

Cadmium

Toxicological overview

Key Points

Kinetics and metabolism

- Cadmium is more efficiently absorbed from the lungs than the gastrointestinal tract
- Cadmium is widely distributed in the body bound mainly to red blood cells. It accumulates in the kidney and liver, where it induces the production of metallothionein that binds approximately 80 - 90 % of cadmium in the body
- There is little or no metabolism of cadmium although it binds to various macromolecules and proteins
- Cadmium is excreted via the urine and faeces

Health effects of acute exposure

- The major route of exposure is by ingestion and inhalation
- Following acute oral exposure, an asymptomatic period of up to 60 minutes may precede clinical symptoms. Lower doses leads to GI irritation, vomiting, abdominal pain and diarrhoea. Higher doses may affect the nervous system, liver, cardiovascular system and may lead to renal failure and death
- Acute inhalation may initially cause irritation of the upper respiratory tract, although symptoms may be delayed for 4-8 hours. Dyspnoea, chest pain and muscle weakness may also occur. Pulmonary oedema, bronchitis, chemical pneumonitis, respiratory failure and death may occur within days of exposure.

Health effects of chronic exposure

- Chronic oral exposure leads to renal failure, characterised by proteinuria. The accumulation of cadmium in the kidney affects renal vitamin D metabolism, leading to osteomalacia and osteoporosis.
- Chronic inhalation causes loss of renal tubular function, leading to proteinuria and impairs lung function by causing bronchitis, obstructive lung disease and in some cases interstitial fibrosis
- Cadmium is a category 1 carcinogen i.e. is carcinogenic to humans

Toxicological Overview

Summary of Health Effects

Following acute oral exposure to cadmium, an asymptomatic period of up to 60 minutes may precede clinical symptoms. Exposure to lower doses of cadmium results in gastrointestinal irritation, vomiting, abdominal pain and diarrhoea [1]. Higher doses may affect the nervous system, liver, cardiovascular system and may lead to renal failure and death [2].

Chronic oral exposure to cadmium leads to renal failure, characterised by proteinuria due to renal tubular dysfunction. The accumulation of cadmium in the kidney affects renal vitamin D metabolism, which subsequently disturbs calcium balance that may lead to osteomalacia and osteoporosis [3]. This, as well as the increased excretion of calcium may result in bone disease [4].

Acute inhalation of cadmium may initially cause irritation of the upper respiratory tract, although symptoms may be delayed for 4-8 hours. Dyspnoea, chest pain and muscle weakness may also occur. Pulmonary oedema, bronchitis, chemical pneumonitis, respiratory failure and death may occur within days of exposure. In the long-term following exposure, progressive pulmonary fibrosis and impaired lung function may occur [5].

Chronic inhalation of cadmium causes loss of renal tubular function, leading to proteinuria and impairs lung function by causing bronchitis, obstructive lung disease and in some cases interstitial fibrosis [2].

In-vitro studies indicate that cadmium compounds have mutagenic potential. They have been shown to induce chromosome damage and DNA strand breaks [3]. Conflicting results have been obtained in *in-vivo* studies including workers exposed to cadmium.

Cadmium has been classified as a category 1 carcinogen i.e. is carcinogenic to humans. Inhalation of cadmium increases the risk of lung cancer. It exerts its genotoxicity via the production of reactive oxygen species and by inhibiting DNA repair, both such mechanisms are expected to have a threshold [3, 6]. However, there is no evidence that cadmium is carcinogenic following oral exposure [7].

In rats, acute inhalation exposure to cadmium compounds predominantly caused interstitial pneumonitis, fibrosis, oedema and emphysema. Oral exposure caused severe necrosis, haemorrhage and ulcers, as well as decreased body weight, and muscle atrophy.

In animals exposed to cadmium prior to and during gestation, skeletal abnormalities of offspring have been reported but no gross teratogenic effects [3, 4]. Adult males exposed to cadmium showed reprotoxic effects such as decreased sperm count and motility and atrophy of the seminiferous tubules [4]. The few human data reporting possible developmental effects of cadmium were inconclusive. Birth weights of newborn infants may be lower following maternal cadmium exposure, but no congenital abnormalities have been reported [5, 7].

Kinetics and metabolism

Cadmium is more efficiently absorbed from the lungs (25-60% absorbed) than the gastrointestinal tract (5-10 % absorbed). It is estimated that on average, adults absorb 1.4-8 µg of cadmium per day by oral exposure.

Absorption following oral exposure is largely dependent on the solubility of the cadmium compound but also physiological and nutritional factors may modify the amount absorbed. Cadmium absorption is reported to be higher in females than males [2].

Absorption of cadmium via inhalation is dependent on solubility and the particle size and hence the site of deposition in the respiratory tract. Absorption from the gastrointestinal tract appears to be a saturable process, as the amount absorbed is decreased at higher doses. Cadmium absorption may be decreased by divalent and trivalent cations (Zn^{2+} , Mg^{2+} , Cr^{3+}) and increased by iron and calcium deficiencies [1].

Cadmium is widely distributed in the body bound mainly to red blood cells or high molecular weight proteins in the plasma. Cadmium is accumulated (50-70% of body burden) in the kidneys and liver, where it induces the production of metallothionein that binds approximately 80-90 % of cadmium in the body [5]. For individuals who are chronically exposed to environmental levels of cadmium either by diet or smoking, the highest concentrations of cadmium are measured in the renal cortex [3]. Cadmium concentrations in the kidney are low at birth but, if exposure to cadmium remains constant, body burden increases in a linear manner with age up until approximately 50 or 60 years of age after which they plateau or decline [3]. Various studies have reported a mean cadmium concentration of 10-50 µg g⁻¹ in the renal cortex at age 40 – 50 [3, 5, 8]. Liver concentrations also are low at birth and increase to approximately 1-2 µg g⁻¹ by the age of 20-25 years, after which time they only slightly increase [5].

There is little or no metabolism of cadmium, although it binds to various macromolecules and proteins [1]. Metallothionein is largely involved in the binding of cadmium, which is generally thought to reduce the toxicity of cadmium. In the liver, its production is sufficient to bind all cadmium accumulated. The metallothionein-bound cadmium is released from the liver into the blood where it is cleared by glomerular filtration in the kidney and taken up by the renal tubules, where the metallothionein is cleaved and cadmium is released. The synthesis of metallothionein in the kidney is lower and insufficient to bind all the free cadmium, resulting in tubular damage or cell membrane destruction via activation of oxygen species [3].

As a small fraction of the cadmium is absorbed from the GI tract following ingestion, most of the oral dose is excreted in the faeces. Following inhalation, excretion via the urine and faeces are approximately equal. In individuals continuously exposed to cadmium, the amount excreted in urine will progressively increase in proportion with body burden. However, the amount excreted is only a small fraction of the total body burden, unless kidney toxicity occurs in which case urinary cadmium increases substantially [4, 8].

Sources and route of human exposure

The main route of exposure to cadmium is via inhalation or ingestion via food or cigarette smoke. Skin absorption is rare.

Cadmium is widely distributed in the Earth's crust (0.1-0.5 µg g⁻¹), the atmosphere (1-5 ng m⁻³), marine sediment (~1 µg g⁻¹) and sea water (~0.1 µg L⁻¹). Environmental levels of cadmium occur following the natural weathering of minerals, forest fires and volcanoes, although larger

amounts are released following human activities. These include the application of phosphate fertilisers, fossil fuel combustion, the production of iron, steel and non-ferrous metals, cement production and waste incineration. The anthropogenic sources of cadmium contribute to human exposure to a greater extent due to production, use and disposal of cadmium products and the incineration of cadmium-containing products [5].

Cadmium is prevalent in the three main environmental compartments, namely air, water and soil. The majority of cadmium exposure arises from air and soil, by atmospheric deposition and by the ingestion of vegetables such as lettuce, spinach, celery and cabbage that accumulate cadmium. Foods such as potatoes and peas take up less amounts [9]. As part of the 2006 Total Diet Survey carried out by the Food Standards Agency, cadmium in the diet was analysed. Toddlers (1.5 – 4.5 years of age) has the highest dietary intake of approximately $0.4 \mu\text{g kg bw}^{-1} \text{ day}^{-1}$ whereas the mean intake across all age groups was about $11 - 13 \mu\text{g day}^{-1}$ [3]. Recent reports have acknowledged that house dust may also be a significant route of exposure to cadmium [9]. Minimal exposure of cadmium arises from water [3].

Cadmium also exists as a number of compounds. Cadmium oxide is of most interest for health effects following inhalation exposure, as it is the main form of airborne cadmium. Both cadmium oxide and cadmium carbonate have similar toxicological profiles as soluble cadmium. Cadmium bound to metallothionein is of interest as they are found in relatively high concentrations of organ meat i.e. liver and kidney.

The inhalation of cadmium also contributes to the total cadmium burden, albeit to a lesser extent than oral intake, with the exception of smokers or those undergoing occupational exposure. Cigarette smoke considerably adds to cadmium exposure. A daily intake of 2-4 μg cadmium was estimated from smoking one packet of cigarettes per day [5].

In the UK, long-term exposure limits (LTEL) for cadmium and cadmium compounds except cadmium oxide fume, cadmium sulphide and cadmium sulphide pigments is 0.025 mg m^{-3} (8 hour time weighted exposure (TWA) reference period). No data was available for the short-term exposure limits (STEL) (15 minute reference period). For cadmium oxide fume the LTEL is set at 0.025 mg m^{-3} and the STEL at 0.05 mg m^{-3} and for cadmium sulphide and pigments, the LTEL is 0.03 mg m^{-3} [10].

In the US, occupational exposure standards were formerly set at $100 - 200 \mu\text{g m}^{-3}$. However, in recent years, occupational exposures have been reduced to $2-50 \mu\text{g m}^{-3}$, as well as requirements to maintain cadmium blood and urine levels below $0-5.0$ or $0-2.6 \mu\text{g L}^{-1}$, respectively, to assure no adverse health effects following occupational exposure [11].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

The acute toxic effects following inhalation of cadmium are summarised in table 1. An initial sign of cadmium inhalation is slight irritation of the upper respiratory tract, although symptoms may be delayed for 4-8 hours. Inhalation of cadmium may also cause a metallic taste, headache, dyspnoea, chest pain and muscle weakness [12]. Following an acute exposure to moderately high concentrations of cadmium (0.01-0.15 mg m⁻³) for nine hours, coughing, slight irritation of the throat and acute gastro-enteritis may occur [5].

Table 1. Summary of toxic effects following acute exposure to cadmium by inhalation.

Dose (mg m ⁻³)	Signs and symptoms
0.01-0.15	Cough, irritation of the throat, gastroenteritis symptoms - vomiting, abdominal cramps, diarrhoea
0.5	Threshold for respiratory effects after 8 hour exposure
1-5	Immediately dangerous to health - facial oedema, hypotension, dysrhythmias, confusion, oliguria, metabolic acidosis and acute centrilobular necrosis of the liver, pulmonary oedema, tracheobronchitis, pneumonitis
5	lethal after 8 hours
39	lethal after 20 minutes
250	Lethal after 10 minutes
2500	Lethal after 1 minute

WHO stated 0.5 mg m⁻³ cadmium as the threshold for respiratory effects resulting from an 8-hour exposure, and exposure to 1-5 mg m⁻³ cadmium was identified as 'immediately dangerous' to humans. Higher doses may lead to extensive fluid loss, metabolic acidosis, pulmonary oedema, facial oedema, hypotension, oliguria, altered metabolism of calcium and zinc and multiorgan failure [1].

Based on lung burdens measured during post mortem examinations, 1- and 10-minute lethal concentrations of 2500 mg m⁻³ and 250 mg m⁻³ have been reported [1].

Hypotension and dysrhythmias have been observed following inhalation of cadmium fumes, as have acute centrilobular necrosis of the liver. However, from the weight of evidence, inhalation exposure to cadmium does not appear to have significant effects on the cardiovascular system or the liver. In addition, gastrointestinal toxicity is not observed after inhalation exposure to cadmium, indicating that gastrointestinal effects are not likely to occur from environmental exposures to cadmium [4].

The time course of acute toxic effects following inhalation of cadmium are summarised in table 2. Following cadmium inhalation there is an asymptomatic period for 4-8 hours that precedes clinical symptoms [1]. Following this time, concentrations of 1 mg m⁻³ and above for 8 hours, or higher concentrations (up to 2.5 mg m⁻³) for shorter time periods may induce metal fume fever-type symptoms. Within 4-7 days wheezing, chest pain and precordial constriction, persistent cough, anorexia, nausea, diarrhoea, abdominal pain, pulmonary

oedema, bronchitis and chemical pneumonitis may occur in more severe cases, which may lead to respiratory failure and death. The mortality following such acute, high level exposures is approximately 15%. If the patient survives, they may experience long-term impaired lung function [1, 11].

Metal fume fever-like symptoms can arise following inhalation of cadmium in an occupational setting, such as welding, galvanising or smelting, and include cough, chest pain, sore throat, headache, rigors, arthralgia (joint pain), myalgia (muscle pain), dyspnoea, malaise, metallic taste, chills, sweating, conjunctivitis and rhinitis, which occur within 3-10 hours of exposure. Such effects may resolve within 24-48 hours [2]

Table 2. Summary of time course of toxic effects following acute exposure to cadmium by inhalation.

Dose (mg m⁻³) and duration of exposure	Time after exposure	Signs and symptoms
1 for 8 hr or 2.5 for shorter periods	4-10 hours	Metal fume fever-type symptoms - acute chemical pneumonitis, cough, chest pain, dyspnoea, malaise, chills, sweating and aching limbs, conjunctivitis and rhinitis
	3 -7 days	Wheezing, chest pain and precordial constriction, persistent cough, weakness and malaise, anorexia, nausea, diarrhoea, abdominal pain, pulmonary oedema, bronchitis and chemical pneumonitis; respiratory failure and death in severe cases
	Longer-term (weeks/months)	Progressive pulmonary fibrosis and impaired lung function

Ingestion

The acute toxic effects following oral exposure to cadmium are summarised in table 3. Following cadmium exposure an asymptomatic period of up to 60 minutes may precede clinical symptoms. The ingestion of cadmium exceeding 15 mg kg⁻¹ body weight (bw) may give rise to gastrointestinal symptoms such as vomiting, abdominal cramps and diarrhoea, whereas doses of 20-30 mg kg⁻¹ bw have caused human fatalities. The lowest emetic dose reported is 0.07 mg kg⁻¹ bw [4]. Fatigue, sleep disturbances, sensory and motor function disturbances, anorexia, peripheral neuropathy and headaches may also arise [5]. The ingestion of cadmium chloride has been reported to produce an elevation in serum haemoglobin and haematocrit [5].

Acute oral exposure to 350 – 8900 mg, corresponding to doses of about 20 to 130 mg kg⁻¹ bw in a 70 kg adult has caused fatal intoxication. In such cases, within 7-14 days of the initial symptoms, hypovolaemia leading to shock, renal failure, hypotension, liver damage and death may occur [5]. No studies were retrieved that reported respiratory effects in humans following oral exposure to cadmium [4].

Table 3. Summary of acute toxic effects following oral exposure to cadmium.

Dose (mg kg ⁻¹ bw)	Signs and symptoms
0.07	Emetic dose
>15	Gastrointestinal symptoms – vomiting, abdominal cramps, diarrhoea
20-30	Extensive fluid loss, shock, pulmonary oedema, hypotension, oliguria, multiorgan failure, death

Delayed effects following an acute exposure

Cadmium exposure may cause long-term health effects. A worker exposed to an acute high level exposure to cadmium fume due to soldering for one hour (dose not determined) continued to have impaired lung function four years following initial insult, showing symptoms such as dyspnoea, cough, myalgia and fever. Similarly, a male welder who developed acute cadmium pneumonitis following a single exposure (dose not determined) continued to show signs of progressive pulmonary fibrosis after nine years [4].

Animal and In-Vitro Data

Inhalation

The form of cadmium can affect the toxicity. Cadmium acetate and cadmium chloride can produce severe respiratory effects from acute exposures of 1-5 mg m⁻³. Exposure to cadmium sulphide (6.29 mg m⁻³) for 6 hours a day for 10 days resulted in an 8% increase in absolute lung weight, compared with a 16% increase observed following exposure to 0.17 mg m⁻³ cadmium chloride. No respiratory effects were observed in rats exposed to cadmium sulphide (99 mg m⁻³) or cadmium selenium (97 mg m⁻³) for 2 hours [4]

Single inhalation exposure of rats to 5-10 mg m⁻³ cadmium oxide dust, cadmium oxide fume or cadmium chloride for 1-5 hours resulted in interstitial pneumonitis, diffuse alveolitis, fibrosis, increased lung weight, reduction in body weight, focal interstitial thickening, oedema, pulmonary haemorrhage and emphysema. A loss of body weight, suppression of the primary humeral immune response, tremors and loss of activity were also reported [4]. Similar results were seen in hamsters exposed to cadmium chloride at 10 mg m⁻³ for 30 minutes and in rabbits exposed to 4.5 mg m⁻³ cadmium oxide for 2 hours. Exposure of rats to cadmium carbonate (132 mg m⁻³) for two hours resulted in stomach erosion. Cats exposed to an undefined concentration of cadmium oxide fume for one day showed several hepatic lesions. Cell granulation was seen at low concentrations and fatty infiltration was observed at higher concentrations [4]

Persistent damage had been reported in animal models following an acute exposure to cadmium as lung fibrosis was reported at least 12 months post-exposure [4]

Ingestion

In rats and mice, severe necrosis, haemorrhage and ulcers in the gastrointestinal epithelium were observed following acute-duration oral exposure to >30 mg kg⁻¹ bw day⁻¹. Decreased body weight was reported following oral exposure to 15.3 mg kg⁻¹ bw over ten days. Acute oral exposure to 30-138 mg kg⁻¹ bw day⁻¹ resulted in liver necrosis, weakness and muscle

atrophy, and in aggression rats, mice and rabbits. The acute oral LD50 for cadmium in rats and mice was estimated to be 100-300 mg kg⁻¹ bw although fatalities have been observed following exposure to 15.3 mg kg⁻¹ bw in rats [4].

Dermal / ocular exposure

Few data are available regarding dermal toxicity from systemic absorption of inhaled or ingested cadmium. Furthermore, few studies were located regarding dermal effects in animals following dermal application. Following exposure to 100 mg m⁻³ cadmium as cadmium pigments for 2 hours, rats had excessive lacrimation 4 hours after exposure, due to direct irritation of the eyes [4].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

The chronic toxic effects following inhalation of cadmium are summarised in table 4. The kidney is the critical organ for long-term low-level exposure. Accumulation of cadmium in the kidney results in loss of tubular function, leading to tubular proteinuria, evidenced by an increase in urinary excretion of β 2-microglobulin, retinol binding protein and α 1-microglobulin. Such proteinuria may occur following inhalation of 25-134 $\mu\text{g m}^{-3}$ cadmium for at least ten years [5].

Cadmium-induced proteinuria has been reported to occur when the concentration of cadmium reaches a critical level. 200 $\mu\text{g g}^{-1}$ (wet weight) cadmium in the renal cortex has been reported to be associated with a 10 % prevalence of tubular effects and proteinuria in the general population and corresponded to a concentration of cadmium in the urine of approximately 10 $\mu\text{g g}^{-1}$ creatinine [3]. However, the recognition that renal effects may be occurring in workers with values cadmium levels substantially below 10 $\mu\text{g g}^{-1}$ creatinine, indicated that a reassessment of the critical concentration in the renal cortex was required [3]. Further research estimated that a cadmium concentration of 200 $\mu\text{g g}^{-1}$ in the renal cortex would be associated with a 30% prevalence of tubular effects. Furthermore, in 2000, Joint Expert Committee on Food Additives (JECFA) noted that a meta-analysis of the epidemiological studies suggested that “the risk from renal dysfunction and progression to clinical disease could be lowered if exposure to cadmium were reduced such that the concentrations of cadmium in the kidney and urine were maintained below 50 $\mu\text{g g}^{-1}$ of renal cortex and 2.5 $\mu\text{g g}^{-1}$ of creatinine, respectively”[7].

Table 4. Summary of chronic toxic effects following inhalation of cadmium.

Dose ($\mu\text{g m}^{-3}$)	Time of exposure	Signs and symptoms
25-134	10 years	Proteinuria
66	20 years	Bronchitis, obstructive lung disease - dyspnoea, reduced vital capacity and increased residual volume
50-356		Emphysema and dyspnoea

Accumulation of cadmium in the kidney may affect vitamin D metabolism and may increase the excretion of calcium and phosphorus into the urine. This may lead to a disruption of the calcium balance, resulting in osteomalacia, osteoporosis and spontaneous fractures. A number of reports have documented disorders of calcium metabolism and bone effects amongst men occupationally exposed to cadmium, and decreased bone density and increased risk of fractures were reported in women in the Cadmibel study. Bone disease resulting from exposure to cadmium in the general environment has only been reported in people from a highly contaminated region in Japan (Itai-itai disease), characterised as osteomalacia, osteoporosis, increased fractures and renal tubular dysfunction [3].

The initial symptoms of respiratory distress observed at higher acute exposures do not always occur following low-level long-term exposures, and it is unclear whether lung impairment results from long-term exposure above critical airborne cadmium concentration or from several episodes of exposure leading to permanent damage [3, 7].

Chronic inhalation however, has been reported to cause emphysema and dyspnoea, and exposure to cadmium for more than 20 years may result in bronchitis, which may lead to obstructive lung disease such as dyspnoea, reduced vital capacity and increased residual volume. This condition may progress to fibrosis of the lower airways and alveolar damage [4, 11].

Ingestion

Following long-term cadmium ingestion, kidney effects such as proteinuria and loss of tubular function may occur, as with inhalation exposure. Osteomalacia, osteoporosis and spontaneous fractures may also as a late manifestation of severe chronic cadmium poisoning [4, 11].

Liver damage is only observed at high concentrations of cadmium due to the presence of a high concentration of metallothionine in the liver. Ingestion of 150 g cadmium chloride was reported to cause focal hepatic necrosis [5].

Genotoxicity

Conflicting data have been presented. Patients with Itai-Itai disease and workers occupationally exposed to cadmium had a higher frequency of chromosome aberrations in peripheral blood lymphocytes, although these data could not be confirmed in subsequent studies [5]. An increase in chromosome aberrations in peripheral blood lymphocytes was observed in workers occupationally exposed to cadmium and lead, but not workers exposed to cadmium alone [4].

Carcinogenicity

IARC has classified cadmium and cadmium compounds as category 1 carcinogens. i.e. is carcinogenic to humans. There is sufficient evidence from occupational studies and animal data to indicate that inhalation of cadmium and cadmium compounds increases the risk of lung cancer [6]. It was assumed that this was induced via a genotoxic mechanism and hence did not to exhibit a dose threshold. However, in a recent assessment EFSA concluded that cadmium exerts its genotoxicity via the production of reactive oxygen species and by inhibiting DNA repair. Both such mechanisms are expected to have a threshold [3].

Evidence that cadmium is associated with an increased risk of prostate cancer remains controversial. With regard specifically to prostate cancer, the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) recently stated that there was no evidence to associate occupational exposure to cadmium and prostate cancer. However, the possibility that cadmium might induce androgen imbalance and thus might potentially be associated with prostate cancer should be monitored [13].

A number of recent case-control studies have reported an association between exposure to cadmium and kidney cancer, stimulating the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) to request that epidemiological studies be critically reviewed. Other recent research has suggested that exposure to cadmium in the general population may increase the risk of cancer of the endometrium, breast, testes, bladder, pancreas and gall bladder [3, 8, 14].

Despite the concerns expressed by some expert groups, there is no convincing evidence that cadmium compounds induce cancer following oral exposure. The JECFA in 2000 stated that “there was no evidence that cadmium is carcinogenic to human exposed via the oral route” [10]. The Agency for Toxic Substances and Disease Registry (ATSDR) came to a more cautious conclusion that ‘neither human nor animal studies provide sufficient evidence to determine whether or not cadmium is a carcinogen by the oral route’ [4]. In 2009, although EFSA reported studies that an association between cadmium exposure and cancer of the lung, endometrium, bladder and breast, it stated that such data were insufficient to carry out human risk assessments and hence that kidney toxicity should be considered to be the critical toxic effect [14].

Reproductive and developmental toxicity

The few data on possible developmental effects of cadmium are inconclusive. Birth weights of newborn infants may be lower following maternal cadmium exposure, but no congenital abnormalities have been reported [5, 7].

Animal and In-Vitro Data

Inhalation

Following exposure to 0.4 mg m⁻³ for 4-6 weeks, rabbits showed signs of type 2 cell hyperplasia and lung interstitial inflammations, whereas at higher doses, (4 mg m⁻³ for 9 months), rabbits developed chronic pneumonia and emphysema, as well as renal damage, evidenced by proteinuria. Gastrointestinal effects (stomach erosion) were observed in rats exposed to 132 mg m⁻³ cadmium carbonate for 2 hours [4].

Ingestion

The chronic toxic effects following oral exposure to cadmium are summarised in table 5. Renal dysfunction in laboratory animals is commonly reported. Proteinuria and histopathologic damage have been observed at doses ranging from 1.8-2.5 mg kg⁻¹ bw day⁻¹ cadmium [4].

Table 5. Summary of chronic toxic effects following oral exposure to cadmium.

Dose (mg kg⁻¹ bw day⁻¹)	Signs and symptoms
> 0.6	Immunosuppression
1.8-2.5	Proteinuria
1-10	Proteinuria, osteomalacia and osteoprosis
5-40	Aggression and anxiety

Sub-chronic oral exposure to cadmium can cause aggressive behaviour, anxiety and alterations in the biochemical activity of the brain in laboratory animals, although the doses that induce such behaviour are generally higher than those causing kidney and bone effects [3]. Cadmium concentrations that cause proteinuria and bone disease such as osteomalacia (softening of the bones as a result of inadequate mineralization of bone matrix, the adult counterpart of rickets) and osteoporosis (an excessive but proportional reduction in the

amounts of both the mineral and matrix phases of bone, resulting in bones that are brittle and liable to fracture) are generally lower ($1-10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$) than those causing aggression and anxiety. In some studies, bone effects have been detected prior to the development of proteinuria or histopathological kidney damage in laboratory animals [4]. Furthermore, immunosuppression has been reported in mice receiving $0.6 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ [1].

Genotoxicity

Cadmium compounds are considered to be mutagenic as human cells treated with cadmium compounds in vitro have shown an increase in chromosome damage or chromosome number, as well as DNA strand breaks, mutations and cell transformation. Thus, these compounds have mutagenic potential [3].

No studies were retrieved regarding genotoxic effects in animals following inhalation exposure to cadmium [4].

Cadmium does not seem to cause germ cell mutations following oral exposure in animals, but does so following subcutaneous exposure [3].

Overall, cadmium appears to have the capability to damage genetic material particularly chromosomes in mammalian cells, but germ cells appear to be protected except at high parenteral dose levels [3, 6]. When making their overall evaluation of cadmium as a proven human carcinogen (group 1), IARC “took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of eukaryotic cells, including human cells”[6].

Although EU RAR suggested that cadmium compounds may be direct acting genotoxins, in the 2009 review, EFSA concluded that it is not a directly genotoxic, as it induces its genotoxicity indirectly by inducing reactive oxygen species and oxidative stress and inhibiting DNA repair. Both mechanisms are expected to exhibit a threshold [14].

Carcinogenicity

IARC concluded there is sufficient evidence in experimental animals for the carcinogenicity of cadmium compounds [6].

Studies in animals provide strong evidence that cadmium or cadmium compounds (above $12.5 \mu\text{g m}^{-3}$) induce lung tumours following chronic inhalation [3, 4, 15]. Two chronic studies in rats have been reported that provide some insight into the carcinogenic potential of orally administered cadmium, only one of which presented increases in the incidence of leukaemia and of benign tumours of the prostate and testis following exposure to $2.5 \text{ mg cadmium chloride kg}^{-1} \text{ bw day}^{-1}$. The positive rat study however, was deemed of questionable relevance to humans due to the anatomical differences between human and rodent prostate [3, 15].

Reproductive and developmental toxicity

The reprotoxicity and developmental toxicity following chronic exposure to cadmium are summarised in table 6 and 7. No reproductive effects were observed in pregnant rats exposed to cadmium concentrations below $5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, with the exception of one study that reported rats ingesting $2.5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ in drinking water had decreased litter sizes and increased intervals between litters [5]. Exposure to $10 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ cadmium

caused a significant decrease in pregnancies per mating. An increased duration of oestrus cycle was reported although no loss of reproductive success. Males exposed to 8-14 mg kg⁻¹ bw day⁻¹ for 10-14 weeks developed necrosis and atrophy of seminiferous tubules, increased testicular weight, prostatic hyperplasia and decreased sperm count [4].

Offspring from female rats exposed to 0.02-0.04 mg kg⁻¹ bw day⁻¹ prior to and during gestation showed reduced exploratory locomotor activity and impaired reflexes [3]. Following exposure to 1-20 mg cadmium kg⁻¹ bw day⁻¹ prior to and during gestation a decreased number of live pups were born and skeletal abnormalities such as sirenomelia (fused lower limbs), amelia (absence of one or more limbs), delayed ossification of the sternum and ribs, dysplasia of facial bones and rear limbs were observed [3, 4]

Table 6. Summary of fertility effects following exposure to cadmium.

	Dose	Signs and symptoms
Females	< 5 mg kg ⁻¹ bw day ⁻¹	No reproductive effects per mating seen in females
	> 10 mg kg ⁻¹ bw day ⁻¹	Decrease in pregnancies and litter size. Increase in intervals between litters
	cadmium sulphate (2.8 mg m ⁻³) or cadmium oxide (1 mg m ⁻³)	Increased duration of oestrus cycle and decreased incidence of pregnancy. No loss of reproductive success
Males	8-14 mg kg ⁻¹ bw day ⁻¹ (chronic exposure)	Necrosis and atrophy of the seminiferous tubule, increased testicular weight, prostatic hyperplasia and decreased sperm count and motility

Table 7. Summary of developmental effects following exposure to cadmium.

	Dose	Signs and symptoms
Inhalation – pregnant females	0.02-0.04 mg m ⁻³	Offspring showed reduced exploratory locomotor activity, delayed ossification and impaired reflexes
	0.16-0.58 mg m ⁻³	Decreased weight gain, osteogenesis and viability
Oral exposure – pregnant females	0.02-0.04 mg kg ⁻¹ bw day ⁻¹	Decreased locomotor activity and impaired reflexes
	1-20 mg kg ⁻¹ bw day ⁻¹	Offspring showed skeletal abnormalities such as sirenomelia (fused lower limbs), amelia (absence of one or more limbs), delayed ossification of the sternum and ribs, dysplasia of facial bones and rear limbs and oedema

In summary, several studies have investigated the effects on development of offspring following exposure of pregnant rodents to cadmium compounds. These indicate that cadmium can be fetotoxic, the most sensitive indicator appearing to be neurobehavioural development, with effects being seen on locomotor activity at around 0.2 – 0.4 mg cadmium kg⁻¹ bw day⁻¹ [3].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.