1,3-Propanediamine, N,N-dimethyl-: Human health tier II assessment

03 July 2015

CAS Number: 109-55-7

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.

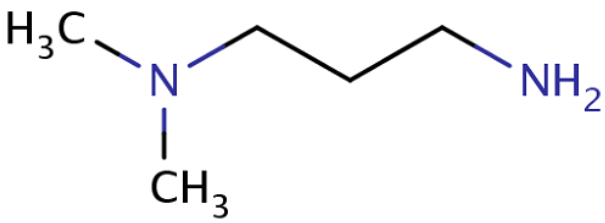
For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

Acronyms & Abbreviations

Chemical Identity

Synonyms	dimethylaminopropylamine (DMAPA) 3-(dimethylamino)propylamine 3-amino-1-(dimethylamino)propane n,n-dimethylpropylenediamine propylamine, 3-(n,n-dimethylamino)-
Structural Formula	
Molecular Formula	C5H14N2
Molecular Weight (g/mol)	102.18
Appearance and Odour (where available)	colourless liquid
SMILES	C(N)CCN(C)C

Import, Manufacture and Use

Australian

The chemical was reported under previous mandatory and/or voluntary calls for information with reported domestic uses in cleaning/washing agents and additives.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation and Authorization of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in the Nordic countries (SPIN) database;
- the Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Report (SIAR);
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and
- the US Department of Health and Human Services, Household Products Database (HPD).

The chemical has reported domestic uses including in:

- cleaning/washing agents;
- paints, lacquers and varnishes;
- adhesives (binding agents) (at concentrations of 1–5 % in paste, powder and liquid home-maintenance products); and
- odour agents.

The chemical has reported commercial uses including:

- as a process regulator;
- as a fuel additive, e.g. additive for petrol;
- in construction materials;
- as an anti-static agent;
- as an anti-shrinking agent for leather;
- as a cross-linking agent for cellulose fibres in the paper industry; and
- as a curing agent for epoxy resins used within the plastics industry.

The chemical has reported site-limited use as an intermediate in producing surfactants and liquid soaps, binding agents, ion-exchange materials (e.g. resins), flocculating agents (water treatment), polyurethane fibres and lubricants, cosmetic agents, agents in the photographic and textile industries, laboratory chemicals (e.g. dye, Basic Blue 22), and washing and cleaning agents (e.g. betaines).

The chemical has reported non-industrial use as an intermediate in agrochemicals (e.g. pesticides) and pharmaceuticals.

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 5, under '*Amines*' 'for use as curing agents for epoxy resins **except** when separately specified in these Schedules' (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

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of Substances which cosmetic products must not contain except subject to the restrictions laid down. The chemical, under the category '*monoalkylamines, monoalkanolamines and their salts*' has restricted use with a maximum secondary amine content in finished cosmetic products of 0.5 %;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain subject to the restrictions laid down.
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III Part 1—List of substances which cosmetic products must not contain except subject to the restrictions laid down.

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):

- Xn; R22 (Harmful if swallowed);
- C; R34 (Causes burns); and
- Xi; R43 (May cause sensitisation by skin contact).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standard is identified for the chemical (Galleria Chemica).

A time weighted average (TWA) exposure limit of 1.14–2 mg/m^3 in different countries such as Canada, Latvia, Russia and the United States of America (USA).

Health Hazard Information

The chemical 1,3-Propanediamine, N,N-dimethyl- (also commonly known as dimethylaminopropylamine (DMAPA)) is a diamine, an organic compound derived from acrylonitrile and a dimethyl amine. The chemical is miscible in water (OECD, 2000) and the alkalinity of the chemical is expected to cause pH-dependent local effects such as corrosion, and also sensitisation that is capable of causing allergic dermatitis (HSDB).

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 data support this classification.

The chemical has moderate acute toxicity based on results from an animal study conducted according to OECD Test Guideline (TG) 401 in male and female Sprague Dawley (SD) rats and in another non-guideline study in rats following oral exposure. The median lethal doses (LD50s) were reported to be 410 and 1600 mg/kg bw, respectively (REACH).

Non-guideline acute oral toxicity studies, as reported by OECD, include LD50 values between 922–1870 mg/kg bw for male rats, 1037 mg/kg bw for female rats and 1500–1640 mg/kg bw for mice (OECD, 2000; US NTP, 2004; RTECS).

Dermal

No data are available for this chemical.

Inhalation

The chemical has low acute toxicity based on results from an animal study conducted according to OECD TG 401 in male and female Wistar rats following inhalation exposure. The median lethal concentration (LC50) was reported to be > 4.31 mg/L (OECD, 2000; US NTP, 2004; REACH).

Observed sub-lethal effects reported included eyelid closure and accelerated respiration during exposure (REACH).

These reported effects in animals and humans (refer to the **Acute toxicity: Observation in humans** section) are most likely due to the corrosive nature of the chemical (refer to the **Corrosivity** section).

Observation in humans

In humans, the chemical vapours caused corneal disturbance and blurred vision in workers exposed to a concentration of 30 ppm in air over several days. Observed reversible effects reported included vision becoming blurred towards the end of the work day (sometimes with the appearance of haloes around lights), pain, photophobia and headaches (HSDB).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (Xn; R34) in the HSIS (Safe Work Australia). The available data support this classification.

In an acute dermal irritation and corrosion study (OECD TG 404) with study deviations (no available Draize scores), 0.5 mL of the chemical was applied to three New Zealand White rabbits, under semi-occlusive conditions on shaved skin for up to four hours, with observation for 14 days (at three minutes, one hour and then 24-hour intervals) after patches were removed. Slight to severe erythema was observed in treated animals after contact for three minutes. One to four hours post-exposure, the treatment areas became necrotic in all animals (REACH).

In another acute dermal irritation and corrosion study (OECD TG 404) with study deviations (no control tested), 0.5 mL of the chemical was applied to six New Zealand White rabbits, under semi-occlusive conditions on shaved and abraded skin for up to

24 hours, with observation for 14 days (immediately after unwrapping; and at 24 hours, 48 hours, 72 hours, 4 days and 14 days) after patches were removed. Moderate to severe erythema was observed immediately after unwrapping following the three-minute contact (mean score at three minutes: ≥ 3.5) with slight oedema (mean score at three minutes: ≥ 1.5). One hour post-exposure, visible necrosis was observed on the treated skin (mean score at 1–24 hours: ≥ 4). Sloughed skin at the application sites was reported one hour and 24 hours following exposure. The primary dermal irritation index was reported to be ≥ 8, indicating severe dermal irritation at four hours and 24 hours post-exposure (REACH).

In a non-guideline dermal irritation and corrosion study, an unspecified dose of the chemical (liquid form) was applied to two Vienna White rabbits, under occlusive conditions for up to 15 minutes, with observation for three weeks (on the same day and at 24 hours, 48 hours, 72 hours, eight days and three weeks) after patches were removed. Haemorrhages was observed in animals after contact for 15 minutes (mean score 24–48 hours: 2). Eight days following the exposure, bean-sized crusting of the skin was reported. Increased hair growth was also observed during the post-observation period (REACH).

According to the OECD, the chemical (depending on its concentration), had a strongly irritating or corrosive effect on the skin and mucous membranes. No further study details were available (OECD, 2000).

In a non-guideline eye irritation study, it was reported that application (one drop) of the chemical to the eyes of two rabbits caused severe, irreversible corrosion. Ten minutes to six days post-exposure, brown-reddish discoloration of conjunctivae, bloody secretions, opacity, slight chemosis and welling up of eye lenses were reported. Post-observation-period evaluation was not possible due to the suppuration (formation of pus) of the eyes (REACH).

Observation in humans

Skin irritation from the chemical has been reported following human exposure.

Occupational exposure to the chemical, which occurred when the chemical was fed into a high-temperature reactor, resulted in a repeated occurrence of a scaly, itchy rash on the subject's face and right hand palm. Patch tests conducted with a 1 % dilution of the chemical reported positive reactions (OECD, 2000).

These reported effects are most likely due to the corrosive and sensitising nature of the chemical (refer to the **Corrosivity** section).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (Xn; R43) in the HSIS (Safe Work Australia). The available data support this classification.

In a study (OECD TG 429), the chemical was reported to be positive for skin sensitisation in a mouse local lymph node assay (LLNA). Female CBA mice (minimum four/dose) were administered daily applications of 0 %, 0.5 %, 1 %, 2.5 %, 5 %, or 10 % (w/v) of the chemical in acetone/olive oil (ratio of 4:1). Stimulation indices of 0, 1.3, 1.1, 3.5, 7.0 and 13.9 were reported, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was reported to be 2.2 % (REACH).

In an additional skin sensitisation study on the chemical, positive results for skin sensitation was also reported. In a guinea pig maximisation test (GPMT) conducted in accordance with OECD TG 406, female Hartley guinea pigs (15/dose) were administered a 1 % (v/v) solution of the chemical (in distilled water) by an intradermal and epicutaneous injection. The animals were topically induced with a 5 % (v/v) concentration of the chemical in distilled water. Skin sensitisation was reported in 1/15 animals challenged with 1 % of the chemical and 1/15 animals challenged with 5 % of the chemical, when observed 48 hours post-challenge (OECD, 2000; HSDB; REACH).

Observation in humans

The previously reported incident provided evidence of sensitisation as well as corrosion (refer to the **Irritation: Observation in humans** section).

Repeated Dose Toxicity

Oral

Based on the data available, repeated oral exposure to the chemical is associated with local effects.

In a repeated dose 28-day oral toxicity study (OECD TG 407), male and female Wistar rats (five/sex/dose) were administered the chemical daily by oral gavage doses of 0, 10, 50 and 250 mg/kg bw/day. At the highest dose, mortality occurred in four females on days 11, 18, 22 and 25, and one male animal exhibited irregular and noisy respiration on days 11 and 12 of the study. Histopathological examinations indicated local irritation at the highest dose. These local effects included lung discoloration with multiple red spots/lesions and foamy content on the surface of lungs of the females that died, indicating congested organs; pulmonary haemorrhage; oedema consistent with cardiorespiratory failure; decreased size of the spleen in one female and focal ballooning degeneration of the squamous epithelium of the forestomach of one male rat. The other observed effects at the highest dose, included decreased spontaneous activity, stilted gait, swollen abdomen, respiratory sounds, gasping and panting in females, which were commonly observed in females that died. The study reported no treatment-related adverse effects for systemic oral toxicity (OECD, 2000; HSDB; REACH).

Dermal

No data are available for this chemical.

Inhalation

No data are available for this chemical.

Observation in humans

Based on the human data available, repeated oral exposure to the chemical, DMAPA, is associated with local effects, most likely due to its corrosive nature (refer to the **Corrosivity** section).

In a US field study (1974), it was reported that workers occupationally exposed through inhalation to 2.34–5.87 mg/m^3 (0.55–1.38 ppm) to DMAPA reported impaired respiration (wheezy breath, constricted chest, and irritated mucosa of the eyes, nose and pharynx) (OECD, 2000).

In a 1977 cross-sectional, serial examination conducted at the same factory with 34 workers, an average DMAPA concentration of 0.55 mg/m^3 (0.13 ppm) was measured in workers. Of the 28 subjects exposed to the chemical, five subjects reported irritation of the nasal mucosa and two subjects reported increased mucous formation in the respiratory tract. Six workers with non-specified tasks had a significant reduction (3.9 %) in vital capacity at the end of the first working day of the week, compared with results obtained before starting work (OECD, 2000).

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic.

Several in vitro assays using the chemical gave negative results (OECD, 2000; HSDB; REACH) in the following studies:

- bacterial mutation assays (various *Salmonella typhimurium* strains) with and without metabolic activation at doses of up to 10000 µg/plate;
- a mammalian cell gene mutation assay in mouse lymphoma L5178Y cells with and without metabolic activation at doses of up to 300 µg/mL;
- chromosomal aberrations in human peripheral blood lymphocytes with and without metabolic activation at doses of up to 715.4 µg/mL.

The chemical gave a negative result in an in vivo mammalian erythrocyte micronucleus test in mouse bone marrow cells at doses up to 100 mg/kg (REACH).

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of this chemical. Based on the available genotoxicity data (refer to **Genotoxicity** section), the chemical is not considered likely to be carcinogenic.

Additionally, the chemical presented no alerts for mutagenicity or carcinogenicity based on its molecular structure as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.2.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not a reproductive or developmental toxicant.

In a combined repeated dose reproductive developmental toxicity screening test (OECD TG 421), SD rats that were administered the chemical by oral gavage showed no treatment-related adverse effects on reproductive or developmental parameters at doses up to 200 mg/kg bw/day (OECD, 2000; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (corrosive effects on the skin, eyes, gastrointestinal and respiratory tracts; and skin sensitisation).

Public Risk Characterisation

The chemical has uses in domestic products and is part of adhesive (binding agent) formulations, including, possibly, epoxy resins. However, it is expected to be present at low concentrations (refer to **Import, manufacture and use** section) in these products. In cleaning and washing agents, the function is assumed to be buffering and very little free amine is in these products. The main route of public exposure is expected to be skin and eye contact, or inhaling vapours. Labelling for DMAPA epoxy formulations is controlled by the *Poisons Standard* (SUSMP, 2015). Provided that the appropriate precautions are taken to avoid skin and eye contact and inhaling vapours, the risk from using domestic products is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal, inhalation and ocular 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, inhalation and ocular 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.

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, 2015).

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 if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)

[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, dermal, inhalation and ocular 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 which 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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