Cadmium cyanide (Cd(CN)2): Human health tier II assessment

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CAS Number: 542-83-6

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.

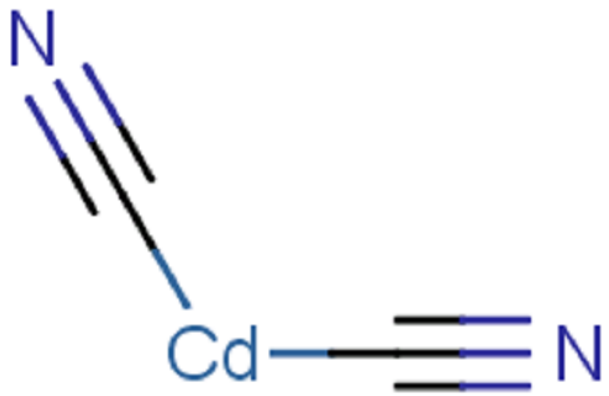
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Cadmium cyanide Cadmium dicyanide
Structural Formula	
Molecular Formula	C2CdN2
Molecular Weight (g/mol)	164.45
SMILES	C{-}(#N).[Cd]{2+}.C{-}#N

Import, Manufacture and Use

Australian

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

International

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

Reported site-limited use including:

- in copper-bright electroplating.

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 Australia Work Health and Safety Regulations 2011 for 'use in abrasive blasting at a concentration of greater than 0.1 % as cadmium' (SafeWork Australia).

International

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

- EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products;

- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The "Hotlist").

Cadmium and its compounds are also restricted in the EU under Annex XVII of the European Chemicals Agency (ECHA) REACH Regulation, including in:

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

Existing 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+; R26/27/28: Very toxic by inhalation, in contact with skin and if swallowed

Xn; R33: Danger of cumulative effects

Muta. Cat. 3; R68: Possible risk or irreversible effects

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

Both components of this salt create concern regarding effects on human health. Cadmium cyanide is expected to dissociate into the cadmium cation and cyanide anion under physiological conditions. Data on other cyanide compounds (NICNAS, 2010; ECHA C&L Inventory; REACH) indicate that exposure to the cyanide ion will contribute to the acute toxicity of this compound, and are discussed in the relevant sections of the report. In general, under conditions of long term low level exposure, the systemic toxicity of cadmium is expected to be the main concern. While there are no data available on this specific chemical, data sources for determining the hazard of the cadmium cation include animal studies on well characterised cadmium compounds, particularly the soluble cadmium salts: cadmium chloride and cadmium sulfate; and a large amount of literature on

observations of cadmium exposure in humans. The toxicity data from cadmium chloride and cadmium sulfate exposure are considered relevant to this cadmium compound, as the chloride and sulfate components have also been assessed by NICNAS and are not considered to contribute to the final recommendations (NICNAS).

Toxicokinetics

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

Dermal absorption of cadmium in rabbits following exposure to 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).

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

Animal studies have demonstrated that absorption of cadmium compounds 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). Specific data for soluble compounds are not available.

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

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 and lactating animals have been shown to absorb more cadmium than non-pregnant adult animals) (OECD, 2004; 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).

In regards to the cyanide anion, cyanide compounds are expected to be readily absorbed through the gastrointestinal tract, lungs and skin. After ingestion, absorbed cyanide is mainly excreted as thiocyanate in the urine. However, traces of cyanide may also be excreted unchanged or as a variety of metabolic products (including carbon dioxide, β-thiocyanoalanine) in expired air, saliva, and sweat (NICNAS, 2010).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Very toxic if swallowed’ (T+; R28) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, data from sodium cyanide, other soluble cadmium salts and observations in humans support this classification.

Sodium cyanide was reported to be very acutely toxic in rats with a LD50 value reported to be between 2.7–8 mg/kg bw (NICNAS, 2010).

Cadmium chloride and cadmium sulfate were reported to be acutely toxic in rats with median lethal dose (LD50) values of 107–327 mg/kg bw and 280 mg/kg bw, respectively (EU RAR, 2007; REACH).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Very toxic in contact with skin’ (T+; R27) in HSIS (Safe Work Australia). While there are no experimental data available for this chemical, the toxicity data for other cyanide compounds indicate high dermal toxicity.

Sodium cyanide and potassium cyanide were reported to be very acutely toxic in rabbits following dermal exposure, with LD50 values of 14.6 mg/kg/bw and 22.3 mg/kg/bw, respectively (NICNAS, 2010; REACH).

A number of soluble cadmium salts are reported to be absorbed through the skin resulting in detectable levels of cadmium in the liver and kidney (see **Toxicokinetics** section).

There are sufficient data to support the existing classification for this chemical.

Inhalation

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

Additionally, cyanide compounds are expected to very acutely toxic through the inhalation route as listed on HSIS due to high systemic availability through this route of exposure from the cyanide ion (See **Toxicokinetics** section) (Safework Australia).

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).

The soluble cadmium salts (cadmium chloride and cadmium sulfate) are also classified as hazardous following acute inhalation exposure, with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia).

Observation in humans

The minimal human lethal dose of inorganic salts of cyanide is reported to be 0.2 grams for adults. Documented signs of oral toxicity include immediate local irritation of the throat, hyperpnoea, apnoea, and convulsions often with cardiovascular failure leading to death. Cases of fatalities have also been reported following skin absorption of 10 % aqueous potassium cyanide (REACH).

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.

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).

Corrosion / Irritation

Respiratory Irritation

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

Skin Irritation

While no specific data are available for the chemical, potential skin irritation was reported following exposure to cadmium chloride (see **Observation in Humans**).

Eye Irritation

No data are available.

Observation in humans

Eczema patients were patch-tested with 0.06, 0.5, 1 or 2 % doses of cadmium chloride in distilled water. At the 2 % dose, skin irritation was reported in 25/1502 patients (1.7 %), but no vesicular reactions (skin blisters) were observed. A lowest observed adverse effect level (LOAEL) value of 2 % was reported. No skin irritation was reported at 1 % in patients (EU RAR, 2007; REACH).

Sensitisation

Skin Sensitisation

While no data are available for this specific compound, there is some evidence of skin sensitisation from human observations following exposure to cadmium chloride (refer to **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 the chemical (in petrolatum) was topically applied to the animals. When challenged, three weeks after the study started, 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 post challenge application (EU RAR, 2007; REACH).

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

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).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Danger of cumulative effects’ (Xn; R33) in HSIS (Safe Work Australia). While there are no data available for this specific chemical, data from animal studies on soluble cadmium compounds, potassium cyanide and observations in humans are provided in the following sections.

A chronic exposure study in male Wistar rats using cadmium chloride reported potential damage to the vertebrae. The animals (10/dose) were orally exposed to cadmium chloride through drinking water for 12 months at 1, 5, 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. A decrease in mechanical strength of the vertebral column at the fourth lumbar vertebra (L4) was reported at 50 mg/L. The L4 was reported to be fractured in 30 % of animals in this group, while 40 % were reported to have L4 deformities. The no observed adverse effect level (NOAEL) and LOAEL for this study were reported to be 0.2 mg/kg bw/day and 0.5 mg/kg bw/day, respectively (Brzoska & Moniuszko-Jakoniuk, 2005; REACH).

In comparison, the NOAEL for potassium cyanide in a 90-day oral toxicity study in Sprague-Dawley (SD) rats was reported as 40 mg/kg bw/day (REACH).

Additionally, the soluble cadmium compounds (cadmium chloride and cadmium sulfate) 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).

There is sufficient evidence from animal studies and observations in humans to warrant this higher, route-specific classification applying to this chemical.

Dermal

No data are available.

Inhalation

While there are no data available for this specific chemical, data from animal studies and observations in humans following exposure to other cadmium compounds are provided in the following sections.

Effects observed in animal studies following repeated-dose exposure to cadmium oxide are reported to be similar to those observed in acute exposure studies including rales (abnormal respiratory sounds), laboured breathing and pneumonia, seen at low doses (EU RAR, 2008).

In a 13-week repeated-dose inhalation study in rats exposed to cadmium oxide, the NOAEL 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).

Additionally, cadmium chloride and cadmium sulfate 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).

There is sufficient evidence from animal studies and observations in humans to warrant this classification applying to this chemical.

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 (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).

An 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 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). While there are no experimental data available for this specific chemical, data from other soluble cadmium salts (cadmium nitrate, cadmium acetate, cadmium chloride and cadmium sulfate) and observations in humans, provided below, support this classification.

In vitro

Cadmium nitrate was reported to induce reversible mutations in four strains of the bacteria *Salmonella typhimurium*, including strains TA 1535 and TA 1538 (HSDB).

Cadmium chloride was reported to not be mutagenic in *S. 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).

Cadmium nitrate was reported to be mutagenic in Chinese hamster ovary (CHO) cells. Dose-dependent effects observed included increased sister chromatid exchanges and chromosome aberrations, which included breaks, acentrics (chromosome or chromosome fragment without a centromere), interchanges, and dicentrics (chromosome or chromatid with two centromeres). There was also a decrease in the mitotic index (the ratio between the number of cells in mitosis and the total number of cells). The inhibitory concentration (IC50) was determined to be 0.015 mM, indicating exposure to cadmium nitrate at that dose resulted in a 50 % inhibition of viable cells (Lin RH et al., 1994).

In another test using 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; and DNA strand breaks and mutations at the K-ras gene were reported in human lung fibroblasts exposed to cadmium sulfate (REACH).

In vivo

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

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

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

While there are no experimental data available for this specific chemical, data from other soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below.

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; REACH).

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

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

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

Additionally, cadmium chloride and cadmium sulfate are classified as hazardous—Category 2 carcinogens—with risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia).

There is sufficient evidence to warrant this classification applying to this chemical.

Observations in humans

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

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).

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). Based on these data, there is only limited evidence of human carcinogenicity from soluble cadmium compounds.

Reproductive and Developmental Toxicity

While there are no experimental data available for this specific chemical, data from other cyanide compounds (sodium cyanide and potassium cyanide) and other soluble cadmium salts (cadmium acetate, cadmium chloride and cadmium sulfate) are reported below.

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. 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, male and female Fischer 344 rats and B6C3F1 mice (10/sex/dose) were administered sodium cyanide in drinking water at 0, 3, 10, 30, 100 and 300 ppm/day for 13 weeks. It was reported that decreased water consumption was observed in the 100 and 300 ppm dose groups in rats and mice, compared with the control group. A decrease in final body weight and body-weight gain was observed in male rats exposed to 300 ppm of the chemical but not in females. No details were reported for mice.

At all doses, decreased weight of the cauda epididymis (tube connecting ducts from the rear of each testicle) in male rats and mice were reported. Decreased sperm motility (at all doses) and sperm head count (at the 300 ppm dose) were only observed in male rats. Pro-oestrus and dioestrus time (time taken for the series of physiological changes in sexual and other organs) were reported to be prolonged in female rats at the 100 and 300 ppm groups compared with controls. These effects were not reported in female mice. No significant treatment-related adverse effects on body weights, organ weights, histopathology or clinical pathology in rats or mice were reported.

The lowest observed effect level (LOEL) of 30 ppm (4.9 mg/kg cyanide ion/kg bw/day) was reported for both decreased cauda epididymal weights in male rats and mice, and prolonged pro-estrus and disoestrus in female rats. Reproductive NOAEL values of 100 ppm (4.9 mg/kg cyanide ion/kg bw/day) for male rats and 300 ppm for mice (equivalent to 24.4 and 28.8 mg/kg cyanide ion/kg bw/day in males and females, respectively) were reported (REACH).

Developmental toxicity

A study using pregnant SD rats reported developmental effects following exposure to cadmium acetate from gestation day (GD) one through to lactation day 21 at doses of 5–8 mg/kg bw/day. Pup body weights were significantly decreased in the cadmium-

exposed pups during lactation. No details on maternal toxicity were reported, although the developmental LOAEL was reported to be 3.1 mg Cd/kg bw/day (EU RAR, 2007).

Effects of cadmium exposure on maternal and foetal zinc metabolism were reported to be investigated in a non-guideline developmental toxicity study. SD rats were orally exposed to cadmium chloride in drinking water at daily doses of 0, 5, 50 and 100 ppm on 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.

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 (REACH; EU RAR 2007).

In another study, cadmium chloride was administered intragastrically at 2, 12 and 40 mg/kg bw/day, to pregnant rats. At the two highest dose groups, reduced foetal body weights and reduced skeletal ossification, compared with controls, were reported. 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).

In another study, female Wistar rats (10 rats/dose) were exposed to potassium cyanide in drinking water at 1, 3 and 30 mg/kg bw/day for 15 days, from gestation days six to 20. In the highest dose group (30 mg/kg bw/day) microscopic lesions of the pancreas, liver and brain were reported in dams and pups, with lesions in dams observed at a higher incidence and intensity than in rat pups. No skeletal or visceral malformations were reported. A developmental NOAEL of 3 mg/kg bw/day and LOAEL of 30 mg/kg bw/day were reported for this study, but potassium cyanide did not show specific developmental toxicity (REACH).

Additionally, cadmium chloride and cadmium sulfate are both individually listed in the HSIS and are classified as hazardous – as Category 2 reproductive and developmental toxins – with the risk phrases 'May impair fertility' (T; R60) and 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia).

There is sufficient evidence to warrant this classification applying to this chemical.

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, dermal and inhalation route of exposure), and toxic effects resulting from repeated exposure following ingestion or inhalation.

Public Risk Characterisation

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

Occupational Risk Characterisation

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

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is 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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Very toxic if swallowed (T+; R28)* Very toxic in contact with skin (T+; R27)* Very toxic by inhalation (T+; R26)*	Fatal if swallowed - Cat. 1 (H300) Fatal in contact with skin - Cat. 1 (H310) Fatal if inhaled - Cat. 1 (H330)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Genotoxicity	Muta. Cat 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 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 label instructions.

Advice for industry

Control measures

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

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

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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