1,4-Cyclohexanedimethanol: Human health tier II assessment

22 November 2013

CAS Number: 105-08-8

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.

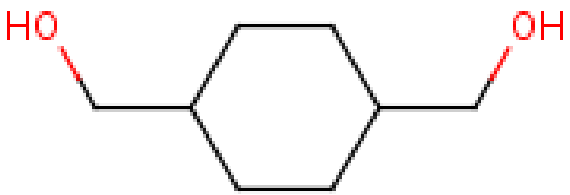
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,4-Bis(hydroxymethyl)cyclohexane Dimethylolcyclohexane Cyclohexanedimethanol Cyclohexane-1,4-dimethanol cyclohex-1,4-ylenedimethanol
Structural Formula	
Molecular Formula	C8H16O2
Molecular Weight (g/mol)	144.24
Appearance and Odour (where available)	Solid paste with mild hydrocarbon odour.
SMILES	C1(CO)CCC(CO)CC1

Import, Manufacture and Use

Australian

No specific Australian use information has been identified.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was 100–1000 tonnes.

International

The following international uses have been identified through 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); Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal; US Household Products Database; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical is included in CosIng database and US Personal Care Products Council INCI directory with the identified functions of a solvent and skin conditioning agent. However, there is currently no documented use of the chemical in cosmetic products in the United States (Personal Care Products Council 2011).

The chemical has reported domestic use including in:

- adhesives (binding agents); and
- paints, lacquers and varnishes.

The chemical has reported domestic use in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical or use of the materials that are produced from chemical reactions using the chemical. Available North American databases do not give evidence for use of the chemical in consumer products, indicating the chemical is not likely to be widely available for domestic use.

The chemical has reported site-limited use including:

- as an intermediate in manufacturing polyester resins, coatings and high performance polyester enamels; polyurethane foams and cyclohexane dimethanol glycidyl ether.

Restrictions

Australian

This chemical is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP, 2013) in Appendix B (Part 3).

Appendix B (Part 3) are the substances that are considered not to require control by scheduling due to low toxicity.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- temporary emergency exposure limits (TEELs) of 12.5 (TEEL-0), 40 (TEEL-1), 250 (TEEL-2), and 500 mg/m³ (TEEL-3) by the US Department of Energy.

Health Hazard Information

There are two geometrical isomers of this chemical, trans-(1,4-cyclohexanedimethanol) and cis-(1,4-cyclohexanedimethanol). The commercial product is a mixture of the two isomers. The two isomers are not listed separately on the Australian Inventory of Chemical Substances (AICS).

Toxicokinetics

Following oral administration of the chemical (70 % trans, 30 % cis-isomers) at dose levels up to 400 mg/kg bw/day in Sprague Dawley (SD) rats, the chemical was rapidly absorbed, and metabolised. The chemical was also rapidly eliminated within 48 hours, mainly in the urine (89–96 %), with smaller amounts in faeces (up to 3 %) and expired CO_2 (up to 0.05 %). The metabolic pathway for the chemical involves a series of oxidation reactions. While a partial oxidation product, 4-hydroxymethylcyclohexanecarboxylic acid, was detected in blood as well as in urine (31 %), cyclohexanedicarboxylic acid (the ultimate oxidation product) was only identified in urine and was the major metabolite (68 %). The cis-trans ratio of metabolites excreted in urine was the same as that of the original dose (OECD, 2011; REACH).

Acute Toxicity

Oral

The chemical had low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw. Observed sub-lethal effects included weakness, prostration and vasodilatation (US EPA, 2007; OECD, 2011; REACH).

Dermal

The chemical had low acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw. Sub-lethal adverse effects were not observed in this study (OECD, 2011).

Inhalation

Although appropriate data are limited, the chemical had low acute toxicity in animal test following inhalation exposure for six hours, with a reported median lethal concentration (LC50) of >1.25 mg/L in rats. In an acute inhalation toxicity study conducted before test guidelines were established, rats were exposed (whole-body) to the chemical at 1.25 mg/mL (calculated 212 ppm) for six hours (instead of standard four hours). There were no abnormal clinical signs or signs of systemic toxicity, and there were also no deaths during a 14-day observation period (OECD, 2011; REACH).

Corrosion / Irritation

Skin Irritation

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

In a skin irritation test (OECD TG 40), the chemical (0.5 g) was applied (semi-occlusive) to the shaved skin of New Zealand White rabbits for four hours. Animals were observed for four days following application. There were no signs of toxicity or ill health in any rabbit during the observation period and dermal irritation was also not observed in any animal throughout the duration of the study. The chemical was considered to be non-irritating to the skin of rabbits (REACH).

Eye Irritation

The chemical produced irritant effects in several eye irritation studies in rabbits. Whilst the reversibility of these effects was not consistent, the persistence of effects on the cornea in at least one animal in two separate studies supports classification (refer to **Recommendation** section). The severity of effects was correlated with the concentration of the chemical and was minimised by washing the eyes.

In an eye irritation study (OECD TG 405), 0.1 mL of the chemical was applied to the conjunctival sac of one eye of three New Zealand White rabbits. Average scores for corneal opacity (1.2), iris lesion (0), conjunctival redness (2) and chemosis (1.85) were reported at 24 and 72 hours for all three animals. At 72 hours following instillation, eyes were noted to have very slight or slight chemosis; slight to substantial discharge, with or without mucus; a crimson-red conjunctival appearance; and diffuse or easily discernible areas of opacity covering up to the entire corneal surface. Slight chemosis, moderate discharge with mucous, crimson-red conjunctival appearance, iritis, and areas of opacity ranging from diffuse to nacreous (milky opalescent) in appearance (covering up to three quarters of the corneal surface) were still evident in one animal on day eight of the study. As no evidence of recovery was evident in this animal on day eight, this animal was killed on humane grounds immediately after the assessment. Injection of the conjunctival blood vessels and periorbital swelling were also apparent in another animal one week after the treatment, which resolved during the subsequent week. The treated eye of the remaining third animal was normal during this time. The chemical was considered to be a moderate eye irritant (REACH).

In an eye irritation study (OECD TG 405), 0.1 mL of the chemical at different concentrations was applied to the conjunctival sac of one eye of New Zealand White rabbits. The chemical was applied initially at 100 % concentration in one rabbit followed by at 50 % concentration in the second rabbit. An additional three rabbits were added to the study and dosed in the same manner as the first two animals with 35 % concentration of the chemical. At 100 % concentration, there was no iritis noted during the study. Conjunctival irritation (redness, chemosis, discharge) cleared by day 21 and average scores for chemosis of 3–72 hours and two at days seven and 14 were noted. An average score of two for corneal opacity persisted up to day 21. At the 50 % concentration, corneal opacity or iritis were not noted during the study up to day 21. An average score of two was noted for chemosis up to 72 hours with conjunctival irritation (redness, chemosis, discharge) cleared by day seven. At 35 % concentration, there was no corneal opacity, iritis or conjunctival irritation noted at any observation period in the treated eyes. It was concluded that the chemical was corrosive in one rabbit eye at 100 % concentration, was an eye irritant in another rabbit eye at 50 % concentration, and was not an eye irritant in another three rabbits' eyes at 35 % concentration (REACH).

In another eye irritation study (OECD TG 405), 0.1 g of the chemical was applied to the conjunctival sac of one eye in each of the two New Zealand White rabbits, which were observed up to 14 days following treatment. While the treated eye of one rabbit was washed immediately with distilled water, the treated eye of the other rabbit was not washed. The scores for conjunctival redness in the unwashed eye were 2, 3, 3, 2, and 0 at 24 hours, 48 hours, 72 hours, seven days, and 14 days, respectively. Corneal opacity and iritis (grade 1) was observed up to 72 hours, but this was reversible. The washed eye only had slight redness one hour into the observation period. Based on conjunctival redness scores, the chemical was considered a Category 2A eye irritant (REACH).

Sensitisation

Skin Sensitisation

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

In a skin maximisation test (OECD TG 406), Dunkin Hartley guinea pigs were induced with intradermal injection of the chemical at 1 % concentration and followed by topical application of the chemical as supplied (undiluted). The challenge phase consisted of topical application of the chemical at 50 % concentration and also as supplied (undiluted). There was no evidence of skin sensitisation in any of the test animals (REACH).

Repeated Dose Toxicity

Oral

Considering the lowest observed adverse effect levels (LOAELs) available from a 13-week rat study (861/1754 mg/kg bw/day in males/females, respectively), and based on the treatment-related effects reported in various repeated dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a repeated dose toxicity study (OECD TG 408), SD rats were administered the chemical in drinking water at doses of 0, 4.0, 8.0 and 12.5 mg/L for 13 weeks. The approximate dose levels achieved were 0, 256/440, 479/754 and 861/1754 mg/kg bw/day in males/females, respectively. While treatment-related effects were not seen in animals receiving the low (4 mg/mL) and mid (8 mg/mL) dose levels, effects were noted in male and female animals treated with the highest dose (12.5 mg/mL). These effects included mortality, bloody or brown/red discoloured urine, softened and/or reduced faeces, reductions in body weight and body weight gains, decreased feed consumption, and increased urinary protein levels. There was no histological evidence of toxicity noted in any tissue. The NOAELs for the repeated dose toxicity were determined to be 479/754 mg/kg bw/day in males/females, respectively, based on effects observed at the highest tested doses (US EPA, 2007; OECD, 2011; REACH).

Similar effects were also observed in a reproductive and developmental screening test in rats where animals were exposed to the chemical for 13 weeks (see **Reproductive and developmental toxicity**).

In a subchronic toxicity study (conducted before the availability of standard guidelines), albino rats were fed the chemical at target concentrations of 0, 0.1 %, and 1 % for 36 days. The dose levels achieved were not reported. There were no significant treatment related effects on mortality, body weight, food consumption and feed efficiency, haematology, clinical chemistry, urinalysis, organ weights or gross or microscopic pathology in either sex of rats consuming diets containing up to 1 % of the test substance for 36 days. Therefore, the no observed adverse effect level (NOAEL) was determined to be 1 % for male and female rats (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical and its main metabolite (4-cyclohexanedicarboxylic acid) are not considered to have mutagenic or genotoxic potential.

The chemical tested negative (with and without metabolic activation) in a bacterial reverse mutation assay conducted using *Salmonella typhimurium* and *Escherichia coli* WP2*uvr*A strains (US EPA, 2007; OECD, 2011; REACH) and in a gene mutation assay conducted with *Saccharomyces cerevisiae* (US EPA, 2007; OECD, 2011). The chemical also tested negative in in vitro chromosomal aberration assays, using CHL/IU and human lymphocytes cells, with and without metabolic activation, as significant increases in cells with chromosomal aberrations and polyploidy were not induced (OECD, 2011; REACH). The primary metabolite of the chemical, 4-cyclohexanedicarboxylic acid, also did not induce mutations at the thymidine kinase locus in a mouse lymphoma assay, using the cell line L5178Y, with and without metabolic activation (REACH).

The chemical also tested negative in an in vivo mammalian bone marrow chromosomal aberration test (OECD TG 475) in SD rats, where the chemical was administered by oral gavage at doses of 0, 500, 1000 or 2000 mg/kg bw. There were no clinical signs indicating toxicity, no mortality, and no evidence of cytotoxicity or clastogenic activity as significant increases in cells with structural chromosome damage, chromosome rearrangements, and a polyploid number of chromosomes, were not observed (OECD, 2011; REACH). Similarly, the chemical also tested negative in a mammalian erythrocyte micronucleus test (OECD TG 474) in CD-1 mice, following the administration of the chemical at single oral doses of 500, 1000 and 2000 mg/kg bw. No statistically significant increases in the frequency of micronucleated immature erythocytes and no substantial decreases in the proportion of immature erythrocytes were observed (REACH).

Carcinogenicity

Although no data are available, the chemical is not likely to be a carcinogen as in vitro and in vivo mutagenic or genotoxic potentials were not noted for the chemical.

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any developmental effects were only observed at high doses and were considered secondary to maternal toxicity (US EPA, 2007; OECD, 2011; REACH).

In a combined repeated dose and reproductive/developmental toxicity study (OECD TG 421), SD rats were administered the chemical in drinking water at doses of 0, 4.0, 8.0 and 12.5 mg/L during pre-mating (56 days), mating (up to 14 days), gestation (21–22 days), and early lactation (four days). The approximate dose levels achieved were 0, 256/385, 479/854 and 861/1360 mg/kg bw/day in males/females, respectively. Clinical abnormalities were observed mainly in the high-dose groups and included mortality, bloody or brown/red discoloured urine, softened and/or reduced faeces, dehydration, reductions in body weight and body weight gains, and decreased feed consumption.

No reproductive or developmental effects (reproductive performance, gestation length, pup survival rate, prenatal loss, number of implantation sites, number of live and dead pups, pup sex ratio, body weights and weight gains) were noted at the lower two doses. Reduced sperm motility was observed in some males dosed at high levels, but this had no effect on fertility. Only litters from highly dosed dams had significant biological changes in the form of decreased body weights and weight gains as well as decreased postnatal survival between days 0–4. These litters were mostly from dams that also exhibited maternal toxicity (reduced body weights and feed consumption, dehydration, discoloured/bloody urine). A NOAEL for parental/systemic toxicity was determined to be 479/854 mg/kg bw/day in males/females respectively, based on effects observed at the highest tested dose (bloody/discoloured urine, reductions in body weights and weight gains, decreased feed consumption). While the NOAEL for developmental toxicity was established as 854 mg/kg bw/day, the NOAEL for reproductive and/or teratogenicity was established as the highest tested dose (1360 mg/kg bw/day).

In another developmental toxicity study (OECD TG 414), SD pregnant rats were administered (gavage) the chemical at doses of 100, 300, and 1000 mg/kg bw/day on days 3–19 of gestation. The relative adrenal weights of pregnant females were significantly increased in the 1000 mg/kg/day dose group compared with controls. However, the increase in adrenal weights was

not considered to be an adverse event as there were no clinical signs, no change in absolute adrenal weight, and no morphologic changes to the adrenals. There was no evidence of foetotoxicity. A NOAEL for maternal toxicity as well as for developmental toxicity was established as 1000 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The main critical effect to human health is the potential for serious damage to eyes. The severity of the effect is correlated with the concentration of the chemical, with the chemical appearing non-irritating in animal tests at 35 % (see **Irritation—eye**).

Public Risk Characterisation

The chemical is currently listed in the Poisons Standard (SUSMP) in Appendix B (Part 3) and there are no restrictions on the use of this chemical in Australia.

The use of this chemical in cosmetic and domestic products in Australia is not known. The main reported uses of this chemical overseas has been as an intermediate reactant to make final products. Although the chemical has also reported uses as a solvent in cosmetic and domestic products, information indicates that it is not widely available for domestic and cosmetic use (see **Import, manufacture and use**).

In addition, although the main critical effect to human health is the potential for serious damage to the eyes, it has also been reported that the chemical was not an eye irritant at 35 % concentration (see **Irritation—eye**). 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

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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 may pose an unreasonable risk to workers, particularly at high concentrations, unless adequate control measures to minimise ocular exposure to the chemical 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 appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

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

Regulatory Control

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

[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 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 may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- 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 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 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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