931 Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for Cadmium

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Summary of Health Effects

Since the ear ly 1950s, when the hazards of occupational cadmium exposure were recognized, a large amount of information has been generated concerning the toxic effects of cadmium exposure in humans and laboratory animals. Toxicological properties of cadmium are similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics. For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd+2 ion regardless of the initial salt. Absorption appears to be simil ar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat. Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion. For the general population, dietary exposure to cadmium is the most likely route of exposure. There is an extensive database on the toxicity of cadmium in environmentally exposed populations and in cadmium workers; however, most of these studies were focused on the presumed sensitive targets. These sensitive targets of cadmium toxicity are the kidney and bone following oral exposure and kidney and lung following inhalation exposure. Studies in animals support the identification of these sensitive targets and provide some suggestive evidence that the developing organisms may also be a sensitive target. There is also evidence to suggest that cadmium is a human carcinogen. Other effects that have been observed in humans and/or animals include reproductive toxicity, hepatic ef fects, hematological effects, and immunological effects.

The earliest indication of kidney damage in humans is an increased excretion of low molecular weight proteins, particularly β2-microglobulin, human complex forming glycoprotein (pHC) (also referred to as α1-microglobulin), and retinol binding protein; increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG); and increased excretion of calcium and

metallothione. Numerous studies of cadmium workers and populations living in areas with low, moderate, or high cadmium pollution have found significant associations between urinary cadmium levels and biomarker levels or significant increases in the prevalence of abnormal biomarker levels. At higher exposure levels, decreases in glomerular filtration rate, increased risk of renal replacement therapy (dialysis or kidney transplantation), and significant increases in the risk of death s from renal disease have been observed. The sensitivity of the kidney to cadmium is related to its distribution in the body and de novo synthesis of metallothionein in the kidney. In the blood, cadmium is bound to metallothionein and is readily filtered a t the glomerulus and reabsorbed in the proximal tubule. Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released; the synthesis of endogenous metallothionein by the tubular cells is then stimulated. However, when the total cadmium content in the renal cortex reaches between 50 and 300 µg/g wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage. Free cadmium ions may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species. Because the toxicity of cadmium is dependent on its concentration in the kidney, adverse effects in humans are typically not observed after shorter durations.

Acute inhalation exposure to cadmium at concentrations above about 5 mg/m3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals. A single, high-level cadmium exposure can result in long-term impairment of lung function. At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphatedehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage. There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema in cadmium workers. Some tolerance to cadmium-induced lung irritation develops in exposed humans and animals, and respiratory function may recover after cessation of cadmium exposure. Another effect of long-t erm inhalation cadmium exposure is damage to the olfactory function and nasal epithelium. Lung damage has also been seen in a few studies of oral cadmium exposure in rats, but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism.

Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition; the occurrence of these bone effects in elderly Japanese women exposed to high levels of cadmium in rice and water was referred to as Itai-Itai disease. Decreases in bone mineral density, increases in the risk of fractures, and increases in the risk of osteoporosis hav e also been observed in populations living in cadmium polluted areas or in cadmium nonpolluted areas. Similar effects have also been observed in young rats orally exposed to cadmium. Animal data strongly suggest that cadmium exposure results in increases i n bone turnover and

decreases in mineralization during the period of rapid bone growth. Although animal studies suggest that these effects are due to direct damage to the bone, it is likely that renal damage resulting in the loss of calcium and phosphate and alteration in renal metabolism of vitamin D would compound these effects.

There are few human data on developmental effects from exposure to cadmium. Some studies indicate that maternal cadmium exposure may cause decreased birth weight in humans, but most of these studies are of limited use because of weaknesses in the study design and lack of control for confounding factors. A number of other studies did not find a significant relationship between maternal cadmium levels and newborn body weight. In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes. Decreased fetal weight, skeletal malformations, and delayed ossification are produced by relatively high maternal doses (1–20 mg/kg/day) due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver. Neurodevelopmental effects have been observed at lower doses. Impaired performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg/m3 or ≥0.04 mg/kg/day.

The results of occupational exposure studies examining the possible association between cadmium exposure and an increased risk of lung cancer are inconsistent, with some studies finding significant increases in lung cancer deaths and other studies not finding increases. Interpretation of the results of many of the studies is complicated by inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, small number of lung cancer deaths, and the lack of significant relationships between cadmium exposure and duration. For prostate cancer, initial studies in European workers indicated an elevation in prostate cancer, but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant. Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Most oral studies in laboratory animals have not found significant increases in cancer incidence. The Department of Health and Human Services concluded that there were sufficient human and animal data to conclude that cadmium is a known human carcinogen; likewise, IARC classified cadmium as carcinogenic to humans (Group 1). The EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1), based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats.