Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-: Human health tier II assessment

03 July 2015

CAS Number: 2855-13-2

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.

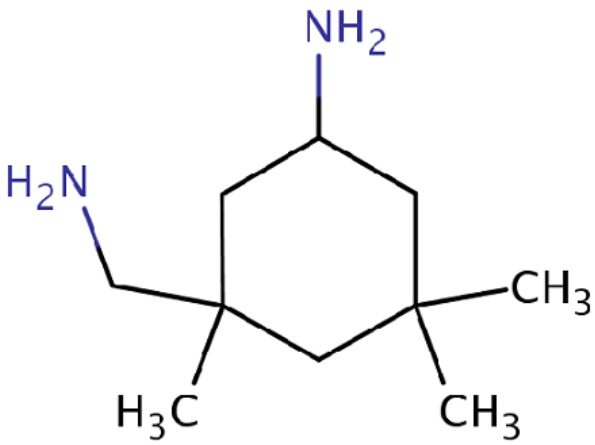
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	isophorone diamine 3-aminomethyl-3,5,5-trimethylcyclohexylamine 5-amino-1,3,3-trimethylcyclohexanemethylamine 1-amino-3-aminomethyl-3,3,5-trimethylcyclohexane 1,3,3-trimethyl-1-aminomethyl-5-aminocyclohexane
Structural Formula	
Molecular Formula	C10H22N2
Molecular Weight (g/mol)	170.30
Appearance and Odour (where available)	colourless liquid
SMILES	C1(C)(C)CC(C)(CN)CC(N)C1

Import, Manufacture and Use

Australian

Under previous mandatory and/or voluntary calls for information, the chemical was reported as having domestic uses in adhesives (binding agents) and unspecificed use in manufacturing other chemicals.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 10,000 and 99,999 tonnes.

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 Nordic countries (SPIN) database;
- the Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset Initial Assessment Report (SIAR);
- the United States (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;
- corrosion inhibitors for metals;
- surface treatments/adhesives (binding agents) (at concentrations of 5–50 % in paste, powder and liquid home maintenance products as epoxy resin hardeners, and in epoxy formulations);
- fillers; and
- insulating materials.

The chemical has reported commercial uses including:

- as a process regulator;
- in construction materials, e.g. paving/floor covering, concrete protection and repair;
- as a solvent;
- as a viscosity adjustor;
- in lubricants and additives;
- as a fixing agents;
- as an anti-static agent; and

- as a curing agent for epoxy resins.

The chemical has reported site-limited uses, including:

- as an intermediate for manufacturing diisocyanates, dyes and hardeners for epoxy resins and coatings; and
- in manufacturing polymers (non-crystalline specialty polyamides), e.g. as a chain extender for polyurethanes.

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

No known restrictions have been identified.

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; R21/22 (Harmful in contact with skin and 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

No specific exposure standards are available.

Health Hazard Information

The chemical cyclohexanemethanamine, 5-amino-1,3,3-trimethyl- (also commonly known as isophorone diamine) is a cycloaliphatic amine, an organic compound derived from the alkaline condensation of acetone to isophorone followed by amination with ammonia and hydrogen (HSDB). The chemical is miscible in water (OECD, 2004) and the alkalinity of the chemical is expected to cause pH-dependent local effects including corrosivity (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 (with study deviations) in male Sprague Dawley (SD) rats following oral exposure. The median lethal dose (LD50) was reported to be 1030 mg/kg bw. Observed sub-lethal effects observed one hour post-exposure included restlessness, thirst, ruffled fur and tiredness. At necrosopy, irritation of the intestinal mucosa was reported. A few animals showed a slight increase in kidney weight and protein in the urine, indicating the kidney as a potential target organ. No further study details were available (OECD, 2004; REACH).

Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn; R21) in the HSIS (Safe Work Australia). While the available data do not support this classification, acute dermal exposure to the chemical is associated with local effects (refer to the **Corrosivity** section).

The chemical has low acute dermal toxicity based on results from an animal study conducted according to OECD TG 402 in male and female SD rats. The LD50 was reported to be >2000 mg/kg bw. Observed sub-lethal effects reported included slight to moderate skin reactions (discolouration/blackened skin in all animals, crust formation on days 1–14 and and scar formation on days 11–14 of the treated skin of some animals) dosed at 2000 mg/kg bw. At necrosopy, crust formation and mild to moderate scarring was observed at the treated sites of all animals and were considered to be skin wounds (REACH).

Inhalation

The chemical has low acute toxicity, based on the available data. An animal study conducted according to OECD TG 403 in male and female SD rats following inhalation exposure (aerosol) indicated the median lethal dose (LC50) as >5.01 mg/L. Observed sub-lethal effects reported included respiratory difficulties (laboured breathing) and a stained nuzzle for all animals. At the highest concentration, one male died during the four-hour exposure and two males during the post-observation period. At necroscopy, discoloured lungs were found in some animals following administration of lethal and sub-lethal doses (REACH).

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

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 a FDA guideline study, 0.5 mL of the undiluted chemical was applied to six New Zealand White rabbits under occlusive conditions on shaved and scarified dorsal skin for up to 24 hours, with observation for 72 hours (at 24 hours and then 48 hours) after the patch was removed. Immediately after unwrapping, and also 48 hours later, erythema scores of four were reported. Scoring for oedema was not possible post-exposure since the skin had become hard and leather-like. The results indicate severe dermal irritation for at least 48 hours post-exposure (REACH).

In another non-guideline study, 50 µL and 100–200 µL of the undiluted chemical was applied to the depilated skin (back) of rats and rabbits, respectively, under occlusive conditions for an unspecified exposure and observation period. Treatment-related effects reported included swelling, irritation and inflammatory effects (these effects were more intensive in rabbits than in rats). Repeated application caused severe effects on the skin including crust formation and necrosis, consistent with corrosivity. No further study details were available (OECD, 2004; REACH).

In an acute eye irritation/corrosion study (OECD TG 405), it was reported that application of 0.1 mL of the undiluted chemical (in liquid form) to the eye (conjunctival sac) of one female rabbit (Small White Russian) caused immediate severe, irreversible corrosion, opalescence of the eye (where scoring was not possible) and nose mucosa. Following 24 hours of exposure, necrosis of the conjunctivae (where lesions were non-reversible) were reported. As a result of this study, it was determined that only one animal be used as the chemical was corrosive. The chemical was euthanised after 24 hours (OECD, 2004; REACH).

Sensitisation

Respiratory Sensitisation

There is inconclusive evidence of respiratory sensitisation in humans (refer to the **Sensitisation: Observation in humans** section).

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 animal and human data (refer to **Sensitisation: Observation in humans** section) support this classification.

In a guinea pig maximisation test (GPMT) conducted in accordance with the OECD TG 406, male Dunkin-Hartley guinea pigs (20/dose) were administered 0.1 % (v/v) solution of the chemical (in 10 % ethanol) by an intradermal injection. The animals were topically induced with a 7.5 % (v/v) concentration of the chemical in 10 % ethanol one week later. Two concentrations, 2.5 % and 5 %, were used in the topical challenge phase two weeks after topical induction. Positive results were reported in 7/20 animals (24 hours post-exposure), 5/20 animals (48 hours post-exposure) and 2/20 animals (72 hours post-exposure) when challenged with 2.5 % of the chemical. At the 5 % challenge concentration, positive results were reported in 18/20 animals (24 hours post-exposure), 15/20 animals (48 hours post-exposure) and 10/20 animals (72 hours post-exposure) (OECD, 2004; REACH).

Skin sensitisation was also reported in two other GPMTs. In one GMPT, 0.5 % of the chemical in acetone was administered by intradermal injection followed by topical induction two weeks later with 0.5 % of the chemical (24 hours occlusive) and a challenge phase using 2 % of the chemical. Positive reactions for all the test animals were reported. In another GMPT, 1 % of the chemical in distilled water was administered by intradermal injection, then topical induction one week later used 1 % of the chemical (48 hours occlusive) and then challenged with 5 % and 10 % of the chemical. Positive reactions were reported in some animals at the highest challenge dose (OECD, 2004; REACH).

Observation in humans

Based on the human data available, sensitisation (occupational contact dermatitis and potential respiratory sensitisation) to the chemical has been reported following human exposure.

Skin sensitisation

Three out of 15 workers manufacturing plastic tennis rackets developed allergic contact dermatitis when exposed concomitantly to the chemical and epoxy resin. Symptoms appeared three months, six weeks or three weeks after starting this work and were reversible within three weeks after exposure to the material ceased. Patch tests were positive with 1, 2, or 5 % of the chemical administered in both ethanol and olive oil (OECD, 2004).

In a poorly documented 1978 study, workers who tested positive for the chemical were patch tested one month later with isophorone diisocyanate (1 %). All four workers were positive, while five control volunteers were negative. This study may indicate a cross-sensitivity between the chemical and its corresponding diisocyanate (OECD, 2004).

A number (142) subjects were identified as having skin disorders from current occupational exposure to epoxy compounds; 135 subjects had allergic contact dermatitis. Patch tests with 0.5 % the chemical were used on the subjects, as this concentration was reported to not induce irritation. It was reported that out of the 53 subjects who were patch tested for the chemical, three tested positive (OECD, 2004).

A 38-year old bricklayer had prolonged skin contact with a work shoe contaminated with the chemical (contained within a two-component glue). The man developed dermatitis on the chest, upper back, arms and legs and patch tests were positive to the chemical (0.5%) two months after the skin had healed (OECD, 2004).

A total of 137 employees across 10 companies preparing and using epoxy resins for coating, flooring, impregnating and repairing concrete, brick and wooden structures were examined. Positive patch tests were reported in 28 of the 137 employees (20 %), predominantly with 1 % epoxy resin in petrolatum (25 subjects tested positive; 18.5 %), but also with 0.1 % of isophorone diamine in olive oil (three subjects tested positive; 2.3 %). Positive correlation with the development of an allergy was reported with the frequency of exposure, the duration of employment and failure of the use of gloves (OECD, 2004).

Respiratory sensitisation

A 44-year-old man reported severe bronchial obstruction after working with resins and hardeners that released fumes of a mixture of trimethyl-1,6-hexanediamine and isophorone diamine. Eight hours after a deliberate challenge with the hardener, a large increase of airway resistance was reported. Seventy-two hours after the challenge, eosinophilia in the bronchioalveolar fluid, combined with a decrease in peripheral eosinophils, was observed, which was reversible when contact with the material ceased (OECD, 2004).

Repeated Dose Toxicity

Oral

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

In a repeated dose 90-day oral toxicity study (OECD TG 408), male and female Wistar rats (20/sex/dose) were administered the chemical daily in drinking water at doses of 0, 20, 60, or 160 mg/kg bw/day. Observations reported included renal effects (reduced absolute and relative kidney weights, morphological alterations in the kidneys indicating tubular nephrosis) in the higher dosed animals. There were no reported treatment-related adverse effects on clinical signs, symptoms or mortality (OECD, 2004; REACH).

Dermal

No data are available for this chemical.

Inhalation

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

In a non-guideline study, male SD rats (10/dose) were exposed (nose-only) to aerosol/vapour concentrations of 0, 18, 200, or 550 mg/m^3 (six hours/day) of the chemical, over 14 days. Effects reported included degeneration/necrosis in the olfactory epithelium of the nose at the lowest dose; and the trachea, larynx and lungs were affected at the highest dose (degeneration/necrosis, hyperplasia, squamous metaplasia). At the highest dose, mortality and significantly reduced mean body weights were reported. Dose-dependent histopathological changes were identified in the respiratory tract. Microscopic alterations in the lower respiratory tract were reversible in the low and medium dose groups after a 20-day recovery period (OECD, 2004; REACH).

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, 2004; REACH) in the following studies:

- bacterial mutation assays (various *Salmonella typhimurium* strains) with and without metabolic activation at doses of up to 50000 µg/plate;
- mammalian chromosome aberrations in CHO (Chinese hamster ovary) cells with and without metabolic activation at doses of up to 1375 µg/mL; and
- a mammalian gene mutation assay in CHO-K1 cells (OECD TG 476) with and without metabolic activation at doses of up to 2000 µg/mL.

The chemical gave a negative result in an in vivo mammalian erythrocyte micronucleus test in NMRI mouse bone marrow cells at doses of 50–500 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 expected to be a reproductive or developmental toxicant.

No studies on reproduction were available. In a 90-day repeated dose oral toxicity study (OECD TG 408) previously described (refer to **Repeat dose toxicity: Oral** section) male and female SD rats that were administered the chemical in drinking water showed no treatment-related adverse effects on reproductive organs at doses up to 160 mg/kg bw/day. No treatment-related adverse effects were observed in female SD rats, acccording to a prenatal development toxicity study (OECD TG 414) testing developmental parameters at doses up to 250 mg/kg bw/day (OECD, 2004; 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, possibly including, epoxy resins and as epoxy resin hardeners. 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 and inhaling vapours. Labelling for isophorone diamine epoxy formulations is controlled by the *Poisons Standard* (SUSMP, 2015). Provided that the appropriate precautions are taken to avoid skin and eye contact, or 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 in contact with skin (Xn; R21)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
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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