Oxiranemethanaminium, N,N,N-trimethyl-, chloride: Human health tier II assessment

01 September 2015

CAS Number: 3033-77-0

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.

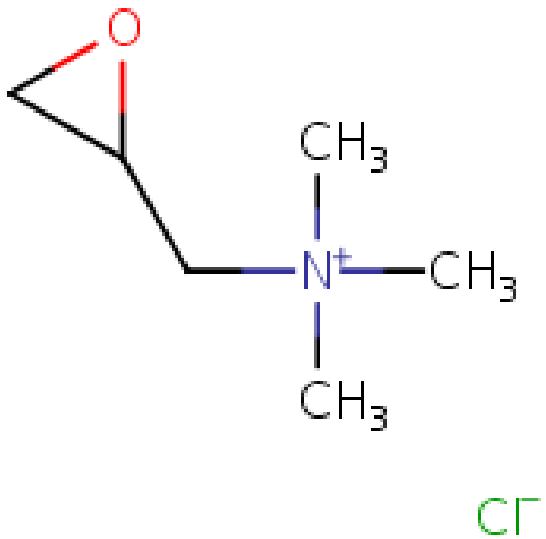
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,3-Epoxypropyltrimethylammonium chloride (EPTAC) glycidyltrimethylammonium chloride (GTMAC)
Structural Formula	
Molecular Formula	C6H14NO.Cl
Molecular Weight (g/mol)	151.63
Appearance and Odour (where available)	white powder
SMILES	C1(CN{+}(C)(C)(C).Cl{-})CO1

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;
- the EU Risk Assessment Report; and
- Galleria Chemica.

The chemical has reported site-limited uses such as in producing cationised starches and quaternisation of other products such as guar, cellulose derivatives and proteins.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)—under *'Quaternary Ammonium Compounds'* in Schedules 6 and 5 (SUSMP, 2015).

Schedule 6:

'QUATERNARY AMMONIUM COMPOUNDS except:

(a) when separately specified in these Schedules;

(b) when included on Schedule 5;

(c) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

(d) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

Schedule 5:

'QUATERNARY AMMONIUM COMPOUNDS in preparations containing 20 per cent or less of quaternary ammonium compounds except:

(a) when separately specified in these Schedules;

(b) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

(c) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

This chemical is also listed in the SUSMP under *'Epoxy resins, liquid'* in Schedule 5 (SUSMP, 2015).

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2015).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2015).

International

No international restrictions are available for the chemical.

Existing Work Health and Safety Controls

Hazard Classification

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

Carc. Cat. 2; R45 (Carcinogenicity)

Muta. Cat. 3; R68 (Mutagenicity)

Repr. Cat. 3; R62 (Reproductive toxicity)

Xn; R21/22 (Acute toxicity)

Xn; R48/22 (Repeat dose toxicity)

Xi; R41 (Eye irritation)

Xi; R43 (Skin sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available information supports the current classification for this chemical.

In an experiment conducted in SPF-albino rats (five animals/sex/dose), a single oral dose of the chemical (20% (v/v) solution diluted from a 71.9% (v/v) solution) was administered at doses of 4.0, 4.8, 5.8, 6.9 or 8.5 mL/kg. Mortalities were observed in all dose groups within 48 hours. The dosed animals showed sedation, dark-coloured eyes, tremors, convulsions, diarrhoea and loss of consciousness. Surviving animals recovered at the end of the observation period and showed no treatment-related histopathological effects. The median lethal dose (LD50) value of the 71.9% solution of the chemical was calculated to be 1513 mg/kg, corresponding to 1088 mg/kg of the pure chemical (EU RAR, 2008).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available information supports the current classification for this chemical.

In a limited study conducted in rabbits (three animals/group), an aqueous solution of the chemical was applied to the skin at a dose of either 1500 or 3000 mg/kg. Two rabbits in the high dose group died within 5 hours. The LD50 value was estimated to be between 1500 – 3000 mg/kg (EU RAR, 2008).

Inhalation

In a study conducted in four female rats (strain not specified), exposure to the chemical for seven hours at a concentration of 8.17 mg/L did not cause deaths or systemic effects. Eye irritation was the only effect reported (EU RAR, 2008).

Corrosion / Irritation

Skin Irritation

In an experiment conducted in accordance with the OECD test guideline (TG) 404, dermal application of 0.5 mL of the chemical (commercial solution of variable concentrations of 70–75%) in three albino rabbits under occlusive conditions did not cause dermal irritation at 1, 24, 48 and 72 hour observation periods (EU RAR, 2008).

In a non-guideline study conducted in 12 albino rabbits, 0.5 mL of the chemical (72% solution) was applied on either intact (six rabbits) or slightly abraded (six rabbits) skin for 24 hours under occlusive patch. Dermal irritation was observed at 24 and 72 hours after application. Severe skin irritation including erythema, slight ischaemia, haemorrhages, slight to distinct encrustation, and slight to moderate oedema was observed. On intact skin, the average irritation scores (using the Draize scoring system) were 4.3 and 3.8 at 24 and 72 hour observation periods, respectively. The average irritation score for abraded skin was 6.3 for both 24 and 72 hour observation periods (EU RAR, 2008).

The chemical in a powder form was shown to be severely irritating to rabbit skin (strain not provided) in an occlusive patch test. In one male rabbit, severe eschar developed 48 hours after application of the chemical. Necrosis and fissuring of the skin was also reported seven days after application (MAK, 1992).

Severe skin irritation (severe dermatitis and thickening of the skin) was seen in a four-week study in mice (see **Repeat Dose Toxicity - Dermal**). Based on the skin irritation effects reported in the irritation studies, the chemical warrants classification as hazardous with risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). The available data support this classification.

In an experiment conducted in three albino rabbits in accordance to the OECD TG 405, 0.1 mL of the chemical (commercial solution approximately 70–75%) was applied into the conjunctival sac of the right eye without rinsing. Eye irritation scores were recorded at 24, 48 and 72 hours post instillation. The rabbits were observed for 21 days. Mean scores for conjunctival redness (3.0 for all animals), conjunctival chemosis (1.7–3.0), iritis (1.3–2.0), and corneal opacity (1.0–1.7) were reported. Congestion of the iris persisted after the 21 day observation period in one animal (EU RAR, 2008).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS (Safe Work Australia). The positive results reported in a guinea pig maximisation test and observation in humans support this classification.

In a guinea pig maximisation test, 20 guinea pigs were induced intradermally with 5% of the chemical. After one week, the chemical (5% in Vaseline) was applied topically for 48 hours under an occlusive dressing. Two weeks after the topical induction, the animals were challenged with the chemical (2.5% in Vaseline) under an occlusive dressing for 24 hours. Slight erythema was observed during the topical induction phase. In the challenge phase, erythema was observed in 11 animals immediately after the challenge and in 14 animals after 24 hours. Skin reactions were still observed in three animals after 48 hours (EU RAR, 2008).

Observation in humans

Various patch test studies conducted in workers at starch cationising plants resulted in positive reactions. These studies have shown that exposure for 24 hours to the chemical at concentrations from 0.1% elicited reactions in workers who developed contact dermatitis within months of employment (EU RAR, 2008). The sensitising potential of the chemical reported from various studies supports the current classification for skin sensitisation.

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure if swallowed' (Xn; R48/22) in the HSIS (Safe Work Australia). The data support the current classification of this chemical.

In a study conducted in Wistar rats (10 animals/sex in the control and high dose groups and five animals/sex in the low- and mid-dose groups), the chemical (72.6% solution) was administered by oral gavage at doses of 0, 3.16, 10.0, 31.6 or 100 mg/kg for 28 days. Half the animals in the high dose and control groups had a four-week post-exposure observation period. In the last week of administration, four females and one male in the high dose group died. In high dose males, reduction in testes and brain weights and testicular atrophy were observed. In high dose females, reduction in absolute liver and heart weights and follicular atrophy were observed. The highest dose group also showed occasional maturation disorders, vacuolisation, and abnormal mitoses in the bone marrow cells, mild focal hyper- and parakeratosis of the forestomach, and mild erosions and haemorrhages in the glandular stomach. However, these effects were reversible after the recovery period.

In the two highest dose groups, body weight, body weight gain and ovary weights were significantly lower compared with controls. Reduced cell lines in the bone marrow were also observed in the two highest dose groups. Proximal tubular hyperplasia was also observed. Vacuolisation in the proximal convoluted tubule (PCT) of the kidneys was observed in all dose groups. Based on the effects in the kidney, the lowest observed adverse effect level (LOAEL) value was determined to be 3.16 mg/kg bw/day (EU RAR, 2008).

Dermal

In a range-finding study conducted in CF1 mice (five animals/sex/dose), 0.2 mL of the chemical (in ethanol/Nonidet P40) was applied (non-occlusively) to the dorsal skin of the test animals at concentrations of 1%, 2.5%, 5% or 10% (w/v) twice a week for four weeks (dose per weight was not provided). Deaths were reported in the high dose groups. Treatment-related skin and kidney damage were also observed. Kidney damage included cellular hypertrophy, karyomegaly, and single cell necrosis in the proximal tubules. The chemical was escharotic with severe dermatitis with epidermal acanthosis (thickening of the skin) observed at the site of application (MAK, 1992). A lowest observed adverse effect level (LOAEL) was not determined for this study.

Inhalation

No data are available.

Genotoxicity

The chemical is classified as hazardous—Category 3 mutagenic substance—with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in the HSIS (Safe Work Australia). The available data support this classification.

In vitro

Based on a number of non-guideline studies, the chemical tested positive for mutagenicity in the following in vitro tests (EU RAR, 2008):

- Ames test in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538;
- fluctuation test in *Klebsiella pneumoniae*, treatment-related increase in mutation rate;
- Ames test in *Escherichia coli* strains WP2 and WP2 uvrA, with and without metabolic activation;
- induced gene conversion in *Saccharomyces cerevisiae* strains JD1 and D7, with and without metabolic activation;
- treatment-related increase in sister chromatid exchange in Chinese hamster V79 cells;
- chromatid aberrations in RL1 rat liver cells; and
- chromosome aberrations in Chinese hamster ovary (CHO).

In vivo

In a micronucleus test conducted in accordance with the OECD TG 407, the chemical was administered through a single intraperitoneal injection in BOR:NMRI mice (18 animals/group) at a dose of 82.5 mg/kg. At 24 hours, there was a statistically significant increase in micronucleated polychromatic erythrocytes (PCE) in females (EU RAR, 2008), indicating a positive result.

Carcinogenicity

The chemical is classified as hazardous—Category 2 carcinogenic substance—with the risk phrase 'May cause cancer' (T; R45) in the HSIS (Safe Work Australia). The available data support this classification.

In a two-year study conducted in CF1 mice (50 animals/sex/dose), the chemical was applied to the skin at concentrations of 0.1, 0.3 and 1.0% (dissolved in ethanol) twice per week. Based on a default assumption that the average weight is 40 g, the applied doses were calculated to be 5, 15 or 50 mg/kg/application or 10, 30, or 100 mg/kg/week. Survival rates in all dose groups were lower compared to controls. The main cause of death was primary systemic neoplasia, mainly of haematopoietic tissues and lungs. In the high dose female group, increased mortality due to mammary gland neoplasms and cutaneous neoplasia was

reported. Apart from the neoplasms, death was also caused by suppurative lesions, renal failure or urethral obstruction (males). Other clinical signs observed in the high dose group were discolouration, epilation and flaking of the skin. Dermal and epidermal tumours, mostly squamous cell carcinoma, were observed except in the low dose group (EU RAR, 2008). Although the relevance of some systemic tumours to chemical exposure was uncertain, the incidences of these tumours cannot be disregarded.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in the HSIS (Safe Work Australia).

No data for developmental effects are available for this chemical. However, chronic exposure to the chemical caused effects in the reproductive organs of Wistar rats (see **Repeat Dose Toxicity - Oral**). The effects included testicular and follicular atrophy, which are consistent with reproductive impairment and would support the current classification for this chemical.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity, mutagenicity, reproductive toxicity), systemic acute effects (acute toxicity from oral and dermal exposure) and local effects (skin sensitisation and eye damage). The chemical can also cause harmful effects following repeated oral exposure as well as skin irritation.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. The chemical is listed in Schedule 5 and 6 of the SUSMP. A number of warning statements, first aid instructions and safety directions apply. These controls are considered adequate to minimise the risk to public health posed by the use of products containing the chemical. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at low 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.

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 under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)* Irritating to skin (Xi; R38)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)*	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	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 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;
- 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.

References

European Union Risk Assessment Report (EU RAR) 2008 for 2,3-epoxypropyltrimethylammonium chloride (CAS No. 3033-77-0). Accessed September 2015 at http://echa.europa.eu/documents/10162/6434698/orats_final_rar_2_3-epoxypropyltrimethylammoni_en.pdf

Galleria Chemica. Accessed September 2015 at http://jr.chemwatch.net/galleria/.

MAK 1992. Glycidyl trimethylammonium chloride (MAK Value Documentation). Wiley-VCH Verlag GmbH& Co. KGaA. Accessed on September 2015 at http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb303377e0004/full

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. 2,3-epoxypropyltrimethylammonium chloride (CAS No. 3033-77-0). Accessed September 2015 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb83d6f-b64d-2e76-e044-00144f67d031/DISS-9eb83d6f-b64d-2e76-e044-00144f67d031_DISS-9eb83d6f-b64d-2e76-e044-00144f67d031.html

Safe Work Australia (SWA). Hazardous Substances Information system (HSIS). Accessed September 2015 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2015. Accessed July 2015 at https://www.comlaw.gov.au/Details/F2015L00844

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