Cadmium: 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.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Colloidal cadmium Cadmium, elemental Cadmium metal
Structural Formula	
Molecular Formula	Cd
Molecular Weight (g/mol)	112.41
Appearance and Odour (where available)	Odourless, soft, blue-white, malleable metal or greyish-white powder.
SMILES	[Cd]

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information:

The chemical has reported domestic use in the colouring of plastics and artists' paints.

The chemical has reported commercial use in photochemicals.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported introduction volume of <1000 tonnes.

International

In general, it is reported that metallic cadmium is mainly used in the production of batteries, cadmium compounds (cadmium oxide and to a lesser extent cadmium hydroxide), and also in coatings, alloys and for other miscellaneous uses (OECD, 2004).

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; US National Library of Medicines (NLM) Household Products Database; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic use in several databases including the SPIN database. However, it should be noted that the sources consulted do not clearly distinguish between direct use of the chemical in the manufacture of a product compared with presence of the chemical in the finished product. The US National Library of Medicines Household Products Database lists only three products with possible domestic use, and again it is not clear these contain cadmium in the metal form. Reports may indicate that a cadmium compound is present, rather than specifically cadmium metal. For example, metallic cadmium is not likely to be used as a colouring agent and the description is more likely to relate to cadmium compounds such as cadmium sulfide.

"Cadmium" has reported domestic use including:

- in paints, lacquers and varnishes, e.g. in protective coatings for metals to prevent rust and in automotive paint protectants (concentration not specified; available in a pump spray product);
- as a colouring agent;
- as a corrosion inhibitor;
- as a filler;
- in adhesives and binding agents; and
- in surface treatments, e.g. industrial ceramic underglaze (< 0.1% concentration; available in an aqueous slurry product).

"Cadmium" has reported commercial use including:

- as low-melting or easily fusible bearing alloys;
- in photography and lithography;
- as a conductive agent;
- as a fixing agent;
- as a process regulator;
- as a reprographic agent;
- in construction materials, e.g. as a colouriser used in home maintenance cement/concrete (concentration not specified; available in a powder product); and

- in automotive products, e.g. motor oil (concentration not specified; available in a liquid product).

"Cadmium" has reported site-limited use including:

- in the manufacture of Ni-Cd batteries;
- in the manufacture of laboratory chemicals such as cadmium oxide, cadmium hydroxide and cadmium-based pigments (cadmium sulfides and cadmium selenides and mixtures containing these pigments);
- in electroplating steel and cast iron (used in automotive, aircraft and electronic applications);
- as a plastic stabiliser in polyvinyl chloride (PVC) products;
- as a chemical intermediate for pigments; and
- as a barrier to control atomic fission.

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 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+; 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. 3; R68 (Possible risk or irreversible effects)

Repr. Cat. 3; R62-63 (Possible risk of impaired fertility and of harm to the unborn child)

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

Cadmium (Cd) is naturally found in the earth's crust but, due to the reactivity of metallic cadmium, only as compounds. Elemental cadmium is a soft silver white metal in its purest form. Environmental cadmium is found in combination with other elements in compounds such as cadmium oxide, cadmium chloride and cadmium sulfate (US EPA).

While there are limited data available on cadmium metal, data sources for determining the hazard of the chemical include animal studies on other well characterised cadmium compounds (where the toxicity is driven by the cadmium cation) such as cadmium oxide, cadmium carbonate, cadmium hydroxide, cadmium chloride and cadmium sulfate, and a large amount of literature on observations of cadmium exposure in humans.

Cadmium oxide is considered an appropriate analogue to cadmium metal due to similarity in physico-chemical properties (relatively low water solubility) and exposure considerations, as cadmium oxide is found as a surface coating on cadmium metal (OECD, 2004). Cadmium oxide and sparingly-soluble cadmium compounds are considered relevant to the acute and chronic effects of cadmium metal, by all routes of exposure. At gastric pH, cadmium metal is expected to be soluble, similarly to cadmium oxide, and behave similarly to soluble cadmium compounds (cadmium sulfate and chloride). The toxicity data for cadmium chloride and cadmium sulfate by the oral route are considered relevant to the chronic systemic toxicity of cadmium metal (NICNASa; NICNASb; NICNASc; OECD, 2004).

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 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; NICNASb).

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; NICNASa).

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; NICNASa).

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).

Acute Toxicity

Oral

While the chemical is listed in HSIS, it is not classified for acute oral toxicity. However, it is classified as toxic by the oral route for repeated dose (refer to **Repeat Dose toxicity- oral** section).

Cadmium metal (powder) has acute oral toxicity with median lethal dose (LD50) values of 890 mg/kg bw in mice and 2330 mg/kg bw in rats (EU RAR, 2007; REACH). These results indicate that the chemical is acutely harmful but no further data are available to support a classification.

Dermal

While the chemical is listed in HSIS, it is not classified for dermal toxicity.

There are no experimental dermal toxicity data available for the chemical. Dermal absorption is expected to be low (OECD, 2004). The chemical is expected to behave similarly to cadmium oxide, which does not have an acute dermal classification (refer to **Toxicokinetics** section) (NICNASa).

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 the chemical, data from other cadmium compounds and observations in humans support this classification.

Cadmium oxide was found to be acutely toxic in rats following inhalation exposure to fumes, with a reported inhalation median lethal concentration (LC50) value of 25 mg/m^3 (measured as cadmium) (NICNASa).

A study in Sprague Dawley (SD) rats reported a LC50 value of <132 mg Cd/m^3 for cadmium carbonate. Rats were exposed 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 tissue analysis) (ATSDR; EU RAR, 2007; REACH; NICNASc).

In humans, eight-hour inhalation exposure to cadmium compounds at 5 mg Cd/m^3 may be lethal; and 1 mg Cd/m^3 is considered to be immediately dangerous to life (EU RAR, 2008; OECD, 2004).

Observation in humans

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 (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; NICNASa).

Corrosion / Irritation

Respiratory Irritation

While limited data are available for the chemical, based on sublethal symptoms observed in acute inhalation and repeated inhalation exposure studies in animals using cadmium oxide (as fumes or dust) and cadmium carbonate, this chemical is expected to be irritating to the respiratory tract (refer to **Acute toxicity- inhalation and Repeat Dose toxicity- inhalation** sections). Humans exposed to cadmium oxide and other cadmium compounds also reported respiratory irritation effects (refer to **Acute toxicity- Observation in Humans and Repeat Dose toxicity- Observation in Humans** sections) (NICNASb; NICNASc).

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Toxic: Danger of serious damage to health by prolonged exposure if swallowed' (T; R48/25) in HSIS (Safe Work Australia). While no data are available for the chemical, 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 and supports this classification.

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).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic: Danger of serious damage to health by prolonged exposure if inhaled' (T; R48/23) in HSIS (Safe Work Australia). While limited data is available for the chemical, adverse effects from animals exposed by repeat inhalation to cadmium oxide and observations in humans exposed to cadmium oxide are provided 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 (EU RAR, 2008; 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 in the lungs was also reported (EU RAR, 2007; NICNASa).

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 (NICNASa).

It is suggested that an increase in residual levels of cadmium oxide 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 (NICNASa).

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

The chemical is classified as hazardous (Category 3 mutagenic substance) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in HSIS (Safe Work Australia). The available data for the chemical and results for other cadmium compounds indicate that absorbed cadmium is a possible mutagen.

In vitro

Cadmium oxide did not induce genotoxic effects in bacterial mutation tests. Cadmium chloride and cadmium sulfate 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.

Carcinogenicity

The chemical is classified as hazardous (Category 2 carcinogenic substance), with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). While limited data are available for this chemical, data from animal studies and observations in humans exposed to cadmium oxide, cadmium hydroxide and soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below, based on similarity in oral bioavailability to the chemical. The available data support this classification.

The chemical (in the form of metallic powder) is reported to produce local tumours when injected (intramuscular and intrathoracic) into hooded and Fischer 344 rats (OECD, 2004; REACH)

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).

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 by inhalation (aerosol) 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 (REACH; NICNASb).

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; NICNASc).

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).

Reproductive and Developmental Toxicity

The chemical 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). While there is limited data available for the chemical, results from cadmium chloride (by oral exposure) and cadmium oxide (by inhalation exposure) indicate that specific reproductive effects (fertility and developmental effects) were detected at dose levels that also caused general toxicity and maternal toxicity. The available 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 the control group were reported in the highest dose group (40 mg/kg bw/day) after six weeks of treatment; this was not reported for other dose groups. However, increased mortality and other signs of toxicity (animals became emaciated, aggressive with ruffled hair coat) were also observed at the highest dose. A reproductive NOAEL of 4 mg/kg bw/day and LOAEL of 40 mg/kg bw/day were reported for this study (EU RAR, 2007; REACH).

In another study, female rats were treated with 0.1, 1 and 10 mg/kg bw/day cadmium chloride by gavage. Male rats treated with the same dose for nine weeks were mated with the treated female rats. Adverse effects including less copulating and fewer pregnant females were reported at 10 mg/kg bw/day. Female rats in this group also showed decreased body and organ weights. A reproductive NOAEL of 1 mg/kg bw/day and LOAEL of 10 mg/kg bw/day were reported for this study (EU RAR, 2007).

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).

Observations in humans

Human epidemiological studies on toxicity to reproduction and fertility associated with occupational cadmium exposure reported no significant reduction in fertility in workers (REACH).

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 (respiratory, renal and skeletal effects) resulting from repeated exposure following ingestion or inhalation. The chemicals is also potential respiratory irritant.

Public Risk Characterisation

The chemical is listed on Schedule 6 of the Poisons Standard under the chemical group 'cadmium and cadmium compounds' (SUSMP, 2013). For the majority of potential public exposure routes, this schedule entry is expected to be appropriate.

Whilst the extent of use of the chemical in domestic products in Australia is not extensively known, there are unreliable reports that the chemical is used in several domestic products overseas (including arts and crafts, automotive and home maintenance products).

Available information indicates that the chemical is not a major constituent in the formulation of automotive or home maintenance products and is used at concentrations <0.1 % in arts and crafts products overseas, (U.S. National Library of Medicines), which are within safe concentration limits and unlikely to be of concern.

Should these products be available to consumers in Australia, there are labelling requirements arising from the schedule entry (refer to **Restrictions- Australia** section). Thus, the public health risk posed by normal use of domestic products containing the chemical is not expected 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 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 as adopted by the relevant state or territory.

Work Health and Safety

This 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)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Very toxic by inhalation (T+; R26)*	Fatal if inhaled - Cat. 2 (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 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
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 - Cat. 2 (H361f) Suspected of damaging the unborn child - Cat. 2 (H361d)

[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 this chemical should be used according to label instructions.

Advice for industry

Control measures

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

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