CADMIUM AND CADMIUM COMPOUNDS

First Listed in the *First Annual Report on Carcinogens* as *Reasonably Anticipated to be Human Carcinogens* -- changed to *Known to be Human Carcinogens* in the *Ninth Report on Carcinogens*

CARCINOGENICITY

Cadmium (CAS No. 7440-43-9) and cadmium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, including epidemiological and mechanistic information which indicate a causal relationship between exposure to cadmium and cadmium compounds and human cancer. In several cohort studies of workers exposed to various cadmium compounds, the risk for death from lung cancer is elevated (IARC 1993). Although confounding factors, such as co-exposure to arsenic, were present in several of these studies, it is unlikely that the increase in lung cancer risk is completely explained by exposure to arsenic. Follow-up analysis of some of these cohorts has not definitively eliminated arsenic as a possible confounding factor, but has confirmed that cadmium exposure is associated with elevated lung cancer risk under some industrial circumstances (Sorahan *et al*. 1995, Sorahan and Lancashire 1997). In some early cohort studies, an increased risk of mortality from prostate cancers was found in cadmium-exposed workers, but later cohort studies have not confirmed this observation. Additional epidemiological evidence (case-control studies, geographic distribution studies, etc.) suggests an association between cadmium exposure in human populations and prostate (Shigematsu *et al.* 1982, Bako *et al.* 1982, Garcia Sanchez *et al.* 1992, van der Gulden *et al.* 1995), renal (Kolonel 1976, Mandel *et al.* 1995), and bladder (Siemiatycki *et al.* 1994) cancers.

The evidence that cadmium and cadmium compounds are human carcinogens is supported by experimental animal studies that have shown cadmium and cadmium compounds induce malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals. Inhalation of a variety of cadmium compounds were reported to produce dose-dependent increases in pulmonary adenocarcinomas in rats, and occasionally to produce pulmonary tumors in mice, but not in hamsters. Intratracheal instillation of cadmium compounds produced malignant lung tumors in rats (IARC 1993). Oral exposure to cadmium chloride produces dose-related increases in leukemia and benign testicular tumors in rats. In several studies, single or multiple injections (subcutaneous, intramuscular, or intraperitoneal) of a variety of soluble and insoluble cadmium compounds caused local sarcomas in rats and mice (IARC 1993, Waalkes and Rehm 1994a). Subcutaneously injected cadmium compounds produce a variety of tumors including prostate tumors in rats, testicular tumors in rats and mice, lymphomas in mice, adrenal tumors in hamsters and mice, and lung and liver tumors in mice (IARC 1993, Waalkes and Rehm 1994a, b, c; Waalkes *et al.* 1994). Based on the carcinogenicity of a wide variety of cadmium compounds, it appears that it is ionic cadmium that is the active, carcinogenic species (IARC 1993). Studies in animals and in isolated cells or tissues suggest that ionic cadmium, or compounds that release ionic cadmium cause genetic damage and are carcinogenic. Thus, the carcinogenic potential of a given cadmium compound would depend on the degree to which the compound releases ionic cadmium under the conditions of exposure.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Increases in chromosomal aberrations have been observed in lymphocytes of workers exposed to cadmium in industrial settings. Many studies of cultured animal cells have shown that cadmium compounds damage genetic material. DNA strand breaks, mutations, chromosomal damage, cell transformations, and disrupted DNA repair have been observed in *in vitro* studies. The accumulated information supports the conclusion that ionic cadmium is the active, genotoxic form of the metal or metal compounds (IARC 1993). No data were available that indicate the mechanisms thought to account for cadmium carcinogenesis in experimental animals would not also operate in humans.

The sensitivity of cells or tissues to cadmium appears to be related, at least in part, to expression of the metallothionein (*MT*) gene. The *MT* protein produced following activation of the *MT* gene functions to sequester cadmium. Activation of the *MT* gene can limit the genotoxic effects of cadmium. Differential expression of the pulmonary *MT* gene appears to be the basis for the sensitivity of rats and the insensitivity of mice to lung tumors induced by inhaled cadmium. Additionally, other target tissues of cadmium carcinogenesis in rodents show minimal basal expression or poor activation upon stimulation of the *MT* gene (Oberdorster *et al.* 1994).

PROPERTIES

Cadmium is an odorless, silver-white, blue-tinged, malleable metal or grayish-white powder. It has an atomic weight of 112.41 and belongs to group IIB of the periodic table. It is a rare element not found in nature in its pure state, but mainly occurs as a sulfide form in zinc deposits. Almost all cadmium compounds have an oxidation state of +2. Cadmium is slowly oxidized in moist air, but forms cadmium oxide fumes when heated. Cadmium and cadmium compounds are not combustible, but may decompose in fires and release corrosive and toxic fumes. Hot cadmium metal reacts with halogens, phosphorus, selenium, sulfur, and tellurium; cadmium vapor reacts with oxygen, carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide, and hydrogen chloride. Cadmium is soluble in dilute nitric acid, ammonium nitrate, and hot sulfuric acid and insoluble in water. Eight stable isotopes and two radioactive isotopes are known. It is commercially available in various purities ranging from 99.0% to 99.9999% in the following forms: powders, foils, ingots, slabs, sticks, and, crystals (IARC 1993, Llewellyn 1994, HSDB 2001).

Commercially important cadmium salts include cadmium chloride, cadmium sulfate, and cadmium nitrate. Cadmium chloride occurs as small, colorless-to-white rhombohedral or hexagonal crystals. It is soluble in water and acetone, slightly soluble in methanol and ethanol, and insoluble in diethyl ether. Commercial cadmium chloride is a mixture of hydrates that is similar to the dihydrate form of cadmium chloride. Cadmium chloride is available in purities ranging from 95.0% to 99.999%. Cadmium sulfate occurs as colorless to white orthorhombic crystals and is commercially available in purities ranging from 98% to 99.999%. It is soluble in water, but insoluble in ethanol, acetone, and ammonia. Cadmium nitrate occurs as a colorless solid. It is very soluble in dilute acids and soluble in ethanol, acetone, water, diethyl ether, and ethyl acetate. Cadmium nitrate is available in technical and reagent grades with a purity ≥99% (IARC 1993, HSDB 2001).

Cadmium oxide occurs as a colorless amorphous powder or dark-brown crystals. It is soluble in dilute acids and ammonium salts; practically insoluble in water, and insoluble in alkali. Commercial-grade cadmium oxide is available in the U.S. with purities ranging from

99% to 99.9999%. Cadmium sulfide occurs as yellow-orange hexagonal or cubic dimorphic semi-transparent crystals or as a yellow-brown powder but may be prepared to range in color from white to deep orange-red. It is soluble in concentrated or warm dilute mineral acids with evolution of hydrogen sulfide, slightly soluble in ammonium hydroxide, practically insoluble in water, and insoluble in alkali. Cadmium sulfide is available in purities ranging from 98% to 99.999%. However, many cadmium sulfide products are complex mixtures that contain other metal compounds (IARC 1973, 1993, HSDB 2001).

USE

Cadmium was discovered in 1817, but was not used commercially until the end of the 19th century. The earliest use of cadmium, primarily in the sulfide form, was in paint pigments. Minor amounts were used in dental amalgams in the early 1900s; during World War I, cadmium was used as a substitute for tin. Since World War II, almost all cadmium has been used in the following five categories: batteries; pigments; stabilizers for plastics; electroplating and coating; and alloys (IARC 1993, Llewellyn 1994).

Over the past several decades, all use categories except batteries declined dramatically. Electroplating and coating accounted for more than half of cadmium consumption in 1960, but declined to approximately 8% by 2000. Cadmium pigments accounted for 20% to 30% of cadmium consumption between 1970 and 1990, but declined to approximately 12% by 2000. Between 1970 and 2000, cadmium use in stabilizers and alloys dropped from 23% to 4% and 8% to 1%, respectively; however, cadmium use in batteries grew from 8% in 1970 to 75% in 2000 (IARC 1993, Plachy 2000).

Cadmium chloride has been used in many industrial applications and products; however, its use is also declining. It is used in electroplating, photocopying, calico printing, dyeing, mirrors, analytical chemistry, vacuum tubes, lubricants, and as a chemical intermediate to produce cadmium-containing stabilizers and pigments (IARC 1993, HSDB 2001). Cadmium chloride was used as fungicides for golf courses and home lawn turf; however, these uses were banned by the EPA in the late 1980s (ATSDR 1999). Cadmium sulfate is used in electroplating, fluorescent screens, vacuum tubes, and analytical chemistry; as a chemical intermediate to produce pigments, stabilizers, and other cadmium compounds; as a fungicide or nematocide; and as a component of Weston cells (portable standards for electromagnetic frequency). Cadmium nitrate is used in photographic emulsions, coloring glass and porcelain, in nuclear reactors, and to produce cadmium hydroxide for use in alkaline batteries (IARC 1993, HSDB 2001).

Cadmium sulfide is primarily used in pigments in paints, glass, ceramics, plastics, textiles, paper, and fireworks. Because of its semiconductive and electroluminescent properties, cadmium sulfide is also used in solar cells, fluorescent screens, radiation detectors, smoke detectors, electron-beam pumped lasers, thin film transistors and diodes, phosphors, and photomultipliers. The primary use for cadmium oxide is in nickel-cadmium batteries; however, it has a wide variety of industrial and commercial uses. These include electroplating, electrical contacts, resistant enamels, heat-resistant plastics, in nitrite rubbers and plastics such as Teflon®, and as a catalyst. Cadmium oxide has been used as nematocide and ascaricide in swine (IARC 1993, HSDB 2001).

PRODUCTION

The U.S. began commercial production of cadmium in 1907 and was the world's leading producer from 1917 to the late 1960s. U.S. cadmium production peaked in 1969 at 5,737 metric tons (Llewellyn 1994). Both production and consumption have declined in recent decades because of increasing environmental concerns and regulations due to its toxicity (Plachy 2000). Greenockite (CdS) is the only cadmium mineral of importance; however, it does not occur in any isolated deposits. Therefore, cadmium is chiefly recovered as a by-product of smelting domestic and imported zinc concentrates. As such, its production is dependent upon the demand for zinc (Llewellyn 1994).

In 2000, there were two U.S. companies that produced primary cadmium as a by-product of zinc smelting and refining, and another company recovered cadmium from scrap (Plachy 2000). In addition, eight U.S. companies were identified as major producers of cadmium compounds (ATSDR 1999). Thirty-three U.S. suppliers of cadmium metal and 16 suppliers of cadmium powder were listed by Chem Sources (2001).

The U.S. was the third largest producer of cadmium in 2000, with approximately 10% of the total world production. Between 1990 and 2000, cadmium production in the U.S. averaged approximately 1,440 metric tons/yr and ranged from a low of 1,010 metric tons in 1994 to a high of 2,060 metric tons in 1997 (Kuck 1994, Plachy 2000). This level of production was similar to the 1980s with an average annual production of approximately 1,500 metric tons, but was much lower than the average production in the 1960s and 1970s with 4,700 and 2,750 metric tons/yr, respectively (Llewellyn 1994). The estimated production of cadmium metal in 2000 was 1,890 metric tons while production of cadmium compounds was approximately 670 metric tons in 1999 and 460 metric tons in 2000 (Plachy 2000).

U.S. imports and exports have fluctuated widely over the past few decades; however, imports have always exceeded exports. Cadmium imports averaged 694, 2,088, and 2,523 metric tons/yr in the 1960s, 1970s, and 1980s, respectively. During this period, U.S. exports averaged 425, 188, and 213 metric tons/yr, respectively (Llewellyn 1994). Imports and exports in the 1990s averaged 1,156 and 485 metric tons, respectively (Kuck 1994, Plachy 1997, 2000). In 2000, the U.S. imported 425 metric tons of cadmium and exported 312 metric tons (Plachy 2000).

EXPOSURE

The general population may be exposed to cadmium through consumption of food and drinking water, inhalation of cadmium-containing particles from ambient air, cigarette smoke, or ingestion of contaminated soil and dust. Tobacco smokers are exposed to an estimated 1.7 μg/cigarette. Food is the major source of cadmium exposure for nonsmokers. Average cadmium levels in the U.S. food supply range from 2 to 40 ppb. The adult intake of cadmium is estimated to be approximately 30 μg/day, with the largest contribution from grain cereal products, potatoes, and other vegetables. Exposures through drinking water or ambient air are typically very low (ATSDR 1999).

Workers in a wide variety of occupations are potentially exposed to cadmium and cadmium compounds (IARC 1993). However, occupations with the highest potential levels of exposure include smelting zinc and lead ores; producing, processing, and handling cadmium powders; welding or remelting cadmium-coated steel; and working with solders that contain cadmium. The major routes of occupational exposure are inhalation of dust and fumes and

incidental ingestion of dust from contaminated hands, cigarettes, or food (ATSDR 1999).

The National Occupational Exposure Survey (NOES) conducted in 1981-1983 estimated that 153,486 workers were potentially exposed to cadmium or cadmium-containing substances. These included workers potentially exposed to unknown cadmium compounds (88,966), cadmium sulfide (42,564), cadmium oxide (15,731), cadmium (4,748), cadmium sulfate (1,313), and cadmium salt of carbonic acid (164) (ATSDR 1999). OSHA estimated in 1990 that approximately 512,000 U.S. workers were exposed to cadmium; however, 70% to more than 80% were exposed to concentrations below occupational standards or guidelines (ATSDR 1999).

EPA's Toxic Chemical Release Inventory (TRI) collects cadmium data in two categories: "cadmium" and "cadmium compounds," and individual facilities may report releases in each category. In 1999, 42 facilities reported releasing approximately 2.2 million lb of cadmium. About 76% was released to land. Releases to air, surface water, and underground injection were approximately 4,300; 690 lb, and 61,000 lb, respectively. The remainder was released off site. Environmental releases of cadmium compounds totaled more than 12 million lb from 98 facilities in 1999 (TRI99 2001).

REGULATIONS

In 1997, U.S. Consumer Products Safety Commission (CPSC) found very low levels of cadmium in children's products made from PVC, and concluded that these levels were not hazardous. Artists' paints containing cadmium are subject to the requirements of the Labeling of Hazardous Art Materials Act (LHAMA).

EPA regulates cadmium and cadmium compounds under the Clean Air Act (CAA), Toxic Substances Control Act (TSCA), Clean Water Act (CWA), Safe Drinking Water Act (SDWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and Superfund Amendments and Reauthorization Act (SARA). Under the SDWA, the maximum contaminant level (MCL) for cadmium is 0.005 mg/L. EPA's Carcinogen Assessment Group includes cadmium oxide, cadmium sulfide, and cadmium sulfate on its list of potential carcinogens. Under CERCLA, the reportable quantities (RQs) for cadmium and compounds are 1 pound (0.454 kg). The RQ for cadmium chloride is 10 lb (4.54 kg). Releases involving cadmium where the mean diameter of the particle is less then 100 micrometers (0.004 inches), however, are exempt from CERCLA reporting requirements. EPA issued a Rebuttable Presumption Against Registration (RPAR) for cadmium-containing pesticides under FIFRA. Also under FIFRA, there are labeling and reporting requirements. By 1997, all cadmium pesticides had undergone voluntary cancellation. Cadmium is no longer used as a pesticide. Both RCRA and SARA subject cadmium and its compounds to reporting requirements.

FDA, under the Food, Drug, and Cosmetic Act (FD&CA), has set a maximum concentration level of 0.005 mg Cd/L in bottled water and limits the amount of cadmium in color additives and direct food additives.

In 1984, NIOSH recommended that exposure to cadmium be reduced to the lowest feasible concentration. OSHA adopted permissible exposure limits (PELs) for toxic effects other than cancer for cadmium: 0.1 mg/m^3 as an 8-hr time-weighted average (TWA) for fumes, 0.3 mg/m^3 as a ceiling for fumes, 0.2 mg/m^3 as an 8-hr TWA for dust, and 0.6 mg/m^3 as a ceiling for dust; the standards were adopted by OSHA. OSHA regulates cadmium and certain cadmium

compounds under the Hazard Communication Standard and as chemical hazards in laboratories. Regulations are summarized in Volume II, Table 28.

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