2-Propanol, 1,1',1''-nitrilotris-: Human health tier II assessment

22 March 2013

CAS Number: 122-20-3

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.

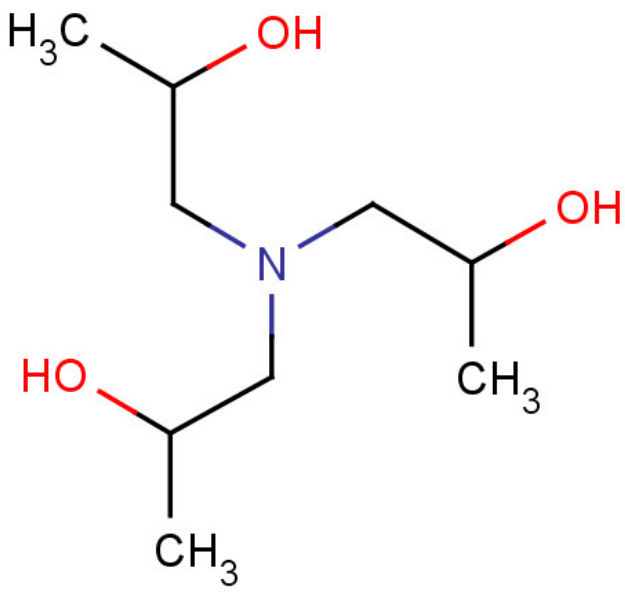
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Triisopropanolamine 1,1',1''-Nitrilotri-2-propanol Tris(2-hydroxypropyl)amine Tris(2-propanol)amine TIPA
Structural Formula	
Molecular Formula	C9H21NO3
Molecular Weight (g/mol)	191.269
Appearance and Odour (where available)	Solid white crystal with a slightly ammonia-like odour
SMILES	C(C)(O)CN(CC(C)O)CC(C)O

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 100 and 1000 tonnes.

The chemical has reported commercial use including:

- an additive in construction materials; and
- as a component of surface-active agents and corrosion inhibitors.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances and Preparations in the Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB):

The chemical has reported cosmetic use as:

- a buffering agent in cosmetic products; and
- an ingredient found in personal care products such as bubble-bath formulations, shampoos, and waterless hand cleaners.

The chemical has reported domestic use including:

- as a component in all-purpose cleaners, fine fabric washes, and light-duty dishwashing liquids.

The chemical has reported commercial use including:

- in coatings as a cross-linker and acid neutraliser;
- grinding aid in cement and concrete;
- in rubber production, electroplating processes, and textile finishing operations; and
- as an additive in fuel, in plastics, and in wood protection.

The chemical has reported site-limited use including:

- as a processing aid in paper, textiles, and leather; and
- in industrial gas treatments and metal working fluids.

Restrictions

Australian

No known restrictions have been identified.

International

Cosmetics

US Cosmetic Ingredient Review (CIR) found the chemical to be safe, with qualifications:

- Safe for use in cosmetic products, but should not be used in products in which N-nitroso compounds can be formed.

Listed on Cosmetics Directive (CosIng) with a Cosmetic restriction - Annex III/62 (List of substances which cosmetic products must not contain, except subject to the restrictions laid down):

- Maximum concentration in ready for use preparation is 2.5%, do not use with nitrosating systems, minimum purity of 99%, maximum secondary amine content of 0.5% (applies to raw materials), maximum nitrosamine content of 50µg/kg, keep in nitrite free containers.

Food Packaging

European Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food - Annex I: Substances.

US FDA Indirect Food Additives: Adhesives and Components of Coatings - Substances for Use Only as Components of Adhesives.

Canada Ingredient Disclosure List (SOR/88-64) if greater than a concentration of 1% w/w.

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):

Xi; R36 (Irritating to eyes).

Exposure Standards

Australian

No exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

Time Weighted Average (TWA) of 5.8 mg/m³ (2 ppm) in Germany.

United States Department of Energy Temporary Emergency Exposure Limits (TEELs):

- TEEL 0 (no effects) at 10 mg/m³;
- TEEL 1 (reversible effects) at 30 mg/m³;

- TEEL 2 (irreversible effects) at 50 mg/m³; and
- TEEL 3 (life-threatening effects) at 250 mg/m³.

Health Hazard Information

Toxicokinetics

The only available study examining the toxicokinetics of the chemical is reported in SIDS (OECD 2009) where rats were administered an equivalent of 10.7 mg/kg bw of the chemical as single oral dose of the chemical salt of 2,4-dichlorophenoxyacetic acid (2,4-D TIPA salt). A minimum of 83.8% of the chemical was reported to be absorbed. The kidney was reported to be the major route of excretion with 80% of the dose excreted in 24 hours via the urine. Excretion via the faeces and expired air accounted for 7% and 5% respectively after 72 hrs.

Acute Toxicity

Oral

The chemical exhibits low acute toxicity in animal tests as evidenced by reported oral LD50 in rats of greater than 2000 mg/kg bw (LD50 = 5994 mg/kg bw and 6500mg/kg bw) (OECD 2009). Observed sub-lethal effects included lethargy, watery eyes and diarrhoea. The oral LD50 in guinea pigs was reported as 1580 mg/kg bw (OECD 2009).

Dermal

The chemical exhibits low acute toxicity in animal tests as evidenced by reported dermal LD50 in rabbits of greater than 2000 mg/kg bw.

No reported systemic toxicity was reported in two female New Zealand White rabbits exposed to 5000 mg/kg of the chemical as an 85% aqueous solution (OECD 2009). Exposure was achieved over an 24 hrs exposure period via an impervious cuff, adhered onto the trunk. The 14 day follow up evaluation period showed no evidence of systemic toxicity.

Inhalation

There are no reliable studies available to determine acute inhalation toxicity due to the low vapour pressure of the chemical.

Corrosion / Irritation

Respiratory Irritation

The chemical was reported to be a respiratory irritant in Swiss Webster mice, with a 50% respiratory rate decrease (RD50) at 815 mg/m³ (OECD 2009). Sensory irritation and pulmonary irritation were observed after exposure to an aerosol concentration range from between 329 mg/m³ to 1070 mg/m³, for 3 hours with a 20 minute recovery period. Moderate to good recovery of animals was observed immediately post-exposure. The RD50 value of the chemical was reported to be of moderate potency.

There is sufficient evidence to classify the chemical as irritating to the respiratory system.

Skin Irritation

Studies were performed in accordance with OECD Test Guideline (TG) 404 (OECD 2009). The chemical irritated the skin of small White Russian rabbits after 4 hours of semi-occlusive application.

In this study (OECD 2009), the chemical was applied to the shaved skin on the dorsal and lateral portion of the rabbit trunk, followed by 14 days' observation. Draize scores of 4 were reported for erythema and oedema, that were reversible within 24 hrs.

In a modified OECD TG 404 study, the chemical was reported as a slight irritating to Vienna White rabbits (REACH 2013) exposed for 1, 5, 15 mins or 20 hours under occlusive conditions. Observations occurred for the following 8 days. The skin was reported as appearing blotched in only the 20 hour application group, with an averaged erythema scrore of 1.5 for 4 animals after 24, 48 and 72 hours. In one animal, the skin remained scaly after 6 days.

In a non guideline study using one New Zealand White rabbit, the chemical was administered for several applications to the abdomen, resulting in continuous contact with intact skin (either unoccluded or under cotton gauze). Moderate redness, very slight swelling, slight exfoliation and development of a superficial burn were reported (OECD 2009).

There is sufficient evidence to classify the chemical as irritating to skin.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The data available indicate that the classification should be amended to 'Risk of serious damage to eyes' (Xi; R41).

In an OECD TG 405 study, the chemical was reported as an eye irritant causing irreversible effects in one animal (OECD 2009). Following application of 0.1 g of the chemical into one eye of 6 Russian White rabbits (washed out after 24 hours), animals were observed at 1, 24, 48 and 72 hours, and 5, 7, 10, 12 and 21 days. Mean 24, 48 and 72 hour irritation/corrosion scores for corneal opacity, iris lesions, conjunctival redness and chemosis were 1.22, 0.67, 3 and 0.94 respectively. All irritation parameters were reversible by day 12 for all animals except one. In one rabbit, corneal opacity, iris lesions, conjunctival redness and chemosis scores of 3, 1, 2 and 2 respectively were still observed at 21 days.

In a modified OECD TG 405 study using two rabbits, the chemical was reported as irritating to the eye causing slight opacity, slight to moderate erythema and chemosis. In one animal, corneal opacity was irreversible by the end of the 8 day observation period. All other irritation parameters were reported as reversible.

Sensitisation

Skin Sensitisation

The chemical is reported to be not sensitising to the skin of guinea pigs (REACH 2013).

In a modified study using the Maguire method for sensitisation, 10 male Hartley albino guinea pigs received four applications of the chemical (22.9% in water) using a gauze patch, within a 10 day period. The animals were challenged after a two week rest period. No test animals reported signs of hyperaemia or oedema. The data indicate that the chemical is not a skin sensitiser.

Observation in humans

A lotion product containing 1.1% of the chemical was reported as not sensitising to the skin (REACH 2013).

The lotion product was applied to 98 volunteers for 48 hrs using open and occlusive patches. After a non-treatment period of approximately 14 days, a second set of open and occlusive patches was applied and scored 48 h later. After scoring the second occlusive patch reactions, these same test sites of all panellists were irradiated for 6 minutes and scored for effects on the skin 48 hrs later. No reactions were observed at the first or second open patch, the first occlusive patch, or 48 h after irradiation.

Weak to strong reactions were reported at the second occlusive patch in seven subjects. These reactions were reported as not clinically significant.

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) of 272 mg/kg bw/day from beagle dog studies, and based on the treatment related effects reported in other studies, the chemical is not considered to cause serious damage to health by repeated oral exposure.

The only reliable study available was a 100 day dietary study in beagle dogs conducted in accordance with the US FDA Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food (OECD 2009). The chemical was administered at 0, 500, 2000 or 7500 ppm to 4 animals/sex/dose (approximate doses of 0, 16.8, 71.2 and 272 mg/kg bw/day in males or 0, 19.7, 78.3 or 288 mg/kg bw/day in females). The NOAEL was reported to be 272 mg/kg bw/day for males, and 288 mg/kg bw/day for females.

In a non-guideline study in Fischer 344 rats, the chemical was administered via drinking water for 14 days at doses of 100, 300, 600, 1200 and 2000 mg/kg bw to 5 animals/sex/dose (OECD 2009). Decreased protein, albumin and glucose, and increased kidney weights were observed in doses greater than or equal to 300 mg/kg bw/day. Histological examinations of the liver, kidney and urinary bladder were reported to not show evidence of an effect.

In another non-guideline drinking water study in Sherman rats, the chemical was administered for 30 days at doses of 140 to 1350 mg/kg bw/day to 5 rats/dose (OECD 2009). Micropathological lesions in liver, kidney, spleen or testes were observed at doses greater than or equal to 260 mg/kg bw/day; the exact nature and extent of these observations were not reported.

Dermal

Considering the NOAEL for local effects available from rat studies (300 mg/kg bw/day), the chemical is not considered to cause serious damage to health by repeated dermal exposure.

In a 28 day OECD Guideline 410 study in Fischer 344 rats, a NOAEL of 3000 mg/kg bw/day for systemic toxicity and a NOAEL of 300 mg/kg bw/day for local effects was reported (OECD 2009). The chemical was administered via a patch at 300, 1000 or 3000 mg/kg bw/day for 5 days/week (21 applications) to 5 animals/sex/dose. Erythema and scabs were reported in one animal at each of the highest two doses. Most animals at 3000 mg/kg bw/day had dermal hyperplasia in the form of minimal thickening. There were no mortalities and no systemic toxicity reported in treated animals.

Inhalation

No data are available.

Observation in humans

The dermal irritancy of a lotion product containing 1.1% of the chemical was evaluated in a 21 day cumulative irritation study using 10 volunteers. Occlusive patches containing 0.3 ml of lotion were applied to the upper back, removed after 23 hrs, washed and then reapplied. Application occurred for 21 consecutive days. Nine out of 10 participants demonstrated a slight skin irritation (REACH 2013).

Genotoxicity

The chemical is not considered to be genotoxic based on an in vivo and several in vitro studies.

The chemical tested negative in several in vitro (Ames reverse mutation assay, Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase assay and chromosomal aberration assays) and one in vivo (micronucleus assay) test for gene mutation and clastogenicity (OECD 2009).

In an OECD TG 474 guideline in vivo micronucleus assay in mice, a single oral dose of the chemical was administered via gavage at 500, 1000 or 2000 mg/kg bw to 5 animals/sex/dose (REACH 2013). In comparison to the negative control no increases in the rate of micronuclei, differences in the number of small or large micronuclei, or inhibition of erythropoiesis were reported. The chemical was reported to be negative for chromosomal aberration. Irregular respiration and piloerection were reported 30 minutes after administration at all three dose levels, but were not observed after 2 to 4 hrs.

The chemical was also reported as negative for genotoxicity in two in vitro guideline studies using mammalian cells (Chinese Hamster ovary cells and rat lymphocyte cells) with and without metabolic activation, and one in vitro study using bacterial cells (several strains of *S. typhimurium*) with and without metabolic activation (OECD 2009).

Carcinogenicity

The chemical was not considered carcinogenic to the liver of male Wistar rats that were fed 1000 mg/kg bw/day of the chemical in their drinking water for a continuous 104 week treatment (REACH, 2013). No tumour formation in the liver was reported after histological examination and as a result, the chemical is considered to have low carcinogenic potential.

Reproductive and Developmental Toxicity

The chemical is not considered to be a reproductive or developmental toxicant.

In a one-generation US FDA guideline study, 25 animals/sex/dose of Sprague Dawley rats were fed concentrations of 0, 500, 2000 or 7000 ppm (approximately 0, 39.7, 160 or 609 mg/kg-bw in males or 0, 43.7, 182 or 700 mg/kg-bw in females) of the chemical, for 5 weeks prior to mating, during gestation and lactation (OECD 2009). Offspring (20/sex/dose only) were also administered the same oral doses for 90 days after weaning. Ophthalmologic exams, clinical chemistry tests and urinalysis were conducted. For the F1 generation controls and high-dose animals, histopathological examinations were conducted on all organs; for the low and intermediate dose animals, examinations were conducted on lungs, liver, kidneys and organs with lesions. No adverse clinical, histological or reproductive effects (gestation length, litter numbers, litter size, survival, body weight) were observed. No differences were seen in the number of litters or litter size, survival, body weight or clinical signs. The NOAEL (F1 generation) was reported to be 609 mg/kg bw/day for males and 700mg/kg bw/day for females.

In an OECD TG 414 guideline study (prenatal developmental toxicity) using Wistar rats, the chemical was administered via oral gavage to 25 animals/sex/dose at 0, 100, 400, 1000 mg/kg bw/day, for 20 days (REACH 2013). Maternal toxicity was observed at 1000 mg/kg bw/day. Gestational parameters were not influenced by the chemical in any test dose group. No signs of embryo/foetotoxicity or induced teratogenicity were reported in the highest dose of 1000 mg/kg bw/day. The NOAEL for paternal rats was 400 mg/kg bw/day and 1000 mg/kg bw/day for the foetus.

Risk Characterisation

Critical Health Effects

The chemical possesses hazardous properties such as serious eye damage and irritation to the skin and respiratory system.

These properties are assumed to be related to the basicity of the chemical. If it is neutralised as a buffering agent in commercial formulations, the irritancy would expect to be greatly reduced.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used overseas as a buffering agent in cosmetics (CosIng) and in personal care products, where the general public may be exposed to the chemical through dermal and/or inhalation routes. However, based on the limited US information derived from the National Library of Medicine (NLM) Household Products Database, the concentration (0.1 - 1%) in these products is not considered to be sufficiently high to cause corrosive effects. If the concentrations in cosmetics are low, irritation effects are not expected. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered low particularly at concentrations below 20% or if adequate control measures to minimise occupational exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls. The existing hazard classification for worker health and safety is considered appropriate based on available data.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient provided that the recommendation is adopted for the amendment of the classification and labelling of the chemical and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Considering the available information to indicate low public exposure from this chemical no regulatory controls are recommended.

Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

[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 label instructions.

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 storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 assist with meeting 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 and physicochemical (physical) hazards) of chemicals are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

References

2006 NICNAS: Australian High Volume Industrial Chemicals List (AHVICL),

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