

## Cadmium (Cd) and its compounds

Most of the cadmium in the environment comes from man made sources, especially from non-ferrous smelting, fuel combustion, disposal of cadmium-containing products and application of phosphate fertilizer. Other contributing sources include metal and phosphate fertilizer production and combustion of fossil fuels, wood and waste incineration.

### 1. Physico-chemical Properties

Cadmium exists in many forms. The most common forms are elemental cadmium, cadmium carbonate, cadmium chloride, cadmium oxide, cadmium sulphate and cadmium sulphide. Their physical and chemical properties are summarized in Table 1.

Table 1. Physical and Chemical Properties of Cadmium and its Compounds (Adapted from ATSDR 1993)

Characteristics	Cadmium	Cadmium carbonate	Cadmium chloride
Synonyms	Colloidal cadmium	Cadmium monocarbonate	Cadmium dichloride
Chemical formula	Cd	CdCO <sub>3</sub>	CdCl <sub>2</sub>
CAS No.	7440-43-9	513-78-0	10108-64-2
Molecular Weight	112.40	172.42	183.32
Valence state	0	2	2
Colour	Blue-white	White	White
Physical state	Solid	Solid	Solid
Melting point	320.9°C	Decomposes at <500°C	568°C
Boiling point	767°C	No data	960°C
Density	8.64 g/cm <sup>3</sup>	4.26 g/cm <sup>3</sup>	4.05 g/cm <sup>3</sup>
Odour	No data	No data	Odourless
<b>Solubility:</b>			
Water	Insoluble	Practically insoluble	1,400 g/L at 20°C; 1,500 g/L at 100°C
Organic solvents	No data	No data	Soluble in acetone
Vapour pressure	1 mm Hg at 394°C	No data	10 mm Hg at 656°C; 40 mm Hg at 736°C 760 mm Hg at 967°

Characteristics	Cadmium Oxide	Cadmium sulphate	Cadmium sulphide
Synonyms	Cadmium fumes; cadmium monoxide	Sulphuric acid, cadmium (2+) salt; cadmium sulphate	Orange cadmium; yellow cadmium
Chemical formula	CdO	CdSO <sub>4</sub>	CdS
CAS No.	1306-19-0	10124-36-4	1306-23-6
Molecular weight	128.41	208.47	144.47
Valence state	2	2	2
Colour	Red or brown	Colourless	Yellow or brown
Physical state	Solid	Solid	Solid
Melting point	1,426°C	1,000°C	1,475°C at 10 atms; 1,750°C at 100 atm
Boiling point	Decomposes at 900°C	No data	Sublimes in N <sub>2</sub> at 980
Density	8.15 g/cm <sup>3</sup>	4.69 g/cm <sup>3</sup>	4.82 g/cm <sup>3</sup>
Odour	Odourless	Odourless	No data
<b>Solubility:</b>			
Water	5 mg/L	750 g/L at 0°C; 680 g/L at 100°	1.3 mg/L at 18°C
Organic solvent	No data	Insoluble in alcohol	Insoluble in cold Colloidal in hot
Vapour pressure	1 mm Hg at 1,000°C	No data	No data

## 2. Environmental Fate

The environmental fate of cadmium and its compounds has been reviewed extensively by ATSDR (1993) and Environment Canada (CEPA, 1994). Only a brief summary will be provided here.

Cadmium is usually found in the form of cadmium oxide, chloride, sulphate or sulphide. In air, cadmium exists as fine particulate (less than 10 µm). The main chemical species in the atmosphere is cadmium oxide although other cadmium salts may also be present. The cadmium compounds in air is stable and undergoes little atmospheric transformation. Cadmium particulate is dispersed by wind and eventually either settled out by rain or snow or dry deposited on land or surface water. The fine particulate containing cadmium can remain airborne for days to weeks and travel hundreds to thousands of kilometres.

In water, cadmium exists either dissolved or as part of insoluble complexes. Solubility is promoted by acidic conditions. Soluble cadmium is quite mobile in water and in soil. Partitioning into the sediment is enhanced by precipitation and sorption to mineral surfaces and organic materials as well as by action of sediment bacteria. The levels in the sediment tend to be at least an order of magnitude higher than in the

overlying water column. High levels of organic material in the water promote formation of organic complexes with cadmium which are poorly soluble. Also in reducing environment, cadmium may precipitate out as cadmium sulfide.

Cadmium in soils may leach into water, especially under acidic conditions. Transformation processes for cadmium in soil are mediated by sorption from and desorption to water, and include precipitation, dissolution, complexation, and ion exchange.

Cadmium can be taken up and retained by aquatic and terrestrial plants and can substantially bioconcentrated in aquatic invertebrates and fish. In terrestrial animals, cadmium is particularly concentrated in the liver and kidney of animals that eat the plants. Low soil pH tends to increase the availability of cadmium.

For non-smokers, ingestion of food is the largest source of cadmium exposure (about 94%), with the rest coming from air. Since only 5-10% of ingested cadmium is absorbed, as compared to 25% absorption for inhaled cadmium (discussed in detail in the next section), after correcting for differences in absorption, food is found to constitute only 80% of total cadmium uptake. Near major point sources of cadmium where ambient air level of cadmium is usually much higher, contribution to body burden by inhalation may increase further. Smoking is a very important source of cadmium exposure. Smoking a pack of cigarette a day contributes about the same amount of cadmium as from the diet. Passive smoking does not appear to increase exposure to cadmium appreciably.

### **3. Toxicokinetics**

The toxicokinetics of cadmium and its compounds have been reviewed in detail elsewhere (ATSDR, 1993). Only a brief summary will be provided in the following paragraphs.

Cadmium and its salts have low volatility and exist in air primarily as fine suspended particular matter. When inhaled, some fractions of the particular matter would be deposited in the respiratory tract and the remaining fractions exhaled. Large particles (greater than 10  $\mu\text{m}$ ) tend to be deposited in the upper respiratory tree, while the finer particulate of about 0.1  $\mu\text{m}$  tends to get deposited in the lungs. Based on the physiology of the human respiratory tree, Norberg *et al.* (1985) has developed a model to predict the kinetics of inhaled cadmium in humans. Modelling results indicate that only about 5% of the large particulate remains deposited in the upper respiratory tract. Much of the particulate that is not exhaled is transported up the respiratory tree and eventually swallowed. In contrast, about 50% the finer particulate is deposited into the lung tissues where it remains available for absorption. About 50 to 100 % of the cadmium deposited in the lungs is eventually absorbed. Therefore, for the purpose of this analysis, about 25% of cadmium fine particulate are considered absorbed.

The absorption of the cadmium from food in the digestive tract is approximately 3-5%, but may be higher (about double) in individuals with iron deficiency. Other dietary factors and physiological factors such as high fat or protein content in the diet, or zinc deficiency may also influence oral absorption of cadmium. Dermal absorption of cadmium is generally very low (0.2-0.8%).

Distribution of cadmium is relatively independent of the route of exposure. It is distributed throughout the body, with particularly high levels in the liver and kidneys. Cadmium is not known to undergo any direct metabolic conversion. But cadmium ion can bind to anionic group such as sulphhydryl group in proteins, in particular albumin and metallothionein. Metallothionein is a small molecular weight protein rich in cysteine, which is capable of binding cadmium efficiently. It is inducible in most tissues by the presence of cadmium. Relatively large amounts of cadmium can be retained in the body in this manner and in this form, cadmium is relatively non-toxic. Cadmium bound to metallothionein is available for filtration in the kidney and reabsorbed. The metallothionein may be degraded releasing cadmium which may then induce fresh synthesis of metallothionein in the kidney. Cadmium induced renal toxicity is believed to be due to the action of cadmium not bound to metallothionein.

Absorbed cadmium is eliminated slowly and about equally in urine and faeces. It is estimated that about 0.007% of body burden is eliminated daily in faeces and about 0.009% in urine. However, faeces generally contain much higher levels of cadmium than urine because most ingested cadmium is never absorbed.

#### **4. Human Health Effects**

The health effects of cadmium have been reviewed extensively elsewhere (ATSDR, 1993; CEPA, 1994; IARC, 1993). Only a brief summary will be presented in the following paragraphs.

In general, the toxicity of cadmium does not depend on its chemical form. Cadmium oxide is of most interest for inhalation exposure because it is the main form of airborne cadmium. However, other forms of cadmium appear to exhibit similar toxicological properties as cadmium oxide on inhalation. For oral exposure, the more soluble salts of cadmium, such as cadmium chloride and carbonate are more important. Cadmium oxide, which can be solubilized at gastric pH, appears to be similar to the soluble forms of cadmium both in absorption and toxicity.

Acute, high level exposure to cadmium by inhalation or oral routes can be fatal. The cause of death is pulmonary edema following inhalation exposure and massive fluid imbalance, and widespread gastrointestinal, liver and other organ damage after oral exposure. The effects are mainly due to destruction of cell membranes at the point of entry.

High levels of cadmium oxide fumes or dust are extremely irritating to respiratory tissues. Typical symptoms include tracheobronchitis, pneumonitis and pulmonary edema. A single high exposure can lead to long term impairment of the lung functions. Long term exposure to levels below those causing lung inflammation results in impairment in lung functions and emphysema. Some tolerance to cadmium-induced lung irritation can develop in some workers.

Oral exposure to acute, high levels of cadmium causes severe irritation to the gastrointestinal epithelium. Common symptoms include nausea, vomiting, abdominal pain, cramps and diarrhea. Gastrointestinal toxicity is not observed after low levels of oral exposure or after inhalation exposure.

Although cadmium can be acutely toxic, it is mainly a cumulative toxicant, and long term exposure is of most concern to humans. Kidney is the main target of cadmium toxicity after intermediate to chronic exposure to this toxicant by either inhalation or oral route. The early sign of kidney damage from cadmium is the presence of a number of low molecular weight proteins due to decreased re-absorption of these proteins, signifying dysfunction of the proximal tubule of the kidney. With longer exposures or at higher doses, there is a reduction in filtration of high molecular weight proteins and even necrosis (cell death). Renal function can deteriorate further, even after cessation of cadmium exposure. The impact of early kidney damage on the overall health of affected individuals is not clear. However, the damage affects the vitamin D metabolism in the kidney. This in turn leads to disruption in calcium absorption and excretion, calcium imbalance and reduction in bone density.

Tubular dysfunction occurs only after cadmium reaches a minimum threshold level, generally referred to as the “critical concentration”, in the renal cortex. The critical concentration of cadmium in the renal cortex associated with increased incidence of kidney dysfunction in an adult human population on prolonged exposure has been estimated to be 200 µg/g wet weight by several investigators (Friberg, 1974; Kjellstrom *et al.* 1977, 1984; Roels *et al.* 1983; US EPA, 1985).

Both oral and inhalation exposure can cause anaemia in humans and animals, likely by reducing gastrointestinal uptake of iron from the diet. Cadmium-induced anaemia is unlikely among populations that have adequate iron intakes to compensate for reduced iron absorption.

Developmental and reproductive effects have been reported in animals following exposure to cadmium by oral and inhalation routes, but the effects are not consistent among humans.

Cadmium has been shown to induce chromosomal aberration in human lymphocytes *in vitro* or from exposed workers in some studies but not in others. In those studies where significant responses were observed, the chromosomal aberrations tended to occur in the more heavily exposed group. Similarly, cadmium was shown to be genotoxic in some of the experimental tests, both *in vivo* and *in vitro*. Overall, cadmium appears to have the capability of altering genetic materials, particularly chromosomes in mammalian cells. Furthermore, cadmium and its compounds inhibit repair of DNA damaged by other agents, thereby enhancing their genotoxicity.

Evidence that inhalation of cadmium is cancer inducing is strong for rats, but relatively weaker in humans. Overall, USEPA (IRIS, 1994) considered the results provide weak evidence of an increased risk of lung cancer in humans following prolonged inhalation exposure to cadmium and has classified cadmium as a probable human carcinogen by inhalation. By the same token, Health Canada (CEPA, 1994) has classified inorganic cadmium compounds as probably carcinogenic to humans by the inhalation route. On the other hand, they did not consider available evidence sufficient to evaluate the potential carcinogenicity of cadmium to humans by the oral and dermal routes. In contrast, International Agency for Research on Cancer (IARC) has re-evaluated the evidence in 1993 and concluded that cadmium and its compounds are carcinogenic in humans (Group 1). The evidence considered include animal studies, which showed an elevated incidence of leukaemia, interstitial-cell tumours of the testis and proliferative lesions of the prostate in male rats with controlled dietary zinc levels.

## 5. Potency Estimates

### Oral-Non-cancer

US EPA (1994) based its oral reference dose (RfD) for cadmium on the highest level of cadmium (i.e. critical concentration) in the human renal cortex not associated with significant proteinuria (i.e. critical effect signalling kidney dysfunction). A toxicokinetic model was used to determine the level of oral chronic exposure (NOAEL) associated with 200 µg/g wet weight of cadmium in the renal cortex. Since the fraction of cadmium absorbed varies with its source, the toxicokinetic model predicted that the no adverse effect levels (NOAELs) for chronic cadmium oral exposure to be 0.005 and 0.01 mg Cd/kg/day for water and food, respectively. The absorption was assumed to be 2.5% of cadmium from food and 5% from water. Applying an uncertainty factor of 10 to the NOAELs, US EPA (1994) calculated a reference dose (RfD) of 0.5 µg Cd/kg/day for cadmium in water and a RfD of 1 µg Cd/kg/day in food. The uncertainty factor is used to account for intrahuman variability to the toxicity of cadmium.

Since the NOAEL was not obtained from a single study, but reflect the data obtained from many studies on the toxicity of cadmium in both animals and humans. Furthermore, these data permit the calculation of pharmacokinetic parameters pertaining to cadmium absorption, distribution, metabolism and elimination, such that a toxicokinetic model can be constructed to allow prediction of exposure from Cd level in the kidney tissues. All these factors give high confidence in the database and in the RfDs thus estimated.

### Inhalation-Cancer

With respect to the risk of lung cancer from inhalation of cadmium, two kinds of risk estimates have been made: one based upon the long term rat bioassay of Takenaka *et al.* (1983) and the other on the epidemiological data of Thun *et al.* (1985). Thun *et al.* considered workers occupationally exposed to cadmium oxide fume and dust. Irrespective of the regulatory body that did the analysis and the extrapolation method used, modelling of these data yielded risk estimates that do not agree. In general, the rat model over-predicts the risk when compared to the observed increase in lung cancer mortality in epidemiological studies.

US EPA (1994) has proposed 1.8 E-3 per µg of cadmium/m<sup>3</sup> of air as the inhalation unit lifetime risk for lung cancer, based on Thun *et al.* (1985). Since substances that exhibit genotoxic properties are generally treated as non-threshold toxicants, extrapolation to low dose was conducted using the two-stage model. Confidence for the estimate was rated high as the study population was relatively large and effects of confounding factors such as arsenic and smoking were accounted for during the quantitative analysis for cadmium effects. US EPA considered the estimate based on human data more reliable than the estimate based on Takenakas *et al.* animal data (9.2 E-2 per µg Cd/m<sup>3</sup>), because of species differences in response.

Health Canada (CEPA, 1994), on the other hand, did not consider available epidemiological studies of workers occupationally exposed to cadmium had adequate accounting for the presence of other confounding substances. As a result, Health Canada derived cadmium carcinogenic potency by inhalation

on the basis of the long-term bioassays (Takenakas *et al.* 1983; Oldiges *et al.* 1984). A multistage model was fitted to the lung tumour incidences to yield a TD<sub>0.05</sub> for the rat, and amortized over the lifetime of the rat. Using standard values for breathing volumes and body weights of rats and humans, the rat TD<sub>0.05</sub> was converted to an equivalent concentration in humans. The resultant TD<sub>0.05</sub> estimated for humans is 5.1 µg Cd/m<sup>3</sup>, which is equivalent to a slope factor of 1 E-2 µg Cd/m<sup>3</sup> at low dose.

World Health Organization (WHO, 1995) had considered derivation of unit risk estimates for lung cancer from exposure to cadmium and its compounds based on both types of data and decided not to give a specific value because of the uncertainties in these calculations.

The US EPA estimate is preferred for the following reasons. The US EPA's assessment is based on human data, circumventing the necessity of species extrapolation and the added uncertainty involved in the extrapolation. If the cancer inducing confounders in the epidemiological study had not been adequately accounted for, as suggested by Health Canada (CEPA, 1994), the potency estimate based on the human study would be higher than what would be expected if the confounders were not present. The observation that the potency estimate based on the animal model is approximately one order of magnitude higher than the potency estimate based on human data does not support such a hypothesis.

### **Inhalation-Non-cancer**

WHO (1995) has pooled the data of seven occupational studies and concluded that the lowest cumulative exposure to airborne cadmium in industrial workers leading to an increased risk of renal dysfunction is 200 µg/m<sup>3</sup>-years for an 8-hour exposure. Extrapolating to a continuous lifetime exposure gives a value around 0.5 µg/m<sup>3</sup>. Because exposure to cadmium occurs mainly via food or tobacco smoking, WHO has stipulated that airborne cadmium levels should not exceed 0.005 µg Cd/m<sup>3</sup> in the rural area or 0.010 µg Cd/m<sup>3</sup> in the urban and industrial areas in Europe. This provision is meant to prevent the cadmium body burden of the general population from reaching a level that might endanger kidney functions.

California Environmental Protection Agency (Cal EPA, 1997) has derived a chronic reference exposure level (REL, equivalent to reference concentration) based on an occupational case-control study (Lauwerys *et al.* 1974). Pulmonary and renal functions were examined in three worker groups, distinguished by sex and whether the workers had more/less than 20 years of exposure. Each exposed group was matched to a control group in terms of age, body size, cigarettes smoked per day, duration of smoking and duration of employment. This study identified kidney as the key target organ of chronic exposure to respirable cadmium, a LOAEL of 21 µg/m<sup>3</sup> for workers exposed for 28 years and a NOAEL of 1.4 µg/m<sup>3</sup> for workers exposed for 4 years. Applying an uncertainty factor of 30 (3 for extrapolating from subchronic to chronic exposure, 10 for intrahuman variation) to the NOAEL, Cal EPA obtained a REL of 0.01 µg/m<sup>3</sup>. The evaluation is strengthened as the REL is based on a human exposure study where the factory process was unchanged over the study period suggesting that exposures may have remained relatively consistent over time.

The exposure limit of 0.01 µg/m<sup>3</sup> is supported by an estimate based on data from other occupational studies (Ellis *et al.* 1985; Mason *et al.* 1988) correlating human cumulative exposures and defects in renal

tubular protein re-absorption. Using similar derivation process, the latter studies yield an REL of 0.02  $\mu\text{g}/\text{m}^3$ , which is similar to the value based on the Lauwerys study.

### **Recommendation**

Based on the US EPA potency for inhalation cancer risk from cadmium exposure, one can calculate the exposure limit associated with a cancer risk of 1 E-6 to be 6 E-4  $\mu\text{g Cd}/\text{m}^3$ . Cancer risk of 1 E-6 is often chosen as the cut-off point for risk management action. The exposure limit based on cancer risk is therefore about one order of magnitude lower than the exposure limit (0.01  $\mu\text{g Cd}/\text{m}^3$ ) estimated based on kidney dysfunction. Adopting the cancer exposure limit would prevent kidney injury arising from cadmium exposure by inhalation alone, it would also provide an additional margin of safety against already elevated cadmium body burden from exposure in the diet. For these reasons, the US EPA potency estimate for lung cancer risk is recommended for health risk evaluation from inhalation exposure to cadmium.

## **6. Reference**

ATSDR (Agency for Toxic Substances and Disease Registry), 1993. Toxicological Profile for Cadmium. And references cited. U.S. Department of Health & Human Services.

California EPA (California Environmental Protection Agency), 1997. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Draft for Public Review. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Berkeley, CA.

CEPA (Canadian Environmental Protection Act), 1994. Priority Substances List Assessment Report: Cadmium and its Compounds. Environment Canada and Health Canada.

Ellis, K.J., Cohn, S.H. and Smith, T.J., 1985. Cadmium inhalation exposure estimates: Their significance with respect to kidney and liver cadmium burden. *J. Toxicol. Environ. Health* 15: 173-187.

Friberg, L., Piscator, M., Nordberg, G.F. and Kjellstrom, T. 1974. *Cadmium in the Environment*. 2nd ed. CRC Press, Boca Raton, FL.

IARC (International Agency for Research on Cancer), 1993. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Volume 58. International Agency for Research on Cancer, Lyon, France.

Kjellstrom, T., Elinder, C.G., Friberg, L., 1984. Conceptual problems in establishing the critical concentration of cadmium in human kidney cortex. *Environ Res* 33: 284-295.

Kjellstrom, T., Evrin, P.E., Rahnster, B., 1977. Dose-response analysis of cadmium-induced tubular proteinuria. A study of urinary beta-2-microglobulin excretion among workers in a battery factory. *Environ Res* 13: 303-317.

Lauwerys, R.R., Buchet, J.P., Roels, H.A., Brouwers, J. and Stanescu, D., 1974. Epidemiological survey of workers exposed to cadmium. *Arch. Environ. Health* 28: 145-148.

Mason, H.J., Davison, A.G., Wright, A.L., Guthrie, C.J.G., Fayers, P.M., Venables K.M., Smith, N.J., Chettle, D.R., Franklin, D.M., Scott, M.C., Holden, H., Gompertz, D. and Newman-Taylor, A.J., 1988. Relation between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. *Brit. J. Ind. Med.* 45: 793-802.

Nordberg, G.F., Kjellstrom, T., Nordberg, M., 1985. Kinetics and Metabolism. In: *Cadmium and Health: A Toxicological and Epidemiological Appraisal. Vol. I. Exposure, Dose, and Metabolism.* Friberg, L., Elinder, C.G., Kjellstrom, T., et al. eds. CRC Press, Boca Raton, FL, pp. 103-178.

Oldgies, H. Hochrainer, D., Takenaka, Sh., Oberdørster, G. and Kønig, H., 1984. Lung carcinomas in rats after low level cadmium inhalation. *Toxicol. Environ. Chem.* 9: 41-51.

Roels, H.A., Lauwerys, R., Dardenne, A.N., 1983. The critical level of cadmium in human renal cortex: A reevaluation. *Toxicol Lett* 15: 357-360.

Takenaka, S., Oldiges, H., Kønig, Hochrainer, D. and Oberdørster, G., 1983. Carcinogenicity of cadmium chloride aerosols in W. rats. *J. Nat. Cancer Inst.* 70: 367-373.

Thun, M.J., Schnorr, T.M., Smith, A.B., Halperin, W.E. and Lemen, R.A. Mortality among a cohort of U.S. cadmium production workers – An update. *J. Nat. Cancer Inst.* 74: 325-333.

US EPA, 1985. *Drinking Water Criteria Document on Cadmium. Final Draft.* United States Environmental Protection Agency, Office of Drinking Water, Washington, DC.

US EPA, 1994. *Integrated Risk Information System. IRIS Database On-Line Search.* US Environmental Protection Agency, Cincinnati, OH. Last update 02/01/1994.

WHO (World Health Organization), 1995. *Updating and Revision of the Air Quality Guidelines for Europe. Report on the WHO Working Group on Inorganic Air Pollutants.* Düsseldorf, Germany. 24-27 October, 1994. WHO Regional Office for Europe, Denmark.