1,3-Propanediol, 2,2-bis(bromomethyl)-: Human health tier II assessment

02 March 2018

CAS Number: 3296-90-0

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.

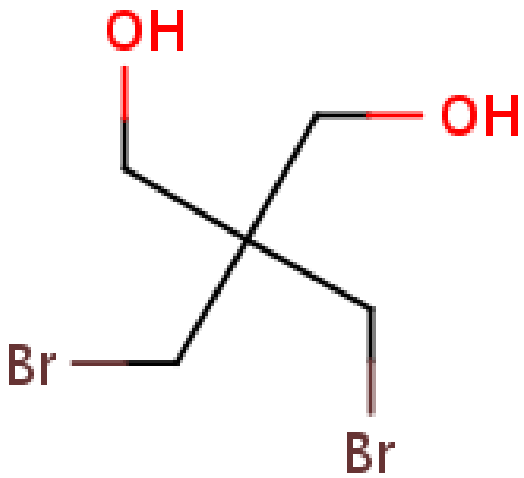
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,2-bis(bromomethyl)propane-1,3-diol (BBMP) dibromoneopentyl glycol (DBNPG) dibromopentaerythritol
Structural Formula	
Molecular Formula	C5H10Br2O2
Molecular Weight (g/mol)	261.9
Appearance and Odour (where available)	Crystalline powder, with a slight, mild and musty odour.
SMILES	C(CO)(CO)(CBr)CBr

Import, Manufacture and Use

Australian

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

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 Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV); the International Agency for Research on Cancer (IARC) monograph; European Chemicals Agency (ECHA) website; National Toxicology Program (NTP); and various international publications.

The chemical has reported site limited uses, including as a reactive flame retardant that is used in the manufacture of unsaturated polyester resins for moulded products and rigid polyurethane foams. The chemical is used in the manufacture of plastic products for construction materials, food packaging and storage, toys, mobile phones, opaque fire retardant laminates and chlorofluorocarbon-free foam products. In the EU, the sole registrant identified that use was primarily (>90 %) in polyester sheets for roofing (Oko-Institut, 2016).

European Food Safety Authority (EFSA, 2012) lists 2,2-bis(bromomethyl)propane-1,3-diol (BBMP) as a novel brominated flame retardant (BFR): 'Novel BFRs are defined as chemicals applied as flame retardants, and with confirmed presence in materials and/or goods in concentrations above 0.1 %'. The chemical is also listed in the United States (US) Environmental Protection Agency (EPA) High Production Volume Program Chemical List.

Restrictions

Australian

No known restrictions have been identified.

International

In the US, the chemical is subject to reporting requirements under Sections 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA) (US EPA Toxic Release Inventory Program).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard is identified (Galleria Chemica)**:**

An exposure limit of 0.2 mg/m^3 time weighted average (TWA) workplace environmental exposure level (WEEL) was reported by the US Toxicology Excellence for Risk Assessment (TERA) and the US American Industrial Hygiene Association (AIHA).

Health Hazard Information

Toxicokinetics

In rats the chemical is rapidly absorbed after oral exposure and efficiently metabolised in the liver to a glucuronide conjugate. The effective elimination of BBMP glucuronide in bile and enterohepatic recycling results in a low systemic bioavailability of BBMP in rats. The urinary excretion rate is slower at higher doses.

The toxicokinetics may differ in humans. The rate of glucuronidation in rodent cells has been shown to be significantly higher than in human hepatocytes. In addition, based in the molecular weight, the glucuronide, if formed in human liver, is expected to be released into blood for excretion in the urine without undergoing the enterohepatic recirculation (Hoehle et al., 2009).

Male Fischer-344 (F344) rats (4/dose) were given either $^{U\text{-}14}$C-labelled or unlabelled BBMP, via gavage or intravenous administration. Within 12 hours after a single oral administration of [^{14}C]BBMP, >80 % of the low dose (10 mg/kg bw) and 48 % of the high dose (100 mg/kg bw) was excreted via urine, mainly as a glucuronide metabolite. This route and rate of elimination were observed to be similar in a repeated daily oral dose study (5 or 10 days). It was reported that the radioactivity recovered in faeces was <15 % in all studies, and the total amount of radioactivity remaining in tissues at 72 hours after a single 100 mg/kg bw dose of [^{14}C]BBMP was less than 1 % of the dose. Adipose tissues, liver, kidneys, muscle and skin contained 0.2 %, 0.7 %, 0.1 %, 0.3 %, and 0.3 % of the initial dose, respectively. Animals in the repeated dose groups did not show an increase in the retention of the chemical in the tissues, and excretion profiles of intravenous administration were found to be similar to those via oral administration. For both oral and intravenous administration, BBMP and its glucuronide product were present in blood plasma. After a 15 mg/kg bw dose of BBMP, hepatic BBMP glucuronide was primarily exported into the bile (>50 % within 6 hour), before it underwent enterohepatic recycling and was subsequently eliminated in the urine (Hoehle et al., 2009; REACH).

In an in vitro study, only one of six human hepatics UDP-glucuronosyltransferase (UGT) enzymes actively converted BBMP to the glucuronide. Less than 3 % was converted over 6 hours. The order of hepatic microsomal glucuronidation activity of BBMP was rats, mice > hamsters > monkeys > humans. The rate of BBMP glucuronidation in rodent cells was 90-fold higher than in human hepatocytes (Rad et al., 2010).

Acute Toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

In an OECD Test Guideline (TG) 401 (Acute oral toxicity) study, Sprague Dawley (SD) rats (5/sex/dose) were orally administered BBMP (98.96 % purity) by gavage at 2000 mg/kg bw. Three animals (one male and two females) were found dead 30–60 minutes after dosing. Clinical signs of systemic toxicity included coma, laboured respiration, hunched posture and lethargy with additional signs of ataxia, ptosis and decreased respiratory rate. Surviving animals appeared normal one or two days after

dosing, and no abnormalities were noted at necropsy of animals that survived until the end of the study. The median lethal dose (LD50) was >2000 mg/kg bw (REACH).

In an older study conducted similar to OECD TG 401, CD-1 rats (5/sex/dose) were orally administered a single dose of BBMP by gavage at 1247, 1484, 1765, 2101 and 2500 mg/kg bw. Coma and death appeared between 1–6 hours after dosing in a total of 22 animals (dose group unspecified). All surviving animals were asymptomatic from day three. The LD50 reported was 1880 mg/kg bw (REACH).

An LD50 of 3458 mg/kg bw was reported for male rats in a study using a commercial formulation of BBMP (containing 81 % of the chemical) (Danish EPA, 2000).

An LD50 of 1200 mg/kg bw in mouse has also been reported (ChemIDPlus). However, supplemental information for deriving these values is not available.

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In an OECD TG 402 (Acute dermal toxicity) study, SD rats (5/sex) were dermally applied BBMP at 5000 mg/kg bw. All animals survived until study termination. The LD50 was >5000 mg/kg bw (REACH).

Inhalation

Limited data are available.

In a study using a commercial formulation of BBMP, exposure of rats to vapours of the chemical at a nominal concentration of 2.49 mg/L for a period of 7 hours resulted in slightly laboured breathing and slight nasal irritation but no mortality (Danish EPA, 2000).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is at most a slight skin irritant.

In a non-OECD TG study, 24 hour exposure to a single dermal application of BBMP (0.5 g in water) produced a primary irritation index of zero in New Zealand White rabbits (n=6) (REACH).

Eye Irritation

Based on the available data, the chemical is at most a slight eye irritant.

In a non-OECD TG study, 100 mg of BBMP was instilled into the conjunctival sacs of New Zealand White rabbits (n=6). Diffuse corneal opacity affecting <1/4 of the corneal surface was observed in four of the test animals within 72 hours. All animals exhibited slight conjunctivitis within 72 hours; however, positive reactions were fully reversible by day eight of experiment (REACH).

Sensitisation

Skin Sensitisation

Based on one available study, BBMP is unlikely to be a skin sensitiser.

In an OECD TG 406 (Skin sensitisation) study using the maximisation protocol, BBMP produced a 0 % (0/10) sensitisation rate in Dunkin-Hartley guinea pigs following two induction exposures (at 5 % intradermally with adjuvant, then up to 75 % epicutaneously) and a challenge exposure at up to 75 % in arachis oil BP epicutaneously (REACH).

Repeated Dose Toxicity

Oral

Based on the available data, the repeated oral toxicity of the chemical are carcinogenic and has reproductive toxic effects (see **Carcinogenicity** and **Reproductive & Developmental Toxicity** sections). Whilst effects in the kidney and urinary bladder were observed in both rats and mice, these occurred only at doses ≥200 mg/kg bw/day.

In a study using a method similar to OECD TG 453 (Combined chronic toxicity / carcinogenicity studies), BBMP was orally administered in the diets of both rats and mice for 13 weeks. F344/N rats (10/sex/dose) were given up to 20000 ppm of BBMP in the diet (equivalent to daily doses of ~1700 mg/kg bw/day for males and ~1600 mg/kg bw/day for females). B6C3F1 mice (10/sex/dose) were given up to 10000 ppm of BBMP (equivalent to daily doses of ~3000 mg/kg bw/day for males and ~2900 mg/kg bw/day for females). No chemical-related mortality or dose-related clinical signs were reported. No significant changes were reported in clinical chemistry or urinalysis results. Significant dose-related decrease in body weight gains were observed in rats dosed ≥5000 ppm and in mice dosed ≥625 ppm. For rats, papillary degeneration was present in both males (dose ≥10000 ppm) and females (dose 20000 ppm). Hyperplasia of the urinary bladder was present in male rats dosed 20000 ppm. In mice, papillary necrosis, renal tubule regeneration, and fibrosis were observed in the kidneys of both males (dose ≥2500 ppm) and females (dose ≥10000 ppm). Urinary bladder hyperplasia was also observed in both sexes (dose ≥5000 ppm) (NTP, 1996; REACH).

Ina gavage study BBMP was administered to both rats and mice for 13 weeks. Deaths were observed in highest dose (800 mg/kg bw/day in rats and 400 mg/kg bw/day in mice) male rats (2/10) and male mice (3/10). Significant dose-related decrease in body weight gains were observed in highest dose rats, and mice dosed at ≥200 mg/kg bw/day of BBMP. Minimal degeneration in the renal papilla was seen in male rats dosed at 800 mg/kg bw/day, and in male rats dosed at 400 mg/kg bw/day. Transitional cell hyperplasia of the urinary bladder was seen in male rats dosed at ≥400 mg/kg bw/day and in both sexes of mice dosed at ≥200 mg/kg bw/day (Elwell et al., 1989; REACH).

Diet containing BBMP at concentrations of 0.1, 0.2 and 0.4 % groups (141, 274, and 589 mg/kg bw/day) was given to CD-1 mice (10/sex/dose) commencing 7 days prior to a 98 day cohabitation period. Exposure at ≥0.2% (≥~274 mg/kg bw/day) of BBMP resulted in significant decreases in postpartum dam weight following delivery of each litter, as well as body weight of parental males at necropsy. Effects observed at the highest dose (0.4 %) included significant decreases in body weight (both sexes) and kidney lesions (Treinen et al., 1989; IARC, 2000).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available data, the chemical is likely to show genotoxicity in humans, warranting hazard classification. Glucuronidation seem to be a detoxification mechanism in BBMP-associated genotoxicity and this may not occur to the same extent in humans compared to rodents.

In a number of bacterial reverse mutation assays, BBMP (purity 84–99.5 %) showed clear evidence of mutagenic activity in *Salmonella* strains TA1535 and TA100 in the presence of 30 % hamster S9 mix. These strains were negative in the absence or presence of rat S9 mix or in the presence of 10 % hamster S9 mix. Results in TA1537 and TA98 were negative despite metabolic activation (hamster and rat) (ECHA, 2017).

In an in vitro mammalian chromosomal aberration test, BBMP (purity not specified) caused chromosomal aberrations in the presence of mammalian metabolic activation (IARC, 2000; ECHA, 2017).

In two in vitro comet assays in human urothelial cells, BBMP (~98 % purity) induced oxidative stress and DNA damage. Strand breaks were not observed in rat hepatocytes. Significantly higher levels of BBMP were found to bind to urothelial cells compared to hepatocytes. This was considered to be associated with metabolism to the glucuronide in the hepatocytes (ECHA, 2017).

In an in vitro sister chromatid exchange assay, BBMP (79 %) did not induce sister chromatid exchanges in Chinese hamster ovary (CHO) cells without S9 (ECHA, 2017).

In an in vivo study, BBMP (oral exposure via dosed feed) induced significant increases in the frequency of micronucleated normochromatic erythrocytes in peripheral blood in B6C3F1 mice of both sexes after 13 weeks of exposure. These increases were observed in both males (≥1300 mg/kg bw/day) and females (dose =600 mg/kg bw/day) (NTP, 1996; IARC, 2000; ECHA, 2017).

A bone marrow micronucleus test was performed in B6C3F1 mice of both sexes following single intraperitoneal injections of 150–600 mg/kg bw BBMP. The study provided clear evidence of BBMP inducing micronuclei in the bone marrow cells of female mice, but not in male mice (NTP, 1996; IARC, 2000; ECHA, 2017).

In an in vivo alkaline comet assay in SD rats (OECD TG 489), DNA damage in the urinary bladder was observed at the highest does (600 mg/kg bw/day). DNA damage was also induced in the liver (ECHA, 2017).

Carcinogenicity

The chemical caused tumours at multiple sites in both rats (two year study and three month stop study) and mice (two year study). Dose response relationships between exposure and carcinogenicity were evident for several tumour types and most sites of cancer are relevant for humans. Classification is considered warranted (see **Recommendation** section).

In a two year study using a method similar to OECD TG 453 (Combined chronic toxicity / carcinogenicity studies), oral administration of BBMP (78.6 % purity) produced clear evidence of carcinogenic activity in both rats and mice. In F344/N rats of both sexes, BBMP increased incidences of neoplasms in the oral cavity, oesophagus, mammary gland and the thyroid gland. In male F344/N rats, the chemical also increased the neoplasms in skin, subcutaneous tissue, Zymbal’s gland, forestomach, small and large intestines, mesothelium, urinary, bladder, lung, seminal vesicle and also increased incidence of mononuclear cell leukaemia. Exposure to BBMP for three months in the diet, followed by maintenance on a control diet for up to two years, caused tumours in male rats at the same tissue sites as the two year study of male rats.

In B6C3F1 mice, BBMP increased incidence of neoplasm in the Harderian gland, lung, kidney (male only) and subcutaneous tissue (female only). The lowest observed adverse effect levels (LOAELs) reported were 2500 ppm (equivalent to 100 mg/kg bw/day in males and 115 mg/kg bw/day in females) in rats and 312 ppm (equivalent to 35 mg/kg bw/day in males and 40 mg/kg bw/day in females) in mice (Dunnick et al., 1997; IARC, 2000; ECHA, 2017).

The International Agency for Research on Cancer (IARC) has classified BBMP as 'possibly carcinogenic to humans (Group 2B)' (IARC, 2000).

Reproductive and Developmental Toxicity

The available data showed that the chemical is a suspected reproductive toxicant, warranting hazard classification. Whilst effects on pup weight and litter size were observed these occurred in the presence of reduced dam weight and insufficient data are available to evaluate whether the decreased litter size was a result of reduced fertility or a developmental effect.

The reproductive toxicity effects of BBMP (87.3 % purity) were evaluated in a continuous breeding protocol consisting of three tasks (Treinen et al., 1989; IARC, 2000). In task 1, diet containing BBMP at concentrations of 0.1, 0.2 or 0.4 % (141, 274, and

589 mg/kg bw/day) were given to CD-1 mice (F0) 7 days prior to and during a 98-day cohabitation period. In task 2, following task 1, crossover mating was performed between control and high dose F0 mice for 7 days to determine the affected sex. In task 3, F1 mice (the last litter) were reared to 74 days and mated with non-siblings of the same treatment group.

BBMP caused generalised toxicity including:

- a significant dose-dependent decrease in body weight gain in both sexes at =0.2 % (F0 and F1)
- decreased postpartum F0 dam weights at =0.2 %
- kidney lesions (such as increased incidence of glomerular atrophy, renal papillary necrosis, tubule degeneration and dilation) at 0.4 % in both sexes of F0 (males more sensitive than females) and in F1 males
- decreased kidney and liver weights in both sexes (F1).

Although BBMP treatment of F0 and F1 animals showed no effects on fertility index (fertile pairs/cohabitated pairs), sperm parameters (e.g. concentration, motility and morphology) or oestrous cyclicity, there were reproductive and developmental effects reported in the high dose group (0.4 %) including:

- decreased number of litters per pair (F0)
- increased cumulative days between delivery of litters with significantly fewer pairs producing fifth litters (F0)
- decreased live pups born per litter (both generations)
- decreased live pup weights (from F0 animals at =0.2 % and F1 animals at 0.4 %), when adjusted for litter size, which occurred in both the absence and presence of decreased litter size
- decreased absolute weights of seminal vesicle, right testis and right epididymis (F1)

In the crossover mating, fertility index in exposed females was reduced; however, this effect was not seen in other tasks of the study.

The chemical BBMP was dietary administered to B6C3F1 mice and F344/N rats (10/sex/dose for both species) for 13 weeks. In both species, reductions in the weight of male reproductive organs in parallel to mean body weight were observed in 5000 ppm and above (corresponding to ~1300 mg/kg bw/day in male mice and ~400 mg/kg bw/day in male rats). Oestrous cyclicity and spermatozoal parameters were not affected (IARC, 2000).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation is carcinogenicity. A genotoxic mode of action cannot be ruled out. The chemical also may cause reproductive and developmental effects.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. The public could come into contact with articles/coated surfaces containing the chemical. However the chemical is a reactive flame retardant and as such, the chemical will be chemically incorporated within the article/coated surface and hence, will not be bioavailable. In addition, overseas use information indicates that the chemical is primarily used in articles to which there would be limited contact i.e. roofing. The chemicals lack of persistence would limit potential for secondary exposure (EFSA, 2012). Therefore, the chemical is not considered to pose an unreasonable risk to public health. Should such information become available indicating exposure to the chemical via secondary exposure or contact with articles, further assessment may be required.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might 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 chemicals at lower concentrations could also

occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed. Oral exposure is also possible but can be prevented by good hygiene practices.

Given the critical systemic long-term health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals 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 HCIS (Safe Work Australia) (see **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

Work Health and Safety

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

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Not Applicable	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility - Cat. 2 (H361f)

[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 industry

Control measures

Control measures to minimise the risk from oral, 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 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.

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