CHAPTER-I
REVIEW OF LITERATURE

The modern civilization depends on wide range of metals and their alloys. They are used in industry, agriculture, food-processing, medicines and household purposes. The rapid industrialization and the use of metals for a variety of purposes have led to their release in significant quantities in the environment. Some of the metals with well recognised toxicity, have been detected in air, water and soil, in quantities higher than the permissible limits. Thus, besides industrial workers handling various metals, general public, animals, flora and fauna are exposed to toxic metals.
Cadmium, placed in group II B of the periodic table, is closely related to zinc. Cadmium is a soft silvery white ductile metal with a faint bluish tinge and possesses following physical properties:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Atomic number</td>
<td>48</td>
</tr>
<tr>
<td>Atomic weight</td>
<td>112.4</td>
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<tr>
<td>Density at 20°C (g/cm³)</td>
<td>8.65</td>
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<tr>
<td>Melting point</td>
<td>320.9°C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>765°C</td>
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<tr>
<td>Valency</td>
<td>2</td>
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Only a few cadmium minerals are known: greenockite (hexagonal CdS), hawleyite (cubic CdS), cadmoselite (CdSe), montemponite (CdO), otavite (CdCO₃), and saukovite or cadmian metacinnabar (Hg, Cd)S. All of these minerals are rare and are not commercial source of the metal. The main source is zinc and lead ores, from which cadmium is obtained as a by product during refining.

Cadmium and its compounds have widespread industrial applications such as in the electroplating: coating steel, iron, copper, brass and other objects with cadmium confers resistance to corrosion; as pigment (cadmium sulphide and sulphoselenides) in a wide variety of products, especially plastics, ceramics, paints, coated fabrics, textiles, rubber, glass,
enamels and printing inks; as plastic stabilizers: cadmium-barium-(zinc)-epoxy organophosphites are used for calendering and plastisols; in batteries: nickel-cadmium storage batteries are the fastest growing segment of the cadmium industry; as alloys: cadmium alloys with most metals offer a wide variety of properties and commercial applications; in nuclear engineering: as a neutron absorber, either as a coating on graphite or in the form of rods. In electrical and electronic industries, the application of cadmium is extremely wide, for example as phosphors and luminescent materials, mixture of cadmium sulfide and zinc sulfide doped with copper and silver gives colour over the entire spectrum. Cadmium phosphors are used for direct conversion of energies of invisible particles (cathode rays, X-ray photon, alpha particles, ultraviolet photons) into visible light. Familiar applications include X-ray fluorescent screens, cathode-ray tubes, television tubes, radar equipment, fluorescent lamps, self-luminscent watch, instrument dials, phosphorescent tapes and markers. Copper-cadmium alloy strip is used for electrical contacts. Cadmium sulfide is used in solar cells and photocells.

Human beings are exposed to cadmium via-food, water, air, cigarette-smoke, emissions from smelters and from combustions of fuels and plastic waste. Grains like wheat, rice and liver and kidney from animals and shellfish contain considerably high content of cadmium.
Toxicity of Cadmium

Cadmium is highly toxic to humans (Gleason et al., 1969). In Japan, itai-itai disease, a particularly disabling and painful illness marked by osteomalacia and proteinuria, is regarded by most investigators as a form of Cd poisoning (Friberg et al., 1974; Tsuchiya, 1976). It was the Japanese experience that has raised the level of awareness and concern that chronic toxicity of Cd is a potentially serious problem in most of the heavily industrialized parts of the world. Once residents of Cd polluted areas or workers occupationally exposed to Cd show effects by accumulating Cd in the renal cortex at a critical concentration (Friberg et al., 1974), the adverse health changes induced by Cd seem essentially irreversible, because Cd in the renal cortex hardly decreases due to its long biological half-life (Friberg et al., 1974; Tsuchiya, 1978), even long after cessation of cadmium exposure. On inhalation or ingestion, Cd causes pulmonary disorders (emphysema, chronic bronchitis, bronchial carcinoma), renal dysfunction (glycosuria, aminoaciduria, hypercalcuria, renal stones), hypertension, anaemia, cardiovascular diseases, congenital abnormalities and even cancer of prostate (Fielder and Dale, 1983). Smokers have higher kidney level and total body burden of Cd than non-smokers (Lewis et al., 1972; Shuman et al., 1974).

Absorption and Excretion of Cadmium

The body accumulates Cd almost entirely by intestinal and
respiratory absorption. The absorption may vary widely, depending on the form in which Cd is bound and on the nature of other constituents of the diet. In animals, the protein content of the diet has an influence on cadmium absorption. Calcium-deficient diets enhance body Cd accumulation. In heavily industrialized areas demonstrating elevated levels of atmospheric Cd, inhalation becomes the primary route of intoxication due to the efficient absorption and retention of Cd through the respiratory tract. Once absorbed, Cd is very efficiently retained in the body, only very small amounts being excreted. The retained material is deposited mainly in liver and kidneys, although small amounts are distributed generally throughout the body.

Excretion is mostly in urine in man, normally only very low levels being present. These levels increase slowly with duration of exposure and tend to reflect the concentration of Cd in the kidneys, and hence total body burden, provided that exposure is not to levels sufficiently high to produce kidney dysfunction. Urinary Cd levels markedly increase if tubular dysfunction occurs. The amount of Cd excreted in faeces would consist of 90 to 95% of unabsorbed ingested Cd, meaning that faecal excretion would correspond approximately to the daily intake of Cd. The excretion of Cd into faeces is the major route of elimination for Cd in mice (Klaassen et al., 1984).
Biochemical Effects of Cadmium

Cadmium exerts its toxic effects by adversely altering various biochemical reactions in the body. It has been specifically implicated in the disturbance of various enzymes and hormone systems associated with carbohydrate and protein metabolism (Singhal et al., 1976). Alterations in carbohydrate metabolism, as manifested by increased exhalation of respiratory carbon dioxide, hyperglycemia, decreased aldolase activity, and increased phosphorylase-a activity, have been reported in mice, rats and rabbits exposed to Cd (Ghafghazi and Menner, 1973; Singhal et al., 1976). In chronic Cd toxicity, increased urinary excretion of glucose and protein occurs. Aminoaciduria and enzymuria in cadmium treated rabbits preceded proteinuria and glucosuria (Nomiyama et al., 1975) and may be considered as early sign of cadmium intoxication. Pyruvate carboxylase, phosphoenolpyruvate carboxykinase, glucose-6-phosphatase and fructose-1,6-diphosphatase comprise the quartet of enzymes that play a rate limiting role in glucose formation from non-carbohydrate sources (gluconeogenesis). The exposure to Cd has been shown to augment the activities of gluconeogenic enzymes as well as to elevate the hepatic cyclic 3,5-adenosine monophosphate (AMP) level (Chapatwala et al., 1982).

Effect of Cadmium on Hematopoetic System

Cadmium induced anaemia in experimental animals has been
shown by few workers (Stowe et al., 1972; Nomiyama et al., 1979). Mild anaemia was found in workers exposed to Cd (Tsuchiya, 1967). Decreased haemoglobin and haptoglobin levels were observed in workers who had high Cd levels in the blood (Piscator, 1971) indicating occurrence of hemolysis in these patients.

The anaemia induced by Cd intoxication is iron sensitive. Berlin and Friberg (1960) reported an increased destruction of red blood cells without any alteration in utilisation of iron for haemoglobin synthesis, indicating that Cd creates only a state of iron deficiency without any blockade in haemoglobin synthesis or erythropoietic activity (Berlin et al., 1961).

**Effect of Cadmium on Kidney**

The kidney is the most sensitive organ; exposure to Cd via inhalation or ingestion may give rise to kidney damage, ranging from minor tubular dysfunction to severe impairment involving tubuli as well as glomeruli. Increased urinary excretion of low molecular weight protein is the earliest sign of chronic Cd toxicity in man. Nomiyama et al. (1974) reported, based on clearance studies on enzymes such as acid phosphatase (AP), alkaline phosphatase (ALP), glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and lactic dehydrogenase (LDH) in urine, that increased
activity of enzymes in urine resulted mainly from renal cellular injury composed of pathological changes in renal tubules. The exposure to Cd significantly inhibited the renal activities of AP, ALP, GOT and GPT as an indication of nephrotoxicity.

Effect of Cadmium on Liver

The effect of cadmium on liver has not been as extensively studied as its effect on kidneys. Hepatotoxicity has been noted following exposure to Cd, but only at dose levels above those producing nephrotoxicity. Evidence of liver dysfunction was reflected by increased serum aspartate- and serum alanine-amino-transferase levels (Chapatwala et al., 1980). Chronic exposure to Cd caused ultrastructural changes (Muto and Omori, 1977; Omori and Muto, 1977; Fingerl et al., 1982), liver lesions (Stowe et al., 1972; Nomiyama et al., 1979) and considerable decrease in liver weights. Light microscopy revealed a depletion of glycogen in the hepatocytes with an increase in collagen deposition (Hoffmann et al., 1975) and in the level of glutathione. Prolonged Cd treatment was found to lower the level of hepatic glycogen through stimulation of glycogenolytic enzyme, phosphorylase-a (Stowe et al., 1972) and increase in the activity of gluconeogenic enzymes (Chapatwala et al., 1980).

Effect of Cadmium on Pancreas

The pancreatic tissue has been found to accumulate fairly high concentration of Cd, surpassed only by kidney and liver.
Cadmium has injurious effects on the cellular architecture as well as the functional capacity of the pancreas. Administration of Cd produced hyperglycemia and reduced the hypoglycemic and convulsant effects of insulin in rabbits. Cadmium accumulation in pancreas has been found to be associated with necrotic lesions of beta cells (Havu, 1969).

**Effect of Cadmium on Central Nervous System**

Cadmium has been shown to inflict morphological as well as biochemical lesions in the central nervous system, leading to behavioural abnormalities. The symptoms in cadmium exposed workers include headache, vertigo, increased knee-joint reflexes, tremor, dermographia and disturbances in both sensory and motor chronaxia (Vorobjeva, 1957). Increased spontaneous motor activity and alterations in the catecholamine metabolism have also been reported on exposure to Cd (Singhal and Merali, 1979). Experimental investigations demonstrated hemorrhagic ganglionic lesions and pathological changes in cerebrum and cerebellum of newborn animals exposed to Cd (Gabbiani, 1966; Gabbiani et al., 1967).

**Cadmium and Protein Malnutrition**

No other disease compares in importance with protein malnutrition in the fields of nutrition or public health in general. Prevalence of protein malnutrition in the third world especially among the industrial labour class, makes it imperative to under-
stand the toxic effects of Cd in protein deficient state of body. Because of interdependence between protein synthesis and trace metal metabolism in the body and the interactions of Cd associated with some of these essential elements, the effects of quality and quantity of dietary protein on Cd toxicity are of some interest. The toxicity of orally administered Cd was enhanced when the protein of diet was reduced while lesser toxic effects were seen when there was significant protein content in the diet (Suzuki et al., 1969). Rats on 11% protein diet are severely affected by Cd toxicity than those on normal diet (Muto and Omori, 1977). Protein in body has profound influence on resistance to Cd toxicity and development of metal induced renal damage. The low protein diet generally enhance Cd toxicity while high protein diet reduce the toxicity (Fox, 1979; Revis, 1981). The low protein diet selectively increases the release of Cd from the liver, reduce the uptake of Cd by the kidney and enhances the urinary excretion of Cd in Cd pre-accumulated rats. In relatively long-term studies, the tissue level of cadmium may be higher in animals fed a high protein diet, but the toxicity of cadmium may be greater in animals fed a low protein diet. These conflicting effects may be associated with the tissue level of metallothionein. Metallothionein synthesis may be reduced in animals fed a low protein diet, which would allow Cd to bind other macromolecules, thus increasing its tissue toxicity.
Cadmium and Alcoholism

The abusive consumption of alcoholic beverages deranges normal function of body system in various ways. Ethanol may directly alter the level of nutrient intake through its effect on appetite, displacement of food in the diet, or by virtue of its deleterious effects at almost every level of the gastrointestinal tract. Through its effect on multiple organs, especially the liver, ethanol alters the transport, activation, catabolism, utilization and storage of almost every nutrient studied. Vitamin absorption, intestinal transport, tissue storage, utilization and conversion to metabolically active forms may also be curtailed when the need for many vitamins and essential nutrients increases (Tomasulo et al., 1968). In addition to causing abnormal vitamin metabolism, chronic alcoholism may have profound effects on mineral, carbohydrate, protein and lipid metabolism. Ethanol is directly toxic to many tissues of the body, and this effect may be potentiated by concomitant exposure to Cd.

Cadmium-Protein Interaction

Cadmium has been shown to interact with a variety of proteins (Vallee and Ulmer, 1972), the most interesting being metallothionein, a low molecular weight (approx. 6,800) cytoplasmic protein, having a characteristic amino acid composition
(high cysteine content, no aromatic amino acids) and possessing high affinity for Cd and several other metals. Metallothionein is normally present in animal tissue in only trace amounts. However, exposure to Cd increases the concentration of MT mainly in liver and kidney (Onosaka and Cherian, 1981). More than 75% of the cadmium found in the liver and kidney was bound to metallothionein. Generally, induction of MT to bind Cd has been considered a protective response of cells to the presence of this toxic metal (Webb and Cain, 1982), thus rendering the metal less toxic by preventing its interaction with other vital macromolecules.

Cadmium-other Metal Interaction

Cadmium can markedly alter the metabolism and functions of some essential elements including Zn, Fe, Mn, Cu, Se and Ca. With individual deficiencies of Fe, Zn, Cu and Ca, the toxicity of Cd and sometimes tissue accumulation of Cd markedly increased. Likewise, an excess above the normal requirement for Zn, Fe, Cu and Se has been shown to protect against the toxic effects of Cd.

1) Cadmium-Copper

Cadmium induced deficiency of Cu as evidenced by a marked decrease in blood Cu and ceruloplasmin activities, low liver concentration of Cu, and reduction in the cortical bone index
has been demonstrated in animals (Campbell and Mills, 1974). However, a few workers (Mogilnicka and Webb, 1982) observed a rise in liver concentration of Cu in rats exposed to Cd with stimulation of ceruloplasmin. Several effects of Cd were prevented by simultaneously increasing the amount of Cu in diet suggesting that Cu is a powerful metabolic antagonist to Cd.

ii) Cadmium-Zinc

Cadmium and Zn appear together in nature. In animals they are biologically antagonistic to each other as they compete for binding sites on various carrier proteins. Exposure to Cd tends to increase the Zn levels in liver and kidney, partly attributed to induced metallothionein. The symptoms of Cd toxicity are quite similar to those of Zn deficiency (Powell et al., 1964). Many of the toxic effects of Cd such as testicular necrosis, anaemia and weight loss could be prevented or corrected by the administration of extra Zn.

iii) Cadmium-Iron

The exposure to Cd results in development of hypochromic, microcytic anaemia associated with increased level of plasma transferrin and decreased Fe stores of the organism. The intestinal absorption of Cd is reported to be enhanced in experimental Fe deficiency in men and animals (Flanagan et al., 1978) as Fe and Cd compete for the binding sites of the Fe
transfer system of the gastrointestinal tract (Schäfer and Forth, 1983). Many Cd toxicity symptoms, such as weight loss and depressed haemoglobin, may be entirely or partially corrected by Fe supplementation.

**Prophylaxis of Cadmium Poisoning**

The most important task for the prophylaxis of Cd poisoning is the diminution of the systemic metal burden. The removal of internally deposited metals by formation of soluble and readily excretable chelates is the most promising approach. Various chelating agents can influence the distribution and toxicity of Cd in the body. The possibilities of chelating agents for modifying the toxicity of Cd depend on the chelating agent used, the molar ratio between the chelate and Cd, the route of exposure and the time lapse between exposure to Cd and administration of the chelating agent. The induction of metallothionein synthesis on Cd exposure results in decreased effectiveness of chelation therapy after a single injection of Cd (Cantilena and Klaassen, 1982). Strong intracellular binding of Cd to metallothionein prevents most of the chelating agents from removing the metal from this natural chelate.

A number of chelating agents, containing thiol group, such as 2,3-dimercaptopropanol (BAL), DL-pencillamine and
dithioerythritol increased the biliary excretion of Cd within a short time (½ hr) after Cd exposure; however, these compounds also increased the deposition of Cd in kidney. The chelating agents, containing carboxylic group, such as ethylenediaminetetraacetic acid (EDTA) and nitrilotriacetic acid (NTA) were able to increase the urinary excretion of Cd with a small decrease in both hepatic and renal deposition, when administered soon after acute exposure (Cherian, 1984). Diethylenetriaminepentaacetic acid (DTPA), and its derivative, Puchel, have also been found to be effective Cd mobilizing agents (Basinger et al., 1981; Planas-Bohne and Lehman, 1983).