Benzoic acid, 2-methyl-, cadmium salt: Human health tier II assessment

18 September 2014

CAS Number: 52337-78-7

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.

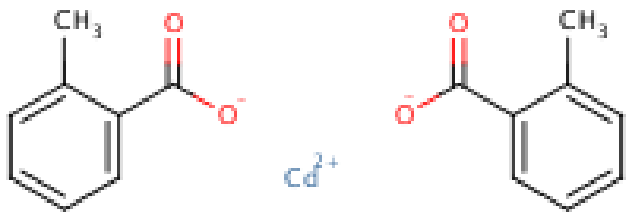
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Cadmium 2-methylbenzoate Cadmium orthotoluate Cadmium o-toluate
Structural Formula	
Molecular Formula	C8H8O2.1/2Cd
Molecular Weight (g/mol)	382.69
SMILES	C(=O)(c1c(C)cccc1)O{-}.[Cd] {2+}.O{-}C(=O)c1c(C)cccc1

Import, Manufacture and Use

Australian

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

International

No specific international use, importation, or manufacturing information has been identified for this chemical.

However, various metal salts of 2-methylbenzoic acid have site-limited use as a component of corrosion inhibitors (SciFinder).

Restrictions

Australian

Cadmium and cadmium compounds are listed in the *Poisons Standard* (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP) (SUSMP, 2013) 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, 2013).

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, 2013).

'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, 2013).

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, 2013).

Cadmium and its compounds are also listed as restricted hazardous chemicals in the Australian 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 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

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

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

Exposure Standards

Australian

Cadmium and cadmium compounds have an exposure standard of 0.01 mg/m^3 time weighted average (TWA) (Safe Work Australia).

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

Most concerns regarding human health are expected to be driven by the cadmium component of this chemical. The adverse health effects of 2-methylbenzoic acid, the parent acid of 2-methylbenzoate, are also taken into account in this assessment where available, and presented as read across in the relevant sections of this report.

2-methylbenzoic acid is a major metabolite of o-xylene and the systemic toxicity can be largely inferred using o-xylene as a worst case for systemic toxicity endpoints. The effects of cadmium are in all cases much greater than those of o-xylene.

The solubility of the chemical in aqueous or acidic solutions is not known. Thus, a ‘worst-case’ scenario is considered where the chemical dissociates into cadmium ions and the respective anion, 2-methylbenzoate, under physiological conditions.

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

Toxicokinetics

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

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

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

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

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

Following long-term low-level exposure, cadmium is reported to be widely distributed in the body and has a biological half-life of 10–20 years. The greatest accumulation occurs in the kidneys and liver, with only 0.005–0.02 % reported to be excreted in urine and faeces each day. Cadmium is also detectable in the placenta, and can cross the placental barrier, although foetal concentrations are lower than placental concentrations. Concentrations of cadmium in newborn blood were 40–50 % lower than the levels in maternal blood (EU RAR, 2007). Cadmium is reported to be found in human breast milk at <1 µg/L (OECD, 2004). In tissue, cadmium is bound to metallothionein, a low molecular weight metal-binding protein thought to play a key role in metabolising and detoxifying cadmium (EU RAR, 2007).

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

Furthermore, it has been shown that o-xylene is endogenously metabolised to 2-methylbenzoic acid, the parent acid of 2-methylbenzoate. The majority of the methyl benzoic acid is excreted in urine in the form of glycine conjugate, methyl hippuric acid (EPA, 2003). Thus, it is expected that in a 'worst-case' estimate, dissociated 2-methylbenzoate ion will be in the form of the parent acid at gastric pH and will be metabolised as such.

Acute Toxicity

Oral

The chemical is not listed in HSIS and by default, it is 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 the chemical, data from cadmium compounds and observations in humans (see **Acute toxicity: Observation in humans** section) indicate that the chemical is likely to be toxic following oral exposure.

Cadmium chloride, cadmium sulfate and cadmium oxide were reported to be acutely toxic in rats with LD50 values ranging from 107–327 mg/kg bw, 280 mg/kg bw and 72–296 mg/kg bw, respectively (NICNASa; NICNASb).

Cadmium chloride, cadmium sulfate, and cadmium oxide are individually classified as hazardous following acute oral exposure, with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). Based on the 'worst-case' estimate where similar bioavailability of this chemical following acute oral exposure is assumed, there is sufficient evidence to warrant this classification applying to the chemical (CAS No. 52337-78-7).

Dermal

The chemical is not listed in HSIS and by default, it is covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful in contact with skin' (Xn; R21) in HSIS (Safe Work Australia).

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

In the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend the classification for the chemical (CAS No. 52337-78-7).

Inhalation

The chemical is not listed in HSIS and by default, it is 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 no experimental data available that are specific to the chemical, data from other cadmium compounds and observations in humans (see **Acute toxicity: Observation in humans** section) are provided below, which support a recommendation to amend the generic 'cadmium compounds' classification applicable to the chemical.

Median lethal concentrations (LC50) of >4.5 mg/m^3 and 25 mg/m^3 were reported from inhalation studies in rats for cadmium chloride and cadmium oxide, respectively. Observed effects included pneumonitis (inflammation of lung tissue), biochemical changes (increased number of alveolar macrophages and decreased lung/body weights) and pulmonary oedema. Abnormal respiratory sounds and laboured breathing were also reported (NICNASa; NICNASb).

Observation in humans

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

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

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

Cadmium chloride, cadmium sulfate and cadmium oxide are 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 information to warrant this classification applying to the chemical (CAS No. 52337-78-7).

Corrosion / Irritation

Respiratory Irritation

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

Skin Irritation

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

Eye Irritation

No data 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 (EU RAR, 2007; NICNASa).

Sensitisation

Skin Sensitisation

While no data are available for this chemical, there is limited evidence of skin sensitisation from human observations following exposure to cadmium compounds and 2-methylbenzoic acid (see **Sensitisation: Observation in humans** section).

In a guinea pig maximisation test, animals (20/dose) were intradermally administered with a 0.007 % cadmium chloride solution in water. After an unreported period, a 5 % solution of cadmium chloride (in petrolatum) was topically applied to the animals. After three weeks, the animals were challenged 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 after the challenge application (EU RAR, 2007; NICNASa).

Observation in humans

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

In a non-guideline experiment, 2-methylbenzoic acid (50 % in polystyrene) was applied by occlusive patch for 24 hours to the upper back of 10 volunteers, for three times a week for three weeks; a total of nine applications. Challenge applications were conducted six weeks after the study began. Both p- and o-toluic acid in 50 % polystyrene were applied to an untreated area of the upper back by occlusive patch for 48 hours. Both chemicals resulted in 50 % of volunteers with sensitisation reactions after 48 hour- and 96 hour-observation periods. Similar results were reported when volunteers were rechallenged using 50 % p-, o-, and m-toluic acid in polystyrene and 5 % p-, o-,and m-toluic acid in petrolatum (Emmett & Suskind, 1973).

Repeated Dose Toxicity

Oral

While there are no data available for the chemical, data from animal studies and observations in humans (see **Repeat dose toxicity: Observation in humans** section) following exposure to cadmium compounds are provided below as read across.

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

Cadmium chloride, cadmium sulfate and cadmium oxide 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; R48/25) in HSIS (Safe Work Australia). Based on the available data, there is sufficient evidence from animal studies and observations in humans to adopt this classification applying to the chemical (CAS No. 52337-78-7).

Dermal

No data are available.

Inhalation

While there are no data available for this chemical, data from animal studies and observations in humans (see **Repeat dose toxicity: Observation in humans** section) following inhalation exposure to other cadmium compounds are provided below 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 (EU RAR, 2008).

In a 13-week repeated dose inhalation study in rats exposed to cadmium oxide, the no observed adverse effect level (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 (EU RAR, 2007).

Cadmium chloride, cadmium sulfate and cadmium oxide 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). The availability of cadmium for this chemical are expected to be high through inhalation exposure similar to cadmium oxide.

Based on the available data, there is sufficient evidence from animal studies and observations in human to adopt the above classification applying to the chemical (CAS No. 52337-78-7).

Observation in humans

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

Respiratory effects

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

It is suggested that an increase in residual levels of 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 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 the chemical 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 or inhalation exposure (EU RAR, 2007; ATSDR, 2012). Initial signs of kidney effects following cadmium exposure include tubular dysfunction, a decreased glomerular filtration rate, and increased proteinuria and enzymuria. Renal dysfunction is considered to occur when renal cortex cadmium concentrations reach 200 ppm (equivalent to 5–10 µg/g creatinine) (EU RAR, 2007). Increased incidence of kidney stones has also been reported in workers exposed to cadmium (18 %), compared with unexposed workers (3 %) (EU RAR, 2007).

Skeletal effects

Oral cadmium exposure is reported to cause bone disease in humans (EU RAR, 2008). While the underlying mechanism is not clearly understood, it is thought that cadmium-induced kidney damage and the resulting 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 a 30-year period. 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

While there are no data available for this chemical, data from other cadmium salts (cadmium chloride and cadmium sulfate) and observations in humans (see **Genotoxicity: Observation in humans** section), which indicate that absorbed cadmium is a possible mutagen, are provided below as read across.

In vitro

Cadmium chloride was not mutagenic in *Salmonella typhimurium* bacterial strains TA 98, TA100, TA 1535 and TA 1537 with and without metabolic activation (REACH). However, cadmium ions have been shown to induce genotoxic effects in vitro (reduction in colony-forming ability and DNA strand breaks in *Escherichia coli*) (EU RAR, 2007).

In another test using Chinese hamster ovary (CHO) cells, cadmium acetate was reported to induce large genomic deletions, base substitutions and splice mutations (HSDB).

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

In vivo

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

Cadmium chloride was reported to be mutagenic in vivo where micronucleus induction and sister chromatid exchanges in mouse bone marrow and chromosomal aberration were investigated, after a single intraperitoneal (i.p.) treatment at doses of 1.9, 5.7 or 7.6 mg/kg bw. A dose-dependent increase of peripheral erythrocytes with micronuclei was reported in this study. Doses of 5.7 and 7.6 mg/kg bw induced bone marrow toxicity, demonstrated by a significant increase in the percentage of polychromatic erythrocytes relative to normal chromatic erythrocytes when compared with the control. The chemical was also reported to induce chromosomal aberrations (excluding metaphases with chromosome or chromatid gaps). The effects were dose-dependent with the maximum effect observable at 24 hours post-treatment. A dose-dependent increase in the frequency of sister chromatid exchanges was reported at the two highest doses (EU RAR, 2007).

Observation 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.

Cadmium chloride and cadmium sulfate are classified as hazardous—Category 2 mutagens—with the risk phrase 'May cause heritable genetic damage' (T; R46) in HSIS (Safe Work Australia).

Based on the available data, there is sufficient evidence to adopt this classification applying to this chemical (CAS No. 52337-78-7).

Carcinogenicity

While there are no data available for the chemical, data from other cadmium compounds (cadmium chloride, cadmium sulfate and cadmium oxide) and human studies (see **Carcinogenicity: Observation in humans** section) are provided below as read across.

Oral administration of cadmium chloride to Wistar rats increased the incidence of large granular lymphocytes, leukaemia, prostate tumours, and testicular tumours. Prostate hyperplasia was also reported in Noble (NBL/Cr) rats orally exposed to the chemical (NTP, 2011; NICNASa).

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

Observation in humans

There are many case studies that explore the link between exposure to cadmium and increased incidences of cancer in workers (NTP, 2011; IARC, 2012). Significantly increased mortalities due to lung cancer were reported in workers in cadmium-processing plants, cadmium recovery plants and those who worked in the nickel-cadmium battery production industry (IARC, 2012). An increased risk of lung cancer was identified in workers with long-term employment in high cadmium-exposure jobs.

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

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

The 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).

Cadmium chloride, cadmium sulfate and cadmium oxide are classified as hazardous, Category 2 carcinogens, with risk phrase '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 human to adopt this classification applying to the chemical (CAS No. 52337-78-7).

Reproductive and Developmental Toxicity

While there are no experimental data available for the chemical, data from other cadmium salts (cadmium chloride and cadmium sulfate), which indicate that absorbed cadmium may cause reproductive and developmental effects, are provided below as read across.

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 the 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 (EU RAR, 2007; NICNASa).

Developmental toxicity

Effects of cadmium exposure on maternal and foetal zinc metabolism were reported to be investigated in a nonguideline developmental toxicity study. Sprague-Dawley (SD) rats were orally exposed to cadmium chloride in drinking water at daily doses of 0, 5, 50 and 100 ppm on gestation days (GD) 6–20. Exposure-related reductions in maternal weights and weight gains were reported at the two highest dose groups (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 (compared with controls) was only observed in the 50 ppm group (NICNASa).

It was reported at the 50 ppm dose that cadmium-induced zinc retention was the cause of 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 (EU RAR 2007; NICNASa).

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

Cadmium chloride and cadmium sulfate are listed in the HSIS and is 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). Based on the available data, there is sufficient evidence from animal studies and observations in human to adopt this classification for the chemical (CAS No. 52337-78-7).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, reproductive toxicity and developmental toxicity), and toxic effects (renal, skeletal and respiratory effects) resulting from repeated exposure. The chemical is also expected to cause acute adverse health effects from all routes of exposure.

Public Risk Characterisation

The uses for this chemical were not identified in Australia and overseas. Based on the use pattern of cadmium compounds, it is unlikely that the public will be exposed to this chemical. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Uses for this chemical are not identified. However, given the reported critical health effects for cadmium and cadmium compounds, the chemical could pose an unreasonable risk to workers when used in industrial applications unless adequate control measures to minimise exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

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

Work Health and Safety

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

The classification proposed below is based on read across principles (see **Health hazard information**) and the existing classifications for cadmium compounds. If empirical data become available for the chemical indicating that a lower (or higher) classification is appropriate for the chemical, these may be used to amend the recommended classification for the 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. 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 - Cat. 1 (H372)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60) Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage fertility. May damage the unborn child - Cat. 1B (H360FD)

[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 chemical should be used according to the instruction on the label.

Advice for industry

Control measures

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

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

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

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective

equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

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

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

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

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

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

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