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Our planet is currently suffering a staggering rate of dramatic environmental change. Environmental change has negatively affected most biological systems on our planet. It has become an increasing concern for the well-being and survival of many species. At an organism level, effects encompass not only endocrine disruptions, sex-ratio changes and decreased reproductive parameters, but also include teratogenic and genotoxic effects, immunosuppression and other immune-system impairments that can lead directly to disease or increase the risk of acquiring disease (Whitehouse and Duffus, 2009). The luxuries enjoyed by our modern lifestyle has brought with it an arsenal of chemical by-products released into the air, land, and water we interact with every day. These includes air, water, and food-borne pesticides, herbicides, fungicides, and insecticides, cleaning products, exhausts from vehicles and heavy metals such as lead, mercury, cadmium, and arsenic that may be present in paint, plastics, food and soil. Development of industries, particularly chemical industries, has lead to increase of heavy metal content in the environment to such concentrations that they produce toxic effects in humans and animals. Study of the mechanism underlying such toxic actions of heavy metals as basic pollutants, thus becomes a necessity. Such studies also help in the realization of a global character of the problem of chemical pollution of environment. (Bozhkov et. al., 2010).

Toxicology (from the Greek words- toxicos "poisonous" and logos "study") is a branch of biology and medicine concerned with the study of the adverse effects of
chemicals on living organism. It also includes investigations of toxins in the environment, how they are distributed, and the risks they present to plants, animals, and people. Toxicology draws on several areas of science including biology, chemistry, mathematics, and physics. Human awareness of poisons predates recorded history. The historical development of toxicology began with early cave dwellers who recognized poisonous plants and animals and used their extracts for hunting or in warfare. However, a parallel gain in knowledge also took place with regard to medicines. In the late Middle Ages, Paracelsus (1493-1541), a physician-alchemist wrote: "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy." At the time, his views were seen as revolutionary, but they mark the beginnings of modern toxicology. Toxicity is thus capacity of a substance to poison. The toxicity of a substance is therefore not an inherent property but the detrimental manifestation of its biochemical effect in a living system. The severity of a substance's toxicity is the function of its interaction with the physiology of a particular organism. Hence, toxicant received by an organism depends on both the routes of exposure and dose. Exposure is a measure of the amount of a toxicant that comes into contact with the organism through air, water, soil, and food. Dose is a measure of the amount of toxicant that comes into contact with the target organ or tissue, within the organism, where it exerts a toxic effect. The dose is largely determined by how effectively the toxicant is absorbed, distributed, metabolized, and eliminated by the body.
Characterizing Toxicity

One measure of response is acute toxicity, which is the amount of a toxicant that will cause an adverse effect within a relatively short period of time (e.g., from instantaneous to within a few days). Another measure of response is chronic toxicity, which is the long-term response to a toxicant (Crosby and Donald, 1998). A local effect refers to an adverse health effect that takes place at the point or area of contact. Systemic effect refers to an adverse health effect that takes place at a location distant from the body's initial point of contact. Again cumulative toxicity is characterized by materials that tend to build up in the body as a result of numerous chronic exposures. Although the same types of dose–response curves are used to measure the chronic toxicity of toxicants, those measurements are more difficult to quantify because the responses are often less absolute and more complex (Needleman, 1998). For example, chronic benzene toxicity causes lung cancer, but it may be years before that benzene-induced cancer appears, and many other factors may retard the development of that cancer (antagonistic effect), contribute to its development (synergistic effect), or independently cause lung cancer (e.g., smoking cigarettes).

Forms of toxicity can also be characterized by the type of adverse response they create. Carcinogens cause cancer, either by the initiation or promotion of an uncontrolled growth of cells. Mutagens cause mutations by altering the DNA sequences of chromosomes. Teratogens cause mutations in the DNA structure of developing fetuses
that can result in developmental abnormalities. (Ohlendorf, et. al., 1986) (Williams, et. al; 2000).

**Differences in Sensitivities**

Resolving the adverse effects of a toxicant is further complicated by the variations in those effects in different species. Some species are more sensitive to certain toxicants than others, and the effects of toxicants on different tissues often vary between species. Because such variations occur between humans and rodents, in spite of the similarity (95%) in their DNA, extrapolations of laboratory studies on the effects of toxicants on rats and mice to human health must always take this into account. Moreover, the toxic effects of a pollutant on the gall bladder of humans cannot be determined in studies involving rats because rats do not have gall bladders.

There are also relatively large differences in the sensitivities and effects of toxicants between individuals of the same species. Fetuses, neonates, and infants are more sensitive to the neurotoxic effects of lead than older individuals, because lead interferes with the development of the central nervous system, which is formed during the first few years of life. Finally, healthy individuals are generally less sensitive to pollutants than individuals with weak immune systems who are less capable of responding to additional threats to their health.

Genomic constituents of a species also play a major role in the sensitivity of individuals. Although some differences have been observed in humans, the most
commonly recognized genetic differences in toxic responses have been observed in other species. These include the acquired genetic resistance of some mosquitoes to DDT and some bacteria to antibiotics. However, the development of molecular techniques used for genotyping human has now made it possible to identify individual sensitivity to different toxicants.

**Dose-response relationship**

The science of toxicology is based on the principle that there is a relationship between a toxic reaction (the response) and the amount of poison received (the dose). An important assumption in this relationship is that there is a dose below which no response occurs or can be measured. A second assumption is that once a maximum response is reached, any further increase in the dose will not result in any increased effect.

One particular instance in which this dose-response relationship does not hold true is in regard to true allergic reactions. Allergic reactions are special kinds of changes in the immune system; they are not really toxic responses. Thus, in an allergic reaction, the chemical acts merely as a trigger, not as the bullet.

For all other types of toxicity, knowing the dose-response relationship is a necessary part of understanding the cause and effect relationship between chemical exposure and illness. As Paracelsus wrote, "The right dose differentiates a poison from a remedy." Keeping that in mind it can be said that the toxicity of a chemical is an inherent
quality of the chemical and cannot be changed without changing the chemical to another form. The toxic effects on an organism are related to the amount of exposure.

Knowledge of the dose-response relationship thus:

- Establishes causality that the chemical has in fact induced the observed effects
- Establishes the lowest dose where an induced effect occurs – the threshold effect
- Determines the rate at which injury builds up – the slope for the dose response.

(Yuill and Miller, 2008)

Dose Estimates of Toxic Effects/ Measures of Exposure

Dose-response curves are used to derive dose estimates of chemical substances. A common dose estimate for acute toxicity is the LD50 (Lethal Dose 50%). This is a statistically derived dose at which 50% of the individuals will be expected to die. Figure A illustrates how an LD50 of 20 mg is derived.

![Dose Response Curve](image)

Figure A.

Other dose estimates also may be used. LD0 represents the dose at which no individuals are expected to die. This is just below the threshold for lethality. LD10 refers
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to the dose at which 10% of the individuals will die. For inhalation toxicity, air concentrations are used for exposure values. Thus, the LC50 is utilized which stands for Lethal Concentration 50%, the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used. The term Lethal Concentration is also used to describe aquatic toxicity, where concentration refers to the concentration in water. Effective Doses (EDs) are used to indicate the effectiveness of a substance. Normally, effective dose refers to a beneficial effect (relief of pain). It might also stand for a harmful effect (paralysis). Thus the specific endpoint must be indicated. Knowledge of the effective and toxic dose levels aides the toxicologist and clinician in determining the relative safety of pharmaceuticals (Yuill and Miller, 2008).

Routes of exposure

A route of administration/exposure in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body. The route of intake and the dosages determine the intensity and duration of the harmful effects of a toxicant. In this context exposure is defined as the contact between an agent and a target. Contact takes place at an exposure surface over an exposure period. Mathematically, exposure is defined as

\[ E = \int_{t_i}^{t_f} C(t) \, dt \]

Where \( E \) is exposure, \( C(t) \) is a concentration that varies with time between the beginning and end of exposure. There are four most common routes by which a substance can enter the body: inhalation, skin (or eye), absorption, ingestion, and injection. Though metal toxicity is usually experienced through oral routes, parenteral administration provides the
desired comparative data needed for comparative toxicology. In some instances, parenteral administration is essential for the drug to be administered in its active form. In clinical studies parenteral administration is advantageous when the subjects are uncooperative, unconscious or unable to retain anything given by mouth. A more common route of administration is the intraperitoneal route. Intraperitoneal injection is the administration of chemicals into the peritoneal cavity of animals for evaluation of their biologic action and toxicity. The peritoneum, a serous or mesothelial membrane lining the abdominal cavity acts as a semipermeable membrane and is connected with an efficient vascular system (Wilkinson, 2001).

Metal compounds that are soluble and stable at the peritoneal fluid pH (5-7) are rapidly absorbed across the visceral peritoneum and transferred to the liver via portal circulation. Hepatic cells possess absorbed material before it reaches other tissues. The microparticulates of the absorbed material are phagocytized by the invading macrophages and scavenged into the reticulo-endothelial system, which includes liver and spleen. Thus although absorption of soluble metal salts from intraperitoneal injections is rapid, the toxicity is less due to possible detoxification by the liver (Schumann et al., 1980).

Metals

Metals are a natural part of our environment. Life has evolved in this natural milieu and requires that metals be present in appropriate levels and combinations. Metals play an important part in modern societies and have historically been linked with
industrial development and improved living standards. Society can draw on metal resources from Earth's crust as well as from metal discarded after use in the economy. (Wernick et. al.,1998). Concentrations of metals that are too low can lead to health problems as a result of nutrient deficiencies, whereas metal concentrations that are too high can be toxic to plants, animals, and humans.

There are 35 metals that concern us because of occupational or residential exposure; 23 of these are the heavy elements or "heavy metals": antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and zinc (Glanze, 1996) Interestingly, small amounts of these elements are common in our environment and diet and are actually necessary for good health, but large amounts of any of them may cause acute or chronic toxicity (poisoning).

For some heavy metals, toxic levels can be just above the background concentrations naturally found in nature. Therefore, it is important for us to inform ourselves about the heavy metals and to take protective measures against excessive exposure. In most parts of the United States, heavy metal toxicity is an uncommon medical condition; however, it is a clinically significant condition when it does occur. If unrecognized or inappropriately treated, toxicity can result in significant illness and reduced quality of life (Ferner, 2001).
What are heavy metals?

"Heavy metals" are chemical elements with a specific gravity that is at least 5 times the specific gravity of water. Some well-known toxic metallic elements with a specific gravity that is 5 or more times that of water are arsenic, 5.7; cadmium, 8.65; iron, 7.9; lead, 11.34; and mercury, 13.546 (Lide, 1992).

Beneficial heavy metals

In small quantities, certain heavy metals are nutritionally essential for a healthy life. Some of these are referred to as the trace elements (e.g., iron, copper, manganese, and zinc). These elements in some forms are found naturally in foodstuffs, fruits, vegetables, and in commercially available multivitamin products (International Occupational Safety and Health Information Centre, 1999). Diagnostic medical applications include direct injection of gallium during radiological procedures, dosing with chromium in parenteral nutrition mixtures, and the use of lead as a radiation shield around x-ray equipment (Roberts, 1999). Heavy metals are also common in industrial applications such as in the manufacture of pesticides, batteries, alloys, electroplated metal parts, textile dyes, steel, and so forth. (International Occupational Safety and Health Information Centre, 1999). Many of these products are in our homes and actually add to our quality of life when properly used.
Toxic Heavy Metals

Heavy metals become toxic when they are not metabolized by the body and accumulate in the soft tissues. Heavy metals may enter the human body through food, water, air, or absorption through the skin when they come in contact with humans in agriculture and in manufacturing, pharmaceutical, industrial, or residential settings. Industrial exposure accounts for a common route of exposure for adults. Ingestion is the most common route of exposure in children (Roberts, 1999). Children may develop toxic levels from the normal hand-to-mouth activity of small children who come in contact with contaminated soil or by actually eating objects that are not food (dirt or paint chips, toys) (Dupler, 2001).

Heavy metal toxicity

Heavy metals constitute a very heterogeneous group of elements widely varied in their chemical properties and biological functions. Heavy metals are kept under environmental pollutant category due to their toxic effects in plants, humans and food. Some of the heavy metals i.e. arsenic (As), cadmium (Cd), lead (Pb), mercury (Hg) are cumulative poison. These heavy metals are persistence, accumulate and not metabolized in other intermediate compounds and do not easily breakdown in environment. These metals are accumulating in food chain through uptake at primary producer level and than through consumption at consumer level. Metals enter the human body either through inhalation or injection. Heavy metals such as Cd, Ni, As, Pb pose a number of hazards to
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humans. These metals are also potent carcinogenic and mutagenic. (Mildvan, 1970). The high concentration intake of cadmium cause itai itai disease and mercury intake lead to minamita disease and other heavy metals cause poisoning due to drinking water contamination. Heavy metals have largest availability in soil and aquatic ecosystem and to relatively smaller proportion in atmosphere at particular vapors. (Raikwar et. al., 2008). There are many evidences of prevailing heavy metal contamination of groundwater in many areas of India (Sharma, et. al., 1989). Sixteen states in India- Andhra Pradesh, Bihar, Delhi, Gujarat, Haryana, Jammu & Kashmir, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Manipur, Orissa, Punjab, Rajasthan, Tamil Nadu and Uttar Pradesh have already been identified endemic to fluorosis (Mariappan et. al., 2000). Arsenic contamination of ground water in eight districts of West Bengal is well documented and more cases are also reported from eastern part of Bihar, Gorakhpur, Balia, Western part of Uttar Pradesh and Chattishgarh (Singh, 2006). The intensive farming belt of Western U.P., Haryana, Punjab, and parts of Rajasthan, Delhi and West Bengal have been reported to contain high NO₃ in groundwater (Malve and Dhage, 1996.) Information on heavy metal toxicity of North Eastern India is scanty. Available literature shows that groundwater of Assam valleys is highly ferruginous (Aowal, 1981; Singh, 2004) The presence of excess fluoride and endemic of Fluorosis was reported in the year 1999 in Karbi Anglong district of Assam, though the disease was prevalent for last twenty years. Subsequently, because of intensified water quality testing and health survey conducted, excess iron and fluoride is getting detected in more and more areas of the region (Akoijam, 1997; Sushella, 2001). Problem of arsenic has been detected in North Eastern India recently (Singh, 2004; Mukherjee et. al., 2006; Singh, 2006).
Wetland sediments in Barak Valley are shown to contain significantly higher levels of several heavy metals such as cadmium, chromium, iron, manganese, nickel, lead and zinc. (Dev et. al., 2010). Statistical observations on Cd in groundwater of teagarden belt of Darrang district, Assam show that this metal exhibits an asymmetric distribution. It is observed that the groundwater of the area is contaminated with cadmium (Borah et. al., 2009).

Physico-chemical property of cadmium

Cadmium (Cd) is a soft, silver-white metal. The physical property of cadmium is atomic number-48, atomic weight 112.411, electro-negativity-1.5, crystal ionic radius (Principal valence state)-0.97, ionisation potential-8.993, oxidation state +2, electron configuration Kr 4d1 5S2, density-8.64 g/cm3, melting point - 320.9°C and boiling point-765°C at 100 kPa. It is usually found as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulfur (cadmium sulfate, cadmium sulfide) (Kumar and Singh, 2010). The soft, bluish-white transition metal is chemically similar to the two other metals in group 12, zinc and mercury. Similar to zinc it prefers oxidation state +2 in most of its compounds and similar to mercury it shows a low melting point for a transition metal. Cadmium is a relatively abundant element. Cadmium was discovered in 1817 by Friedrich Strohmeyer as an impurity in zinc carbonate.
Distribution of cadmium in the environment

The natural presence of cadmium in the environment results mainly from gradual phenomena, such as rock erosion and abrasion, and of singular occurrences, such as volcanic eruptions. Cadmium is therefore naturally present in air, water, soil and foodstuffs. Cadmium levels in the environment vary widely. Cadmium is widely distributed in the Earth's crust at an average concentration of about 0.1 mg kg\(^{-1}\) and is commonly found in association with zinc. Higher levels are present in sedimentary rocks: marine phosphates often contain about 15 mg kg\(^{-1}\) (GESAMP, 1984). Weathering and erosion result in the transport by rivers of large quantities of cadmium to the world's oceans and this represents a major flux of the global cadmium cycle; an annual gross input of 15,000 tones has been estimated (GESAMP, 1987). Volcanic activity is also a major natural source of atmospheric cadmium release.

Non-ferrous metal mines represent a major source of cadmium to the aquatic environment. At the global level, the smelting of non-ferrous metal ores has been estimated to be the largest human source of cadmium release to the aquatic environment (Nriagu and Pacyna, 1988). The manufacture of phosphate fertilizer results in a redistribution of the cadmium present in the rock phosphates between the phosphoric acid product and gypsum waste. The atmospheric fall-out of cadmium to fresh and marine waters also represents a major input of cadmium at the global level (Nriagu, and Pacyna, 1988). Cadmium has many industrial uses, which can result in its release to air, water,
and land. Cadmium is today regarded as the most serious contaminant of the modern age (Borah et. al., 2009). It ranks seventh on the Agency of Toxic Substances and Disease Registry/Environmental Protection Agency (ATSDR/EPA) list of Hazardous Substances (ATSDR, 2007).

**Uses and Sources:**

Cadmium is a naturally occurring element, used for a variety of purposes including silver solder; metal plating; pigments in plastics, ceramics and glass; nickel-cadmium batteries; electronic devices; PVC stabilizers; coatings on steel and nonferrous metals; components of specialized alloys; and as a catalyst. The largest sources of cadmium to the environment are fossil fuel emissions and incineration of municipal wastes. Cadmium is also released in smelter emissions. Cadmium as a major consumer product is used in nickel-cadmium (Ni-Cd) batteries, pigments, petrol and plastics. Some sources of phosphate in fertilizers contain cadmium in amounts of up to 100 mg/kg. (Trueman, 1965) which can lead to an increase in the concentration of cadmium in soil ( Taylor, 1997). Nickel-cadmium batteries are one of the most popular and most common cadmium-based products.

**Routes of Human Exposure:**

The major ways of cadmium exposure in the general population are through:
• Ingestion of cadmium found in certain foods, and
• Cigarette smoking since the tobacco plant takes up cadmium avidly from the environment.

The non-smoking public receives the majority of their exposure through food. The main route of cadmium exposure for smokers is via tobacco smoke (National Toxicology Program 2004; Mannino et. al., 2004). Cadmium exposure in the workplace takes place during mining and work with cadmium containing ores. Additional occupational exposure may occur during manufacture of products containing cadmium such as paints and during work such as plating, soldering, and welding (National Institute of Occupational Safety and Health, 1990).

Because of cadmium’s strong tendency to accumulate in plants and other living organisms, consumption of contaminated food is the primary non occupational route of exposure to cadmium. People are exposed to cadmium by drinking contaminated water, by breathing contaminated air (including cigarette smoke), or by swallowing small quantities of contaminated soil or dust. Cigarette smokers can have approximately twice the cadmium in their bodies as non-smokers. Cadmium released into the air by industry, incinerators, smelters, and fossil fuel emissions is deposited onto soils or surface water where it tends to accumulate in plants (including food crops), fish, and shellfish. Cadmium is also a contaminant in sewage sludge from industrial sources. Crops grown on soils treated with sewage sludge can take up cadmium, increasing the potential for human exposure.
Cadmium cycle

Cadmium is a relatively volatile element not essential to plants, animals and humans. Its presence in live organisms is unwanted and harmful. An increased level of cadmium in the air, water and soil increases its uptake by live organisms. It is taken up by plants and animals and through them also by humans. This leads to the cadmium cycle soil - plant - animal - man. Pavlik et al. (1997) have stated that up to 90% Cd taken up by plants originates from soil and only 10% from the atmosphere. Uptake of cadmium by plants occurs through roots and leaves. Plants take up cadmium from water only in the form of Cd$^{2+}$ ions (after release from the sorption complex or from soil solution). Additional cadmium is transported to roots by diffusion and mass soil flow. Green plants are the starting link of the food chain, which is the principal source of cadmium for animals and humans. Plants convert solar energy to chemical energy and store it in the form of organic compounds. They also accumulate unwanted substances including cadmium. Plants are consumed mostly by herbivores, which then become a source of food for carnivores. Omnivores consume plant products, herbivores and carnivores. The main port of entry of cadmium to the organism of animals is the digestive tract and alveolar absorption (Friberg, 2005).
Mechanism of action

The toxicity of cadmium is generally related to its chemical similarity to zinc, an essential trace element required for normal growth, wound healing, reproduction and prevention of skin disorders. As a component of wide variety of metalloenzymes, zinc is involved in the fundamental process of nucleic acid and protein synthesis and degradation of carbohydrate metabolism. Cadmium has a higher affinity for sulfhydryl groups than zinc and therefore is able to replace the native zinc ion in zinc metalloenzymes. Hence the toxicity of cadmium is related to its affinity for active cellular sulfhydryl and imidazole nitrogen groups. (Gupta, 2010). Cadmium initially binds to metallothionein and is transported to the kidney. Toxic effects are observed once the concentration of cadmium exceeds that of available metallothionein, and it has also been shown that the cadmium-metallothionein complex may be damaging. Accumulation of cadmium in the kidney results in increased excretion of vital low and high molecular weight proteins. Cadmium which is high affinity zinc analog and can interfere in its biological processes. It also binds to and activates the estrogen receptor, likely stimulating the growth of certain types of cancer cells and causing other estrogenic effects, such as reproductive dysfunction. Cadmium causes cell apoptosis by activating mitogen-activated protein kinases (MAPK).
Toxicokinetics

a. Absorption

**Inhalation route:**

Inhalation exposure primarily occurs in the workplace. Cadmium compounds are inhaled as particulate matter, either as fumes with very small particle size or as dust. After inhalation exposure, the absorption of cadmium compounds may vary greatly and depends upon the particle sizes and their solubility. Thus particle size, which controls alveolar deposition, is a key determinant of cadmium absorption in the lung. The respiratory Cd intake can be diverted to the gastro-intestinal tract due to the clearance of Cd deposited on the mucosa of nasopharynx, trachea or bronchi. It can also be deposited in the alveoli and from there be absorbed into the blood.

**Oral route:**

Depending on the dietary intake and the iron status, it has been estimated that ingested cadmium is poorly absorbed. Animal studies have shown that the intestinal absorption of Cadmium is about less than 5% but both the absorption and tissue distribution of Cadmium can be affected by the form of Cadmium and nutritional deficiencies (Ohta and Cherian, 1991, 1995). Cadmium absorption increases with iron or calcium deficiency. Absorption from the gut appears to take place in two phases, uptake from the lumen into the mucosa and transfer from the mucosa into the circulation. Cadmium is distributed throughout the body, but the major portion is found in the liver.
and kidney. The majority of absorbed cadmium is retained in the tissues. For a given individual, the absorption following oral exposure to cadmium is likely to depend on physiologic status (age; body stores of iron, calcium, and zinc; pregnancy history; etc.) and, also, on the presence and levels of ions (Zinc) and other dietary components ingested with the cadmium.

Dermal route:

Absorption of cadmium through the skin is extremely low (0.5%) and would be of concern only in situation where concentrated solutions would be in contact with the skin for several hours or longer duration.

b. Distribution

Cadmium is widely distributed in the body, with the major portion of the body burden located in the liver and kidney. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure (30% of Cd body burden in the kidney). Cadmium can be detected in virtually all tissues in adults from industrialized countries, with greatest concentrations in the liver and kidney. Average cadmium concentrations in the kidney are at birth near zero, and rise roughly linearly with age to a peak (typically around 40-50 µg/g wet weight) between ages 50 and 60 years, after which kidney concentrations plateau or decline. Liver cadmium concentrations also begin near zero at
birth, increase to typical values of 1-2 µg /g wet weight by age 20-25 years, then increase only slightly thereafter.

c. Metabolism

The most dangerous characteristic of cadmium is that it accumulates throughout lifetime. Cadmium accumulates in the liver and kidneys and has a long biological half-life, from 17-30 years in man (Goyer, 1997). After uptake from the lung or the gastrointestinal tract, cadmium is transported in blood plasma initially bound to albumin, as shown in experimental animals. Cadmium bound to albumin is preferentially taken up by the liver. In the liver, cadmium induces the synthesis of metallothionein and a few days after exposure metallothionein-bound cadmium appears in the blood plasma. Because of its low molecular weight, cadmium-metallothionein is efficiently filtered through the glomeruli and thereafter taken up by the tubules. Cadmium accumulates in the human kidney over the entire lifetime (Jin et. al., 1992). Cadmium does not undergo metabolic conversion, but the cadmium ion can readily bind to anionic groups, especially sulphhydryl groups, in proteins and other molecules. Cadmium is bound to the protein metallothionein in the liver, which releases the metallothionein-cadmium complex, rather than free cadmium, into the bloodstream. Metallothionein is a low-molecular-weight, sulphydryl-rich protein that normally binds zinc. Metallothionein-bound cadmium is readily filtered by the renal glomerulus and reabsorbed from the glomerular filtrate by the proximal tubule cells, at which point the “exogenous” metallothionein is catabolized in tubular lysosomes, releasing free cadmium. Although initially non-toxic, the cadmium-
metallothionein complex can be nephrotoxic as it accumulates in the kidneys (Dorian et al., 1995). The free cadmium stimulates the synthesis of metallothionein in the tubular cells, is then bound to the tubular metallothionein, and remains in the cells.

d. Elimination

Most cadmium that is ingested or inhaled and transported to the gut via mucociliary clearance is excreted in the feces. Most absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal. Cadmium is also eliminated through hair and breast milk, but these routes are of limited importance for total excretion and do not significantly alter the biological half-time. The placenta is only a partial barrier to fetal exposure to cadmium. The amount of cadmium excreted represents only a small fraction of the total body burden unless renal damage is present.

Toxicity of cadmium

Acute human poisoning

Acute human poisoning by ingestion is characterized by increased salivation and severe nausea, vomiting which occur within 15 minutes to 2 hours and last for 7 to 24 hours. (Gupta, 2010). Acute exposure to cadmium fumes may cause flu like symptoms including chills, fever, and muscle ache. Symptoms may resolve after a week if there is no respiratory damage. More severe exposures can cause tracheo-bronchitis, 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. In more severe cases, these symptoms can be followed by collapse with signs of shock, hematemeses, diarrhea and tinesmus. (Hunter, 1978).

**Chronic human poisoning**

Chronic cadmium poisoning, are similar to a type of osteomalacia in which the patient suffers from lumbar pains, leg myalgia and increase in pain when pressure is applied to the bones. Specific symptoms related to chronic exposure to cadmium fumes and dust include weight loss, cough and dyspnea, gross pulmonary emphysema and appearance of low molecular weight proteins in the urine (Hunter, 1978). Studies have shown that chronic exposure to cadmium can lead to serious health effects including lung cancer, emphysema and other lung diseases, and kidney damage. More detailed studies of specific cases have shown impairment of renal tubular functions indicated by low insulin clearance values, a diminished capacity of kidneys to concentrate urine, and an increased formation of kidney stones. (Gupta, 2010). Cadmium is known to alter neurotransmitter levels in the brain, and may inhibit calcium entry into neurons (ATSDR 1999). Testicular effects of cadmium may be due to cadmium interference with zinc-protein complexes that control DNA transcription, subsequently leading to apoptosis. Other adverse effects shown in chronic animal studies include effects on the liver, lungs, immune system, blood and nervous system. There is little evidence for many of these effects in humans. It
is important to note, however, that few studies on human beings have assessed the effects of cadmium at low levels of exposure.

**Health effects of cadmium exposure on different organ systems**

**Cardiovascular effects**

Cadmium produces specific and multiple effects on the cardiovascular system. In rabbit treated with cadmium the increased aortic vascular resistance and the reduced myocardial contractility contribute to preserve a haemodynamic equilibrium without alteration of blood pressure and heart rate (Boscolo and Carmignani, 1986). It has been shown that a low intake of dietary cadmium induces specific dose-dependent functional and biochemical changes in the cardiovascular tissues of rats. (Kopp et. al., 1982) Exposures to cadmium, pollutant gases, solvents, and pesticides have been linked to increased incidence of cardiovascular disease. Mechanistically, these effects have been attributed to changes in the synthesis or reactivity of nitric oxide that may be caused by environmental oxidants or increased endogenous production of reactive oxygen species. (Bhatnagar, 2006).

**Neurological Effects**

Cadmium adversely affects a number of organs and systems, including the central nervous system, in humans and other mammals (Mendez and Rios, 2011). Neurological
effects consisting of decreased motor activity, weakness and muscle atrophy, aggressive behavior, increased passive avoidance, and alterations in brain dopamine, 5-hydroxytryptamine, succinic dehydrogenase, and monoamine oxidase levels have been observed in rats exposed to 3.1–24 mg Cd/kg/day for an intermediate duration (ATSDR 1999a). In mice, necrosis of the choroid plexus epithelial cells have been observed following intermediate duration exposure to 1.4 mg Cd/kg/day as cadmium chloride in drinking water, but not after exposure to 0.2 mg Cd/kg/day (Valois and Webster, 1989). Chronic exposure to 3.6 mg Cd/kg/day as cadmium chloride in drinking water resulted in peripheral neuropathy in rats. The inhalation of cadmium can result in olfactory epithelial injury, an altered sense of smell, and direct delivery of the metal from the olfactory epithelium to the olfactory bulbs and other parts of the central nervous system. Cadmium delivered to the olfactory bulbs, most likely along the olfactory nerve, thereby bypassing the intact blood-brain barrier. Reports showed that cadmium can penetrate olfactory epithelium and hence be transported to olfactory bulbs. The olfactory route could therefore be a likely way to reach the brain and should be taken into account for occupational risk assessments for this metal (Bondier et. al., 2008). Again cadmium was detected in the blood and the brain after treatment and Cd + IS (immobilization stress) exposure modified cadmium distribution in tissues. This result suggests that exposure to low levels of Cadmium associated with stress may lead to increased aggressiveness in rats (Terçariol et.al., 2011).
Renal Effects

Numerous human and animal studies indicate that the kidney is the main target of cadmium toxicity (ATSDR 1999a). The first sign of renal effects is tubular damage, characterized by increased urinary excretion of low-molecular-weight proteins or intracellular tubular enzymes. More important, in succession to the tubular effects, Cd may affect glomerular function (Åkesson et. al., 2005). The kidney damage is characterized as decreased reabsorption of filtered low molecular weight proteins and mild tubular lesions progressing to necrosis. Cadmium reaches the kidney in form of cadmium-metallothionein (Cd-MT) where it is filtrated in the glomerulus, and subsequently reabsorbed in the proximal tubules. This causes the excretion of essential proteins and sugars from the body and further kidney damage. It takes a very long time before cadmium that has accumulated in kidneys is excreted from a human body. It then remains in the tubulus cells and makes up for the major part of the cadmium body burden (Svartengren et. al., 1986). The circulating Cd-MT complexes, released during liver damage or formed by binding plasma Cd are freely filtered through the renal glomeruli and efficiently taken up by the tubular epithelial cells, where they are rapidly degraded by lysosomal enzymes. The liberated Cd binds to endogenous MT but excess Cd interacts with intracellular machinery to elicit toxicity (Konar et.al., 2010).
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Respiratory effects

Inhalation of high levels of cadmium can also cause severe, life-threatening effects on the lungs. An exposure to significantly higher cadmium levels occurs when people smoke. Tobacco smoke transports cadmium into the lungs. Blood transports it through the rest of the body where it can increase effects by potentiating cadmium that is already present from cadmium-rich food. If a high concentration of cadmium reaches the lungs, symptoms usually do not appear for 4 to 10 hours, at which point the tiny air sacks in the lungs, the alveoli, may begin to hemorrhage, the Agency for Toxic Substances and Disease Registry reports. The person may experience fever and chills. Cadmium may also increase blood flow to the lungs, further complicating the alveolar hemorrhage. On cadmium exposure the lungs become inflamed and swell, causing difficulty in breathing. Blood clots may form in the small blood vessels throughout the lungs. The effects usually worsen over time and may result in permanent lung damage or death. (Agency for Toxic Substances and Disease Registry: Cadmium Toxicity). It has been shown that inhalatively resorbed cadmium reaches blood circulation usually in form of cadmium-cysteine complexes (Zalups, 2003).

Skeletal effects

- A serious bone disease found in the Jinzu River basin of Japan first hinted that cadmium might cause serious bone loss. Itai-itai disease, which means "ouch, ouch," is a
painful result of chronic cadmium poisoning from mining byproducts dumped upstream. The patients showed extreme bone demineralization (Wilson and Bhattacharya, 1997). Long-term exposure to this metal leads mainly to the damage of kidney and bones. Cadmium (Cd) exposure induces bone resorption \textit{in vitro} and \textit{in vivo} that can lead to low bone mass and increased incidence of fracture (Wilson and Bhattacharya, 1997). A correlation between the cadmium in bones and the decrease in the strength of the bone showed that cadmium directly affects the mechanical properties of bones of young rats (Ogoshi et. al., 1989). Cadmium causes bone loss by increasing the formation and activity of bone-dissolving cells. In human beings, this response might lead to the bone disease osteoporosis. Cadmium treatment affects bone collagen by decreasing its content and increasing its solubility. Skeletal injury such as osteopenia, osteoporosis and/or osteomalacia with increased incidence of fractures and pathological fractures are also noted as a result of human and animal exposure to cadmium (Galicka et. al., 2004). Moreover studies have suggested bone mineral density (BMD) correlation with previous kidney impairment caused by cadmium exposure, especially to tubular damage for female (Chen et.al., 2011).

\textbf{Gastrointestinal effects}

Ingestion of very high doses of cadmium can irritate the stomach, leading to vomiting and diarrhea and even death (ATSDR, 1999). The uptake through the human gastrointestinal is approximately 5\% of an ingested amount of cadmium, depending on
the exact dose and nutritional composition (Jin et. al., 2002). Several factors can increase this amount, such as low intakes of vitamin D, calcium, and trace elements like zinc and copper (Godt et. al., 2006). Furthermore a high fiber diet increases the dietary cadmium intake (Jarup et. al., 1998). 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 (Flanagan et. al., 1978). This is the main reason for the higher cadmium resorption in people with anemia and habitual iron deficit, such as children or menstruating women (Godt et. al., 2006). Oral cadmium exposure reduces gastrointestinal uptake of iron, which can result in anemia if dietary intake of iron is low. The intestinal adaptive response to iron deficiency may enhance cadmium toxicity, whereas sequestration and subsequent excretion of cadmium by the intestinal mucosa serves to protect the body against toxic effects. The duodenum, particularly in iron-deficient mice, is especially vulnerable to the toxic effects of cadmium. (Valberg et. al., 1976). Research suggests that high cadmium intake facilitates the occurrence of stress-induced mucosal lesions by diminishing the mucin content and PGE2 generation in gastric mucosa (Oner et. al., 1995). The reduced PGE2 and mucin levels in mucosa and increased leakage of hemoglobin into the luminal fluid in cadmium exposed rats are the overt evidences of injury in mucosal barrier (Izgut- Uysal et. al., 1993).
Hematological Effects

In animal studies, administration of additional iron prevents the anemia. Anemia has been observed in some human oral studies and in a number of animal oral studies of cadmium. Following intermediate-duration exposure, anemia has been observed in rats, mice, and rabbits exposed to doses of 0.8 mg Cd/kg/day and higher (ATSDR 1999). Because the hematological effects are secondary to decreased iron intake rather than a direct effect of cadmium on the hematological system, it is not likely that the effect is duration-related, thus, an uncertainty factor was not used to account for the use of an intermediate-duration study. In blood, cadmium is predominantly bound to the red blood cells and albumin (Hays et al., 2008; ATSDR, 1999). Cadmium enters the liver where it is then bound to metallothionein and redistributed to the bloodstream. Because of its small size, cadmium- metallothionein is efficiently transported to the kidney tubules via glomerular filtration (Nordberg et al., 2007).

Reproductive Effects

Cadmium appears to interfere with the ovarian steroidogenic pathway in rats. It is evaluated the direct effects of in vitro cadmium exposure on steroidogenesis in rat ovaries. The most affected were productions of progesterone and testosterone (Piasek, and Laskey, 1999). Low dosages of cadmium are reported to stimulate ovarian progesterone biosynthesis, while high dosages inhibit it (Henson and Chedrese, 2004).
Maternal exposure to cadmium is associated with low birth weight and an increase of spontaneous abortion (Shiverick and Salafia, 1999; Frery et al., 1993). Some evidence exists also that cadmium is a potent nonsteroidal estrogen in vivo and in vitro. Studies in rats showed that cadmium precipitates enhanced mammary development and increased uterine weight (Johnson et al., 2003). Testicular effects have also been observed in animals exposed to cadmium for acute or intermediate durations; the testicular effects included necrosis and atrophy of seminiferous tubule epithelium, increased testes weight, and decreased sperm count and motility (ATSDR 1999).

**Oxidative stress**

The mechanisms of heavy metal damage include the production of free radicals that alter mitochondrial activity, affecting cellular types like neurons and muscular fibers (Armenta et al., 2011). Reactive oxygen species (ROS) are often implicated in Cd toxicology. Direct evidence of the generation of free radicals in intact animals following acute Cd overload in association of ROS in chronic Cd toxicity have been found. Cd-generated superoxide anion, hydrogen peroxide, and hydroxyl radicals in vivo have been detected by the electron spin resonance spectra, which are often accompanied by activation of redox sensitive transcription factors (e.g., NF-kappaB, AP-1 and Nrf2) and alteration of ROS-related gene expression. It is generally agreed upon that oxidative stress plays important roles in acute Cd poisoning. However, following long-term Cd exposure at environmentally-relevant low levels, direct evidence for oxidative stress is often obscure. Alterations in ROS-related gene expression during chronic exposures are also less significant compared to acute Cd poisoning. This is probably due to induced
adaptation mechanisms (e.g., metallothionein and glutathione) following chronic Cd exposures, which in turn diminish Cd-induced oxidative stress. In chronic Cd-transformed cells, less ROS signals are detected with fluorescence probes. Acquired apoptotic tolerance renders damaged cells to proliferate with inherent oxidative DNA lesions, potentially leading to tumorigenesis. Thus, ROS are generated following acute Cd overload and play important roles in tissue damage. Adaptation to chronic Cd exposure reduces ROS production, but acquired Cd tolerance with aberrant gene expression plays important roles in chronic Cd toxicity and carcinogenesis (Liu et. al., 2009).

Hepatotoxic effects

The liver is an important organ performing vital functions including biotransformation, migration of lipids, glycogen storage and release of glucose into the blood. Moreover liver contain many enzymes and proteins, heavy metal chelation may disrupt the liver tissue by disintegrating the functional and structural properties the cells. Cadmium exposure can induce acute, lethal hepatocellular necrosis in rodents (Sauer, 1997). Histological and histochemical alterations in the liver and kidneys of the frog Rana ridibunda, which were exposed to 200 ppm aqueous solutions of cadmium for 4, 10 and 30 days, respectively was seen. In both the liver and kidneys, essential changes appeared after 10 days' exposure, the maximum changes being apparent after 30 days of exposure. In the liver, what was very characteristic was an increase in the area occupied by Kupffer cells, with the area in the animals exposed to cadmium for 30 days being the largest observed. What was also apparent was karyomegaly, polyploidy and infiltration.
In comparison with 10 days' exposure, fibrosis around the blood vessels and between hepatocytes, as well as Proliferating Cell Nuclear Antigen (PCNA) reactivity and apoptotic bodies increased lightly in the liver (Loumbourdis, 2005). Histopathological changes like cytoplasmic vacuolization of the hepatocytes, blood vessel congestion, inflammatory leucocytic infiltration and necrosis were induced in the liver of the fish *Channa striatus* due to cadmium exposure (Radhakrishnan and Hemalata, 2010).

**Endocrinological effects**

Cadmium can act as an endocrine disruptor by altering the homeostatic balance of a variety of hormones. Circulating concentrations of pituitary hormones, such as prolactin, adrenocorticotropic hormone, growth hormone, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone, were altered in male rats exposed to Cd (Lafuente et. al., 2003). Acute exposure to Cd can also decrease progesterone production in female rats, and this effect is dependent on the stage of the estrus cycle at the time of exposure (Piasek and Laskey, 1994, 1999). More recently, it has been reported that Cd may have estrogenic properties. 17b-Estradiol (E2) mediates its effects via two nuclear estrogen receptor (ER) isoforms, ERa and ERb (Hall et. al., 2001). Cd has been reported to bind and activate ERa in vitro and in vivo can mimic the effects of E2 on the uterus and mammary gland (Johnson et. al., 2003; Stoica et. al., 2000). Hormones are known to influence the immune system, and a strong sexual dimorphism exists in the immune response. Female steroids such as E2 are important factors responsible for gender differences of immune system in mammals. E2 affects all aspects
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of the immune response: the production, differentiation, and maturation of immune cells as well as the nonspecific immune response, the humoral- and cell-mediated immune responses (Ansar Ahmed et. al., 1985; Grossman, 1984, 1985, 1989; Medina et al., 2000). ERs are differentially expressed according to immune cell type, and the relative expression ratio of ERa to ERb may be one of the factors determining the cell type-specific effects of E2 on immune cells (Phiel et. al., 2005). The immunotoxic effects of Cd have been reported on the development of immune organs, on the differentiation of immune cells, and on specific and nonspecific immune responses (Descotes, 1988, 1992; Koller, 1998). This indicates an impact on the immune system as a whole, which can lead to a significant decrease in host resistance. However, the variability of experimental results has revealed that the immunotoxicity of Cd not only depends on the speciation of the metal employed, the route, dose, and duration of exposure but also on the physiological status of the animal. Cadmium specifically modify amine metabolism at the central nervous system and pituitary hormone secretions. Thus, the physiological functions controlled by these hormones can be modulated by cadmium. This xenobiotic is associated with deleterious effects on the gonadal function and with changes in the secretory pattern of other pituitary hormones like prolactin, ACTH, GH or TSH. (Lafuente and Esquifino, 1999).

Effect of cadmium on immune system

Cadmium exposure has multiple effects on the immune system (Blobaum et.al., 2010 Fowler, 2009, Ohsawa, 2009). Immunotoxicity investigation of metals in rodents
with subsequent extrapolation to man, forms the basis of human risk assessment. When
the immune system acts as a target of xenobiotic insults, the result can be a decreased
resistance to infection, cancer, or immune dysregulation that can induce the development
of autoimmunity. Extensive experimental investigations indicated that heavy metals alter
a number of parameters of the host's immune system and lead to increased susceptibility
to infections, autoimmune diseases, and allergic manifestations (Bernier et. al., 1995).
Studies have documented the direct immunotoxicity caused by short-term exposure to
heavy metals; still others observed genotoxic, apoptosis, or even chronic effects resulting
from long term exposure (El-Sherbiny et.al., 2010). A number of investigations have
suggested that cadmium may exert immunosuppressive effects in animals even though
conflicting findings, mainly to due varying conditions of exposure, have been reported.
Overall, cadmium has been shown to enhance humoral immune responses at low levels of
exposure, whereas higher ones may result in either no effect or decreased antibody
production. By contrast, cell-mediated immunity was more consistently shown to be
depressed. Similarly, phagocytosis, natural killer cell activity and host resistance toward
experimental infections were markedly impaired in most instances. Very few data are
available regarding cadmium immunotoxicity in humans. Hypersensitivity reactions have
so far not been described. No immune alterations were found to be associated with
"chronic cadmium disease", whereas a depressed phagocytosis, the clinical relevance of
which remains to be established, was recently documented in cadmium-exposed workers.
Further investigations are therefore needed to determine how immunotoxic cadmium
actually is and what health consequences are to be expected in occupationally or
environmentally exposed humans. (Descotes, 1992) Presently, only little is known about
the influence of heavy metals (Co, Cr (VI), Cd, Pb or Ni) on the immune system in human populations (Hengstler et. al., 2003). No studies on diseases possibly related to suppressive immunotoxicity except of cancer studies have been carried out. Evidence has been published that the humoral immune system might be susceptible to the exposure of Cd (Jung et. al., 2003). In animal experiments as well as in vitro investigations Cd, suppress the ability of B- and T-cells to proliferate. The mechanisms causing these disturbances in proliferation may be due to DNA damage (Hengstler et. al., 2003) by production of oxygen radicals, but may also be due to DNA repair inhibition (Hengstler et al., 2003). However, different mechanisms seem to be responsible for the generation of reactive oxygen species, and depletion of sulfhydryl groups for Cd (Stohs et. al., 2000). The effect on DNA-repair of Cd is reversed by the addition of zinc (Hartwig et. al., 1998). The activation of protein kinase and the induction of c-fos and c-jun by Cd, on the other hand, point to a stimulating effect of these metals on cell proliferation (Bagchi, et. al., 1997; Beyersmann et. al., 1997). The effect of Cd on cell proliferation has been reported to depend on dose, whereby lower concentrations (1 μM) lead to a stimulation and higher concentrations to a suppression of proliferation (McCabe et. al., 1990).

The immunotoxicity of cadmium also has been suggested by impaired resistance to L. monocytogenes as well as by the inhibition of antigen-specific T cell responses and the induction of abnormalities in antibody production. It has been reported that cadmium cause the destruction of the cell membrane of human lymphocytes and monocytes (Fuente, 2002). Cadmium (Cd) toxicity also includes increased reactive oxygen species (ROS) generation (Olmos et. al., 2003; Garnier et. al., 2006), but the biochemical
mechanism of ROS production during this metal stress is not completely elucidated. It is observed that the accumulation of cadmium is higher in thymus than in spleen, the metal affected CD4+ and CD8+ lymphocytes at the spleen but not at the thymus (Lafuente, 2003). Some study concludes the occurrence and changes in melano macrophage centres (MMC) and appearance of pigments in MMC of spleen, kidney and liver due to cadmium exposure. This indicates that the MMC could be considered as a biomarker of stress induced by the various pollutants or toxicants which are present in the environment (Suresh, 2009).

Carcinogenity

Cadmium (Cd), a heavy metal of considerable occupational and environmental concern, has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC). The carcinogenic potential of Cd as well as the mechanisms underlying carcinogenesis following exposure to Cd has been studied using in vitro cell culture and in vivo animal models. Exposure of cells to Cd results in their transformation. Administration of Cd in animals results in tumors of multiple organs/tissues. Also, a causal relationship has been noticed between exposure to Cd and the incidence of lung cancer in human. It has been demonstrated that Cd induces cancer by multiple mechanisms and the most important among them are aberrant gene expression, inhibition of DNA damage repair, induction of oxidative stress, and inhibition of apoptosis. The available evidence indicates that, perhaps, oxidative stress plays a central role in Cd carcinogenesis because of its involvement in Cd-induced aberrant gene expression,
inhibition of DNA damage repair, and apoptosis (Joseph, 2009). Waalkes et al. (1988) have shown that a subcutaneous injection of cadmium chloride can induce prostate cancer in Wistar rats. This group also postulated that high doses of cadmium can cause severe testicular necrosis in rats, followed by a higher incidence of testicular interstitial tumors. In contrast to laboratory data though, epidemiological studies could not convincingly prove cadmium to be a cause of prostate cancer (Sahmoun, 2005). Early publications however suggested an association of cadmium and renal cancer in humans (Kolonel, 1976). This assumption was confirmed in 2005 by a systematic review of seven epidemiological and eleven clinical studies (Il'yasova, 2005). Although molecular mechanisms of cadmium-induced carcinogenesis are not yet understood, several factors may contribute to it: Up-regulation of mitogenic signalling, perturbation of DNA-repairing mechanism, and acquisition of apoptotic resistance by cadmium exposure (Goyer et al., 2004). Cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities. Cd^{2+} does not catalyze Fenton-type reactions because it does not accept or donate electrons under physiological conditions, and it is only weakly genotoxic. Hence, indirect mechanisms are implicated in the carcinogenicity of cadmium. Multiple mechanisms such as modulation of gene expression and signal transduction, interference with enzymes of the cellular antioxidant system and generation of reactive oxygen species (ROS), inhibition of DNA repair and DNA methylation, role in apoptosis and disruption of E-cadherin-mediated cell-cell adhesion are discussed in this context. Cadmium affects both gene transcription and translation. The major mechanisms of gene induction by cadmium known so far are modulation of cellular signal transduction pathways by enhancement of protein phosphorylation and activation of transcription and
translation factors. Cadmium interferes with antioxidant defense mechanisms and stimulates the production of reactive oxygen species, which may act as signaling molecules in the induction of gene expression and apoptosis. The inhibition of DNA repair processes by cadmium represents a mechanism by which cadmium enhances the genotoxicity of other agents and may contribute to the tumor initiation by this metal. The disruption of E-cadherin-mediated cell-cell adhesion by cadmium probably further stimulates the development of tumors. The Fas down regulation induced by Cd2+ seems to be also responsible for the carcinogenic and the immunomodulatory effects of this metal (Tsangaris et. al., 2004). It thus became clear that there exist multiple mechanisms which contribute to the carcinogenicity of cadmium, although the relative weights of these contributions are difficult to estimate (Waisberg et. al., 2003).

Apoptosis

Apoptosis is a form of active cell death characterized by cell shrinkage, membrane blebbing, aggregation of cytoplasmic organelles, chromatin condensation and DNA fragmentation into oligonucleosomal fragments due to the activation of endogenous endonucleases. Apoptosis can be induced by a wide variety of stimuli such as glucocorticoids, radiation and pesticides, and it plays an important role in many fundamental biological process such as embryogenesis, metamorphosis, tissue homeostasis, development and regulation of the immune system (Krichah et. al., 2003). It is well known that apoptosis plays a key role in the homeostasis of the immune system, and in recent years it has become clear that programmed cell death is also involved in
many pathological conditions, either as the result of its enhancement or inhibition. Thus, abnormalities in programmed cell death are involved in different immunological diseases, including AIDS. In this regard, it seems evident that the uncontrolled elimination of immune cells may account for immunosupression or immune dysregulation, depending on the lymphoid cell subset affected. Recently, the number of toxic agents with an apoptotic-inducing effect on immune cells has increased, and these substances seem to be responsible for immunodeficiency (Fuente et al., 2002). It has been shown that administration of CdCl₂ to rodents induced apoptosis in liver and testicular cells. However, other studies using isolated nuclei from mammalian cells, indicate that Cd has a dual effect, inhibiting the endonuclease activity triggered by calcium, but inducing this enzymatic activity in the absence of calcium, probably by replacing it. It is worth mentioning that experiments with Cd were performed in the presence of Ca^{2+}, and that under such experimental conditions it was observed, the induction of apoptosis in all mononuclear cells (MNC) samples tested (Fuente et al., 2002). A previous study on a human T-cell line (CEM-C12) showed that Cd²⁺ exerts its toxic effect via apoptosis, while a comparative study of the apoptotic effect of Cd²⁺ in immune system's cell lines showed a differential Cd-induced apoptosis, which may disturb the immune system's normal growth and development (Tsangaris et al., 2004).

Though cell death resulting from cadmium (Cd) intoxication has been confirmed to occur through apoptosis by morphological and biochemical studies, it is still not clear whether Cd itself or metallothionein (MT) induced by Cd is the major factor responsible
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for the apoptosis. Although apoptosis is inducible by exposure of cells to various stimuli, the common pathway involved is generally accepted to be activation of endonucleases that induce internucleosomal cleavage of DNA, resulting in the 'ladder' formation observed upon agarose gel electrophoresis and the chromatin condensation seen by electron microscopy. Cd does not seem to activate the endonuclease in vitro. However, Cd itself can be associated with apoptosis through indirect oxidative stress by inhibition of antioxidant enzymes and possible interaction with zinc finger protein. In addition to the direct effect of Cd, MT appears to play dual roles in apoptosis induction: one as a Cd carrier by which Cd accumulates in the nucleus, and the other as an inhibitor of zinc finger proteins, which include transcriptional factors related to apoptosis such as the product of the apoptosis resistance gene A20. In this context, it is demonstrated that the mode of cell death following Cd exposure is associated with intracellular movement of Cd and MT; a possible mechanism for Cd-induced apoptosis (Hamada et al., 1997). Cadmium treatment could accelerate testis apoptosis (Li et al., 2000). The results of some experiments suggest that Cd-induced apoptosis is partly caused by caspase-9 activation triggered by Cyt c (Kondoh et al., 2002). Again, some other have demonstrated that cadmium potently initiates the cell cycle arrest at early hours and finally induces p53-dependent apoptosis at later part of the event (Chatterjee et al., 2009).

Treatment

At present, there is no effective treatment for cadmium intoxication, and patients are given supportive treatment according to their symptoms. However, it is thought that
some of the new chelating agents may be effective. The results of some experiments suggested that immunotoxicity induced by Cd was significantly restored or prevented by metallothionein. The NK cell and phagocytic activity used for evaluation of non-specific immunocompetence was significantly increased in Cd plus MLT-treated mice when compared with the treatment of Cd alone. The number of peripheral leukocytes was significantly increased in Cd plus metallothionein-treated mice when compared with treatment of Cd alone (Kim et. al., 2000). Other than symptomatic treatment, there are no good options for dealing with cadmium poisoning. Hemodialysis may be used to remove circulating cadmium from the bloodstream, although the literature on the subject is scarce. Addition of a chelating agent, particularly ethylenediamine tetra acetic acid (EDTA), will increase the amount of cadmium removed by the dialysate (the fluid used in dialysis to carry substances to or remove from the kidney during hemodialysis).