Xanthylium, 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)phenyl]-2,7-dimethyl-, chloride: Human health tier II assessment

26 October 2018

CAS Number: 3068-39-1

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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.

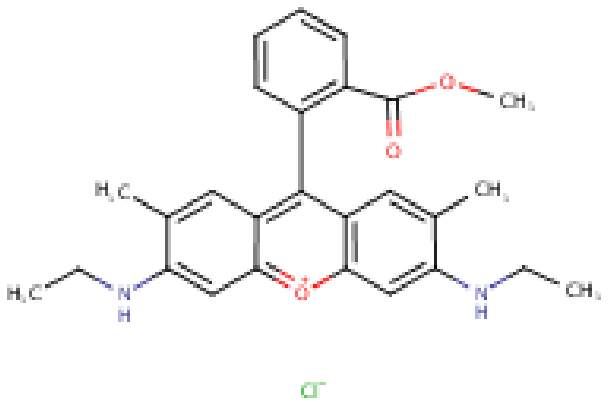
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Basic Red 1:1 3,6-bis(ethylamino)-9-(2-(methoxycarbonyl)phenyl)-2,7-dimethylxanthylium chloride
Structural Formula	
Molecular Formula	C27H29N2O3.Cl
Molecular Weight (g/mol)	464.98
Appearance and Odour (where available)	Red/orange powdered solid material.

SMILES	C(=O)(c1c(-c2c3c(cc(NCC)c(C)c3)o{+}(.Cl{-})c3c2cc(C)c(NCC)c3)cccc1)OC

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 European Commission Cosmetic Ingredients and Substances (CosIng) database; and the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

The chemical has reported cosmetic uses, including in hair dyes.

Although cosmetic use has been identified, it is not expected to be widespread. The chemical is not listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS) or on the US Department of Health and Human Services, Household Products Database (HPD). The Environmental Working Group (EWG) Skin Deep Cosmetics Database indicates that the chemical has been used in 4 discontinued products.

The chemical has reported domestic uses, including in:

- paints, lacquers, and varnishes; and
- water-based printer inks.

The chemical has reported commercial uses, including as a pigment in a range of textiles and other products.

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Xanthylium, 3,6-bis(ethylamino)-9-[2-(methoxycarbonyl)phenyl]-2,7-dimethyl-, chloride (CAS No. 3068-39-1) also known as Basic Red 1:1 (and referred to as such hereafter) is used as a colourant in hair dyes and in other industrial applications.

Toxicokinetics

No toxicokinetic studies have been conducted on Basic Red 1:1 in mammals; however, the physical and chemical properties of the compound, together with data from toxicological studies, provides some information on the absorption, distribution and excretion of the compound. No data are available on the metabolism of the compound.

Although the molecule is relatively large (molecular weight of 464.98 g/mol), oral absorption is expected to occur given its partition coefficient (1.7). At pH values ranging from 4 to 9, hydrolysis half-lives are long, which suggest that any systemic effects observed would occur as a result of the parent molecule. Adverse effects observed in inhalation studies indicate the chemical is likely to be absorbed via inhalation. Given the positive reaction observed in a skin sensitisation study, some level of dermal absorption is also expected to occur (REACH).

Red colourisation of internal tissues has been observed in an acute oral toxicity study, which suggests widespread distribution following oral administration. Staining of internal tissues has also been observed in other studies involving oral administration (REACH).

A repeat dose toxicity study showed some non-adverse renal effects at 15 mg/kg bodyweight (bw)/day which, together with observations of red stained urine, may indicate that some renal/urinary clearance of the chemical occurred. Given the compound's high molecular weight, coupled with observed red staining of the gastrointestinal tracts of animals in an acute oral toxicity study and in a repeat oral toxicity study, faecal excretion of the chemical is expected to be a major elimination route (REACH).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats ranges from 449–500 mg/kg bw. The chemical is recommended for hazard classification (see **Recommendation** section).

A study was conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 (acute oral toxicity). Albino Sprague Dawley (SD) rats of both sexes (5 animals per sex per dose) were administered the chemical via oral gavage at 0, 100, 316, 1000 or 3160 mg/kg bw. There were no mortalities in the 100 mg/kg bw group. At 316 mg/kg bw, 2 females and 1 male died. In the 1000 mg/kg dose group, 5 males and 4 females died, and all animals died in the high dose group. Clinical signs observed were apathy, diminished response to external stimulus, narrow eyelids, bristled fur, soft

stools and reduced quantity of stools. The following findings were observed in animals that died during the observation period: Cardiac lesions, pulmonary lesions (including apical lung collapse), cryptorchism, dark brown discolouration of the livers and red/violet discolouration of the gastrointestinal tracts and internal tissues. Under the conditions of the study, the LD50 of the test material was found to be 449 mg/kg bw for males and females combined (REACH).

In a study conducted according to OECD TG 423 (acute oral toxicity – acute toxic class method), female SD rats were orally administered the chemical at 0, 300 or 2000 mg/kg bw. Mortalities were 1/4 and 3/3 in the 300 and 2000 mg/kg bw dose levels, respectively. Sublethal effects observed within 6 hours of dosing at 300 mg/kg bw included reduced locomotor activity, ataxic gait and tremors. Dosing at 2000 mg/kg bw resulted in diarrhoea, piloerection, reduced locomotor activity, ataxic gait, loss of righting reflex and convulsions with onset within 10 to 60 minutes of dosing. The material also produced red stained faeces and urine at both doses and gross pathological examination revealed unabsorbed residual test item imparting reddish discolouration to stomach, small intestine and large intestine. On the basis of this study, the oral LD50 was 500 mg/kg bw (REACH).

In a non-guideline study, an unknown number of rats of unspecified strain were orally administered Basic Red 1:1 at 500 mg/kg bw. No mortalities were recorded; therefore, the LD50 was considered to be >500 mg/kg bw (REACH).

Dermal

No data are available.

Inhalation

The chemical has very high acute toxicity based on results from animal tests following inhalation exposure. The median lethal concentration (LC50) in rats ranges from 0.05–0.5 mg/L (equivalent to 50–500 mg/m^3). The chemical warrants hazard classification (see **Recommendation** section).

The potential for Basic Red 1:1 to produce acute toxicity via inhalation was assessed in a study conducted according to OECD TG 403 (acute inhalation toxicity). The aerosolised test material was administered via nose-only inhalation to Wistar rats (5/sex/dose) at 0.05, 0.5 and 1 mg/L (equivalent to 50, 500 and 1000 mg/m^3, respectively) for up to 4 hours. At 0.5 and 1 mg/L, all animals were found dead (or were sacrificed for ethical reasons) within 3 hours of the start of exposure. At 0.05 mg/L, 2 males were sacrificed for ethical reasons by day 6. No other mortalities occurred during the 14 day observation period. Animals in the 0.05 mg/L group exhibited slow breathing during the exposure period. Following exposure, animals in the 0.05 mg/L group exhibited lethargy, hunched posture, laboured respiration, rales, gasping, swelling of the abdomen and piloerection up until day 12. Reduced body weight gain was observed in all surviving animals in the first week after exposure. Animals that died or were euthanised following exposure showed: Purple discolouration of the trachea and dark red discolouration of the lungs (1 mg/mL and 0.5 mg/L animals), purple discolouration of the stomach, accentuated lobular pattern of the liver and isolated reddish lesions in the thymus (0.5 mg/L). One animal euthanised at the end of the study showed an irregular stomach surface and a reduction in thymus size. Another euthanised animal showed distended gastrointestinal tract. No abnormalities were seen in the surviving animals. Under these test conditions, a 4 hour LC50 via the inhalation route was within the range 0.05–0.5 mg/L (equivalent to 50–500 mg/m^3) (REACH).

Corrosion / Irritation

Skin Irritation

The chemical did not produce any evidence of skin irritation in several studies. No hazard classification is warranted.

A study was conducted to assess the potential for Basic Red 1:1 to cause skin irritation in a study conducted according to OECD TG 404 (acute dermal irritation/corrosion). The clipped skin of 3 New Zealand White (NZW) rabbits was dermally exposed to the test chemical (0.5 g) under semiocclusive conditions for 4 hours. Animals were observed for 72 hours following removal of the dressings. No signs of irritation or corrosion were observed in any of the animals. Investigators noted; however, that the

assessment of erythema was hindered by the pink staining of the skin from the test material. On the basis of this finding, the chemical was not considered to be a skin irritant (REACH).

The chemical was tested in a non-guideline study in which the material was dermally applied to the entire unclipped inner ear of a single NZW rabbit (sex not specified). No erythema or any other signs of irritation were observed. Given no adverse dermal effects were observed, the chemical was not tested on any other animals. The investigators reported the chemical to be non-irritating (REACH).

A non-guideline skin irritation study was conducted with an albino Himalayan rabbit. The chemical (0.5 g) was dermally applied to the intact skin of 1 animal. No skin reactions were elicited and; therefore, the investigators reported the chemical was not a skin irritant (REACH).

The test chemical (0.5 g) was applied topically to 1 intact and 1 additionally abraded flank of 6 albino Himalayan rabbits under occlusion for a 24 hour exposure period. The scoring of skin reactions was performed immediately, 48 hours and 73 hours after removal of the occlusive patch. Since the test chemical did not elicit any skin reactions at the application site of any animal, the test chemical was considered to be non-irritating (REACH).

The chemical was assessed for its potential to produce skin irritation in a study conducted according to OECD TG 431 (in vitro skin corrosion: reconstructed human epidermis test method). Due to the chemical producing colour interference in the medium, the test material was not compatible with the test system and no conclusion could be made on the corrosive potential of the test material (REACH).

Eye Irritation

In an eye irritation study in rabbits, the chemical was found to be highly irritating with conjunctival swelling, discharge and opacification. Effects were not reversible within the 7 day observation period, warranting hazard classification (see **Recommendation** section).

Basic Red 1:1 was assessed for its potential to produce eye irritation in a study conducted similarly to OECD TG 405 (acute eye irritation/corrosion). A single dose of the test material (0.1 g) was applied to 1 eye in each of 6 animals (sex not specified) and animals were observed for signs of irritation at 1, 24, 48 and 72 hours. One hour after instillation, investigators reported significant conjunctival swelling along with mild to severe discharge from the eyes. Slight corneal opacification was observed in 4 animals. From 24 hours post application, until the end of the observation period, the edges of the eyelids were hardened with dried discharge in all animals. Mucus hypersecretion was observed, which later became purulent. Redness induced by the material was difficult to determine given the extreme swelling of the eyes. Following a 7 day observation period the adverse effects were not reversed. Under these test conditions, the chemical is a severe ocular irritant (REACH).

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive result seen in a single local lymph node assay (LLNA) (EC3 is 10 %). Hazard classification is warranted (see **Recommendation** section).

A mouse LLNA was conducted on Basic Red 1:1 according to OECD TG 429 (skin sensitisation). Female CBA:J mice (5/dose) were administered the test chemical at concentrations of 10, 25 or 50 % w/w (in acetone/olive oil (4:1 v/v)) on 3 consecutive days by dermal application to the ears. Three days following the final exposure, all animals were administered ^{3}H-methyl thymidine via injection, and after a subsequent 5 days, draining auricular lymph nodes were excised and assessed for lymphocyte proliferation. No erythema was observed at the site of application; however, the material produced pink/red/brown staining of the skin, but this was reported not to have affected the assessment of skin reactions. No mortalities occurred and no clinical signs of systemic toxicity were observed. The stimulation indices calculated for the 3 doses assessed were 3.0, 5.7 and 3.6 for the concentrations 10, 25 and 50 %, respectively. The calculated EC3 value (estimated concentration to produce a 3-fold increase in the proliferation of lymph node cells) was 10 %. Under these test conditions, the chemical is considered to be a skin sensitiser (REACH).

The chemical had no structural alerts for sensitisation in the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox (OECD Toolbox).

The chemical had no structural alerts for sensitisation in the VEGA QSAR software; however, the reliability of this result was determined to be 'low' (VEGA QSAR).

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) available from 28-day rat studies (1.5 mg/kg bw/day) and based on the treatment-related effects, repeated oral exposure to the chemical is considered to cause serious damage to health. Hazard classification is warranted (see **Recommendation** section).

Basic Red 1:1 was assessed in a study conducted according to OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test). Wistar rats (10 animals/sex/dose) were dosed by oral gavage at 1.5, 5 or 15 mg/kg bw/day, 7 days per week for 4 weeks. Males were dosed for 2 weeks prior to mating, and during mating and up until the time of euthanasia. Females that delivered offspring were treated for 2 weeks prior to and during mating, during pregnancy and for at least 13-15 days of lactation (for 50 days total). Three females in the high dose group were euthanised for ethical reasons early in the post-coitum period, 1 female was euthanised for ethical reasons on day 17 post-coitum, and 1 female was deceased on day 3 of lactation. The primary cause of moribundity/death in 3 of these animals was treatment related effects in the respiratory tract. Prior to euthanasia, animals exhibited clinical signs of toxicity including rales, gasping, a lean appearance and/or piloerection, body weight loss and reduced food intake. The primary cause of morbundity in the female animal euthanised on day 17 post-coitum was reported to not be treatment related. Two females in the 5 mg/kg bw/day group showed rales, hunched posture, piloerection and a lean appearance. These same animals also exhibited body weight loss as well as reduced food intake during the first 4 days of the post-coitum period. Reduced body weight gain and reduced food intake were observed in females treated at 15 mg/kg bw/day during the lactation phase. Two males in the high dose group showed purple discolouration of the stomachs, and 2 surviving females had purple discolouration and distended intestinal tracts. No parental toxicity was observed in males treated up to 15 mg/kg bw/day and females treated at 1.5 mg/kg bw/day. On the basis of these findings, the NOAEL is 1.5 mg/kg bw/day.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro genotoxicity studies, the chemical is not considered to be genotoxic.

Basic Red 1:1 was assessed in an Ames bacterial reverse mutation assay according to OECD TG 471 (bacterial reverse mutation test). The compound was incubated with *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 strains, and *Escherichia coli* WP2 uvr A strain at concentrations up to 1000 µg/plate, both with and without S9 metabolic activation. The investigators reported that the chemical was negative for genotoxicity in all strains tested, both with and without metabolic activation (REACH).

The chemical was assessed in a study conducted according to OECD TG 490 (in vitro mammalian cell gene mutation tests using the thymidine kinase gene). Mouse lymphoma L5178Y cells were incubated with the test chemical at concentrations up to

20 µg/mL in the presence and absence of metabolic activation with S9. The chemical was negative for genotoxicity at all doses below the cytotoxic threshold (REACH).

A study was conducted according to OECD TG 473 (in vitro mammalian chromosome aberration test). Human lymphocytes were incubated with the test chemical at concentrations up to 0.05 µg/mL (without S9 metabolic activation) and 0.15 µg/mL (with S9 metabolic activation). The chemical did not produce any biologically significant increase in the number of chromosome aberrations, either in the presence or absence of metabolic activation. The chemical was not clastogenic in this test system (REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not show specific reproductive or developmental toxicity.

Basic Red 1:1 was assessed in a study conducted according to OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) (for more details on the repeated dose toxicity study see **Repeated dose toxicity**: **Oral** section). Wistar rats (10 animals/sex/dose) were dosed by oral gavage at 1.5, 5 or 15 mg/kg bw/day, 7 days a week for 4 weeks. Males were dosed for 2 weeks prior to and during mating and up to sacrifice. Females that delivered offspring were treated for 2 weeks prior to and during mating, during pregnancy and for at least 13–15 days of lactation. No reproductive toxicity was observed up to the highest dose level tested; therefore, the NOAEL of the test material was determined to be >15 mg/kg bw/day for reproductive toxicity. Pup body weight gain was slightly reduced in the high dose group, although the reduction did not reach statistical significance. This reduced pup weight gain occurred in the presence of maternal toxicity (clinical signs, reduced body weight gain, reduced food weight gain). Pup body weight at birth was similar across all groups (including the controls). No macroscopic findings were noted among pups that were considered to be related to treatment. No external malformations were observed in any of the pups. Elevated thyroxine levels were observed in pups at 15 mg/kg bw/dose; however, this was not considered to be treatment related. Under the conditions of this study, the NOAEL for offspring developmental toxicity was 15 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral and inhalation exposure) and local effects (eye irritation, skin sensitisation). The chemical can also cause harmful effects following repeated exposure through oral exposure.

Public Risk Characterisation

Based on overseas use information (see **Import, Manufacture and Use** section) use in cosmetic products in Australia is not expected to be widespread, The risk to the Australian public is currently considered to be low. If information becomes available indicating use of the chemical in Australia, risks to the public may require management through the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

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 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 systemic long-term systemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking 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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)
Repeat Dose Toxicity	Not Applicable	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)

[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, ocular, 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;
- 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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