Furan, tetrahydro-: Human health tier II assessment

17 May 2013

CAS Number: 109-99-9

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.

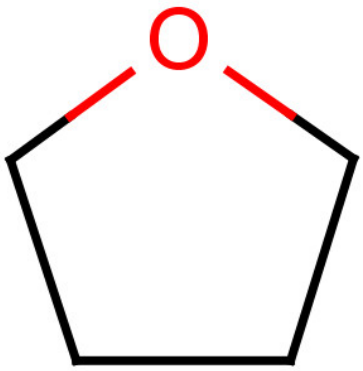
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tetrahydrofuran (THF) 1,4-epoxybutane butylene oxide diethylene oxide cyclotetramethylene oxide
Structural Formula	
Molecular Formula	C4H8O
Molecular Weight (g/mol)	72.11
Appearance and Odour (where available)	Colourless clear liquid.
SMILES	C1CCCO1

Import, Manufacture and Use

Australian

The chemical was reported during the 2006 High Volume Industrial Chemicals List (HVICL) compilation with a total reported introduction volume of less than 1000 tonnes.

No specific Australian uses have been identified.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances in Preparations in Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic use including:

- in cleaning agents;
- in adhesives; and
- in stain removers.

The chemical has reported commercial use including:

- as a solvent in the production of high polymers such as polyvinyl chloride, bulk pharmaceutical manufacturing, synthetic perfumes, printing inks, dyes, adhesives, lacquers, and other coatings;
- as a reagent for chemical reactions;
- in the synthesis of butyrolactone, succinic acid and 1,4-butanediol diacetate;
- in the synthesis of motor fuels;
- in PVC cement up to 75 %;
- in the fabrication of articles for packaging, transporting, or storing of food (if residual amount does not exceed 1.5 % of the film); and
- in metal working fluids.

The chemical has reported site-limited use including:

- as an intermediate for manufacturing unvulcanised rubber, resins and plastics.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xi; R36/37 (irritation).

Exposure Standards

Australian

The chemical has an exposure standard of 295 mg/m³ (100 ppm) Time Weighted Average (TWA).

International

The following are identified (Galleria Chemica):

An exposure limit (OEL, TWA, STEL, PEL or STV) of 147–590 mg/m³ (50-200 ppm) in different countries such as USA, Canada, Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed via oral, dermal and inhalation routes. It is also systemically distributed and rapidly metabolised. The chemical is proposed to be oxidatively metabolised to succinic acid (an intermediate in the citric acid cycle). The chemical undergoes a series of reactions leading to the release of carbon dioxide. Intermediate metabolites (γ-hydroxybutyric acid) can be converted to neurotransmitters (γ-aminobutyric acid). Enzymes such as cytochrome P450 (CYP450), paraoxonase (PON1) and dehydrogenases may be involved in metabolising the chemical (US EPA, 2012).

Rapid excretion is observed in inhalation studies in rats. Human volunteer studies also suggested that the chemical is rapidly excreted in exhaled air (as carbon dioxide, volatile organics or possibly unmetabolised chemical) and urine (US EPA, 2012).

Acute Toxicity

Oral

The chemical is of low acute oral toxicity.

One study reported a rat oral LD50 of 1650 mg/kg bw (no details available) (ChemIDplus), while at least five other studies reported LD50 > 2000 mg/kg bw (2050 − 6210 mg/kg bw) (Galleria Chemica).

The oral LD50 is 2300 mg/kg bw in mice and guinea pigs; and 3120 mg/kg bw in rabbits (ChemIDplus; Galleria Chemica).

Dermal

No data are available.

Inhalation

The chemical is of low acute inhalation toxicity.

Rat inhalation LC50 = 80975 ppm/1-h; 62000 ppm/2-h (HSDB); 21000 ppm/3-h; 53.9 mg/L/4-h (18271 ppm) (OECD, 2000). The effects reported include nausea or vomiting, and respiratory stimulation (ChemIDplus).

Mouse inhalation LCLo (lowest published lethal concentration) = 24000 mg/m³/2-h. The effects reported in mice are somnolence (general depressed activity), dyspnoea and muscle weakness (ChemIDplus).

Observation in humans

A number of occupational exposure studies in humans exposed to the chemical (concentrations not available) in the presence of other chemicals, showed effects on the nervous system and the liver (US EPA, 2012).

Lowest published toxic concentration (TCLo) for humans is reported as 25000 ppm (ChemIDplus).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The available data support this classification.

In rats, structural changes in the respiratory tissue and respiratory tract irritation were observed following inhalation. The effects observed included congested mottled lungs, oedema and haemorrhage in lungs and bronchi. Sprague Dawley rats exposed to vapours at 200 ppm (4 hours/day, 5 days/week for 12 weeks) displayed signs of mild irritation on the nose, ears, and eyelids. Irritation increased with the exposure concentration. At 5000 ppm, animals displayed intense salivation, teary eyes, and bleeding from the nose (US EPA, 2012).

Skin Irritation

Although the skin irritation scores are not available, the available studies indicate the chemical as a mild to moderate, or strong skin irritant. Therefore, the chemical is considered a skin irritant and a hazard classification is warranted.

The chemical was reported to irritate skin (OECD, 2000; EU IUCLID, 2000).

When tested in 10 guinea pigs (intact skin), the chemical at 100 % concentration produced mild to moderate irritation. When tested on abraded skin, the chemical produced mild irritation. At 50 % concentration, the chemical produced strong irritation on both intact or abraded skin (irritation scores or the diluent details are not available) (HSDB).

Administering 1 mL of the concentrated chemical on rabbit skin caused reddening, and the skin later thickened and sloughed off (US EPA, 2012).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study in rabbits, the chemical was found to cause oedema of the eyelid, vasodilation (widening of blood vessels) and corneal opacity (US EPA, 2012).

The chemical is reported to irritate the eyes at vapour levels of 100−200 ppm in animals (HSDB).

Observation in humans

Irritation was observed when the chemical was applied to the skin of six people (occlusive and non occlusive) (US EPA, 2012).

Sensitisation

Skin Sensitisation

No data are available.

Observation in humans

There was no contact dermatitis or sensitisation observed in 196 volunteers exposed to the chemical dermally (exposure concentration not reported) (US EPA, 2012).

Repeated Dose Toxicity

Oral

There are no long term, repeat dose oral toxicity studies. Based on the limited data available, the chemical is not considered to cause serious damage to health by repeated oral exposure.

Mortality, body weight loss, stomach and liver lesions, and nephrosis were observed in rats exposed to the chemical at high oral doses of 1780, 2225 or 2670 mg/kg bw/day for 2 − 4 weeks. In another oral study, rats (F344) were exposed to 0, 125 or 2000 mg/kg bw/day for > 14 days (duration of exposure not specified). During the first 14 days, increased mortality and body weight loss (20 % in males and 13 % in females) occurred at the highest dose. Acute inflammation of the trachea and serofibrinous (containing serum and fibrin) exudate in tracheal lumen were observed in all treated groups. Increased lung weight, hyperplasia, hyperkeratosis and inflammation of the epithelium and mucosa of the forestomach were also observed in all treated groups (EU IUCLID Dataset, 2000).

In mice, the only effect reported in a 49 days repeat dose gavage study was decreased liver weight in all treated groups at 63, 125, 250, 500 or 1000 mg/kg bw/day. This effect was significant at 250 and 500 mg/kg bw/day, compared with the control groups (EU IUCLID Dataset, 2000).

Dermal

No data are available.

Inhalation

Based on the data available, the chemical is not considered to cause serious damage to health by repeated inhalation exposure.

Signs of narcosis, skin and mucosal irritation were the only effects observed in rats that inhaled doses of 10 − 193 mg/L (3333 − 64333 ppm) for 2 − 6 hours/day up to 30 days.

Rats (F344/N) were exposed to the chemical at 0, 0.2, 0.6, 1.8, 5.4, or 15 mg/L (0, 66, 200, 600, 1800 or 5000 ppm), 6 hours/day, 5 days/week for 13 weeks. Toxic effects on the central nervous system (e.g. lack of muscle coordination) were observed at 15 mg/L. At necropsy, significant local irritation symptoms and morphological damage of the mucous membrane in the nasal and tracheal mucosa; histopathologic lesions in the lung (papillar hyperplasia), liver and respiratory tract; renal lesions; significant changes of the relative organ weights; and muscular chronaxy (minimum time to elicit a response) were also observed at 15 mg/L. The no observed adverse effect concentration (NOAEC) was 5.4 mg/L (1800 ppm), as the only finding at this dose level was nasal and ocular secretions in one animal (out of 20) (EU IUCLID Dataset, 2000; OECD, 2000).

In another study, mice (B6C3F1) were exposed to the chemical at 0, 0.2, 0.6, 1.8, 5.4, or 15 mg/L (0, 66, 200, 600, 1800 or 5000 ppm), 6 hours/day, 5 days/week for 13 weeks. Mice receiving the highest dose showed mortality, inflammation of the urinary tract and toxic effects on the central nervous system (CNS). Significantly reduced thymus and spleen weights; enhanced liver weights; minimal to mild centrilobular hepatocytomegaly (enlargement of hepatocytes); atrophy of the uterus and degeneration of the inner cortex of the adrenal gland were also observed at this highest dose. Toxic effects on the CNS and minimal to mild centrilobular hepatocytomegaly were also seen at 5.4 mg/L. Significantly reduced thymus weights and enhanced liver weights were observed from 1.8 mg/L. The NOAEC was 0.6 mg/L, as the only finding at this level was nasal and ocular secretions (1/20) (EU IUCLID Dataset, 2000).

Genotoxicity

Based on the data available, the chemical is not genotoxic.

The chemical was not genotoxic in three in vitro genotoxicity studies (two Ames assays (one according to OECD TG 471) with *Salmonella typhimurium* strains and a reverse mutation assay (OECD TG 471) with *Escherichia Coli* strain WP 2 uvrA), with and without metabolic activation. Another reverse mutation assay with *E. Coli* strain WP 2 uvrA gave positive results at 1 µmol/L, without metabolic activation (US EPA, 2012; OECD, 2000).

Negative results were observed in two in vivo genotoxicity studies: an unscheduled DNA synthesis assay in rat hepatocytes (no details on concentrations tested) and a mammalian bone marrow chromosomal aberration test in male mice treated with a single intraperitoneal injection (with up to 2000 mg/kg bw/day) (US EPA, 2012; OECD, 2000).

In a sister chromatid exchange (SCE) assay in male mice, although equivocal results were reported in the initial test, the repeated tests gave negative results in mouse bone marrow cells (with doses up to 2500 mg/kg bw). In a micronucleus assay with male and female mice with doses up to 5000 ppm (inhaled 6 h/day for 4 days/week for 14 weeks), equivocal results were reported for males, but the highest effect observed was within the historical control levels. Females showed negative results (REACH, 2009; OECD, 2000).

Carcinogenicity

The chemical showed some evidence of carcinogenicity in rodents, when exposed through inhalation. However, the evidence is not conclusive as to the human relevance of the observed tumours and it is not possible to determine the need for classification at this level of assessment (IMAP Tier II).

Two-year carcinogenicity studies in rats and mice are available (NTP, 1998). Groups of 50 rats (F344) and mice (B6C3F1) were exposed to the chemical at 0, 200, 600 or 1800 ppm for 6 hours/day, 5 days/week for 105 weeks. At 600 ppm and 1800 ppm, the chemical produced some evidence of carcinogenicity in male rats (increased incidences of renal tubule adenoma or carcinoma; 1/50, 1/50, 4/50 and 5/50 at 0, 200, 600 and 1800 ppm, respectively). The incidences of adenoma and carcinoma combined in 600 and 1800 ppm male rats were not statistically significant, but exceeded the historical control range (NTP, 1998). In the 2-year study (NTP, 1998), there was clear evidence of carcinogenicity in female mice, with increased incidences of hepatocellular neoplasms (hepatocellular adenoma: 12/50, 17/50, 18/50, 31/48; hepatocellular carcinoma: 6/50, 10/50, 10/50, 16/48; hepatocellular adenoma or carcinoma: 17/50, 24/50, 26/50, 41/50 at 0, 200, 600 and 1800 ppm, respectively). There was no evidence of carcinogenic activity in female rats or male mice exposed to the chemical at 200, 600 or 1800 ppm (NTP, 1998;

OECD, 2000 and US EPA, 2012). The NTP (1998) stated that the lower incidence of hepatocellular neoplasms in the male mice at 1800 ppm was due to the low survival rate at this dose group (12/50, compared with 32/50, 31/50 and 28/50 for 0, 200 and 600 ppm groups, respectively). The survival rate of female mice at 1800 ppm was 32 out of 50.

NTP (1998) also stated that the liver is the major site for carcinogenicity for the structurally related chemicals furan and 1,4-dioxane. 1,4-Dioxane was carcinogenic in rats and guinea pigs when administered by gavage.

The presence of kidney lesions in male rats in the carcinogenicity study was described as a possible result of degenerative hyaline droplet nephropathy that progressed to neoplasm formation. This is stated as a species and gender specific lesion, possibly mediated through non-genotoxic modes of action (Swenberg, 1993 cited in NTP, 1998). However, another 12 week inhalation study reported the kidney as the target organ for toxicity of this chemical (Kawata and Ito, 1984 cited in NTP, 1998).

By evaluating the NTP (1998) studies on carcinogenicity, the US EPA (2012) stated that, 'Under the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for THF provides "suggestive evidence of carcinogenic potential" by all routes of exposure'.

In a dermal study, 0.1 mL of the chemical (89 mg/mouse) was applied to the skin of mice (n = 25), twice a week for 25 weeks. Following completion of the exposure, 11 mice survived to 17.5 months. At necropsy, benign tumours were observed in four mice (details not available) (EU IUCLID Dataset, 2000; HSDB).

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies are available in both rats and mice. Based on the data available, the chemical is not considered a reproductive or developmental toxin.

In a developmental toxicity study, pregnant groups of rats (Sprague Dawley) and mice (Swiss CD-1) were exposed to the chemical vapour at 0, 600, 1800 or 5000 ppm (0, 1770, 5310 or 14750 mg/m^3), 6 hours/day during the gestation days (GD) 6 to 19 (rats) or GD 6 to 17 (mice) (OECD, 2000; US EPA, 2012). Rats showed lethargy and a reduction in mean body weight at the highest dose. No symptoms of toxicity were observed in rats/dams that received other doses. Mean foetal body weights in the highest dose group were significantly less than those in the control group. There were no effects on implantations or malformations in rat foetuses. Based on decreased maternal and foetal weights, a NOAEL of 1800 ppm (5310 mg/m^3) is reported for rats (US EPA, 2012). Seven treated mice died during the first six days of exposure in the highest dose group. Mean body weights and uterine weights of pregnant mice in the two high dose groups were significantly less than those of the controls at the end of the study. In the same dose groups, reduction in the percentage of live pups per litter, and delayed ossification of the sternum were observed. Survived pregnant mice at the highest dose group had litters with high resorptions, but there were no effects on implantations, foetal sex ratio or foetal abnormalities. Based on the gravid uterine weights in dams and foetal survival, the NOAEC was reported as 600 ppm (1770 mg/m^3) in mice (US EPA, 2012).

No effects on reproductive performance was observed in a two-generation oral study in rats. The NOEL for reproductive toxicity is 300 mg/kg bw/day (OECD, 2000).

Other Health Effects

Neurotoxicity

Based on the limited data available, the chemical may cause transient sedation but it is not considered a neurotoxin. However, the chemical is reported as a depressant of the central nervous system by the US Occupational Safety and Health Administration (OSHA).

In a neurotoxicity study (OECD, TG 413), Sprague Dawley rats were exposed (via inhalation) to the chemical at 0, 1.5, 4.5 or 9 mg/L (0, 500, 1500 or 3000 ppm), 6 hours/day, 5 days/week for 14 weeks. At high doses (4.5 or 9 mg/mL), rats showed decreased startle responses to an auditory alerting stimulus, indicating possible transient sedation. There were no neurological effects. The chemical, up to 3000 ppm, did not produce any persistent or cumulative effects on the nervous system structure or function. The no-observed effect concentration (NOEC) was 500 ppm (1.5 mg/L) (Malley et al., 2001).

Several acute inhalation studies in animals exposed to the chemical (once only exposure ranging from 30 minutes to several hours) indicated CNS toxicity. The symptoms of CNS toxicity reported were sedation, coma, altered respiration, and decreased response to external stimuli (US EPA, 2012).

Risk Characterisation

Critical Health Effects

The main critical effects to human health are irritation to the eyes, skin and respiratory system from short term exposure. Rodent carcinogenicity data indicate that even if the observed effects are relevant to humans, the exposures leading to these tumours are outside the range considered relevant for long term human exposure, particularly as the irritant concentrations in rodents are lower than the concentrations at which tumours were observed. Transient neurotoxic effects may also be possible from short term exposure.

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemical is reported to be used in domestic products overseas, including in the fabrication of articles for packaging or storing of food (if the residual amount does not exceed 1.5 % of the film), in cleaning agents, adhesives and stain removers. There are no restrictions on the use of this chemical in Australia.
Considering the potential health effects, there is a concern in the use of this chemical as an ingredient in domestic products. Exposure of the public is expected to be limited by the possible irritant effects of the chemical (which occur at low doses compared with the doses that produced tumours in rodents). It is therefore not expected that long term exposures will cause carcinogenic effects arising from concentrations used in domestic/consumer products.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The control measures to protect workers from possible irritation effects will be adequate to protect them from potential long term effects, as the doses which caused long term effects are lower than the doses which caused irritation effects in rodents. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend the chemical to be risk managed for public safety from its potential use in domestic products through scheduling, and occupational health and safety through classification and labelling. Further assessment (Tier III) is recommended to examine the need for a hazard classification for potential carcinogenicity of the chemical.

Regulatory Control

Public Health

The chemical is recommended for scheduling to mitigate risk from its use in domestic products. Matters to be taken into consideration include the irritation effects, potential for carcinogenicity and transient neurotoxic effects.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

[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

The products containing the chemical should be used according to the label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular 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 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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