Cadmium chlorides and sulfates: Human health tier II assessment

22 November 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Cadmium chloride, hydrate (2:5)	7790-78-5
Sulfuric acid, cadmium salt (1:1), hydrate (3:8)	7790-84-3
Cadmium chloride (CdCl2)	10108-64-2
Sulfuric acid, cadmium salt (1:1)	10124-36-4

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.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of four chemical compounds consists of cadmium chlorides and sulfates, with or without water of hydration. On the AICS (Australian Inventory of Chemical Substances), hydrates are regarded as a mixture of the anhydrous form and water, therefore, anhydrous forms are taken to cover all hydrates and these chemicals should be considered equivalent. These compounds have been included in this group due to the expectation that the physico-chemical properties will not vary greatly, as all compounds are relatively water soluble, leading to the compounds within this group having related end uses. The anions in each case are not considered to contribute to the toxicity of the chemicals. In addition, information outlined in the Organisation for Economic Co-operation and Development (OECD) guideline on the Grouping of Chemicals (OECD, 2007) provides guidance on grouping chemicals based on physico-chemical or toxicological criteria.

Import, Manufacture and Use

Australian

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

International

Cadmium chloride, cadmium sulfate and its hydrates have one or more of the following reported uses, which have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; EU Risk

Assessment Reports (EU RAR); Substances and Preparations in the Nordic countries (SPIN) database; the International Agency for Research on Cancer (IARC) report; the United States (US) National Toxicology Program's Report on Carcinogens (NTP RoC); Galleria Chemica and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Reported commercial use including:

- in galvanoplasty (electrotyping);
- in photography;
- dyeing and calico printing;
- fluorescent screens;
- in vacuum tubes;
- as lubricants, e.g. in the processing of PVC;
- in manufacturing special mirrors;
- in electroplating, e.g. electrodeposition of Cd, Cu, and Ni;
- as an electrolyte in batteries, e.g. in Weston cells (wet-chemical cells); and
- as a pH regulation agent.

Reported site-limited use including:

- as a laboratory chemical in the analysis to test for pyridine bases, in the analysis of sulphides in detecting H2S and detecting fumaric acid;
- as a chemical intermediate in producing cadmium-containing stabilisers and pigments, and other cadmium compounds;
- in preparing metallic soaps for vinyl stabilisers; and
- as a process regulator, e.g. as an accelerator in cement formation and catalyst in the Marsh Test for arsenic.

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).

'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, including in:

- plastic materials;
- paints;
- metal plating; and
- brazing (soldering/welding) fillers.

Existing Worker Health and Safety Controls

Hazard Classification

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

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)

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

T; R25 (Toxic if swallowed)

T+; R26 (Very toxic by inhalation)

However, cadmium chloride, hydrate (CAS No. 7790-78-5) and cadmium sulfate, hydrate (CAS No. 7790-84-3) are not individually listed in HSIS, therefore, by default, both are covered by the generic 'cadmium compounds' classification as hazardous with the following risk phrases 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^3 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^3 in different countries such as Canada, USA, Latvia and Switzerland.

Health Hazard Information

The health hazards identified in this report for cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4), are considered to apply to their respective hydrated forms.

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.

Dermal absorption of cadmium in rabbits following exposure to a 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).

Only 2 % of a subcutaneously injected dose of cadmium chloride (CAS No. 10108-64-2) was reported to be excreted by rats though faeces six days after exposure. The chemical was reported to be readily available in plasma, but disappeared rapidly. For cadmium sulfate (CAS No. 10124-36-4), 20 % of an intravenously (i.v) injected dose was reported to be excreted though faeces in 72 hours (HSDB).

In rodent dietary exposure studies using cadmium oxide, a 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 increase in bone, blood or urine levels of cadmium was detected. Absorption rates following oral exposure to low doses of the chemical were reported to be much greater than those determined for exposure to higher doses (EU RAR, 2007).

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

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 via urine and faeces per day. Cadmium is also detectable in the placenta, and can cross the placenta, 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 the metabolism and detoxification of cadmium (EU RAR, 2007).

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

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

Acute Toxicity

Oral

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are classified as hazardous following acute oral exposure, with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). The available data support this.

Cadmium chloride is reported to be acutely toxic in animal tests following oral exposure. The oral median lethal dose (LD50) values in Sprague Dawley (SD) rats range from 107–327 mg/kg bw (EU RAR, 2007, REACH).

Cadmium sulfate is reported to be acutely toxic in rats through oral exposure. The LD50 was reported to be 280 mg/kg bw (HSDB).

There is sufficient evidence to warrant this classification applying to all compounds in this the group.

Dermal

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are not classified for dermal toxicity in HSIS, although the generic cadmium compounds classification includes dermal toxicity (Safe Work Australia).

While there are no experimental dermal toxicity data available specific to these chemicals, cadmium chloride is reported to be substantially absorbed by the skin resulting in detectable levels of cadmium in the liver and kidney (see **Toxicokinetics** section).

In the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend the classification for this group of chemicals.

Inhalation

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are classified as hazardous following acute inhalation exposure, with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia). The available data from observations in humans support this classification.

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

A study in SD rats reported a median lethal concentration (LC50) for cadmium chloride of >4.5 mg/m^3 (REACH). However, animals were only exposed to the chemical for a two-hour period. Observed effects reported included pneumonitis (inflammation of lung tissue) and biochemical changes (increased number of alveolar macrophages and decreased lung/body weights).

There is sufficient information about the chemical similarity to warrant this classification applying to all compounds in this group.

Observation in humans

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).

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.

Corrosion / Irritation

Respiratory Irritation

While no specific data are available, based on inhalation studies in animals and observations in humans (described under **Acute toxicity**), these compounds are expected to be irritating to the respiratory tract (EU RAR 2007).

Skin Irritation

While no specific data are available, based on observations in humans, cadmium chloride (CAS No. 10108-64-2) is potentially irritating to the skin (refer to **Observation in humans** section).

Eye Irritation

No data are available.

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 % in patients (EU RAR, 2007; REACH).

Sensitisation

Skin Sensitisation

In a guinea pig maximisation test, animals (20/dose) were intradermally administered a 0.007 % cadmium chloride solution in water. After an unreported period, a 5 % solution of the chemical (in petrolatum) was topically applied to the animals. When challenged three weeks later with 0.05 % cadmium chloride solution by intradermal injection, and with a 7.5 % topical application, no contact sensitisation was reported at 24 or 48 hours (EU RAR, 2007; REACH).

While there is evidence of potential skin sensitisation from human observations, there is insufficient evidence to classify these chemicals as skin sensitisers.

Observation in humans

Skin patch tests using cadmium chloride and cadmium sulfate tested positive in seven out of approximately 150 patients attending a dermatological department between 1979–1981 (EU RAR, 2007).

Repeated Dose Toxicity

Oral

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are 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). The available animal and human data 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 through drinking water for 12 months at 1, 5, 50 mg/L. No treatment-related signs were reported at 1 mg/L. At ≥5 mg/L, increased lumbar spine deformities and a decrease in lumbar spine mineralisation (including calcium, magnesium, zinc, copper, iron and phosphate) were reported. A decrease in 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. The remaining animals in this group (30 %) had intact L4s. The NOAEL (no observed adverse effect level) and LOAEL (lowest observed adverse effect level) for this study were reported to be 0.2 mg/kg bw/day and 0.5 mg/kg bw/day, respectively (REACH).

In a non-guideline, subchronic repeated dose toxicity study, male and female Wistar rats (20/sex/group) were administered cadmium chloride in their diet at doses of 1, 3, 10, 30 ppm for three months. While cadmium accumulation in the kidneys and liver was reported, no signs of systemic toxicity in the blood, liver or kidney were observed (up to 30 ppm were tolerated by rats over three months). No signs of any alterations were reported after autopsies and histopathology of animals. The NOAEL for this study was reported as 30 ppm (3 mg/kg bw/day) (REACH).

There is sufficient information about the chemical similarity to warrant this classification applying to all compounds in this group.

Dermal

No data are available.

Inhalation

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are 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 experimental data available specific to these chemicals, data from studies using other cadmium compounds and observations in human 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 exposure studies including rales (abnormal respiratory sounds characterised by fine crackles), laboured breathing and pneumonia, seen at low doses (EU RAR, 2008).

In a 13-week repeated dose inhalation study in rats exposed to cadmium oxide, the NOAEL for the chemical was reported to be 0.025 mg/m^3. At higher doses (≥0.05 mg/m^3), treatment-related lesions in the lungs were observed, including inflammation and fibrosis. A dose-related increase in hyperplasia (elevated cell production in lungs) was also reported (EU RAR, 2007).

Observation in humans

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

Respiratory effects

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

It is suggested that an increase in residual levels of the chemical 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 LOAEL of 0.0031 mg/L, based on lung effects (increased residual levels of the chemical), was derived from a study on workers exposed to the chemical fumes at <0.5 mg/m^3 over several years.

Renal effects

The kidney is considered to be the main target organ for cadmium toxicity following repeated oral and inhalation exposure (ATSDR, 2012; EU RAR, 2007). Initial signs of kidney effects following cadmium exposure include tubular dysfunction, 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).

An increased frequency of kidney stones have also been reported in workers exposed to cadmium (18 %), compared with unexposed workers (3 %) (EU RAR, 2007).

Skeletal effects

Cadmium exposure through the oral route 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 resulting hypercalcinuria (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 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).

Genotoxicity

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are classified as hazardous, as Category 2 mutagens, with the risk phrase 'May cause heritable genetic damage' (T; R46) in HSIS (Safe Work Australia). The available data support this classification.

In vitro

Cadmium chloride was reported to not be mutagenic in *Salmonella typhimurium* bacterial strains TA 98, TA 100, 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*) (EU RAR, 2007).

Cadmium chloride and cadmium sulfate were clastogenic in tests using mammalian cells. An increase in sister chromatid exchanges were 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 (REACH).

In vivo

Cadmium chloride was reported to be mutagenic in vivo in male albino rats that were injected intraperitoneally (i.p) with a 4 mg/kg bw dose of the chemical. Single strand DNA breaks were observed following exposure, notably in the kidney (EU RAR, 2007).

Cadmium chloride was reported to be mutagenic in vivo in a study where the induction of micronuclei, sister chromatid exchanges in mouse bone marrow and chromosomal aberration were investigated, after a single i.p treatment of the chemical at doses of 1.9, 5.7, 7.6 mg/kg bw.

A dose-dependent increase of peripheral erythrocytes with micronuclei were reported, where doses of 5.7 and 7.6 mg/kg bw induced bone marrow toxicity as noted by a significant increase in the percentage of polychromatic erythrocytes when compared with the control. The chemical was also reported to induce chromosomal aberrations (excluding metaphases with chromosome or chromatid gaps). The intensity of effects was dose-dependent, and at a maximum 24 hours post-treatment. A dose-dependent increase in the frequency of sister chromatid exchanges was reported at the two highest doses (EU RAR, 2007).

There is sufficient information about the chemical similarity to warrant this classification applying to all compounds in this group.

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

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are classified as hazardous, as Category 2 carcinogens, with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

Oral administration of cadmium chloride to Wistar rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testis tumours. Prostate hyperplasia (increased cell production in prostate) was also reported in Noble rats orally exposed to the chemical (NTP, 2011; REACH).

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 (REACH).

Rats were exposed to cadmium chloride at 0.03 and 0.09 mg/m^3 for 22 hours a day, seven days a week over an 18-month exposure period. The LOAEL for carcinogenicity was reported to be 0.03 mg/m^3 air, as lung bronchioalveolar adenomas (benign glandular tumour of the lung), adenocarcinomas (malignant glandular tumours) and squamous cell carcinomas (cancer of the outer layer of skin or of the lining of the internal organs) were noted at this dose. In male and female rats, a high incidence of lung nodules and lung tumours were reported for 0.03 mg/m^3 exposure (lung nodules in 33/38 rats; primary lung tumours in 28/38 rats). Bronchioalveolar adenomas were observed in 6/38 animals, adenocarcinomas were observed in 19/38 animals and combined squamous cell carcinomas and adenocarcinomas were observed in 3/38 animals.

In another study, rats were exposed to cadmium sulfate at 0.09 mg/m^3 for 22 hours a day, seven days a week over an 18-month exposure period. Lung bronchioalveolar adenomas, adenocarcinomas and squamous cell carcinomas were noted. In another study using cadmium sulfate, a significant incidence of lung tumours was observed following chronic inhalation exposure to 0.09 mg/m^3 over a 29–30 month period (REACH).

There is sufficient information about the chemical similarity to warrant this classification applying to all compounds in this group.

Observations in humans

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

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 NTP has also classified cadmium and cadmium

compounds as ‘Known to be human carcinogens’ (NTP, 2011).

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

In some of these cases, workers may have potentially 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) has concluded 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).

Reproductive and Developmental Toxicity

Cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4) are both individually listed in HSIS and are classified as hazardous, as Category 2 reproductive and developmental toxins, with the risk phrases 'May impair fertility' (T; R60) and 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia). The available data support these classifications.

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).

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).

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).

There is sufficient information about the chemical similarity to warrant this classification applying to all compounds in this group.

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 route of exposure), and toxic

effects resulting from repeated exposure following ingestion or inhalation. The chemicals are also potential respiratory irritants.

Public Risk Characterisation

Given the uses identified for these chemicals, 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 chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemicals are implemented. The chemicals 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

Assessment of the chemicals is considered to be sufficient, provided that the recommended amendments to the classification are adopted, and labelling and all other 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 chemicals should be labelled in accordance with state and territory legislation (SUSMP).

Work Health and Safety

The chemicals are 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.

The classification proposed below is based on read across principles (refer to section on **Grouping rationale**) and the existing classifications for cadmium chloride (CAS No. 10108-64-2) and cadmium sulfate (CAS No. 10124-36-4). It should be used as a default for all members of the group i.e. it should be adopted for the hydrates of the respective chemicals. If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for the specific chemical, these may be used to amend the default classification for that chemical.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Harmful in contact with skin (Xn; R21)* Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Harmful in contact with skin - Cat. 4 (H312) Fatal if inhaled - Cat. 1 (H330)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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 or the unborn child - Cat. 1B (H360F) May damage fertility or the unborn child - Cat. 1B (H360D)

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

[b] 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 chemicals should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemicals 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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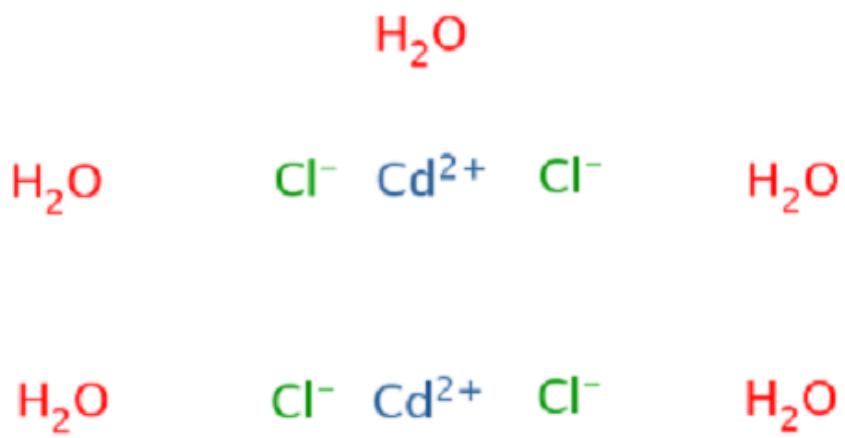
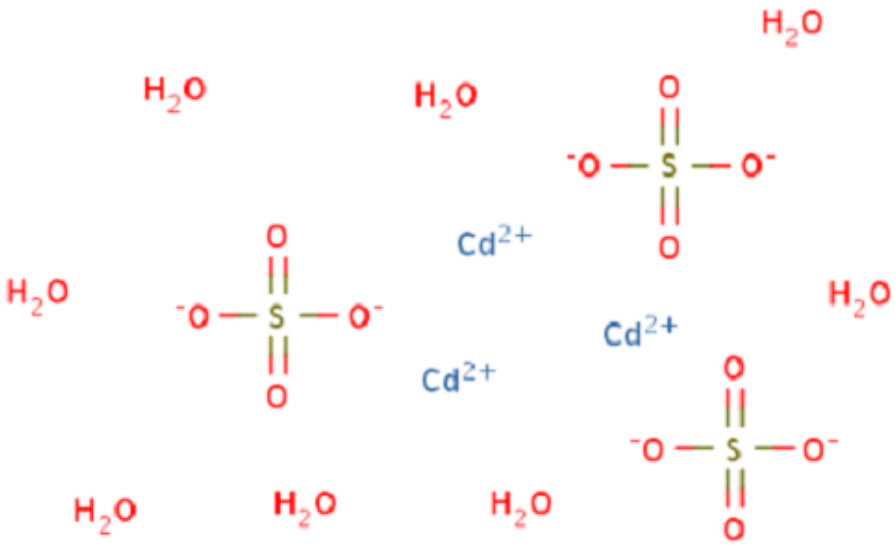
Chemical Identities

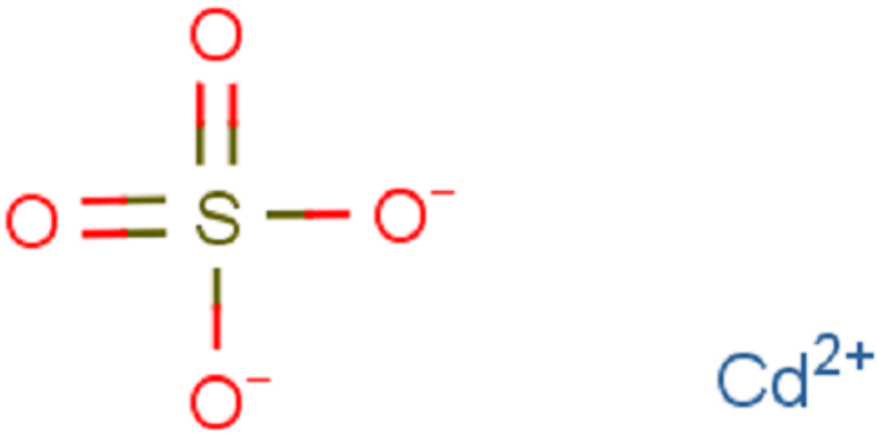
Chemical Name in the Inventory and Synonyms	**Cadmium chloride, hydrate (2:5)** Cadmium chloride, hydrate Cadmium chloride hydrate (1:2.5) Cadmium chloride hemipentahydrate Cadmium chloride pentahydrate
CAS Number	7790-78-5
Structural Formula	

Molecular Formula	CdCl2.5/2H2O
Molecular Weight	183.32

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, cadmium salt (1:1), hydrate (3:8)** Cadmium sulfate, hydrate Cadmium sulfate hydrate (3:8) Cadmium sulfate octahydrate
CAS Number	7790-84-3
Structural Formula	
Molecular Formula	Cd.H2O4S.8/3H2O
Molecular Weight	226.49

Chemical Name in the Inventory and Synonyms	**Cadmium chloride (CdCl2)** Cadmium chloride Cadmium dichloride Dichlorocadmium
CAS Number	10108-64-2
Structural Formula	

	
Molecular Formula	CdCl2
Molecular Weight	183.32

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, cadmium salt (1:1)** Cadmium sulfate Cadmium sulfate (1:1) Cadmium monosulfate Cadmium sulfuricum
CAS Number	10124-36-4
Structural Formula	
Molecular Formula	Cd.H2O4S
Molecular Weight	208.47

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