

# Cadmium fluoride (CdF<sub>2</sub>): Human health tier II assessment

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## Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

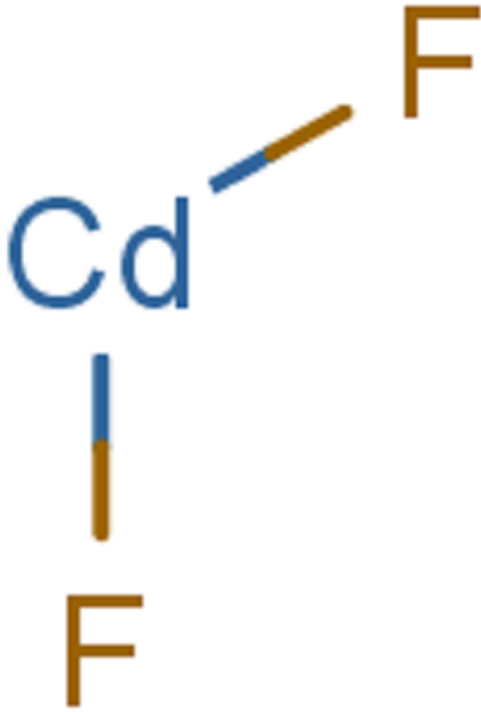
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### Acronyms & Abbreviations

## Chemical Identity

Synonyms	Cadmium fluoride Cadmium difluoride
Structural Formula	
Molecular Formula	CdF <sub>2</sub>
Molecular Weight (g/mol)	150.41
SMILES	<chem>F{-}.[Cd]{2+}.F{-}</chem>

# Import, Manufacture and Use

## Australian

No specific Australian use, import, or manufacturing information has been identified.

## International

The chemical has the following reported uses, which have been identified through Galleria Chemica:

Reported commercial use including:

- in the manufacture of phosphors and glass.

Reported site-limited use including:

- in nuclear reactor controls.

## Restrictions

### Australian

Cadmium and cadmium compounds are listed in the *Poisons Standard* (the Standard for the Uniform Scheduling of Medicines and Poisons – SUSMP (SUSMP, 2012)) under the following Schedules:

#### **Appendix I, The uniform paint standard**

The following applies to paints containing cadmium or cadmium compounds at >0.1 %. 'The proportion of a substance for the purposes of this Schedule is calculated as a percentage of the element present in the non-volatile content of the paint' (SUSMP 2012).

'A person must not manufacture, sell, supply or use a paint containing >0.1 % of cadmium or cadmium compounds for application to:

- a roof or any surface to be used for the collection or storage of potable water; or
- furniture; or
- any fence, wall, post, gate or building (interior or exterior) other than a building which is used exclusively for industrial purposes or mining or any oil terminal; or
- any premises used for the manufacture, processing, preparation, packing or serving of products intended for human or animal consumption' (SUSMP, 2012).

Additionally, 'a person must not manufacture, sell, supply or use a paint for application to toys unless the paint complies with the specification for coating materials contained in Australian/New Zealand Standard AS/NZS ISO 8124.3:2012 entitled *Safety of toys Part 3: Migration of certain elements* (ISO 8124-03:2010, MOD)' (SUSMP, 2012).

'**Schedule 6** except when:

(a) included in Schedule 4; or

(b) in paints or tinters containing 0.1 per cent or less of cadmium calculated on the non-volatile content of the paint or tinter' (SUSMP, 2012).

Schedule 6 substances are considered to have 'moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label' (SUSMP, 2012).

Cadmium and its compounds are also listed as restricted hazardous chemicals in the Australia Work Health and Safety Regulations 2011 for 'use in abrasive blasting at a concentration of greater than 0.1 % as cadmium' (SafeWork Australia).

## International

Cadmium and cadmium compounds are listed on the following (Galleria Chemica):

- EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada list of prohibited and restricted cosmetic ingredients (The "Hotlist").

Cadmium and its compounds are also restricted in the EU under Annex XVII of the European Chemicals Agency (ECHA) REACH Regulation. Cadmium compounds (as Cd) cannot be used in substances and preparations placed on the market for sale at the following concentrations in:

- plastic materials  $\geq 0.01$  % by weight of the plastic material;
- paints with a zinc content of  $>10$  % by weight of the paint  $\geq 0.1$  % by weight;
- metal plating; and
- brazing (soldering/welding) fillers  $\geq 0.01$  % by weight.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

T; R25 (Toxic if swallowed)

T+; R26 (Very toxic by inhalation)

T; R48/23/25 (Danger of serious damage to health by prolonged exposure through inhalation and if swallowed)

Carc. Cat. 2; R45 (May cause cancer)

Muta. Cat. 2; R46 (May cause heritable genetic damage)

Repr. Cat. 2; R60-61 (May impair fertility and may cause harm to the unborn child)

Cadmium compounds not individually listed on the HSIS are, by default, covered by a generic 'cadmium compounds' classification (Safe Work Australia) as hazardous with the following risk phrase for human health.

Xn; R20/21/22: Harmful by inhalation, in contact with skin and if swallowed.

## Exposure Standards

## Australian

Cadmium and cadmium compounds have an exposure standard of 0.01 mg/m<sup>3</sup> time weighted average (TWA).

## International

For cadmium and cadmium compounds the following exposure limits were identified (Galleria Chemica).

An exposure limit (TWA) of 0.01 - 0.2 mg/m<sup>3</sup> in different countries such as Canada, USA, Latvia and Switzerland.

## Health Hazard Information

Both components of this salt are associated with toxic effects on human health. Cadmium fluoride is expected to dissociate into the cadmium cation and fluoride anion under physiological conditions. Fluoride is a normal constituent of the human body. It increases the structural stability of teeth and bones through interactions with calcium phosphates at physiological concentrations. However, increased exposure to fluoride can have adverse effects on teeth and bones (NHMRC; OSU, 2001).

It is reported that fluoride poisoning can be induced by any soluble compound which dissociates the fluoride ion (HSDB). Thus, data on other fluoride compounds (ECHA C&L Inventory; HSDB; REACHc), particularly sodium fluoride and zinc fluoride (where sodium and zinc are not expected to contribute to toxicity), indicate that exposure to the fluoride ion can contribute to the acute and chronic oral toxicity of metal fluoride complexes, and are discussed in the relevant sections of the report. In general, under conditions of long term low level exposure, the systemic toxicity of cadmium is expected to be the main concern.

While there are no data available on this specific chemical, data sources for determining the hazard of the cadmium cation include animal studies on other well-characterised cadmium compounds, particularly soluble cadmium salts (cadmium chloride and cadmium sulfate) and a large amount of literature on observations of cadmium exposure in humans (NICNASa; NICNASb). The toxicity data from cadmium chloride and cadmium sulfate exposure are considered relevant to the chemical, as the bioavailability is expected to be similar following ingestion.

## Toxicokinetics

There is a large amount of information on the toxicokinetics of the cadmium ion in humans. This information is mostly related to general cadmium exposure in workers, and is not specific to particular cadmium compounds.

Human data available on cadmium indicate that gastro-intestinal absorption is low (5–10 %), and varies depending on the source of the cadmium, presence of zinc in the diet, the body's iron stores (deficiencies are linked with increased cadmium absorption) and the person's age and physiological condition (young or pregnant or lactating animals have been shown to absorb more cadmium than non-pregnant adult animals) (OECD, 2004; EU RAR, 2007).

Dermal absorption of cadmium in rabbits following exposure to cadmium chloride solution was considered to be substantial, resulting in accumulation of up to 0.8 % of the administered dose in the kidney and liver (EU RAR, 2007).

Animal studies have demonstrated that absorption of cadmium oxide following inhalation exposure ranges from 30 % (dusts, size-dependent) to 50 % (fumes). In humans, inhalation absorption of 10–30 % (dusts, size-dependent) was reported (OECD, 2004).

In rodent dietary exposure studies using cadmium oxide, significant accumulation of cadmium was detected in the liver, kidneys, lungs and spleen. Levels in the liver and kidneys were reported to be dose-dependent. However, no significant increases in blood or urine levels of cadmium were detected. Absorption fractions following oral exposure to low doses of cadmium oxide were reported to be much greater than those determined for exposure to higher doses (EU RAR, 2007).

Following long-term low-level exposure, cadmium is reported to be widely distributed in the body and has a biological half-life of 10–20 years. The greatest accumulation occurs in the kidneys and liver, with only 0.005–0.02 % reported to be excreted in urine

and faeces each day. Cadmium is also detectable in the placenta, and can cross the placental barrier, although foetal concentrations are lower than placental concentrations. Concentrations of cadmium in newborn blood were 40–50 % lower than the levels in maternal blood (EU RAR, 2007). Cadmium is reported to be found in human breast milk at <1 µg/L (OECD, 2004). In tissue, cadmium is bound to metallothionein, a low molecular weight metal-binding protein thought to play a key role in metabolising and detoxifying cadmium (EU RAR, 2007).

It should be noted that higher levels of cadmium (particularly in the kidney) are detected in smokers compared with non-smokers, as cadmium has been shown to accumulate in tobacco plant leaves (WHO, 2010).

The fluoride ion is expected to be readily absorbed via the gastrointestinal tract and lungs and the degree of absorption is correlated with the solubility of the fluoride compound. It is expected that dermal absorption will be low due to its ionic nature. After ingestion, absorbed fluoride is mainly excreted by the kidney through urine, however small amounts of fluoride are present in sweat, milk and intestinal secretions. It is reported that 90 % of fluoride is filtered by the glomerulus and reabsorbed by the renal tubules (HSDB).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, data from sodium fluoride, soluble cadmium salts (cadmium chloride and cadmium sulfate) and observations in humans following acute oral exposure to zinc fluoride and other cadmium compounds, support this classification.

Cadmium chloride and cadmium sulfate were reported to be acutely toxic in rats with LD50 values ranging from 107–327 mg/kg bw and 280 mg/kg bw, respectively (NICNASa).

Sodium fluoride (NaF) was reported to be acutely toxic in rats with LD50 values of 148.5 mg/kg bw and 223 mg/kg bw, for females and males respectively (REACHc).

### Dermal

The chemical is not classified for dermal toxicity in HSIS, although the classification for cadmium compounds not individually listed in HSIS includes dermal toxicity (Safe Work Australia).

While there are no experimental dermal toxicity data available specific to this chemical, a number of soluble cadmium salts are reported to be absorbed through the skin resulting in detectable levels of cadmium in the kidney and liver. Fluoride ion is expected to have low dermal absorption (see **Toxicokinetics** section).

In the absence of more comprehensive information, there is insufficient evidence to recommend a classification for this chemical.

### Inhalation

The chemical is classified as hazardous with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, data from other cadmium compounds and observations in humans support this classification.

A median lethal concentration (LC50) for cadmium chloride of >4.5 mg/m<sup>3</sup> was reported from a 2-hour inhalation study in rats (REACH). Observed effects included pneumonitis (inflammation of lung tissue) and biochemical changes (increased number of alveolar macrophages and decreased lung/body weights). Even after considering the lower percentage of cadmium in these chemicals compared with cadmium chloride, this suggests that the chemicals in this group should be considered toxic (NICNASa).

## Observation in humans

Several cases of cadmium poisoning (compound not specified) as a result of ingesting contaminated food or drinks have been documented. Signs and symptoms of toxicity reported include nausea, vomiting, diarrhoea and abdominal cramps.

Eight-hour inhalation exposure to cadmium levels of 5 mg/m<sup>3</sup> is reported to be potentially lethal, while 1 mg/m<sup>3</sup> is considered to be immediately dangerous to life (EU RAR, 2008).

In addition, there are many case studies of acute poisoning following inhalation of cadmium oxide fumes, or fumes produced by heating cadmium-containing materials to high temperatures. Documented signs of toxicity include nausea, fever, difficulties in respiration and severe respiratory irritation. Pulmonary oedema, resulting in mortality, was commonly reported following acute exposure (EU RAR, 2007).

A number of cases of fluoride poisoning have been reported. Symptoms of acute toxicity include vomiting within 10-60 mins after ingestion, diarrhoea, dehydration, rapid or weak pulse, low blood pressure, drowsiness, dilated pupils, hyporeflexia (absent reflexes) and rapid and shallow respiration (HSDB).

At higher doses, symptoms include haemorrhagic gastroenteritis and haemorrhages, congestion, and oedema in several organs including the brain. Reported clinical manifestations include excitability, muscle tremors, weakness, urination, defaecation, salivation, emesis, sudden collapse, clonic convulsions, coma, cyanosis and eventually death due to respiratory and cardiac failure (HSDB).

## Corrosion / Irritation

### Respiratory Irritation

While no data are available for this chemical, based on sublethal symptoms observed in inhalation studies in animals and observations in humans, the chemical is expected to irritate the respiratory tract.

### Skin Irritation

While no specific data are available for this chemical, potential skin irritation was reported following exposure to cadmium chloride (see **Irritation/Corrosivity - Observations in Humans**).

### Eye Irritation

No data are available for the chemical. Sodium fluoride was reported to be slightly irritating to the eyes of rabbits exposed to a solution containing 100 ppm NaF. Slight conjunctivitis was reported one hour post-exposure and irritation effects were fully reversible after 24 hrs (REACHc).

## Observation in humans

Eczema patients were patch-tested with 0.06, 0.5, 1 or 2 % doses of cadmium chloride in distilled water. At the 2 % dose, skin irritation was reported in 25/1502 patients (1.7 %), but no vesicular reactions (skin blisters) were observed. A lowest observed adverse effect level (LOAEL) value of 2 % was reported. No skin irritation was reported at 1 % dose (NICNASa).

## Sensitisation

## Skin Sensitisation

While no data are available for this chemical, there is limited evidence of skin sensitisation from human observations following exposure to cadmium chloride (see **Irritation/Corrosivity - Observation in humans** section).

In a guinea pig maximisation test, animals (20/dose) were intradermally administered a 0.007 % cadmium chloride solution in water. Topical induction used a 5 % suspension of cadmium chloride in petrolatum. After three weeks, the animals were challenged at 0.05 % cadmium chloride solution by intradermal injection and at 7.5 % by topical application. No contact sensitisation was reported at 24 or 48 hours post challenge application (NICNASa).

There is insufficient evidence to classify this chemical as a skin sensitizer.

## Observation in humans

Skin patch tests using cadmium chloride and cadmium sulfate were positive in seven out of approximately 150 patients attending a dermatological department between 1979 and 1981 (NICNASa).

## Repeated Dose Toxicity

### Oral

The chemical is classified as hazardous following repeated oral exposure, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure if swallowed' (T; R48/R25) in HSIS (Safe Work Australia). While no data are available for this specific chemical, data from animal studies and observations in humans following oral exposure to sodium fluoride and soluble cadmium salts (cadmium chloride and cadmium sulfate), which have similar oral bioavailability, support this classification.

A chronic exposure study in male Wistar rats using cadmium chloride reported potential damage to the vertebrae. The animals (10/dose) were orally exposed to cadmium chloride for 12 months through drinking water at 1, 5, or 50 mg Cd/L (calculated daily dose ranges were 0.049–0.223, 0.238–0.977, and 2.073–10.445 mg/kg bw/day, respectively). No treatment-related signs were reported at 1 mg/L. At  $\geq 5$  mg/L, increased lumbar spine deformities and a decrease in lumbar spine mineralisation (measurements included calcium, magnesium, zinc, copper, iron and phosphate) were reported. Decreased mechanical strength of the vertebral column at the fourth lumbar vertebra (L4) was reported at 50 mg/L. The L4 was reported to be fractured in 30 % of animals in this group, while 40 % were reported to have L4 deformities (NICNASa).

Manifestations of chronic oral exposure to excess fluoride in cattle are dental fluorosis and osteofluorosis. The animals with moderate to severe osteofluorosis also exhibited an intermittent, non-specific stiffness that may be associated with calcification of periarticular structures (body joints) and tendon insertions. This stiffness was reported to be transitory; and limited feeding or grazing time, which impaired the animals' well-being (HSDB).

A chronic oral study using SD rats exposed to sodium fluoride at doses of 4, 10 or 25 mg/kg bw/day, reported effects including decreased weight gain, dose-related macroscopic and microscopic changes in teeth, bone and stomach of the rats. The LOAEL was reported to be 4 mg/kg bw/day based on dental effects observed in rats (REACHc).

### Dermal

No data are available.

### Inhalation

The chemical is classified as hazardous following repeated inhalation exposure, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/R23) in HSIS (Safe Work Australia). While there are no



data available for the chemical, data from animal studies and observations in humans following inhalation exposure to other cadmium compounds are provided below as read-across and support this classification.

Effects observed in animal studies following repeated-dose exposure to cadmium oxide are reported to be similar to those observed in acute inhalation exposure studies including rales (abnormal respiratory sounds), laboured breathing and pneumonia, seen at low doses (NICNASb).

In a 13-week repeated-dose inhalation study in rats exposed to cadmium oxide, the NOAEL was reported to be 0.025 mg/m<sup>3</sup>. At higher doses ( $\geq 0.05$  mg/m<sup>3</sup>), treatment-related lesions in the lungs, including inflammation and fibrosis, were observed. A dose-related increase in hyperplasia (elevated cell production) in the lungs was also reported (NICNASb).

## Observation in humans

Exposure to low levels of cadmium over a long period of time has been linked to chronic cadmium poisoning. The effects of cadmium on specific target organs following exposure in humans are summarised below.

### **Respiratory effects**

There are a number of documented case studies of workers chronically exposed to cadmium fumes (EU RAR, 2007). Effects reported included fatigue, respiratory irritation, shortness of breath, decreased lung function and recurrent bronchitis.

It is suggested that an increase in residual levels of cadmium in lungs may lead to chronic obstructive airway disease and (in some cases) mortality, all of which have been documented following exposure (EU RAR, 2007). A lowest observed adverse effect concentration (LOAEC) of 0.0031 mg/L, based on lung effects (increased residual levels of the chemical), was derived from a study on workers exposed to cadmium fumes at  $<0.5$  mg/m<sup>3</sup> over several years.

### **Renal effects**

The kidneys are considered to be the main target organ for cadmium toxicity following repeated oral or inhalation exposure (ATSDR, 2012; EU RAR, 2007). Initial signs of kidney effects following cadmium exposure include tubular dysfunction, a decreased glomerular filtration rate, and increased proteinuria and enzymuria. Renal dysfunction is considered to occur when renal cortex cadmium concentrations reach 200 ppm (equivalent to 5–10 µg/g creatinine) (EU RAR, 2007).

Increased incidence of kidney stones has also been reported in workers exposed to cadmium (18 %), compared with unexposed workers (3 %) (EU RAR, 2007).

### **Skeletal effects**

Oral cadmium exposure is reported to cause bone disease in humans (EU RAR, 2008). While the underlying mechanism is not clearly understood, it is thought that cadmium-induced kidney damage and the resulting hypercalcaemia (elevated levels of calcium in the urine) may promote osteoporotic effects in bone (EU RAR, 2007).

In a case study in Japan, a high incidence of Itai-Itai disease was diagnosed in patients from specific geographical locations. It was found that farms in these areas were irrigated by a river being polluted by cadmium sludge from an upstream mine, and the patients may have been exposed to cadmium for over 30 years. Samples of rice taken from those areas were reported to contain cadmium at 0.68 mg/kg, compared with 0.066 mg/kg in other areas (EU RAR, 2007). Itai-Itai disease is characterised by osteomalacia (softening of the bones), osteoporosis, severe renal tubular disease, and is associated with severe pain (WHO, 2011). A limited number of case reports have also documented clinical bone disease in workers exposed to cadmium compounds (EU RAR, 2007).

Additionally, chronic ingestion of fluoride is reported to cause mottled enamel and osteosclerosis (increased bone density and calcification) resulting in anatomical abnormalities. Intake of more than 6 mg/day results in fluorosis; symptoms include weight loss, brittleness of bones, anaemia, weakness, general ill health and joint stiffness (HSDB)

## Genotoxicity

The chemical is classified as hazardous, as a Category 2 mutagen, with the risk phrase 'May cause heritable genetic damage' (T; R46) in HSIS (Safe Work Australia). While there are no experimental data available for this specific chemical, data from other soluble cadmium salts (cadmium chloride and cadmium sulfate) and observations in humans, provided below as read-across data, support this classification. Sodium fluoride gave negative results based on available data.

### ***In vitro***

Cadmium chloride was reported to not be mutagenic in *Salmonella typhimurium* bacterial strains TA 98, TA100, TA 1535 and TA 1537 with and without metabolic activation (REACH). However, cadmium ions have been shown to induce genotoxic effects in vitro (reduction in colony-forming ability and DNA strand breaks in *Escherichia coli*) (NICNASa).

Cadmium chloride and cadmium sulfate were clastogenic in tests using mammalian cells. An increase in sister chromatid exchanges was reported in male and female mouse splenocytes exposed to cadmium chloride, and in human lung fibroblasts exposed to either cadmium chloride or cadmium sulfate; chromosomal aberrations were observed in male and female Swiss mouse splenocytes following exposure to cadmium chloride; and DNA strand breaks and mutations at the K-ras gene were reported in human lung fibroblasts exposed to cadmium sulfate (NICNASa).

Sodium fluoride was reported not to be mutagenic in *S. typhimurium* bacterial strains TA 98, TA100, TA 1535 and TA 1537 with and without metabolic activation (REACHc)

In a mammalian cell gene mutation test using Chinese hamster V9 cells, sodium fluoride was reported not to be mutagenic at concentrations ranging from 10 to 400 µg/mL after 24 hours of incubation (REACHc).

### ***In vivo***

Cadmium chloride was reported to be mutagenic in vivo in male albino rats that were injected intraperitoneally with a 4 mg/kg bw dose of the chemical. Single strand DNA breaks were observed following exposure, notably in the kidney (NICNASa).

Cadmium chloride was reported to be mutagenic in vivo where micronucleus induction and sister chromatid exchanges in mouse bone marrow and chromosomal aberration were investigated, after a single intraperitoneal (ip) treatment at doses of 1.9, 5.7 or 7.6 mg/kg bw. A dose-dependent increase of peripheral erythrocytes with micronuclei was reported in this study. Doses of 5.7 and 7.6 mg/kg bw induced bone marrow toxicity demonstrated by a significant increase in the percentage of polychromatic erythrocytes relative to normal chromatic erythrocytes when compared with the control. The chemical was also reported to induce chromosomal aberrations (excluding metaphases with chromosome or chromatid gaps). The effects were dose-dependent with the maximum effect observable at 24 hours post-treatment. A dose-dependent increase in the frequency of sister chromatid exchanges was reported at the two highest doses (NICNASa).

Sodium fluoride was reported not to be mutagenic in a micronucleus test in male B6C3F1 mice that were administered concentrations of fluoride (up to 400 ppm) in the drinking water. No treatment-related effects were reported as there were no increases in micronuclei in peripheral erythrocytes and chromosome aberrations in bone marrow cells.

### ***Observations in humans***

Chromosomal aberrations, increased frequency of micronuclei, and sister chromatid exchanges have been detected in humans environmentally exposed to cadmium (EU RAR, 2007). However, the specific cadmium compounds involved are not identified.

## **Carcinogenicity**

The chemical is classified as hazardous, as a Category 2 carcinogen, with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, data from sodium fluoride, other soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below as read-across data. Based on similarity in oral bioavailability to the chemical, there is sufficient evidence to support this classification.

Oral administration of cadmium chloride to Wistar rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testicular tumours. Prostate hyperplasia was also reported in Noble (NBL/Cr) rats orally exposed to the chemical (NICNASa).

A non-guideline inhalation study reported an increase in lung tumours in male and female Wistar rats (20/sex/dose) exposed to aerosolised cadmium chloride, cadmium sulfate, cadmium oxide dusts, cadmium oxide fumes or cadmium sulfide (NICNASa).

In separate studies, rats were exposed to cadmium chloride (0.03 and 0.09 mg/m<sup>3</sup>) and cadmium sulfate (0.09 mg/m<sup>3</sup> for 22 hours a day, seven days a week for 18-months. Effects reported included: lung bronchioalveolar adenomas (benign glandular tumour of the lung), adenocarcinomas (malignant glandular tumours) and squamous cell carcinomas (cancer of the outer layer of the lining of the airways). A LOAEL for carcinogenicity of 0.03 mg/m<sup>3</sup> air was reported for cadmium chloride. In a follow-up study using cadmium sulfate, a significant incidence of lung tumours was observed following chronic inhalation exposure to 0.09 mg/m<sup>3</sup> over a 29-30 month period (NICNASa).

### **Observations in humans**

There are many case studies that explore the link between exposure to cadmium and increased incidences of cancer in workers (NTP, 2011; IARC, 2012).

Significantly increased mortalities due to lung cancer were reported in workers in cadmium-processing plants, cadmium recovery plants and those who worked in the nickel-cadmium battery production industry (IARC, 2012). An increased risk of lung cancer was identified in workers with long-term employment in high cadmium-exposure jobs.

A few cases of cancer of the prostate, pancreas and kidney have also been reported following exposure to cadmium (either from occupational exposure or by contamination).

In some of these cases, workers may have been exposed to other chemicals, including arsenic and nickel. Both IARC and the US NTP concluded that the increase in lung cancers could not be solely due to co-exposure to other chemicals (NTP, 2011; IARC, 2012). However, the Agency for Toxic Substances and Disease Registry (ATSDR) disputed that the interpretation of these observations in humans is complicated by co-exposure with other metals, and that there is a 'lack of significant relationship between cadmium exposure and duration' (ASTDR, 2012). These data suggest that there may be limited evidence of cancer of the prostate, pancreas and kidney occurring from exposure to cadmium compounds in these studies.

The International Agency for Research on Cancer (IARC) has classified cadmium and cadmium compounds as 'Carcinogenic to humans (Group 1)' based on sufficient evidence in humans and experimental animals (IARC, 2012). Additionally, the US National Toxicology Program (NTP) has also classified cadmium and cadmium compounds as 'Known to be human carcinogens' (NTP, 2011).

Fluoride ion is not reported to be a human carcinogen (HSDB).

## **Reproductive and Developmental Toxicity**

The chemical is classified as hazardous, as a Category 2 reproductive and developmental toxin, with the risk phrases 'May impair fertility' (T; R60) and 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, data from sodium fluoride, other soluble cadmium salts (cadmium chloride and cadmium sulfate), provided below as read-across data, support this classification.

### **Reproductive toxicity**

In a study in female Wistar rats, animals were exposed to cadmium chloride by oral gavage at 0.04, 0.4, 4 and 40 mg/kg bw/day for 14 weeks. Increased oestrous cycle lengths and decreased body weights compared with controls were reported in rats in the highest dose group (40 mg/kg bw/day) after six weeks of treatment; this was not reported for other dose groups. A reproductive NOAEL of 4 mg/kg bw/day and LOAEL of 40 mg/kg bw/day were reported for this study (REACH; EU RAR, 2007; NICNASa).

In a three-generation oral study, SD rats were exposed to sodium fluoride in drinking water at levels up to 250 ppm (equivalent to 28.4 mg/kg bw/d of sodium fluoride or 12.8 mg/kg bw/day of fluoride). No treatment-related or cumulative toxic effects were reported throughout three generations (REACHc).

### **Developmental toxicity**

Effects of cadmium exposure on maternal and foetal zinc metabolism were reported to be investigated in a non-guideline developmental toxicity study. SD rats were orally exposed to cadmium chloride in drinking water at daily doses of 0, 5, 50 and 100 ppm on gestation days 6–20. Exposure-related reduced maternal weights and weight gains were reported at the highest dose groups at 50 and 100 ppm but not in the 5 ppm group. In the 100 ppm dose group, reduced foetal weights were reported to

be a secondary effect to decreased maternal weights (attributed to maternal reduced food and water intake). A significant difference in the foetal weight to maternal weight ratio (as compared with the controls) was only observed in the 50 ppm group.

It was reported at the 50 ppm dose that cadmium-induced zinc retention was the cause for impaired foetal growth as zinc retention in maternal liver and kidney, and decreased concentration of zinc in the foetal liver were observed. A maternal and developmental NOAEL of 5 ppm (0.63 mg/kg bw/day) and a maternal and developmental LOAEL of 50 ppm (4.7 mg/kg bw/day) were reported (REACH; EU RAR 2007; NICNASa).

In another study, cadmium chloride was administered intragastrically at 2, 12 and 40 mg/kg bw/day, to pregnant rats. At the two highest dose groups, reduced foetal body weights and reduced skeletal ossification, compared with controls, were reported. However, reduced body weight gains during pregnancy of treated females at all dose levels were also reported. NOAEL or LOAEL estimates were not reported for this study (EU RAR 2007; NICNASa).

In a prenatal developmental toxicity study, SD rats were exposed to sodium fluoride at 50, 150 and 300 ppm dose concentrations (approximately 7.5, 22.5, and 45 mg/kg/day, respectively) in drinking water. Maternal exposure to the chemical at concentrations up to 300 ppm (approximately 27 mg/kg bw/day) during organogenesis (GD 6 to 15) did not significantly affect post implantation loss, mean foetal body weight/litter, or external, visceral or skeletal malformations (REACHc).

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, reproductive toxicity and developmental toxicity), systemic acute effects (acute toxicity by the oral and inhalation routes of exposure), and toxic effects (renal, respiratory and skeletal effects) resulting from repeated exposure following ingestion or inhalation. The chemical is also a potential respiratory irritant.

### Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from these chemicals is not considered to be unreasonable.

### Occupational Risk Characterisation

Given the critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

## NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

### Regulatory Control

#### Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP).

## Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS) <sup>a</sup>	GHS Classification (HCIS) <sup>b</sup>
Acute Toxicity	Toxic if swallowed (T; R25)* Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Fatal if inhaled - Cat. 1 (H330)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)* Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)*	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)*	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60)* Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

<sup>a</sup> Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

<sup>b</sup> Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

\* Existing Hazard Classification. No change recommended to this classification

## Advice for consumers

Products containing the chemical should be used according to label instructions.

## Advice for industry

### Control measures

Control measures to minimise the risk from exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;

- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

### ***Obligations under workplace health and safety legislation***

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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