Cadmium (CAS No. 7440-43-9) and Cadmium Compounds

Known to be human carcinogens
First Listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Cadmium and cadmium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans, including epidemiological and mechanistic information that indicate a causal relationship between exposure to cadmium and cadmium compounds and human cancer. Cadmium and cadmium compounds were first listed as *reasonably anticipated to be human carcinogens* in the *First Annual Report on Carcinogens* (1980); however, the listing was revised to *known to be human carcinogens* in the *Ninth Report on Carcinogens* (2000). Several cohort (epidemiological) studies of workers found that exposure to various cadmium compounds increased the risk of death from lung cancer (IARC 1993). Although other factors that could increase the risk of cancer, such as co-exposure to arsenic, were present in several of these studies, it is unlikely that the increased risk of lung cancer was due entirely to confounding factors. 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). Some early cohort studies found an increased risk of mortality from prostate cancer among cadmium-exposed workers, but later cohort studies have not confirmed this observation. Additional epidemiological evidence (including case-control studies and geographic distribution studies) suggests an association between cadmium exposure and cancer of the prostate (Bako *et al.* 1982, Shigematsu *et al.* 1982, Garcia Sanchez *et al.* 1992, van der Gulden *et al.* 1995), kidney (Kolonel 1976, Mandel *et al.* 1995), and bladder (Siemiatycki *et al.* 1994).

The findings in humans are supported by studies in experimental animals demonstrating that cadmium and cadmium compounds by multiple routes of exposure induce malignant tumor formation at various sites in multiple species of experimental animals. Inhalation exposure to a variety of cadmium compounds caused lung tumors (pulmonary adenocarcinoma) in rats, and the tumor incidence increased with increasing exposure. In other species exposed to cadmium compounds by inhalation, lung tumors were observed occasionally in mice, but not in hamsters. Intratracheal instillation of cadmium compounds also caused malignant lung tumors in rats (IARC 1993). When administered orally to rats, cadmium chloride caused dose-related increases in the incidences of leukemia and benign testicular tumors. In several studies with rats and mice, single or multiple injections (subcutaneous, intramuscular, or intraperitoneal) of a variety of soluble and insoluble cadmium compounds caused tumors (sarcoma) at the injection site (IARC 1993, Waalkes and Rehm 1994a). Subcutaneously injected cadmium compounds caused tumors at various tissue sites, including prostate tumors in rats, testicular tumors in rats and mice, lymphoma in mice, adrenal-gland tumors in hamsters and mice, and lung and liver tumors in mice (IARC 1993, Waalkes *et al.* 1994, Waalkes and Rehm 1994a, 1994b, 1994c). 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).

Since cadmium and cadmium compounds were reviewed for listing in the *Ninth Report on Carcinogens* (2000), studies in rats have been published suggesting that cadmium compounds cause tumors at additional tissue sites (the pituitary gland and kidney). Subcutaneous administration of cadmium chloride significantly increased the incidence of pituitary-gland tumors in rats (Waalkes *et al.* 1999b). The incidence of kidney tumors in rats increased with increasing oral dose of cadmium chloride; however, the tumor incidence was not significantly higher at the highest dose than in the unexposed control animals (Waalkes *et al.* 1999a).

Additional Information Relevant to Carcinogenicity

Studies in experimental 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 is expected to depend on the degree to which the compound releases ionic cadmium under the conditions of exposure. Increased frequencies of chromosomal aberrations (changes in chromosome structure or number) have been observed in lymphocytes (white blood cells) of workers occupationally exposed to cadmium. Many studies of cultured mammalian cells have shown that cadmium compounds cause genetic damage, including gene mutations, DNA strand breaks, chromosomal damage, cell transformation (a step in tumor formation), and disrupted DNA repair. The accumulated information supports the conclusion that ionic cadmium is the active, genotoxic form of cadmium and its compounds (IARC 1993). There is no evidence to suggest that the mechanisms thought to account for cadmium's carcinogenicity 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 their ability to produce metallothionein (MT), a protective protein that binds heavy metals, including cadmium. Activation of the *MT* gene in response to cadmium exposure results in production of metallothionein, which sequesters cadmium, thus limiting its genotoxic effects. The difference between rats and mice in sensitivity to cadmium as a lung carcinogen appears to be due to differential expression of MT in lung tissue following inhalation exposure to cadmium. Other tissues in which cadmium causes cancer in rodents also show minimal basal expression of the *MT* gene or limited activation of MT in response to cadmium exposure (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. Eight stable isotopes and two radioactive isotopes are known. Almost all cadmium compounds have an oxidation state of +2. Cadmium is soluble in dilute nitric acid, ammonium nitrate, and hot sulfuric acid and insoluble in water. It 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, and cadmium vapor reacts with oxygen, carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide, and hydrogen chloride. Cadmium is commercially available in purities ranging from 99.0% to 99.9999%, as powders, foils, ingots, slabs, sticks, and crystals (IARC 1993, Llewellyn 1994, HSDB 2003).

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 similar to the dihydrate form of cadmium chloride. It is available in purities ranging from 95.0% to 99.999%. Cadmium sulfate occurs as colorless to white orthorhombic crystals. It is soluble in water but insoluble in ethanol, acetone, and ammonia, and is available in purities ranging from 98% to 99.999%. 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 of 99% or higher (IARC 1993, HSDB 2003).

Other commercially important cadmium compounds include cadmium oxide and cadmium sulfide. 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 alkalies. Commercial-grade cadmium oxide is available in purities ranging from 99% to 99.9999%. Cadmium sulfide occurs as yellow-orange hexagonal or cubic dimorphic semitransparent 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 alkalies. 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 2003).

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 batteries, pigments, alloys, electroplating and coating, and stabilizers for plastics (IARC 1993, Llewellyn 1994). However, all uses except in batteries declined dramatically in the late 20th century. Electroplating and coating accounted for more than half of cadmium consumption in 1960 but declined to about 8% by 2000. Cadmium pigments accounted for 20% to 30% of cadmium consumption between 1970 and 1990 but declined to about 12% by 2000. Between 1970 and 2000, cadmium's use in stabilizers decreased from 23% to 4%, and its use in alloys from 8% to 1%. In contrast, cadmium's use in batteries grew from 8% in 1970 to 75% in 2000 (IARC 1993, Plachy 2000).

Cadmium chloride is used in electroplating, photocopying, calico printing, dyeing, mirrors, analytical chemistry, vacuum tubes, and lubricants and as a chemical intermediate in production of cadmium-containing stabilizers and pigments (IARC 1993, HSDB 2003). However, its uses are declining. Cadmium chloride was used as a fungicide for golf courses and home lawn turf, but these uses were banned by the U.S. Environmental Protection Agency (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 an electrolyte in Weston cells (portable voltage standards). Cadmium nitrate is used in photographic emulsions, to color glass and porcelain, in nuclear reactors, and to produce cadmium hydroxide for use in alkaline batteries (IARC 1993, HSDB 2003).

Cadmium sulfide is used primarily in pigments for paints, glass, ceramics, plastics, textiles, paper, and fireworks. It also is used in solar cells, fluorescent screens, radiation detectors, smoke detectors, electron-beam-pumped lasers, thin-film transistors and diodes, phosphors, and photomultipliers. Cadmium oxide is used primarily in nickel-cadmium batteries, but also as a catalyst and in electroplating, electrical contacts, resistant enamels, heat-resistant plastics, and manufacture of plastics (such as Teflon) and nitrile rubbers. Cadmium oxide has been used as a nematocide and ascaricide in swine (IARC 1993, HSDB 2003).

Production

Cadmium is a rare element not found in nature in its pure state. It occurs mainly as cadmium sulfide (CdS, or greenockite) in zinc deposits. Cadmium is chiefly recovered as a byproduct of zinc concentrates, and its production depends on the demand for zinc (Llewellyn 1994).

The United States 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 (12.6 million pounds) (Llewellyn 1994). Cadmium production and consumption have declined in recent decades, because its toxicity led to increasing environmental concerns and regulations (Plachy 2000). In 2002, the United States was the seventh largest producer of cadmium, accounting for about 4% of the world production (Plachy 2002). Estimated U.S. production of cadmium metal was 1,890 metric tons (4.2 million pounds) in 2000, but declined to about 700 metric tons (1.5 million pounds) in 2001 and 2002 (Plachy 2002). U.S. production of cadmium compounds was about 670 metric tons (1.5 million pounds) in 1999, 460 metric tons (1 million pounds) in 2000, 31 metric tons (68,000 lb) in 2001, and 33 metric tons (73,000 lb) in 2002 (Plachy 2000, 2002).

Eight U.S. companies were identified as major producers of cadmium compounds in the 1990s (ATSDR 1999). In 2000, two U.S. companies produced primary cadmium as a byproduct of zinc smelting and refining, and another company recovered cadmium from scrap (Plachy 2000). In 2003, 28 U.S. suppliers of cadmium metal, 18 suppliers of cadmium metal powder, and numerous suppliers of various cadmium compounds were identified (ChemSources 2003).

U.S. imports and exports fluctuated widely in the late 20th century, with imports always exceeding exports. Annual cadmium imports averaged 694 metric tons (1.5 million pounds) in the 1960s, 2,088 metric tons (4.6 million pounds) in the 1970s, 2,523 metric tons (5.6 million pounds) in the 1980s, and 1,156 metric tons (2.5 million pounds) in the 1990s. Annual U.S. exports averaged 425 metric tons (937,000 lb) in the 1960s, 188 metric tons (414,000 lb) in the 1970s, 213 metric tons (470,000 lb) in the 1980s, and 485 metric tons (1.1 million pounds) in the 1990s. In 2000, the United States imported 425 metric tons (937,000 lb) of cadmium and exported 312 metric tons (688,000 lb) (Llewellyn 1994, Buckingham and Plachy 2002).

Exposure

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

Workers in a wide variety of occupations potentially are exposed to cadmium and cadmium compounds (IARC 1993). However, occupations with the highest potential levels of exposure include smelting zinc and lead ores, welding or remelting cadmium-coated steel, working with solders that contain cadmium, and producing, processing, and handling cadmium powders. 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 (1981–1983) estimated that about 250,000 workers potentially were exposed to cadmium and selected inorganic cadmium compounds. These included workers potentially exposed to unknown cadmium compounds (88,968), cadmium sulfide (42,562), cadmium mercury sulfide (19,707), cadmium selenide (17,939), cadmium oxide (15,727), cadmium chloride (4,748), cadmium nitrate (1,878), and cadmium sulfate (1,313) (NIOSH 1984). The Occupational Safety and Health Administration estimated in 1990 that approximately 512,000 U.S. workers were exposed to cadmium; however, 70% to over 80% were exposed to cadmium at concentrations below occupational standards or guidelines (ATSDR 1999).

EPA's Toxics Release Inventory (TRI) collects cadmium data in two categories, "cadmium" and "cadmium compounds," and individual facilities may report releases in both categories. From 1988 to 1997, reported releases of cadmium to the environment ranged from about 106,000 to 635,000 lb (48 to 288 metric tons) and releases of cadmium compounds from about 825,000 to 4.1 million pounds (374 to 1,860 metric tons). Since 1998 (when the numbers of industries covered by the TRI was increased), cadmium releases have ranged from a low of about 740,000 lb (336 metric tons) in 2000 to a high of about 2.8 million pounds (1,270 metric tons) in 1998. In 2001, 34 facilities reported releasing approximately 844,000 lb (383 metric tons) of cadmium, of which over 75% was released to land on site. Reported releases of cadmium compounds since 1998 have ranged from a low of nearly 8.9 million pounds (4,037 metric tons) in 2000 to a high of over 15 million pounds (6,804 metric tons) in 2001, reported by 97 facilities, of which over 80% was released to land on site (TRI01 2003).

Regulations

DOT

Cadmium and cadmium compounds are considered hazardous materials and special requirements have been set for marking, labeling, and transporting these materials

EPA

Clean Air Act

NESHAP: Cadmium Compounds listed as a Hazardous Air Pollutant (HAP)

Urban Air Toxics Strategy: Cadmium Compounds identified as one of 33 HAPs that present the greatest threat to public health in urban areas

Clean Water Act

Biosolids Rule: Ceiling concentration of total cadmium for land application = 85 mg/kg

Effluent Guidelines: Listed as a Toxic Pollutant (cadmium and cadmium compounds)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 10 lb (cadmium, cadmium acetate, cadmium bromide, cadmium chloride)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cadmium and cadmium compounds are listed substances subject to reporting requirements

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for cadmium chloride have been cancelled

Resource Conservation and Recovery Act

Characteristic Toxic Hazardous Waste: TCLP Threshold = 1.0 mg/L (cadmium)

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance - F006, K061, K064, K069, K100

Cadmium and Cadmium Compounds each listed as a Hazardous Constituent of Waste

Safe Drinking Water Act

Maximum Contaminant Level (MCL) = 0.005 mg/L (cadmium)

FDA

Maximum permissible level of cadmium in bottled water = 0.005 mg/L

Various specified color additives may contain cadmium at levels no greater than 15 ppm

Specified food additives may contain cadmium at maximum levels that range from 0.05-0.13 ppm

Action levels for cadmium in pottery (ceramics) range from 0.25-0.5 μg/mL leaching solution

OSHA

Ceiling Concentration = 0.3 mg/m^3 (fume); 0.6 mg/m^3 (dust)

Permissible Exposure Limit (PEL) = 0.1 mg/m^3 (fume); 0.2 mg/m^3 (dust)

"Comprehensive Standards" for occupational exposure to cadmium have been developed

Guidelines

ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 0.01 mg/m^3; 0.002 mg/m^3 (respirable fraction)

NIOSH

Immediately Dangerous to Life and Health (IDLH) = 9 mg/m^3 (cadmium dust & fume)

Listed as a potential occupational carcinogen (cadmium dust & fume)

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