1-Propanaminium, 3-chloro-2-hydroxy-N,N,N-trimethyl-, chloride: Human health tier II assessment

21 April 2016

CAS Number: 3327-22-8

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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.

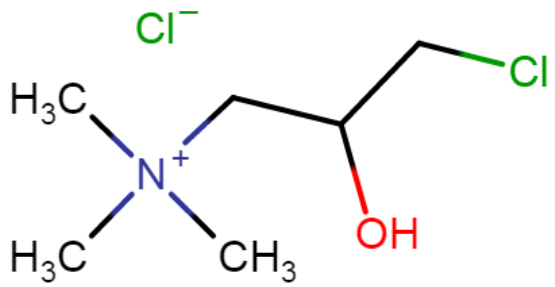
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	3-chloro-2-hydroxypropyltrimethylammonium chloride (CHPTAC) Dextrosil
Structural Formula	
Molecular Formula	C6H15ClNO.Cl
Molecular Weight (g/mol)	188.12
Appearance and Odour (where available)	white crystalline solid
SMILES	C(O)(CN{+}(C)(C)(C).Cl{-})CCl

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 quaternary ammonium substituted starches, guar, cellulose derivatives and proteins. The cationic materials have a variety of uses such as in cosmetic products, production of paper products, and in food packaging.

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, 2016).

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.'

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, 2016).

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, 2016).

International

No international restrictions are known 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. 3; R40 (Carcinogenicity).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Typically, the chemical contains approximately 2–3 % 2,3-epoxypropyltrimethylammonium chloride (CAS No 3033-77-0; EPTAC) as an impurity. The chemical undergoes hydrolytic conversion into EPTAC, and subsequently into the *diol* form (2,3-dihydroxypropyltrimethylammoniumchloride; CAS No 34004-36-9), in aqueous media (EU RAR, 2008). The data for EPTAC will be included in the assessment of the chemical where this interconversion is expected to occur.

Toxicokinetics

Limited data are available for the chemical. The chemical was shown to be absorbed via the oral and dermal route (EU RAR, 2008). An *in vitro* test was conducted in viable human and mouse skin membrane using a radiolabelled form of the chemical at concentrations of 0.1, 1, 20 and 65 % in water. In human skin, the amount of radioactivity was higher in the skin (between 0.5 and 6.8 fold) and stratum corneum (between 1.1 to 21 fold) compared to the receptor fluid. However, in the mouse skin, the amount of radioactivity on the skin was 5.3 to 17.6 times lower than in the receptor fluid (EU RAR, 2008).

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 a study conducted in Sprague Dawley (SD) rats (10 animals/sex/dose), the chemical (60% solution) was administered once by oral gavage at doses of 3670, 4440, 5170 or 6520 mg/kg bw. No mortality was observed at the lowest dose tested. All of the

animals in the high dose group died during the study. Mortality and decrease in mean body weights also occurred in the mid-dose groups. Observed sub-lethal effects included sedation, miosis (excessive constriction of the the pupil of the eye), dyspnoea, tremors and cramping. The calculated median lethal dose (LD50) values were determined to be 4810 mg/kg and 4700 mg/kg for males and females, respectively (EU RAR, 2008).

Other studies conducted in rats resulted in LD50 values of 2170–2213 mg/kg bw (EU RAR, 2008). Sub-lethal effects reported included piloerection, an abnormal body carriage, abnormal gait, lethargy, decreased respiratory rate, pallor of the extremities and increased salivation. Post-mortem examinations revealed congestion or haemorrhage of the lungs and pallor of the liver, spleen and kidneys (EU RAR, 2008).

Dermal

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

In a separate dermal–limit study conducted in CD rats (five animals/sex) and Wistar rats, the chemical (65% aqueous solution) was applied to a shaved dorso-lumbar area under an occlusive dressing for 24 hours at approximate dose of 2000 mg/kg bw with observation for 14 days. No deaths occurred and no clinical signs were observed. The dermal LD50 values in both studies are > 2000 mg/kg bw (EU RAR, 2008).

Inhalation

The chemical was of low acute toxicity in animal tests following inhalation exposure.

Based on a limited seven-hour inhalation study conducted in four rats (strain and sex unspecified), exposure to the chemical at a dose of 12.05 mg/L did not cause deaths or toxic effects. No other information was reported (EU RAR, 2008).

Corrosion / Irritation

Skin Irritation

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

In studies conducted in New Zealand White (NZW) and albino rabbits, application of 0.5 mL of the chemical (reported concentrations ranged from 60–65 % aqueous solution) under occlusive or semi-occlusive patches for four hours did not produce skin irritation effects (EU RAR, 2008).

Eye Irritation

Based on studies conducted in rabbits, the chemical is not considered to be irritating to the eyes.

In a study conducted in six NZW rabbits, 0.1 mL of the chemical (55 % solution) was applied to one eye of each rabbit. The eyes remained unwashed and were observed at 24, 48 and 72 hours and seven days after treatment. All ocular scores were zero except in one animal which had a conjunctival redness score of 1 after 24 hours. In another study conducted in NZW rabbits (three animals/sex/dose), 0.1 mL of the chemical was applied to one eye as 12.5, 25.0 or 50.0 % solutions with observations for up to 72 hours after treatment. All scores were zero at the 72 hour observation period (EU RAR, 2008).

In a more detailed study conducted in three NZW rabbits, the chemical (65% solution) was applied to one eye with observations at 1 hour, and 1, 2, 3, 4 and 7 days after treatment. Temporary conjunctival redness (mean score 24–72 hr timepoints: 1.7) and chemosis (mean score 24–72 hr timepoints: 1.0) were observed in all animals but reversed by day 4 (EU RAR, 2008).

Sensitisation

Skin Sensitisation

The chemical was not found to induce dermal sensitisation when tested in guinea pigs according with OECD Test Guideline (TG) 406.

In a guinea pig maximisation test in accordance to OECD TG 406, induction was carried out using the chemical (70% solution) for both intracutaneous and epidermal induction in 10 female Pirbright White guinea pigs. Challenge was performed 22 days following induction using an occluded patch of 0.2 mL of 30 % chemical in 0.9 % saline. No effects were observed during the induction and challenge periods (EU RAR, 2008).

In a Buehler test conducted in ten female Hartley/Dunkin guinea pigs, application of the chemical (65 % solution) did not cause any effects during the induction phase. Challenge phase was conducted at the same concentration as the induction phase. In the challenge phase, slight localised erythema was observed in two out of ten animals (EU RAR, 2008).

Repeated Dose Toxicity

Oral

Considering the lowest observed-effect levels (LOELs) available from a 28-day limit study in rats (1085 mg/kg bw/d), and based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a limit-test conducted in Bor:WISW rats (five animals/sex), the chemical (69.54% purity) was administered by oral gavage at a daily dose of 1085 mg/kg bw/d, seven days per week, for four weeks. Clinical findings included slightly red coloured salivation and alopecia in the legs or neck. Statistically significant decreases in glucose levels were observed in treated groups. In males, there was a slight but statistically significant decrease in absolute and relative heart weights and increase in kidney weights. The kidneys also exhibited slight to moderate vacuolisation of proximal tubule cells of the inner cortical and outer medullar region; minimal or slight tubular hyperplasia and hypertrophy were also observed. No changes in organ weights were observed in treated females. Given the organ effects observed in males, the lowest observed adverse effect level (LOAEL) of 1085 mg/kg bw/d was determined (EU RAR, 2008).

Dermal

Considering the LOAEL available from a mice rat study (approximately 5750 mg/kg bw/week equivalent to 1643 mg/kg bw/d), the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a study conducted in NMRI mice (50 animals/sex/dose), the chemical (65.79 % solution) was applied to skin twice per week at doses of 0, 0.018 and 0.18 mL (equivalent to 2875 mg/kg for the high dose and 288 mg/kg for the low dose per application) for 105 weeks (for males) or 89 weeks (for females) (refer to **Carcinogenicity** section). At the application site, slight treatment-related increase in the incidence of acanthosis (thickening of the skin) and hyperkeratosis (thickening of the outer layer of the skin) was observed. High dose females had increased absolute and relative liver and adrenal weights (EU RAR, 2008). The lowest observed adverse effect level (LOAEL) value was determined to be 5750 mg/kg bw/week equivalent to 1643 mg/kg bw/d.

Inhalation

No data are available.

Genotoxicity

Positive results were reported for several *in vitro* point mutation assay (Ames test) in *Salmonella typhimurium* strains TA100, 1535 and 1537, with or without metabolic activation. Positive results were also observed in other *in vitro* assays using the chemical. A negative result was reported for one *in vivo* assay (mouse micronucleus test). The genotoxic potential of the chemical was determined to be equivocal based on the results from available mutagenicity studies.

The chemical in its purified form converts pH-dependently into the more reactive epoxy form, EPTAC. The chemical also undergoes hydrolytic conversion into EPTAC in aqueous media. EPTAC is a mutagen and was determined to be responsible for some of the positive results in *in vitro* tests (EU RAR, 2008).

In vitro

The chemical was found to be genotoxic in an Ames test using *Salmonella typhimurium* strains TA100 and TA1535, with or without metabolic activation. The chemical was found to be clastogenic in a cultured human lymphocytes in a lymphocyte chromosome analysis and elicited unscheduled DNA synthesis in rat hepatocytes at concentrations higher than 0.1 mg/mL. The chemical also significantly increased the forward mutation frequency of the hypoxanthine phosphoribosyl transferase (HGPRT) gene locus in Chinese hamster ovary (CHO) cells, with and without metabolic activation (EU RAR, 2008; REACH).

In vivo

The chemical gave negative results in a micronucleus test conducted in BOR:NMRI mice at a dose of 147 mg/kg bw (EU RAR, 2008; REACH).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in the HSIS (Safe Work Australia). The data support this current classification.

In a two-year dermal painting study conducted in NMRI mice (50 animals/sex/dose), the chemical (65.79 % solution) was applied to skin twice per week at a dose of 0, 0.018 and 0.18 mL (equivalent to 2875 mg/kg bw for the high dose and 288 mg/kg bw for the low dose per application) for 105 weeks (for males) or 89 weeks (for females). There were treatment-related and statistically significant increases in the incidence of lung carcinomas and adenomas. The high dose group incidence exceeded the spontaneous tumour incidence in this species historically. A statistically significant increase in the incidence of focal hyperplasia in the glandular mucosa of the stomach in both sexes combined was also observed (EU RAR, 2008).

Reproductive and Developmental Toxicity

In the absence of more comprehensive information, the available study does not show specific reproductive or developmental toxicity of the chemical.

In a two-year study conducted in NMRI mice (refer to **Carcinogenicity** section), statistically significant decrease in absolute and relative testes weight was reported in high dose males. The relevance of this effect for this particular endpoint is uncertain.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity).

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Although the public could come into contact with cationic materials made from the chemical, it is expected that the chemical will be bound within the cationic

materials and hence will not be bioavailable. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

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 systemic long-term 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.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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]
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[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:

- 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. (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CAS No. 3327-22-8). Accessed March 2016 at http://echa.europa.eu/documents/10162/7ce22d7d-8793-4da1-903d-60fbf738aacd

Galleria Chemica. Accessed March 2016 at http://jr.chemwatch.net/galleria/

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CAS No. 3327-22-8). Accessed March 2016 at http://echa.europa.eu/registration-dossier/-/registered-dossier/8186

Safe Work Australia. Hazardous Substances Information System (HSIS). Accessed March 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Accessed March 2016 at https://www.comlaw.gov.au/Details/F2016L00036

Last update 21 April 2016