Sparingly-soluble cadmium salts: Human health tier II assessment

04 July 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Carbonic acid, cadmium salt (1:1)	513-78-0
Cadmium hydroxide (Cd(OH)2)	21041-95-2

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 two chemical compounds consists of sparingly-soluble cadmium salts with water solubilities in the range of 1 mg/L to 1 g/L but much higher solubility in acidic solutions. These compounds have been included in this group due to the expected similarity in their physico-chemical properties, leading to the compounds within this group having related end uses. The toxicity of these cadmium compounds is considered to result entirely from the presence of the cadmium component (cation). The anion components are not expected to contribute to the toxicity of the chemical compounds in comparison to the cadmium cation. As the chemicals vary in solubility, there may be some differences in acute toxicity associated with bioavailability differences. However, all the chemicals are expected to be bioavailable in the longer term, therefore chronic systemic toxicity is expected to be similar. In addition, information outlined in the Organisation for Economic Co-operation and Development (OECD) guideline on Grouping of Chemicals (OECD, 2007) provides guidance on grouping chemicals based on physico-chemical or toxicological criteria (H. Lawrence Clever et al., 1992).

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; EU Risk Assessment Reports (EU RAR); the International Agency for Research on Cancer (IARC) report; the United States (US) National Toxicology Program's Report on Carcinogens (NTP RoC); and Galleria Chemica.

Cadmium hydroxide has reported commercial use including:

- in Ni-Cd battery electrodes.

Both chemicals have reported site-limited use including:

- in electroplating; and
- in the manufacture of cadmium salts.

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

Existing Worker Health and Safety Controls

Hazard Classification

The members of this group are not individually listed in the Hazardous Substances Information System (HSIS). Therefore, by default, they are covered by the generic 'cadmium compounds' classification as hazardous with the following risk phrases for human health (Safe Work Australia):

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 main concern regarding effects on human health is expected to be driven by the cadmium component (cation) of these compounds. The compounds are expected to dissociate into the cadmium and their respective anions under physiological conditions. The anions of the chemicals (carbonate and hydroxide) in this group have been screened by NICNAS and are not considered to contribute to the final recommendations of this assessment.

While there are limited data available on these specific chemicals, data sources for determining the hazard of the cadmium cation include animal studies on well characterised cadmium compounds such as cadmium oxide, cadmium chloride, cadmium sulfate, and a large amount of literature on observations of cadmium exposure in humans. The toxicity data for cadmium chloride and cadmium sulfate by the oral route are considered relevant to the chronic systemic toxicity of cadmium compounds

in this group as the bioavailability is expected to be similar. Cadmium oxide, a relatively insoluble cadmium compound, is also considered relevant to the acute and chronic effects of the cadmium compounds in this group, by all routes of exposure (NICNASa; NICNASb).

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.

Cadmium oxide and cadmium carbonate are reported to be relatively water-insoluble. In vitro studies have demonstrated the solubility of the cadmium oxide to be 94 % in artificial gastric juice and 0.15 % in artificial intestinal juice (EU RAR, 2007). It was also reported that some water-insoluble compounds including cadmium carbonate can be changed to water-soluble cadmium salts by interaction with light or oxygen (ATDSR).

Human data available on cadmium indicate that gastro-intestinal absorption rates are low (5-10 %), and vary depending on the source of the cadmium, the 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 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 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).

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) is 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 increase in blood or urine levels of cadmium was detected. Absorption rates 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).

A study reported cadmium was detectable in the liver of male rats that were injected intraperitoneally (ip) with acetic acid, cadmium salt (CAS No. 543-90-8) at a dose equivalent to 1 mg cadmium/kg, daily for eight days (HSDB).

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 that may play a key role in the metabolism and detoxification of cadmium (EU RAR, 2007).

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).

An acute inhalation study reported that approximately 60% of the inhaled dose of cadmium carbonate aerosols was found in the gastrointestinal tract, transported by mucociliary clearance (ATDSR).

In a two-hour rat inhalation exposure to cadmium carbonate, cadmium was primarily eliminated in the faeces, with a minor component (approximately 1% of faecal excretion) in the urine. Cadmium excretion by both routes increased over time post-exposure, with significantly elevated excretion found at 7 days, but not 30 days, post-exposure. It was reported that most of the cadmium initially excreted in the faeces was unlikely to have been absorbed but rather be particles transported from the lung to the gastrointestinal tract (ATDSR).

Acute Toxicity

Oral

The compounds in this group are not individually listed in HSIS and by default, they are covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). While there are no experimental data available for these specific chemicals, data from cadmium oxide and soluble cadmium salts (cadmium chloride and cadmium sulfate), which have similar oral bioavailability, support a recommendation to amend the classification.

Cadmium oxide, cadmium chloride and cadmium sulfate have high acute oral toxicity in rats with median lethal dose (LD50) values ranging from 72–296 mg/kg bw, 107-327 and 280 mg/kg bw, respectively (NICNASa; NICNASb).

Cadmium oxide and cadmium salts (cadmium chloride and cadmium sulfate) are classified as hazardous, with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). Based on similarity in bioavailability following acute oral exposure, there is sufficient evidence to warrant this classification applying to the compounds in this group.

Dermal

The compounds in this group are not individually listed in HSIS. Therefore, by default, they are covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful in contact with skin' (Xn; R21) in HSIS (Safe Work Australia).

There are no experimental dermal toxicity data available for these specific chemicals; dermal absorption is expected to be low due to the ionic nature of the compounds in this group. The chemicals in this group are expected to behave similarly to cadmium oxide which does not have an acute dermal classification.

In the absence of more comprehensive information, there is insufficient evidence to support the generic cadmium compound acute dermal toxicity classification for this group of chemical compounds.

Inhalation

The compounds in this group are not individually listed in HSIS and by default, they are covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful if inhaled' (Xn; R20) in HSIS (Safe Work Australia). While there are limited experimental data available for these specific chemical compounds, data from the less soluble cadmium oxide support a recommendation to amend the classification for the compounds in this group.

A study in Sprague-Dawley (SD) rats reported an inhalation median lethal concentration (LC50) for cadmium carbonate of <132 mg Cd/m^3. Rats were exposed by inhalation through aerosol to cadmium carbonate for a two-hour period, followed by a 30 day observation period. Mortality was observed within one week with signs of toxicity including rales (abnormal respiratory sounds) and laboured breathing. Adverse effects reported included lung discoloration and erosions of the stomach of animals at necroscopy. Rapid uptake and greater body burden of cadmium carbonate were observed as seen from the tissues (ATSDR; EU RAR, 2007; REACH).

Cadmium oxide was also found to be acutely toxic in rats following inhalation exposure to cadmium fumes of with an LC50 value of 25 mg/m^3 (measured as cadmium) (NICNASa).

In humans, inhalation exposure to cadmium at 1 mg/m^3 is considered to be immediately dangerous to life (EU RAR, 2008).

Cadmium oxide is classified as hazardous following acute inhalation exposure, with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia). There is sufficient evidence to warrant this classification applying to the compounds in this group.

Observation in humans

The first cases of acute poisoning by cadmium carbonate were reported in 1858 and noted symptoms of pulmonary and gastrointestinal irritation in three individuals who had polished silverware (EU RAR 2007).

There are many case reports 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) from ingesting contaminated food or drinks have been documented. Reported signs and symptoms of toxicity include nausea, vomiting, diarrhoea and abdominal cramps.

Corrosion / Irritation

Respiratory Irritation

While limited data are available for the specific cadmium compounds in this group, based on sublethal symptoms observed in acute inhalation studies in animals using cadmium carbonate and cadmium oxide these compounds are expected to be irritating to the respiratory tract. Humans exposed to cadmium carbonate and other cadmium compounds also reported respiratory irritation effects.

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Respiratory Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

While no data are available for the specific cadmium compounds in this group, data from animal studies and observations in humans following oral exposure to soluble cadmium salts (cadmium chloride and cadmium sulfate), which have similar oral bioavailability are provided below as read-across.

A chronic oral exposure study in male Wistar rats (1, 5, 50 mg/L, calculated daily dose ranges were 0.049–0.223, 0.238–0.977, and 2.073–10.445 mg/kg bw/day, respectively), over 12 months, reported no treatment related signs 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. Decreased mechanical strength of the vertebral column at the fourth lumbar vertebra (L4) was reported at 50 mg/L. 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 (ATSDR; NICNASb).

Cadmium salts (cadmium chloride and cadmium sulfate) are classified as hazardous, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure if swallowed' (T; R48/R25) in HSIS (Safe Work Australia). Based on the available data on repeat oral exposure, there is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the compounds in this group.

Dermal

No data are available.

Inhalation

While no data available for these specific chemicals, adverse effects from animals exposed by repeat inhalation to cadmium oxide and observations in humans exposed to cadmium oxide and cadmium are provided as read-across.

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 (NICNASa).

In a 13-week repeated-dose inhalation study in rats exposed to cadmium oxide, the NOAEL was reported to be 0.025 mg/m^3. At higher doses (≥0.05 mg/m^3), 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 (NICNASa).

Cadmium oxide is classified as hazardous, with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/R23) in HSIS (Safe Work Australia). Based on the available data on repeat inhalation exposure, there is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the compounds in this group.

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 and provided below.

Respiratory effects

There are a number of documented case studies of workers chronically exposed to cadmium oxide 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 repeated inhalation exposure to cadmium oxide (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 oxide fumes at <0.5 mg/m^3 over several years.

Renal effects

The kidneys are 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, 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 frequency 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 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 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).

Genotoxicity

There are limited experimental data available for the specific chemical compounds in this group. Cadmium oxide and cadmium carbonate have been reported to be acid soluble, thus expected to have similar oral bioavailability to soluble cadmium salts (cadmium chloride and cadmium sulfate). In the absence of *in vivo* studies specific to the chemical compounds in this group, *in vivo* data from soluble cadmium salts are relevant and are provided below as read-across.

In vitro

Cadmium carbonate (up to 100 µM) produced significant chromosome aberration but not in sister chromatid exchange using Chinese hamster ovary (CHO-W8) cells (Wang TC et al., 2001).

Cadmium oxide did not induce genotoxic effects in bacterial mutation tests. Cadmium chloride and cadmium sulphate predominantly produced positive results in sister chromatid exchange, chromosomal aberration and DNA strand breaks (NICNASa; NICNASb).

In vivo

Results were generally positive in in vivo studies (micronucleus assay, sister chromatid exchange and chromosomal aberration in mouse bone marrow) for cadmium chloride. However, one study on cadmium oxide reported a negative result in a micronucleus assay using human peripheral blood (NICNASb)

Other cadmium compounds

Cadmium salts (not specified) have been shown to induce genotoxic effects in both in vitro (reduction in colony-forming ability and DNA strand breaks in *Escherichia coli*) and in vivo studies (sister chromatid exchange and chromosomal aberration in mice, and DNA strand breaks in rats) (EU RAR, 2007; IARC, 2012).

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.

Soluble cadmium salts (cadmium chloride and cadmium sulfate) are classified as hazardous, Category 2 mutagens, with the risk phrase ‘May cause heritable generic damage’ (T; R46) in HSIS (Safe Work Australia). Based on the available data, there is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the compounds in this group.

Carcinogenicity

While limited data are available for the specific cadmium compounds in this group, data from animal studies and observations in humans exposed to cadmium oxide and soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below, based on similarity in oral bioavailability to the specific compounds in this group.

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 rats orally exposed to the chemical (NICNASb).

In separate studies, rats were exposed to cadmium chloride (0.03 and 0.09 mg/m^3) and cadmium sulfate (0.09 mg/m^3 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^3 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^3 over a 29-30 month period (NICNASb).

In chronic inhalation studies in rats, cadmium oxide (dusts and fumes) induced carcinogenic effects (malignant lung tumours) at 0.03 mg/m^3. However, lower incidences of tumours were reported in rats exposed to fumes, compared with dusts, which was shown to be related to the level of pulmonary deposition of cadmium oxide from the two forms (NICNASa).

Observations in humans

Human epidemiological studies on mortality rates of lung cancer associated with occupational cadmium exposure, reported that cumulative exposure to cadmium hydroxide dust (co-exposed with cadmium oxide, nickel hydroxide and oxyacetylene fumes) in 3,025 nickel-battery factory workers employed from the period 1923-2000 resulted in significantly increased cancer of the respiratory tract where levels of exposure were high. Cadmium hydroxide exposure levels were reported to be 0.6 – 2.8 mg/m^3 (1949), <0.5 mg/m^3, <0.2 mg/m^3 (1967) and 0.05 mg/m^3 (since 1975), with an increase in lung cancer deaths in workers with the highest exposure (2.8 mg/m^3) first employed between 1926 and 1946 (REACH).

Furthermore, there are many case studies that explore the link between exposure to cadmium compounds (not specified) 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) 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). 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).

Cadmium oxide and cadmium salts (cadmium chloride and cadmium sulfate) are classified as hazardous (Category 2 carcinogens) with the risk phrases ‘'May cause cancer' (T; R45) in HSIS (Safe Work Australia). Based on the available data, there is sufficient evidence from animal studies and observations in humans to warrant this classification applying to the compounds in this group.

Reproductive and Developmental Toxicity

While no data available for these specific chemicals, adverse effects from animals exposed by inhalation to cadmium oxide are provided as read-across.

Reproductive toxicity

In a study in male and female F344/N rats and male and female B6C3F1 mice, animals were exposed to cadmium oxide by inhalation at 0.025, 0.5, 0.1, 0.25 or 1 mg/m^3 for 13 weeks. Decreased spermatid counts and increased oestrous cycle lengths were reported in rats in the highest dose groups, as well as decreased body weight gain and increased mortality. No treatment-related histopathological changes of the reproductive organs were seen. In mice, there was no reproductive toxicity reported at any exposure level (NTP, 1995). A reproductive LOAEL of 1 mg/m^3 was reported for this study based on the effects observed in rats (NICNASa).

Developmental toxicity

In a developmental toxicity study in Sprague Dawley (SD) rats, animals were exposed to cadmium oxide by inhalation at 0.05, 0.5 or 2 mg/m^3 on gestation days (GD) 4–19. Exposure-related foetal skeletal variations (reduced ossification of the pelvis and the sternebrae) and reduced foetal weights (statistically significant in the highest dose group) were reported. However, significantly decreased maternal body weights and reduced absolute liver and kidney weights were also recorded at the highest dose, in addition to one mortality at GD 17. Signs of toxicity were observed in dams in all treatment groups. The effects included dyspnoea (difficult or laboured breathing) and hypoactivity (NTP, 1995). A maternal NOAEL of <0.05 mg/m^3 and a developmental NOAEL of 0.5 mg/m^3 were reported for this study (NICNASa).

In another study, Swiss mice were exposed to cadmium oxide by inhalation at 0.05, 0.5 or 2 mg/m^3 on GD 4–17. An increased frequency in reduced ossification of the sternebrae was reported in foetuses (statistically significant at the highest dose), while significantly reduced foetal weights were reported at =0.5 mg/m^3. Signs of toxicity, including dyspnoea and hypoactivity, were observed in dams from all treatment groups, in addition to significantly reduced maternal body weights and five mortalities (euthanised moribund) from the highest dose group (NTP, 1995). A maternal NOAEL of <0.05 mg/m^3 and a developmental NOAEL of 0.05 mg/m^3 were reported for this study (EU RAR, 2007). Placental and lactational transfer of cadmium to the offspring (see **Toxicokinetics**) are also considered to be adverse to development (NICNASa).

Cadmium oxide is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrases ‘Possible risk of impaired fertility’ (Xn; R62) and ‘Possible risk of harm to the unborn child’ (Xn; R63) in HSIS (Safe Work Australia). Based on the available data on inhalation exposure from animal studies, there is sufficient evidence to warrant this classification applying to the 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 routes of exposure), and toxic effects (renal and respiratory effects) resulting from repeated exposure following ingestion or inhalation. The chemicals in this group are also potential respiratory irritants.

Public Risk Characterisation

Given the uses identified for the chemicals in this group, 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 in this group may pose an unreasonable risk to workers unless adequate control measures to minimise exposure 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 these chemical compounds 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

Work Health and Safety

These chemical compounds 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). It should be used as a default for all members of the group. 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) 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 through inhalation - Cat. 1 (H372) Causes damage to organs through prolonged or repeated exposure if swallowed - 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 3 - Possible risk of impaired fertility (Xn; R62) Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

[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 these chemical compounds should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to these chemical compounds 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 chemicals has not been undertaken as part of this assessment.

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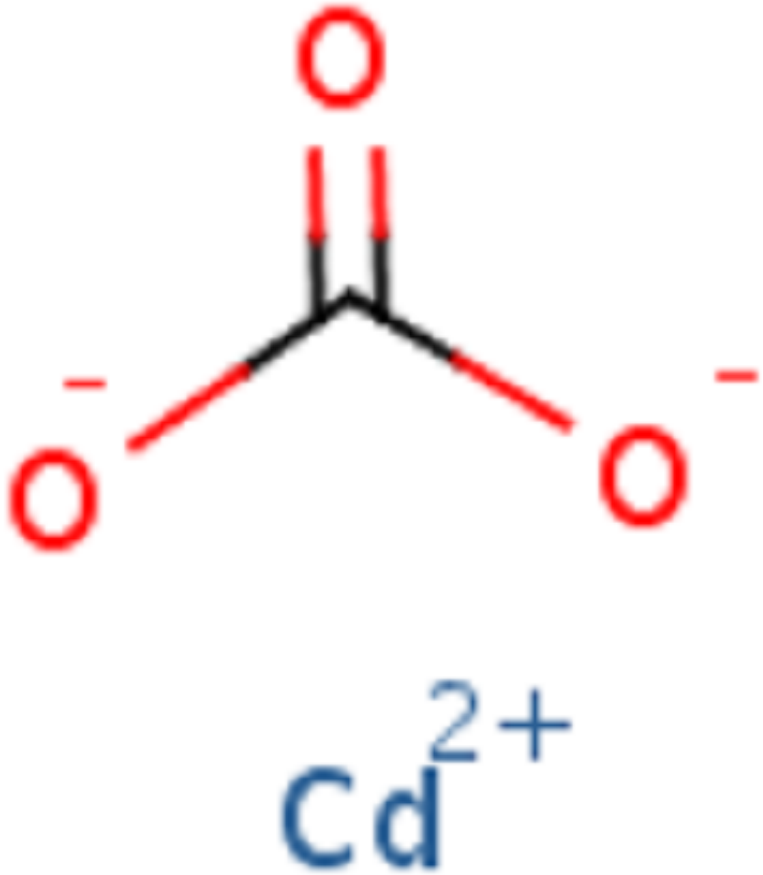
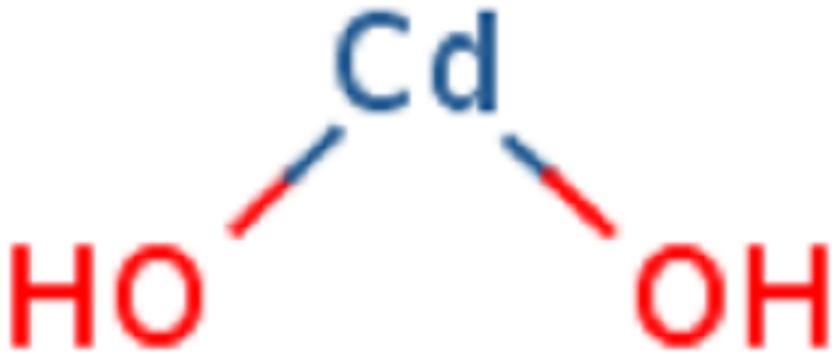
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Carbonic acid, cadmium salt (1:1)** Cadmium carbonate Cadmium carbonate (CdCO3) Carbonic acid, cadmium salt Cadmium monocarbonate Carbonic acid, cadmium(2+) salt (1:1)
CAS Number	513-78-0
Structural Formula	

	
Molecular Formula	CH2O3.Cd
Molecular Weight	172.42

Chemical Name in the Inventory and Synonyms	**Cadmium hydroxide (Cd(OH)2)** Cadmium hydroxide Cadmium dihydroxide
CAS Number	21041-95-2
Structural Formula	

	
Molecular Formula	CdH2O2
Molecular Weight	146.42

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