Cadmium, bis(diethylcarbamodithioato-S,S')-, (T-4)-: 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.

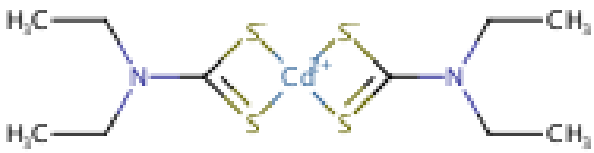
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Cadmium diethyldithiocarbamate Rubber accelerator CED
Structural Formula	
Molecular Formula	C10H20CdN2S4
Molecular Weight (g/mol)	408.95
Appearance and Odour (where available)	white or yellow powder
SMILES	C(=S)(N(CC)CC)S{-}.[Cd]{2+}.S{-}C(=S)N(CC)CC

Import, Manufacture and Use

Australian

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

International

The following site-limited uses for the chemical were identified (SciFinder; ChemNet):

- as an accelerator in the vulcanisation process of rubber substrates;
- as a constituent in thermoparticulating coatings to detect overheating in gas-cooled generators.

Restrictions

Australian

Cadmium and cadmium compounds are listed in the *Poisons Standard* (the *Standard for the Uniform Scheduling of Medicines and Poisons*) (SUSMP, 2014) 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, 2014).

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, 2014).

'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, 2014).

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, 2014).

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' (Safe Work Australia).

International

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

- European Union (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 Registration, Evaluation, Authorisation and Restriction of Chemicals (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 Hazardous Substances Information System (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, the USA, Latvia and Switzerland.

Health Hazard Information

The chemical is a non-ionic metal complex of the cadmium cation and the diethyldithiocarbamate (DDTC) anion.

Toxicokinetics

This chemical is known to be highly insoluble in water, acidic and basic solutions, human serum, and carbon tetrachloride (Gale et al., 1981).

However, studies have shown that separate administration of the organic ligand (as either sodium diethyldithiocarbamate (Na-DDTC) or diethyldithiocarbamic acid (DDTC), and cadmium (as cadmium chloride) in Sprague Dawley (SD) rats causes the cadmium content to distribute differently within the body/organism compared with ionic cadmium, thereby increasing the concentrations of cadmium in the brain and the lungs (Cantilena et al., 1982; Tatrai et al., 2001).

Male SD rats pre-treated with diethyldithiocarbamic acid exhibited a 10-fold increase in cadmium concentrations in the brain compared with the non pre-treated rats. The partition coefficient of the chemical was also significantly increased (375 times greater than that of cadmium) consistent with the highly lipophilic nature of the chemical (Cantilena et al., 1982).

Further evidence of the lipophilicity of the chemical was also obtained from incubation studies using rat hepatocyte cultures where a rapid uptake of the chemical was reported compared with cadmium chloride (Hellstrom-Lindahl & Oskarsson, 1989; Hellstrom-Lindahl & Oskarsson, 1990). Intratracheal co-administration of cadmium chloride and Na-DDTC in male SD rats increased cadmium content in the lungs compared with rats treated with cadmium only (Tatrai et al., 2001).

In a study to investigate the effects of DDTC on cadmium metabolism, BDF_1 male mice (the first filial generation from a cross between C57BL/6 female mice with DBA/2 male mice) were exposed to cadmium in drinking water [deionised water containing sucrose, cadmium chloride and radiolabelled cadmium chloride ($^{109}CdCl_2$)] for 15 days prior to intraperitoneal (i.p.) injections (seven injections over a 14-day period) of Na-DDTC. Cadmium liver and brain concentrations were increased compared with the controls (treated with cadmium alone) (Gale et al., 1985).

In a follow-up study to the above, male F_1 mice (10 animals) received i.p. injections of cadmium in saline solution containing ^{109}Cd prior to feeding DDTC (500 mg/kg) in saline solution for four consecutive days. Treatment with Na-DDTC had no significant effect on hepatic or pulmonary cadmium concentration (Gale et al., 1989). Additionally, although reduction of cadmium levels in the kidney, spleen, testes, and pancreas were reported compared with animals treated with cadmium alone, significant increases in cadmium levels in the brain and in the heart were also observed.

In another study, male CBA/Bom mice were fed with milled pellets containing Na-DDTC (100 µg/g) for seven days prior to administering ^{109}Cd-labelled cadmium chloride (22.7 µg/mL) through their drinking water for 35 days (Andersen & Nielsen, 1989). Combined exposure to cadmium chloride and Na-DDTC did not increase the retention of cadmium in the organs compared with controls (animals exposed to cadmium, but not pre-exposed to Na-DDTC). The relative organ distribution of cadmium in the pre-exposed group did not differ significantly from the controls, especially in the liver and brain.

Although the chemical is insoluble in a range of media, given the high lipophilicity of the chemical, it is expected that absorption of the chemical will occur through all routes of exposure (oral, dermal, and inhalation). Acute toxicity data showed limited alleviation of acute symptoms (see **Acute toxicity** section), but there are no data to indicate that increased elimination occurs. While the absorption and distribution differ from ionic cadmium salts due to lipophilicity of the complex, it is expected that metabolism of the chemical will release free cadmium ions. Therefore, the toxicokinetic information of the cadmium ion in humans and cadmium compounds in experimental animals below, are relevant in this chemical assessment.

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 kidneys) are detected in smokers compared with non-smokers, as cadmium has been shown to accumulate in tobacco plant leaves (WHO, 2010).

Acute Toxicity

Oral

The chemical is not listed in the HSIS and by default, it is covered by the generic 'cadmium compounds' hazard classification with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). While there are no experimental data available for the chemical, data from studies in which cadmium and DDTC are separately administered orally indicate that the chemical is likely to be at least harmful.

In BDF_1 male mice, delayed i.p. administration of Na-DDTC after exposure to a lethal dose of cadmium chloride alleviated the acute toxic effects of cadmium through endogenous formation of the chemical (Gale et al., 1981). The i.p. median lethal dose (LD50) value of Na-DDTC was 650 mg/kg; the authors of the study proposed using Na-DDTC as an antidote for acute lethal cadmium poisoning.

However, oral administration of DDTC did not affect the mortality rates in mice previously exposed to cadmium chloride through oral administration. Furthermore, enhancement of cadmium-induced intestinal paralysis was observed in animals orally administered with Na-DDTC 15 minutes after being exposed to cadmium chloride. It was proposed that the properties of Na-DDTC are responsible for the enhanced toxicity to cadmium from oral exposure, compared with exposure by i.p. injection (Andersen et al., 1988).

Given the high lipophilicity of the chemical (see **Toxicokinetics**), it is expected that oral exposure to the chemical will lead to rapid intestinal uptake and that cadmium-induced damage would be, at the very least, equivalent to that of cadmium and cadmium compounds (NICNAS a; NICNAS b). Thus, the information on cadmium compounds following oral exposure would be relevant for the assessment of the acute toxicity of the chemical.

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 (NICNAS a; NICNAS b).

Given that the bioavailability of the cadmium is enhanced by the lipophilic nature of the chemical following oral exposure, the default classification of cadmium compounds is expected to be applicable for the chemical.

Dermal

The chemical is not listed in the 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 the HSIS (Safe Work Australia).

Although the chemical is likely to be lipophilic in nature (see **Toxicokinetics** and **Acute toxicity: Oral** sections), there are no experimental dermal toxicity data available for this specific chemical. However, a number of soluble cadmium salts are reported to be absorbed through the skin, resulting in detectable levels of cadmium in the kidneys and liver (see **Toxicokinetics** section). The lipophilic nature of the chemical complex is expected to increase dermal absorption compared with ionic cadmium.

In the absence of more comprehensive information, there is insufficient evidence to amend the default classification for this chemical.

Inhalation

The chemical is not individually listed in the HSIS, therefore, by default, it is covered by the generic cadmium compounds hazard classification with the risk phrase 'Harmful if inhaled' (Xn; R20) in the HSIS (Safe Work Australia). While there are no experimental data available specific to this chemical, data from co-administration studies using cadmium chloride and Na-DDTC, as well as other cadmium compounds, indicate that the chemical is likely to be at least harmful following inhalation exposure.

In a pulmonary toxicity study, male SD rats (five animals/group) were exposed to a single intratracheal instillation of cadmium chloride (10 µg/mL), sodium diethyldithiocarbamate trihydrate (1 mg/mL), or both (Tatrai et al., 2001). Compared with rats exposed to cadmium chloride only, blood cadmium concentration in the combined exposure group were higher at day three. It

was also shown that co-administration of cadmium chloride and DDTC caused morphological changes in alveolar tissues, which were more severe compared with rats exposed only to cadmium chloride (Tatrai et al., 2001). The combined exposure resulted in the increased retention of cadmium in the lungs. This information, together with the information below on the effects from exposure to cadmium compounds through inhalation, indicates that acute effects should be expected.

Median lethal concentrations (LC50) of >4.5 mg/m^3 and 25 mg/m^3 were reported from inhalation studies in rats using 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 (NICNAS a; NICNAS b).

Given the enhanced bioavailability of the cadmium ion due to the lipophilic nature of the chemical, there is sufficient evidence to support the default classification of cadmium compounds being applied to this chemical.

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).

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. The current information is insufficient to classify the chemical as a respiratory irritant.

Skin Irritation

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

Eye Irritation

No data are available for the chemical.

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 concentration (LOAEC) value of 2 % was reported (EU RAR, 2007; NICNAS a).

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 chloride (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. Topical induction used a 5 % solution of cadmium chloride (in petrolatum). After three weeks, the animals were challenged with a 0.05 % cadmium chloride solution by intradermal injection and with a 7.5 % topical application. No dermal reactions were reported at 24 or 48 hours post challenge application (EU RAR, 2007; NICNAS a).

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

While there are no data available for the chemical, data from combined exposure studies using cadmium chloride and DDTC, animal studies and observations in humans following exposure to cadmium compounds can be used to infer relevant toxicological properties of this chemical.

The toxicity from chronic oral exposure to the chemical will depend on the release of ionic cadmium in various organs. Initial distribution of the chemical is likely to be different from that of ionic cadmium compounds and could lead to toxic effects in organs other than those affected by ionic cadmium. Thus, over the longer term, metabolism of the chemical will produce similar toxicity to ionic cadmium. The relevant information on cadmium and cadmium compounds is reported below.

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 (NICNAS a).

Dermal

While the chemical is lipophilic and likely to have higher dermal bioavailability than that of ionic cadmium compounds (see **Toxicokinetics**), there are no experimental dermal toxicity data available for this specific chemical.

Inhalation

Cadmium chloride, cadmium sulfate and cadmium oxide are classified as hazardous following repeated inhalation exposure (Safe Work Australia). Furthermore, a combined exposure study (see **Acute toxicity: Inhalation**) showed that the ligand causes increased retention of cadmium in the lungs. Observations in humans (see **Repeat dose toxicity: Observations in**

humans section) also demonstrate the inhalation toxicity of cadmium compounds and can be used to infer relevant toxicological properties of this chemical.

Observation in humans

Exposure to low levels of cadmium over a long period has been linked to chronic cadmium poisoning. The effects of cadmium compounds 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 cadmium in the lungs may lead to chronic obstructive airway disease and (in some cases) mortality, all of which have been documented following exposure (EU RAR, 2007). An LOAEC value 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 (EU RAR, 2007).

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, 2014). 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 mg/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 (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, 2010). A limited number of case reports have also documented clinical bone disease in workers exposed to cadmium compounds (EU RAR, 2007).

Given this information above, the available data for cadmium compounds and the combined exposure studies, there is sufficient evidence from animal studies and observations in humans following repeated exposure to warrant the following classification applying to the chemical in the HSIS: 'Toxic: danger of serious damage to health by prolonged exposure' (T; R48).

Genotoxicity

Exposure to ionic cadmium was shown to be mutagenic in animal tests (EU RAR, 2007; NICNAS a). Cadmium exposure also leads to genotoxic effects in humans as reported below.

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 were not identified.

Although there are no genotoxicity data available for the chemical, genotoxic effects following exposure to the chemical could reasonably be expected.

Carcinogenicity

There are no data available for the chemical. The toxicokinetics of the chemical differ significantly from cadmium compounds. However, ionic cadmium is expected to be released during metabolism of the chemical (see **Toxicokinetics** section). Thus, data for cadmium compounds (cadmium chloride, cadmium sulfate, and cadmium oxide) and human studies (see **Carcinogenicity: Observations 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 cadmium chloride (NTP, 2011; NICNAS a).

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 (NICNAS a; NICNAS b).

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 tumours 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 (NICNAS a).

Cadmium chloride and cadmium sulfate are classified as hazardous—Category 2 carcinogens—with the risk phrase 'May cause cancer' (T; R45) in the 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.

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). 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' (ATSDR, 2014). 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).

Reproductive and Developmental Toxicity

While there are no experimental data available for the chemical, data from combined exposure studies and other soluble cadmium salts (cadmium chloride and cadmium sulfate) are provided below as read across.

Reproductive toxicity

In a rat study, Na-DDTC showed protective effects against cadmium-induced testicular toxicity. Male Wistar rats were injected subcutaneously with cadmium chloride (3 mg). Thirty minutes after cadmium chloride exposure, Na-DDTC was administered

intraperitoneally at doses of 0.1, 0.2, 0.5 or 1 mmol/kg (approximately 17, 34, 86, or 171 mg/kg). Seven days after exposure, the animals were euthanised and the testes were removed for investigation. At doses of 34 mg/kg and above, application of Na-DDTC completely prevented the increase in lipid peroxidation and weight decreases in the testes. Na-DDTC also significantly decreased cadmium concentrations in the testes and completely prevented the increase of testicular iron concentration. Increased iron concentration is indicative of testicular haemorrhage. Furthermore, sterility was almost completely prevented at 17 mg/kg dose (Ono et al., 1997).

Developmental toxicity

The distribution of intravenously administered cadmium was studied in pregnant C57BL mice with or without DDTC pre-treatment. Female mice were pre-exposed to Na-DDTC (171 mg/kg bw) by gavage on gestation day (GD) 18 prior to administration of cadmium chloride (0.137 mg/kg bw) intravenously two hours later, followed by a second oral dose of Na-DDTC (171 mg/kg bw). The chemical, DDTC, increased the concentration of cadmium in the brain and on most maternal organs. The chemical, DDTC, also increased the cadmium concentrations in whole foetuses and foetal organs. The results suggest the formation of a lipid-soluble metal-dithiocarbamate complexes in vivo, and the increase levels of cadmium after DDTC pre-treatment, indicate a risk for higher cadmium foetotoxicity (Danielsson, 1984).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity), and toxic effects (renal, skeletal, and respiratory effects) resulting from repeated exposure. Based on the health effects from cadmium compounds and DDTC, the chemical is also expected to cause acute adverse health effects from all routes of exposure. Other toxic effects, such as genotoxicity, reproductive or developmental toxicity cannot be ruled out.

Public Risk Characterisation

The uses for this chemical were not identified in Australia. Furthermore, based on the use pattern of this chemical overseas, 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

The uses for this chemical were not identified in Australia. However, given the reported critical health effects for cadmium compounds, the chemical could 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. The controls expected to be in place due to the carcinogenicity classification are expected to be sufficient to protect workers from any potential genotoxic, reproductive, and developmental effects.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment 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, 2014).

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 indicating that a lower (or higher) classification is appropriate for the chemical, these may be used to amend the default classification for the chemical.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (T; R48/23/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)

[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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