absorbed than cadmium in food (5% in water versus 2.5% in food) (IRIS 2006). The presence of elevated zinc or chromium in the diet decreases cadmium uptake.

Digestive system

The uptake through the human gastrointestinal is approximately 5% of an ingested amount of cadmium, depending on the exact dose and nutritional composition. An average citizen has a daily intake of 30–35 µg cadmium; 95% of this taken up with food and drinks. An average smoker has an additional intake of 30 µg per day. Several factors can increase this amount, such as low intakes of vitamin D, calcium, and trace elements like zinc and copper. Concerning zinc and calcium,

it is assumed that their molecular homology could be a reason for a compensatory higher cadmium resorption. Furthermore, a high fiber diet increases the dietary cadmium intake. The most important metabolic parameter for cadmium uptake is a person's possible lack of iron. People with low iron supplies showed a 6% higher uptake of cadmium than those with a balanced iron stock.

This is the main reason for the higher cadmium resorption in people with anemia and habitual iron deficit, such as children or menstruating women.

Respiratory system

The major source of inhalative cadmium intoxication is cigarette smoke. The human lung reabsorbs 40–60% of the cadmium in tobacco smoke. A 50-year-old average non-smoker has a cadmium body burden of 15 mg. While a comparable life-long smoker shows a value of 30 mg. Smokers generally have cadmium blood levels 4–5 times those of non-smokers. Workers exposed to cadmium-containing fumes have been reported to develop acute respiratory distress syndromes. Inhalativly resorbed cadmium reaches blood circulation usually in form of cadmium-cysteine complexes.

Dermal resorption

The resorption from cadmium-contaminated soil and water solutions by human skin in a diffusion cell model. They could demonstrate a penetration of 8.8 % (soil) and 12.7% (water) of the applied cadmium dose into the skin; while the plasma uptake from soil was 0.01% and 0.07% from water.

Cadmium concentration in blood, liver and kidney increased, thus indicating percutaneous absorption.

Excretion of Cadmium

Absorbed cadmium is eliminated from the body primarily in urine. The rate of excretion is low, probably because cadmium remains tightly bound to metallothionein, MTN, which is almost completely reabsorbed in the renal tubules. Because excretion is slow, cadmium accumulation in the body can be significant. Cadmium concentration in blood reflects recent exposure; urinary cadmium concentration more closely reflects total body burden. However, when renal damage from cadmium exposure occurs, the excretion rate increases sharply, and urinary cadmium levels no longer reflect body burden.

Accumulation of Cadmium

The total cadmium body burden at birth is non-detectable (CDC 2005). It gradually increases with age to about 9.5 mg to 50 mg (ATSDR 1999). The kidneys and liver together contain about 50% of the body’s accumulation of cadmium (HSDB 2006).

Cadmium Half-Life

The biologic half-life of cadmium in the kidney is estimated to be between 6 to 38 years; the half-life of cadmium in the liver is between 4 and 19 years (ATSDR 1999). These long half-lives reflect the fact that humans do not have effective pathways for cadmium elimination. Cadmium has no known biologic function in humans. Bioaccumulation appears to be a by-product of increasing industrialization. Any excessive accumulation in the body should be regarded as potentially toxic.

Handling of cadmium in the body

Once taken up by the blood, the majority of cadmium is transported bound to proteins, such as Albumin and Metallothionein. The first organ reached after uptake into the GI-blood is the liver. Here cadmium induces the production of Metallothionein. After consecutive hepatocyte necrosis and apoptosis, Cd-Metallothionein complexes are washed into sinusoidal blood. From here, parts of the absorbed cadmium enter the entero-hepatical cycle via secretion into the biliary tract in form of Cadmium-Glutathione conjugates. Enzymatically degraded to cadmium-cysteine complexes in the biliary tree, cadmium re-enters the small intestines. The main organ for long-term cadmium accumulation is the kidney. Here the half-life period for cadmium is approx. 10 years. A life-long intake can therefore lead to a cadmium accumulation in the kidney, consequently resulting in tubules cell necrosis. The blood concentration of cadmium serves as a reliable indicator for a recent exposition, while the urinary concentration reflects past exposure, body burden and renal accumulation. Excretion of Cadmium takes place via faeces and urine.

Hazards to human health

Carcinogenesis: Long-term exposures to cadmium may turn carcinogen in humans, where normal epithelial cells transform to malignant cells inhibiting the biosynthesis of DNA, RNA, and proteins. Cadmium inhibits binding of xeroderma pigmentosum group A (XPA) to DNA which recognizes DNA damages. Cadmium also reduces the binding efficiency of tumor suppressor p53 to DNA that is responsible for base excision repair of UV light exposure in DNA. Cadmium inhibits an enzyme Human 8-oxo-dGTPase that protects against the incorporation of 8-oxo-dGTP into DNA. Thus cadmium exposures may lead to genomic instability and tumor genesis by inhibiting DNA repairs at various levels.

Infertility: Sperm concentration in semen is very important factor in reproduction cadmium exposures decreases sperm count in semen. Cadmium enters the testicular cells in ion transporter chains and voltage-dependent calcium channels. Sertoli and testicular germ cells contains expression of sperm-head voltage-dependent calcium channeling where with elevated testicular cadmium levels there is a deletion in exons 7 and/or 8 which cadmium levels decreasing the sperm count.

Cardiovascular abnormality: Cadmium found in tobacco, air and food by in-vitro exposures effects endothelial dysfunctions and in-vivo accelerates atherosclerotic plaque formation (artery wall thickening) causing cardiovascular diseases. Cadmium interferes with anti-oxidative stress by binding to metallothionein (protein that regulates zinc homeostasis and free radical scavenger and increase reactive oxygen species formation.

Osteotoxicity: There are many Cadmium-induced hormone disturbances like affect in vitamin D metabolic pathways that is cadmium-related bone changes due to release of calcium from bone occurring in the absence of circulating parathyroid hormone, and calcitonin. In estrogen hormone pathways, cadmium concentrations activate the estrogen receptor (ER) and blocks it's binding to estrogen indirectly affect the skeleton causing Osteotoxicity and multiple bone fractures.

Renal disorder: Exposures to high-dose cadmium causes Itai-itai disease characterized by severely impaired tubular and glomerular function. Long-term exposure of low-dose cadmium leads to tubular impairment include zinc and copper bound to the metal binding protein metallothionein (MT), glucose, amino acids, phosphate, calcium, β2-MG, and retinol-binding protein (RBP) losses. Kidney reabsorptive capacity for nutrients, vitamins, and minerals decreases. There is abnormal urination with low-molecular-weight proteins, calcium, amino acid, phosphate and glucose similar in Fanconi's syndrome, a genetic disorder of renal tubular transport develops kidney damage, and blood cadmium as the indicator.

Other disorders: Urinary cadmium has various effects on other tissues such as lungs, periodontal tissues, hypertension, diabetes and mammary glands. There is a reduction of forced expiration (reflection of lung function) with increased urinary cadmium in smoking individuals. Urinary cadmium with creatinine level is estimated to be to more in periodontal disease affected individuals than the unaffected individuals. It was studied that the cadmium blood pressure association disorder was greatest among nonsmokers, intermediate among former smokers, and small or absent among current smokers. Increased urinary cadmium level increases the risk of prediabetes and diabetes. The estimated risk for abnormal individuals fasting glucose and diabetes were almost the same. Cadmium level in breast milk with elemental composition of milk, including manganese, iron, and calcium levels had changes, due to mammary gland metal transport chain.

Environmental effects of cadmium

Cadmium waste streams from the industries mainly end up in soils. The causes of these waste streams are for instance zinc production, phosphate ore implication and bio industrial manure. Cadmium waste streams may also enter the air through (household) waste combustion and burning of fossil fuels. Because of regulations only little cadmium now enters the water through disposal of wastewater from households or industries.

Another important source of cadmium emission is the production of artificial phosphate fertilizers. Part of the cadmium ends up in the soil after the fertilizer is applied on farmland and the rest of the cadmium ends up in surface waters when waste from fertilizer productions is dumped by production companies. Cadmium can be transported over great distances when it is absorbed by sludge. This cadmium-rich sludge can pollute surface waters as well as soils.

Cadmium strongly adsorbs to organic matter in soils. When cadmium is present in soils it can be extremely dangerous, as the uptake through food will increase. Soils that are acidified enhance the cadmium uptake by plants. This is a potential danger to the animals that are dependent upon the plants for survival. Cadmium can accumulate in their bodies, especially when they eat multiple plants. Cows may have large amounts of cadmium in their kidneys due to this.

Earthworms and other essential soil organisms are extremely susceptive to cadmium poisoning. They can die at very low concentrations and this has consequences for the soil structure. When cadmium concentrations in soils are high they can influence soil processes of microorganisms and threat the whole soil ecosystem. In aquatic ecosystems cadmium can bio

accumulate in mussels, oysters, shrimps, lobsters and fish. The susceptibility to cadmium can vary greatly between aquatic organisms. Salt-water organisms are known to be more resistant to cadmium poisoning than freshwater organisms. Animals eating or drinking cadmium sometimes get high blood-pressures, liver disease and nerve or brain damage.

Conclusion: Cadmium is heavy metal hazardous to all living organisms. Cadmium involves different machineries to induce its harmful effect on many biological activities in humans and various other organisms. In human's cadmium adverse effect is not only restricted to kidney and bone but it includes almost every organ and tissue where it accumulates which argues needs for public health measures aimed at reducing exposure. There are many methods by which this heavy metal can be suppressed in its activities forming the future prospective for reduced metal toxicity involving cadmium. The preventive measures in high-risk patients must be practiced and it is important to make population-based preventive strategies, such as promoting public and private smoke-free environments, reviewing food safety policies maintaining cadmium safety standards, and limiting cadmium industrial releases into the environment helping to avoid cadmium toxicity.

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