Thioperoxydicarbonic diamide ([(H2N)C(S)]2S2), tetraethyl-: Human health tier II assessment

25 November 2016

CAS Number: 97-77-8

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.

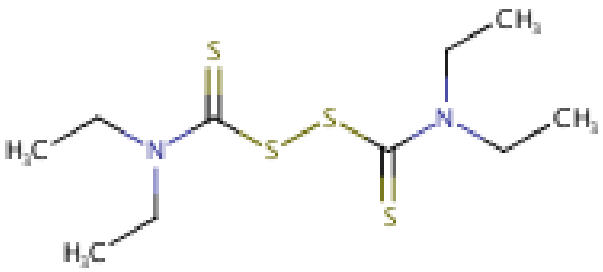
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tetraethylthiuram disulfide disulfiram antabuse tetraethylthioperoxydicarbonic diamide
Structural Formula	
Molecular Formula	C10H20N2S4
Molecular Weight (g/mol)	296.55
Appearance and Odour (where available)	Odourless white, yellowish, or light-gray powder.
SMILES	C(=S)(N(CC)CC)SSC(=S)N(CC)CC

Import, Manufacture and Use

Australian

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

The chemical has reported non-industrial use in the treatment of alcohol addiction (Therapeutic Goods Administration—TGA).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the National Center for Biotechnology Information; and various international assessments (Petersen, 1992; United States (US) Department of Health (DoH) and Human Services (HS), 1995; Ranek et al., 1997; Ehrlich et al., 2011).

The chemical has reported domestic uses, including as a component in:

- paints and coatings;
- adhesives; and
- binding agents.

The chemical has reported commercial uses, including:

- as a process regulator;
- as a formulation component;
- in water treatment product; and
- as a pH regulator.

The chemical has reported site-limited use as an accelerator in rubber products.

The chemical has reported non-industrial uses, including as:

- a medication for treatment of alcoholism; and
- a seed disinfectant and fungicide.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 4 and 6 (SUSMP, 2016) as follows:

Schedule 4

Disulfiram for therapeutic use

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State of Territory legislation to prescribe and should be available from pharmacist on prescription' (SUSMP, 2016).

Schedule 6

Disulfiram except when included in Schedule 4 for therapeutic use

Schedule 6 chemicals are described as 'Substances with a 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'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2016).

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’); and
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

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):

- Xn; R22 (acute toxicity)
- Xn; R48/22 (repeat oral toxicity via oral route)
- Xi; R43 (sensitisation)

Exposure Standards

Australian

The chemical has an exposure standard of 2 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica):

TWA

- The TWA is 2 mg/m^3 in different countries such as Argentina, Canada, China, Colombia, Dubai, Italy, Mexico, New Zealand, Nicaragua, Norway, Peru South Korea, US (Alaska, Hawaii, Michigan, Minnesota, North Carolina, Tennessee and Vermont) and Uruguay.

Short term exposure limit (STEL)

- The STEL is 2–5 mg/m^3 in different countries such as the US (Washington and Alaska) and Argentina.

Health Hazard Information

Tetraethylthioperoxydicarbonic diamide, also known as disulfiram (CAS No. 97-77-8), has similar toxicological activity to tetramethylthioperoxydicarbonic diamide, also known as thiram (CAS No. 137-26-8). Disulfiram and thiram have identical metabolism pathways; the metabolites differ by two methylene (i.e. –CH_2–) groups. Both chemicals have relatively similar physicochemical properties; however, disulfiram has higher lipophilicity. Therefore, in the absence of hazard data for disulfiram, information for thiram was used to read across the hazards.

Toxicokinetics

Disulfiram blocks aldehyde dehydrogenase (ALDH) in the liver—responsible for removing the toxic metabolite of ethanol, acetaldehyde. It can also block the enzyme dopamine beta (β)-hydroxylase which is responsible for converting dopamine to noradrenaline causing an increase of dopamine in the brain (Pratt-Hyatt et al., 2010; NCCMH, 2011). Following oral administration, the chemical has been reported to be rapidly absorbed and distributed in the body. During metabolism, reduction cleaves the disulfide (S-S) bond, creating two molecules of diethyldithiocarbamate (DDC). Three metabolites of the chemical have been identified including DDC, carbon disulfide, and a glucuronide conjugate of DDC (DDC-glucuronide). The metabolite DDC has been reported to undergo further metabolism by the cytochrome CYP2E1 enzyme to yield a highly reactive intermediate that ultimately deactivates the enzyme (Pratt-Hyatt et al., 2010). The chemical is excreted in the urine as DDC and DDC glucuronide, and in exhaled air as carbon disulfide (REACH a).

Male Sprague-Dawley (SD) rats (n=3/group) were orally and intraperitoneally (i.p.) dosed with 7 mg/kg bw of radiolabelled chemical in 0.5% methyl cellulose. Groups were euthanised after 0.5, 2, 4, 6, 12, 24 or 48 hours. The chemical was reported to be rapidly absorbed (after oral and i.p. administration) and metabolised to DDC-glucuronide and inorganic sulfate. Radioactivity was observed in the kidney, pancreas, liver and gastrointestinal tract (GIT). After 24 hours, 20% of the dose was excreted in the faeces (7%) and breath as CS_2 (12%). Of the remaining radiation dose, 93% was accounted for after 48 hours. After i.p. injection and oral administration, maximum plasma concentrations were reported between 30 minutes and 1 hour and between 4 and 6 hours, respectively (REACH a).

Rats (strain, number and sex not specified) were orally treated with a single dose of the chemical at 25 or 250 mg/kg bw. Approximately 90% of the dose was absorbed, of which the metabolite DDC was identified in the gastrointestinal tract (GIT). The chemical and its metabolite were reported to be distributed throughout the liver, kidney and muscle (REACH a).

In a study conducted in three human volunteers (sex not reported), the chemical was orally administered as a single dose of 200 mg. Carbon disulfide (0.6 µg/mL) and DDC (0.2–1.0 µg/mL) were found in the blood samples collected 10–12 hours after administration. Over 90% of the dose was excreted in the urine as DDC and DDC-glucuronide after 3 days of administration (REACH a).

Acute Toxicity

Oral

Based on a weight of evidence from the available animal studies, the chemical is considered to be harmful via oral administration. This supports the current classification as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia).

In a study conducted in SD rats (n=10/sex/dose) the chemical in corn oil was orally administered at doses of 500, 650, 845, 1000, 1300, 1700, 2200, 2860, 3850 and 5000 mg/kg bw, and the animals were observed for 14 days. Mortality was reported 1–7 days post-treatment at doses ≥ 1000 mg/kg bw. At 650 and 845 mg/kg bw, slight motor ataxia was observed. The median lethal dose (LD50) was determined to be 1860 and 1090 mg/kg bw in males and females, respectively (REACH a).

In another study, the LD50 value in rats (number, strain and sex not specified) was reported to be 500 mg/kg bw. Ataxia, hypothermia and paralysis were reported after dosing. No further details were provided (REACH a).

In SD rats (n=5/sex/dose), the chemical in corn oil was administered via gavage at doses of 2500, 2606, 5200 or 7500 mg/kg bw and observed for 14 days. Signs of toxicity included ataxia, tremors and an abnormal gait. The LD50 value was determined to be 4573 mg/kg bw in females and >5200 mg/kg bw in males (REACH a).

The LD50 value from combined exposure to the chemical and alcohol was reported to be 650 mg/kg bw in rabbits (number, strain, sex not specified) (REACH a).

Dermal

The chemical has low acute dermal toxicity based on results from animal tests following dermal exposure. The LD50 value in rats was >2000 mg/kg bw.

New Zealand White (NZW) rabbits (n=5/sex) were treated with 2000 mg/kg bw of the chemical in saline, occlusively, for 24 hours. Erythema was observed in several animals up to 48 hours after dosing. A pathological examination revealed one male and two females with off-white fibrous tissue, and a marbled appearance of the hepatic lobes. Two out of the three animals were reported to have hard, yellow foci on all the lobes of the liver and pale colouration of the kidneys. One out of the three animals had an area of green necrotic hepatic tissue. Tapeworm cysts were found in these animals. The LD50 value was determined to be >2000 mg/kg bw (REACH a).

Inhalation

No data are available for the chemical. However, thiram is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in the HSIS (Safe Work Australia). The available data from the analogue chemical is applicable to the chemical warranting hazard classification.

Median lethal concentration (LC50) values of 3.46 and <5.04 mg/L/4-hours were reported in female and male SD rats, respectively, following exposure to thiram as an aerosol (combined LC50 for rats = 4.42 mg/L/4-hours) (REACH b).

Corrosion / Irritation

Skin Irritation

Based on the available animal studies, the chemical is not irritating to the skin.

In a study conducted in NZW rabbits (n=6; sex not specified), the chemical (500 mg; 3 M) was applied under an occlusive patch to the shaved skin for 4 hours. The animals were observed 1, 24, 48 and 72 hours, 7 and 14 days after application. The mean irritation score was reported to be 0.13/8, indicating minimal skin irritation (REACH a).

Rabbits (NZW; n=3/sex) were treated with the chemical (500 mg in saline; concentration not specified) to abraded skin under an occlusive patch, for 24 hours. The animals were observed 1, 24, 72 hours and 7 days after treatment. The mean erythema score was determined to be 0.25 over 24–72 hours; and irritation was fully reversible after three days. The mean oedema score was 0 after 24–72 hours (REACH a).

Eye Irritation

The chemical was reported to slightly irritate the eyes. In the absence of more comprehensive information, classification for eye irritation is not warranted.

Rabbits (NZW; n=3/sex) were treated with a single dose of the neat chemical to the unrinsed eye for 24 hours. The following scores were determined 24 – 72 hours after treatment:

- Overall irritation score was 4.2/110—fully reversible within 7 days.
- Mean cornea score was reported to be 0/4.
- Iridial scores in two animals were 0.32/2—reversible within 48 hours.
- Conjunctival scores (sum of redness, chemosis and discharge) were given as 16/20; 2.66/20; 4/20; 3.33/20; 3.33/20 in five animals, respectively, after 24 hours and reversed within 72 hours–7 days (REACH a).

In a study conducted in NZW rabbits (n=6; sex not specified), neat chemical (100 mg) was applied to the unwashed eye for 24 hours and observed at 24, 48, 72 hours and 7 days after treatment. Irritation scores for the cornea (0.17/4), iris (0.17/2), conjunctivae (0.94/3) and chemosis (0.67/4) were determined over the period 24–72 hours after treatment. All effects reversed within 7 days (REACH a).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). Limited data (see **Observation in humans**) are available for the chemical; however, data for thiram (CAS No. 137-26-8) supports this classification.

In a split adjuvant test for skin sensitisation (US EPA OPP 81-6), female Dunkin-Hartley guinea pigs (n=10 control and n=20/test group) were induced epicutaneously with thiram at 25 % (w/w in petrolatum) and challenged epicutaneously (timing not available) with the same concentration. During the challenge phase, clinical observations including red spots and, moderate and diffuse skin reaction were reported in 8/20 animals at 24 hours and in 6/20 animals at 48 hours (REACH b).

Observation in humans

Positive reactions were reported in human (number and sex not specified) subjects after exposure to the chemical as "dry material". However, no positive reactions were observed when the chemical was formulated into rubber products (REACH a).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘danger of serious damage to health by prolonged exposure if swallowed’ (Xn; R48/22) in HSIS (Safe Work Australia). Limited animal studies are available for the chemical. However, human data (see **Observation in humans**) available for this chemical supports this classification.

In a study conducted in Fischer 344 (F344) rats (n=5/sex/dose), the chemical was administered in diet at concentrations of 0, 1500, 1100, 3200, 4600 or 6800 ppm (equivalent to 75, 110, 160 or 340 mg/kg bw/d) for seven weeks. Mortality was reported in the high dose group (one male). There was a linear decrease in body weights, with 50% reduction in the high dose group, compared to the control. Based on body weight measurements, the lowest observed effect level (LOEL) was determined to be 75 mg/kg bw/d (REACH a).

Dermal

No data are available for the chemical. However, a subacute study is available for the structurally related chemical, thiram (CAS No. 137-26-8). The lowest observed adverse effect level (LOAEL) available from a 21–22 day rabbit study (1000 mg/kg bw/d), identifies that thiram is not considered to cause serious damage to health from repeated dermal exposure. Considering that the lipid solubility is much lower for thiram compared to disulfiram, systemic toxicity from repeated dermal exposure to the chemical cannot be ruled out.

Rabbits (NZW; n=5/sex/dose) were treated with thiram at doses of 0, 100, 300 or 1000 mg/kg bw, under occluded patches for 6 hours/day for 21 (males) or 22 (females) consecutive days. No deaths occurred in any dose groups. Slight to well-defined erythema with or without oedema was reported in all dose groups. Reduced bodyweight gain was observed in females at the highest dose. Histopathological examinations revealed minimal generalised or focal acanthosis (thickening of the skin) of the epidermis in all dose groups. The LOAEL was determined to be 1000 mg/kg bw/d (REACH b).

Inhalation

No data are available.

Observation in humans

Several case studies have indicated that repeated oral exposure to the chemical through medication at doses ranging from 100–400 mg/day can lead to severe drug reactions, especially when subjects were exposed to alcoholic substances.

Chronic alcoholic patients (n=9–33 treated; n=24 control; sex not specified) were treated with 125 or 250 mg of the chemical for one, three or six months. Patients treated with 250 mg showed a significant decline in peripheral nerve function; no significant electrophysiological abnormalities were reported (HSDB).

Six cases of adverse outcomes in patients continuing to use alcohol have been reported. In all cases, the patients received treatment of 200–400 mg/day of disulfiram. All patients died. Symptoms of toxicity include fatigue and abdominal distension; fever, anorexia, and vomiting; jaundice (a yellowish or greenish pigmentation of the skin and whites of the eyes due to high bilirubin levels). At necropsy, liver weights ranged from 500–2000 g; the surface was smooth with a few regenerating nodules. Microscopic examination of the liver showed that the lobular architecture was disturbed. There was extensive fibrosis and liver cell necrosis; proliferation of bile ducts and liver cell necrosis (Ranek et al., 1997).

A self-employed artist who was given treatment with disulfiram (100 mg daily) suffered an ongoing feeling of malaise with symptoms including nausea, palpitations, numbness of the head and chest discomfort. Physical examinations and serum biochemistry revealed that alcohol and drugs were not consumed; however, an elevated urinary acetone concentration was reported indicating solvent absorption. The artist identified that solvents including methylated spirits, spray paints, spray glue and metal polishes are used in the artworks, with exposure of 12 hours/day, 7 days/week. The symptoms experienced by the artist were considered to be from the interaction of disulfiram with ethanol (Ehrlich et al., 2011).

Genotoxicity

Based on the available data, the chemical is expected to have some genotoxic potential. In addition, the analogue chemical, thiram, was also considered to have some genotoxic potential (See NICNAS report on thiram—CAS No. 137-26-8). Therefore, the chemical is recommended to be classified as a Category 3 mutagen.

In vitro

In vitro genotoxicity studies showed both positive and negative results for the chemical:

- negative for DNA damage/repair in rat hepatocytes tested at concentrations up to 500 µg/L (REACH a);
- negative in a bacterial reverse mutation assay with *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA1538 with and without metabolic activation tested at concentrations up to 5000 µg/plate (REACH a);
- positive in a bacterial reverse mutation assay in *S. typhimurium* strains TA100, TA98 and TA1538 with and without metabolic activation tested at concentrations ≥20 µg/plate (REACH a); and
- positive in a mammalian cell gene mutation assay in mouse lymphoma L5178Y cells tested at concentrations ranging from 0–4 µg/mL without metabolic activation. It was reported that the experiment 'failed to meet quality control thus the results were ambiguous' (REACH a).

In vivo

Male mice (strain not specified; n=5/group) were administered the chemical at doses of 200, 400 and 800 mg/kg bw by oral intubation. A statistically significant increase in the number of sister-chromatid exchanges (SCEs) at the highest dose (800 mg/kg bw) was reported in mouse bone marrow cells. In spermatogonial cells, statistically significant increases in the number of SCEs were reported in all three doses tested. The results indicated a genotoxic response (Madrigal-Bujaider et al., 1999).

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

Rats (F344; n=50/sex/dose; 20 control) were administered with the chemical in diet at concentrations of 0, 300 or 600 ppm (equivalent to 15 or 30 mg/kg bw/d) for 107 weeks. Mortalities and neoplastic changes in treated groups were not dose-dependent and were comparable to controls. The NOAEL was determined to be 600 ppm (REACH a).

Mice (B6C3F1; number and sex not specified) were administered the chemical daily in diet at concentrations of 500 or 2000 ppm (equivalent to 25 or 100 mg/kg bw/d) for 108 weeks. Females in all dose groups showed treatment-related incidences of alveolar/bronchiolar adenomas or carcinomas. However, the statistical significance of these results were ambigous. Under the test conditions, the potential for carcinogenicity is not established (REACH a).

The International Agency for the Research of Cancer (IARC) has classified the chemical as 'Non classifiable as to its carcinogenicity to humans' (Group 3), based on inadequate evidence for carcinogenicity in humans and in experimental animals (IARC, 1976).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not show specific reproductive or developmental toxicity. The observed developmental effects were secondary to maternal toxicity.

Pregnant CD-1 Swiss mice (n=50 female) were dosed with the chemical at 245 mg/kg bw/d via gavage on days 6–13 of gestation. Toxic effects were not observed in the dams based on litter size, birth weight, neonatal growth and survival of pups (HSDB).

Guinea pigs (number, strain and sex not provided) were treated daily with 125 mg/kg bw/d of the chemical in diet on days 17–19 or 19–21 of pregnancy. Brain weights were reduced in the offspring of dams dosed during days 19–21 of pregnancy (HSDB).

Rats administered 100 mg per day of the chemical from day 3 of gestation had 88% resorptions on day 13 (HSDB).

In a study conducted on the analogue, thiram (CAS No. 137-26-8), NZW rabbits (n=4/sex/dose) and SD rats (n=6/sex/dose) were administered the chemical via gavage at doses of 0, 1, 3, 5, 7.5, 10, 20, 40 or 80 mg/kg bw/d, on days 6-19 of gestation. Maternal toxicity was reported at concentrations =10 mg/kg bw/d with clinical signs of toxicity including decreased body weight. At the two highest doses, all the animals died; at 20 mg/kg bw/d, one animal died; at 10 mg/kg bw/d a transient decrease in body weight gain was reported. Foetotoxic effects were reported at 20 mg/kg bw/d in rabbits: including litter resorption and increases in post-implantation loss. These effects were also seen in rats at =40 mg/kg bw/d (REACH b).

Other Health Effects

Neurotoxicity

Neurotoxic effects were observed in humans and rats following acute or repeated oral exposure to the chemical.

Three case studies have reported symptoms of basal ganglia disease after treatment with disulfiram. Symptoms of toxicity include parkinsonism, blepharospasm (involuntary tight closure of the eyelids) and pseudobulbar palsy (the inability to control facial movements). One of the three patients did not show signs of motor disorder; however, he exhibited a loss of drive or psychic self-activation—resembling symptoms of schizophrenia (associated with basal ganglia lesions) (Laplane et al., 1992).

Male Wistar rats and SD rats were administered 220–580 mg/kg (equivalent to 11–29 mg/kg bw/d), daily for one or three weeks. The ileum was isolated from each rat and analysed for acetylcholine (ACh) and serotonin (5-HT) activity. Responses to 5-HT were decreased in the treated groups compared to the control. A decrease in the histochemical reactivity for ACh esterase was observed in the nerve plexus of the gut wall—indicating nerve damage (Savolainen et al., 1984).

Endocrine Disruption

The chemical is considered to affect the ALDH enzyme. The ALDH enzyme has been shown to regulate osteoblast function which may affect the endocrine system (Mittal et al., 2014).

Disulfiram has been reported to have 'the most potent cytotoxic effect on osteoblasts'. In an in vivo study, rat calvarial osteoblasts were treated with disulfiram, acetaldehyde, GSH or GSH + disulfiram for 24 hours. The chemical was reported to diminish osteoblast proliferation and induce apoptosis. A significant decrease in total GSH content in osteoblasts was observed, leading to oxidative stress and apoptosis (Mittal et al., 2014).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (skin sensitisation).

The chemical may have some genotoxic potential, can also cause harmful effects following acute inhalation exposure, and harmful effects including neurotoxicity, following acute and repeated oral exposure.

Public Risk Characterisation

Although domestic industrial use in Australia is not known, the chemical is reported to be used as a preservative in paints overseas.

The chemical is currently listed on Schedule 6 of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP 2016) except when included in Schedule 4 for therapeutic use.

The critical health effects identified above are not expected to occur from use of the chemical as a preservative in paint. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

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

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

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, 2016).

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)*	May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)

[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 instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and inhalation 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 that could 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 help meet 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.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

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Last update 25 November 2016

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