Ethanol, 2-butoxy-, phosphate (3:1): Human health tier II assessment

25 November 2016

CAS Number: 78-51-3

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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.

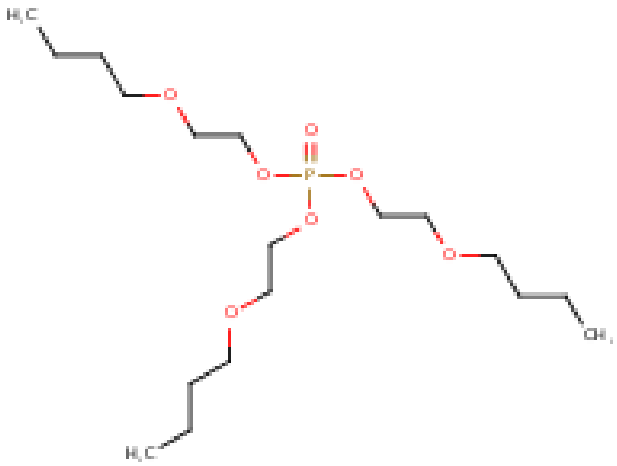
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tri(butoxyethyl) phosphate TBOEP TBEP 2-butoxyethanol phosphate TBXP
Structural Formula	
Molecular Formula	C18H39O7P
Molecular Weight (g/mol)	398.47
SMILES	C(CCC)OCCOP(=O)(OCCOCCCC)OCCOCCCC

Import, Manufacture and Use

Australian

The chemical referred to as TBOEP in this assessment, was reported under previous mandatory and/or voluntary calls for information.

The following domestic uses were identified based on available safety data sheets (SDSs) in Australia:

- cleaning supplies; and
- floor finish products.

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 United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US Household Products Database (US HPD); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and Agency for Toxic Substances & Disease Registry (ATSDR, 2012), World Health Organisation (WHO) Environmental Health Criteria 218 (WHO, 2000), National Toxicology program (NTP); Commission for Environmental Cooperation (CEC, 2015) and Joint Assessment of Commodity Chemicals report (JACC, 1992).

The chemical has reported domestic uses as a component of the following products:

- shoe care;
- cleaning and washing;
- paints, laquers, varnishes; and
- floor polishes.

The chemical has reported commercial uses including in:

- colourants;
- levelling agents; and
- building materials.

The chemical has reported site-limited uses including:

- as a plasticiser or anti-foam agent in synthetic rubber, plastics and lacquers;
- as a solvent and plasticiser in manufacturing of resins and elastomers;
- as surface treatment for paper, cardboard and other non-metals;
- in textile and leather manufacturing; and
- as flame retardant in the manufacture of various consumer products containing rigid plastic.

A number of products formulated to contain TBEOP, including electrical and electronic products, automotive products and textiles (CEC, 2015), are used in domestic settings and TBEOP is commonly detected in indoor dust (de Boer et al., 2016; Cequier et al., 2014).

Restrictions

Australian

No known restrictions have been identified.

International

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

- Switzerland Ordinance of the Federal Department of Home Affairs (FDHA) on articles and materials - Annex 6, List of additives, Part A: evaluated substances with the specific migration limit (SML) of 0.05 mg/kg; and
- United States (US) Toxic Substances Control Act (TSCA) Section 8 (a) - Preliminary Assessment Information Rules (PAIR) - Reporting List and Section 8 (d) - Health and Safety Data Reporting.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS)(Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards were identified (Galleria Chemica).

Temporary Emergency Exposure Limits (TEELs) defined by the US Department of Energy (DOE) for the chemical are reported as:

TEEL-1 = 1.3 mg/m^3; TEEL-2 = 15 mg/m^3; TEEL-3 = 590 mg/m^3.

Health Hazard Information

Toxicokinetics

No specific studies are available on the toxicokinetics of the chemical.

Bis (2-butoxyethyl) phosphate (CAS No 14260-98-1) is considered to be a metabolite of TBOEP (Fromme et al., 2014; Van den Eede et al., 2015). In addition, 2-butoxyethanol (CAS No 111-76-2) is assumed to be a metabolite (WHO, 2000; Sassaki et al., 2011).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw.

In an OECD test guideline (TG) 401 Acute oral toxicity study, Sprague-Dawley (SD) rats (n=5/sex/dos) were treated with a single dose of TBOEP at 2000 mg/kg body weight (bw) by oral gavage. No deaths were reported. The acute oral LD50 was >2000 mg/kg bw in both sexes (REACH).

Additionally, the following oral LD50 values have been reported in rats for the chemical:

- 13,278 mg/kg bw in males (ATSDR, 2012);
- 5,383 mg/kg bw in females (ATSDR, 2012); and
- 3,000 or 4,700 mg/kg bw (sex not specified; WHO, 2000).

Reported signs of toxicity observed include ataxia, laboured breathing, red stains on the nose or eyes, rough coat, soft faeces, urine stains, depression, prostration, and tremors (ATSDR, 2012; WHO, 2000; REACH).

In a non-guideline study, SD rats (n=10/sex/dose) were treated with a single dose of TBOEP at 1000, 1500, 1750, 2000 or 3200 mg/kg bw (females) and 1000, 3200, 6800, 8000 or 9000 mg/kg bw (males). Mortality was not formally recorded, however the number of rats subjected to electrophysiological measurements indicated mortality for females of 7/10 at 1750, 8/10 at 2000, and 9/10 at 3200 mg/kg bw. In males, the mortality was at least 6/10 at up to 8000 and 8/10 at 9000 mg/kg bw (ATSDR, 2012; REACH). This indicates that there is potentially greater TBOEP acute toxicity.

Dermal

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

Dermal LD50 values of >5,000 and 10,000 mg/kg bw were reported for rabbits (WHO, 2000).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure. The median lethal concentration (LC50) in rats is >4 mg/L.

In an OECD TG 403 (Acute inhalation toxicity) study, Wistar rats (n=5/sex/dose) were exposed to measured TBOEP concentrations of 3.3, 3.4 or 6.4 mg/L for 4 hours. No animals died, and no changes or abnormalities were observed in body weight or gross necropsy. At all concentrations, the animals exhibited depressed and irregular respiration, increased salivation, sneezing, unsteadiness and tremor. All symptoms cleared in most animals by nine days or later. The inhalation 4-hour LC50 is reported as >6.4 mg/L (WHO, 2000; REACH).

Other reported LC50 values include:

- >4.43 mg/L in rats (4-hour; WHO, 2000); and

- >20.1 mg/L in rats (1-hour; REACH).

Corrosion / Irritation

Skin Irritation

The chemical is acutely irritating to the skin, but the effects do not warrant hazard classification.

In a study equivalent to OECD TG 404 (Acute dermal irritation/corrosion), New Zealand White (BZW) rabbits (n=3) were treated with 0.5 mL of undiluted TBOEP under a cellulose patch on surgical plaster, covered with a semi-occlusive bandage. After the 4 hour exposure period, any residual test material was removed with warm tap water. Exposure sites were examined at 30-60 minutes, 24, 48 and 72 hours and scored for erythema, eschar and oedema according to the Draize scoring system.Two rabbits showed erythema (mean score 1.66) and slight oedema (mean scroe 0.66) up to 72 hours. All effects were reversible within 14 days (REACH).

In the 21-day dermal toxicity study in NZW rabbits (n=6/sex/dose), the animals were treated 5 days/week for three weeks with TBOEP applications of 0, 10, 100 or 1000 mg/kg bw/day on unabraded dorsal clipped skin. The test sites were occluded for 6 hours after each exposure. No animals died. Slight to moderate erythema was noted up to 72 hours. The skin irritation was dose related and severity progressed over time. Two rabbits showed very slight to slight oedema, with roughness and scaling of the skin up to seven days. All effects were reversible within 14 days. Microscopic observations of the skin (highest dose group) included squamous cell hyperplasia and hyperkeratosis (WHO, 2000; REACH).

The chemical, TBOEP was reported as non-irritating to intact and abraded skin when applied topically to albino rabbits (WHO, 2000). No other details were available.

Eye Irritation

The chemical TBOEP is considered not to be irritating to eyes.

In four studies TBOEP was non-irritating to the eyes of albino rabbits. No study details were available (WHO, 2000).

Observation in humans

A repeat human insult patch test indicated minimal skin irritation. No other experimental details are available (HSDB; REACH).

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser and warrants hazard classification.

In a study performed according to OECD TG 429 (Skin sensitisation: local lymph node assay), CBA female mice (n=4/dose) received TBOEP at 10, 25 or 50 % concentrations in acetone/olive oil (4:1 v/v) vehicle or vehicle alone. Stimulation index (SI) was reported >3 for 25 and 50% concentrations of TBOEP (SI 3.1 and 5.5, respectively), suggesting that the chemical may be a sensitiser (REACH).

In another study, equivalent to OECD TG 406 (Skin sensitisation), Buehler test was conducted in albino guinea pigs (sex not specified). Ten guinea pigs were treated with 0.5 mL of the neat chemical applied to the skin. There were no signs of irritation at 24 or 48 hours after challenge applications suggesting that TBOEP is not a sensitiser (REACH).

The chemical contains a structural alert for binding to proteins as indicated in the profiling functionality of the OECD Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (v.3.4). Additionally, the chemical has a positive prediction for skin sensitisation based on OASIS-TIMES (v.2.27.19); however, the structural parameter is outside the applicability domain of the model.

A weight of evidence analysis of the experimental data (positive result for LLNA) and QSAR modelling indicate that the chemical is likely to be a skin sensitiser.

Observation in humans

A repeat human insult patch test did not indicate skin sensitisation. No other experimental details are available (HSDB; REACH).

In industrial health records, no cases were reported indicating skin (or respiratory) sensitisation effects from exposure to TBOEP either from medical surveillance during 1990-2010 or from available company medical records dating back to the commencement of TBOEP manufacture in 1971

(REACH).

Repeated Dose Toxicity

Oral

Based on the available information, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a study equivalent to OECD TG 408 (Repeated dose 90-day oral toxicity in rodents), SD rats (n=20/sex/dose) were fed diets containing TBOEP at 0, 300, 3000 or 10000 mg/kg for 18 weeks (adult rats). The chemical TBOEP had no effect on body weight or food intake. Increase in serum gamma-glutamyltranspeptidase and decrease in plasma cholinesterase activity were seen in both sexes in the 3000 and 10000 mg/kg groups. Liver weight was increased at the highest dose in both sexes. Mild periportal hepatocellular hypertrophy and periportal vacuolisation was seen in males at two highest doses. The no observed effect level (NOEL) was 300 mg/kg diet, equivalent to appr 15-20 mg/kg bw/day (WHO, 2000; REACH).

In another study equivalent to OECD TG 408, pubertal Wistar rats (n=8/sex/dose) were given a diet containing TBOEP at 0, 300, 3000 or 30000 mg/kg for 14 weeks. Body weight gain was reduced in both sexes at the highest dose. Serum cholinesterase activity was significantly decreased in both sexes at 3000 and 30000 mg/kg, and serum gammaglutamyl transferase activity was significantly increased in both sexes at 30000 mg/kg. Moderate periportal hepatocyte swelling in livers of male rats was seen at the highest dose. The NOEL, based on reduced serum cholinesterase activity, was 300 mg/kg diet (appr 20 mg/kg bw/day) (WHO, 2000; REACH).

In another study equivalent to OECD TG 408, SD rats (n=12/sex/dose) were administered 0, 0.25 or 0.5 mL/kg bw (appr 250 and 510 mg/kg bw/day) undiluted TBOEP on 5 days/week for 18 weeks. During the first week, two high-dose females showed muscular weakness and ataxia; these disappeared by the end of the fourth week. After about 7 weeks, nearly all animals exhibited some signs of toxicity including breathing difficulties, tremors, lacrimation and increased urination. These were reported as treatment related. All treated animals appeared less active, and one female from high dose group died during week 13. Significant increase in serum gammaglutamyltransferase was seen in females at the highest dose. Liver weight was significantly increased (about 20%) in both high- and low-dose groups. Kidney weight was increased by about 20% in both groups and the increase was statistically significant in high-dose groups. Histopathological changes were seen in hearts of males at both doses. The authors concluded that TBOEP may have accelerated the development of focal myocarditis, which is a normal feature of older male SD rats. A NOEL was not ascertained in this study. The lowest observed adverse effect level (LOAEL) in this study was 250 mg/kg bw/day (WHO, 2000; REACH).

In a non-guideline study, SD rats (n=10/dose/sex) were treated with 0, 1, 10 and 100 mg TBOEP/kg bw/day for 14 days. The chemical TBOEP did not have any reported effects on body weight gain, organ weights, haematology or histopathology (REACH).

Dermal

Based on the available information, the chemical is not considered to cause serious damage to health.

In a study equivalent to OECD TG 410 (Repeated dose dermal toxicity: 21/28-day study), NZW rabbits (n=6/sex/dose) received undiluted TBOEP applied to the unabraded dorsal skin at doses of 0, 10, 100, or 1000 mg/kg bw/day, five days a week for three weeks. After each application, the area was covered for six hours. There were no deaths and no adverse clinical signs of toxicity observed in treated rabbits. No adverse systemic toxicity was observed following dosing at 1000 mg/kg bw/day. The no observed adverse effect level (NOAEL) for systemic toxicity was 1000 mg/kg bw/day (ATSDR, 2012; REACH).

Inhalation

No data are available.

Genotoxicity

The chemical TBOEP is considered non-genotoxic.

Mutagenic acitivity of TBOEP was tested in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 at concentrations 0, 50, 100 and 500 µg/plate with and without metabolic activation. TBOEP did not cause any mutagenic response with or without metabolic activation (ATSDR, 2012; REACH).

The chemical TBOEP was not mutagenic in mammalian Chinese hamster ovary (CHO) and mouse L5178Y lymphoma cells with and without metabolic activation (ATSDR, 2012; REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical TBOEP does not show specific reproductive or developmental toxicity.

Reproductive toxicity

The chemical TBOEP has not been tested for effects on fertility, but acute- and intermediate-duration studies in rats reported no gross or microscopic alterations in the reproductive organs of males and females (ATSDR, 2012).

In a previously described non-guideline study (see **Repeat Dose Toxicity: Oral**), no effects were reported on the weight or gross or microscopic morphology of the testes or ovaries in SD rats given TBOEP up to 100 mg/kg bw/day of for 14 days. Similar findings were reported in rats given TBOEP up to 510 mg/kg bw/day via the diet for 18 weeks (ATSDR, 2012; REACH).

This is supported by a recent non-guideline study showing minimal effects of TBOEP on chicken embryos when exposed up to a dose of 45400 ng/g (Egloff et al., 2014).

Developmental toxicity

In a study equivalent to OECD TG 414 (Prenatal developmental toxicity study), female Charles River CD rats were treated by gavage with TBOEP at 0 (corn oil), 250, 500 or 1500 mg/kg bw/day on gestation days (GD) 6 to 15. The study was terminated on GD 20. Treatments had no effect on foetal resorption, foetal viability, post-implantation loss, total implantations or the incidence of foetal malformations. The NOAEL for developmental toxicity was 1500 mg/kg bw/day, the highest dose level tested. Some dams in the 1500 mg/kg bw/day group occasionally exhibited signs of toxicity such as ataxia and lethargy, and had significantly reduced weight gain when compared to controls (ATSDR, 2012; WHO, 2000; REACH).

Other Health Effects

Neurotoxicity

Organophosphate esters are commonly associated with neurological effects. Based on the limited information available for the chemical, the neurotoxicity is not considered to cause serious damage to health.

In a previously described study (see **Repeat Dose Toxicity: Oral**), nerve conduction measurements were made with all rats treated with approximately 250 or 510 mg/kg bw/day of TBOEP at the end of weeks 6, 12, and 18. Significantly reduced conduction velocity in the caudal nerve was measured at 6, 12, and 18 weeks. The absolute refractory period was increased in both males and females by week 18, with males being more sensitive. The relative refractory period was increased in both males and females at 12 and 18 weeks. Morphological changes in sciatic nerves (two days after last dose) included axonal degeneration and demyelination seen in at both doses, with a greater incidence in the high dose animals (5/6) as compared to the low dose animals (3/6). Both myelinated and unmyelinated nerves were adversely affected. No NOAEL was determined in this study. The LOAEL for neurotoxicity was 0.25 mL/kg bw/day (approximately 250 mg/kg bw/day) (REACH).

In an in vitro assay, TBOEP was tested for acetylcholinesterase inhibition using the Ellman method of colorimetric analysis. Acetylcholinesterase inhibition was not dose-dependent and at 10, 100 and 1000 ppm TBOEP was measured at 11.9, 14.3 and 10.8 % respectively. Therefore, TBOEP was concluded not to show neurotoxicity in this test system (REACH).

A non-guideline acute delayed neurotoxicity study was carried out using groups of 20 hens. Dermal or oral (in gelatin capsules) TBOEP doses of 5000 mg/kg bw were administered at the start of the study and again 21 days later. Tri-ortho-cresyl phosphate (TOCP) was used as a positive control. Negative controls were either untreated (dermal study) or given empty capsules (oral study). All hens were treated with 15 mg/kg bw of atropine sulfate three times a day for five days following each dosing. Neurotoxicity was assessed 21 days after the final dose. No treatment-related histological lesions were detected in the brain, spinal cord and peripheral nerves of TBOEP-treated hens. The TBOEP had no effect on neuropathy target esterases. Only brain acetylcholinesterase and plasma butrylycholinesterase activities were inhibited in TBOEP treated hens. These findings suggest that TBOEP does not induce delayed neurotoxicity in the adult hens (Carrington et al., 1990; REACH).

Endocrine Disruption

In a recent in vitro study, TBOEP induced oxidative stress and altered steroidogenesis (testosterone production) in TM3 Leydig cells (Jin et al., 2016).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

Public Risk Characterisation

Given the uses identified for the chemical, there is a low likelihood that the public will be exposed. Although the public could come into contact with articles and coated surfaces containing the chemical, it is expected that the chemical will be bound within the article or coated surface. However, the chemical may become available by product decomposition or aging and it has been commonly measured in indoor dust (de Boer et al., 2016; Cequier et al., 2014). Exposure via this route is not expected to be at harmful levels.

Occupational Risk Characterisation

During product formulation, dermal 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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.

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 used according to the instructions on the label.

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]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 dermal 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:

- 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 is 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.

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