1-Cyclohexene-1-methanol, 4-(1-methylethenyl)-: Human health tier II assessment

CAS Number: 536-59-4

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.

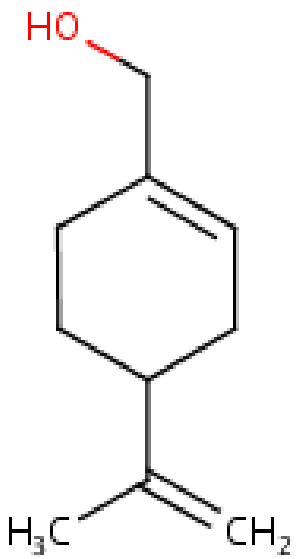
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	p-mentha-1,8-dien-7-ol perillyl alcohol (POH) perillol isocarveol
Structural Formula	
Molecular Formula	C10H16O
Molecular Weight (g/mol)	152.20
Appearance and Odour (where available)	colourless to pale yellow, dense, oily liquid with characteristic odour
SMILES	C(=C)(C)C1CC=C(CO)CC1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through the European Union (EU) Food Safety Authority (EFSA); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); Fragrance Material Review (Bhatia et al, 2008); Flavour Extract Manufacturers Association (FEMA) Review (Cohen et al, 2016); and the Research Institute for Fragrance Materials (RIFM) reviews (Api et al, 2018; Belsito et al, 2008).

The chemical has reported cosmetic and domestic uses as a fragrance ingredient in perfumes and a wide range of personal care and domestic products. Other cosmetic functions include antimicrobial, antioxidant, masking and skin protecting.

The chemical has reported non-industrial use as a food flavouring ingredient.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is a terpenoid and therefore is subject to the EU Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Annex III: List of Substances which cosmetic products must not contain except subject to the restrictions laid down. Peroxide levels must be less than 10 mmoles/L. This limit applies to the substance and not to the finished cosmetic product (CosIng).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 150–300 mg/m^3 (25–50 ppm) time weighted average (TWA) and 111–300 mg/m^3 (20–50 ppm) short-term exposure limit (STEL)/occupational exposure limit (OEL) in various countries such as Canada (Alberta), Denmark, Estonia and Sweden.

Health Hazard Information

Toxicokinetics

Perillyl alcohol (POH) is rapidly absorbed via oral and dermal route. It is rapidly metabolised to perillic acid, dihydroperillic acid and perillaldehyde by alcohol and aldehyde dehydrogenases in rats, dogs and humans (Belanger, 1998; Belsito et al, 2008). Peak plasma concentrations of perillic acid in humans were achieved approximately 1.5–3.5 hours after ingestion (Belanger, 1998).

In a study conducted in male Wistar rats, around 50 % of the administered POH was excreted in bile as acyl glucuronide (PCOO-GA) and ether-glucuronide (PO-GA) 120 mins post-exposure (Bhatia et al, 2008).

Female Wistar-Furth rats (4–10/group) were administered 2 % POH in diet for up to 10 weeks. Plasma levels of terpene metabolites including perillic acid (59 %), dihydroperillic acid (28 %), perillic acid methyl ester (10 %) and dihydroperillic acid (4 %) were reported (Bhatia et al, 2008).

In a pharmacokinetics study in rats and dogs, POH was orally administered at dose levels ranging from 20 to 500 mg/kg/dose, either via single or multiple doses. Mean C_{max} values of perillic acid in dogs (both sexes) were 477–383 µM (at 100 mg/kg bw), 544–434 µM (at 200 mg/kg bw), and 959–987 µM (at 400 mg/kg bw). In rats, mean C_{max} values of perillic acid were 86 µM (at 100 mg/kg bw/day), 190 µM (300 mg/kg bw/day) and 544 µM (500 mg/kg bw/day) (Bhatia et al, 2008).

In a beagle dog study (n=1/sex), 250 mg/kg POH in sesame oil was administered intragastrically via gavage into the stomach. Peak plasma concentration of POH was reported at 1–5 hours and of dihydroperillic acid at 5 hours with elimination via urine and faeces in 2.2–3.4 hours (Bhatia et al, 2008).

Acute Toxicity

Oral

Based on the available animal data, the chemical has low acute oral toxicity with a median lethal dose (LD50) of 2100 mg/kg in rats.

In an acute toxicity study, rats (n=10/group) were treated with the chemical at doses of 1220, 1950, 2470 or 5000 mg/kg by gavage. Mortalities were recorded as 4/10 animals (1950 mg/kg), 8/10 (2470 mg/kg) and 10/10 (5000 mg/kg), with most of the deaths occurring between days 0–2. Sublethal effects included lethargy, piloerection, ptosis, coma and ataxia. Yellow exudate in the nose and mouth areas, red and yellow colouration of the intestines, red areas in the stomach, dark areas in the lungs, kidneys and large spleen were recorded at necropsy. The LD50 in rats was determined to be 2100 mg/kg (95 % confidence interval of 1700–2600 mg/kg) (Bhatia et al, 2008).

Dermal

Based on the available animal data, the chemical has low acute dermal toxicity with an LD50 of >5000 mg/kg bw in rats.

In an acute dermal toxicity study, neat chemical was applied to the skin of rabbits (n=10) at 5.0 g/kg bw. Mortality was recorded in 2 rabbits between days 3 and 5 following dermal exposure. Clinical signs included negative righting reflex, ptosis, ataxia, flaccid tone, lethargy and anorexia. Additional effects observed at necropsy included: brown exudate in anogenital region, yellow exudate in the nose and mouth, red or yellow discolouration, bloating, hard faecal matter in intestines, dark mottled liver and kidneys, and dark areas in the lungs in 1–2 animals. An LD50 of >5000 mg/kg bw was established in rats (Bhatia et al, 2008).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is slightly irritating to the skin. The effects were not sufficient to warrant hazard classification.

Topical application of the chemical (pure) to rabbits (n=4) for 4 hours under semiocclusive conditions caused slight irritation with erythema (mean score of 2.0) and oedema (mean score of 1.3). The effects increased in severity with time and did not reverse by 72 hours (Bhatia et al, 2008).

Neat chemical was applied to the skin of rabbits (n=10) (duration of exposure not reported) with observation for five days. Severe erythema (10/10), and moderate (2/10) and severe oedema (8/10) were reported (Bhatia et al, 2008).

Eye Irritation

No data are available.

Observation in humans

Male and female volunteers (n=25/sex) exposed to the chemical (4 % in petrolatum) for 48 hours under occlusion showed no signs of irritation (Bhatia et al, 2008).

Sensitisation

Skin Sensitisation

Animal studies are not available. The chemical at 4 % was not sensitising in a human maximisation test (see **Observation in humans** section). The chemical is susceptible to auto-oxidation leading to formation of hydroperoxide species. These oxidised species may induce sensitisation.

The profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox v4.2 was used to determine the presence of potential structural alerts for skin sensitisation. While the unmetabolised chemical did not display any mechanistic alerts for skin sensitisation, several auto-oxidation products and potential skin metabolites displayed alerts for protein binding.

Skin sensitisation was predicted using Laboratory of Mathematical Chemistry OASIS–TIMES (tissue metabolism simulator) software (version 2.28.1). The chemical was predicted to be a non-sensitiser (100 % in domain). Several auto-oxidised

metabolites of the chemical were predicted to be sensitisers which were supported by mechanistic alerts for hydroperoxide free radical decomposition and michael type addition on alpha,beta-aldehydes.

Observation in humans

In a human maximisation test (n=25 males and females), the chemical at 4 % in petrolatum was applied under occlusion for 48 hours to the same site on 5 alternate days. No irritation responses were observed (Bhatia et al, 2018).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause serious damage to health following repeated oral exposure.

In a 2-week study, rats (n=3–4/group) were administered the chemical in feed at 1000 mg/kg bw/day. Decreased food intake and body weight gain, and increased liver weight and cholesterol levels were reported (Belsito et al, 2008).

In another 14-day feeding study, male Wistar rats were administered 1 % of the chemical in commercial rat feed. Increases in liver weight and cholesterol, and decreases in triacylglycerol levels and apolipoprotein (Apo) A-1 levels were reported (Bhatia et al, 2008).

In a sub-chronic 90-day study, groups of male F344/N rats were fed the chemical in diet at 310, 630, 1250, 2500 or 5000 ppm of perillyl alcohol/kg food. Significant reduction in body weights at 5000 ppm were observed. A maximum tolerated dose (MTD) of 2500 ppm was reported (Bhatia et al, 2008).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available *in vitro* genotoxicity studies, the chemical is not considered to be genotoxic.

In an Ames test conducted according to OECD Test Guideline (TG) 471, the chemical was tested in *Salmonella typhimurium* strains TA98, TA 100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A at concentrations of 1, 3.33, 10, 33.3, 100, 333, 1000 or 3333 µg/plate, with and without metabolic activation. The chemical caused no increase in the mean number of revertant colonies with or without metabolic activation (EFSA, 2017).

In another Ames test, the chemical was negative for genotoxicity in *S. typhimurium* strains TA98, TA 100, TA1535 and TA1537) and *E. coli* WP2*uvr*A at concentrations up to 5000 µg/plate, with and without metabolic activation (Api et al, 2018).

In an in vitro micronucleus assay (OECD TG 487), human peripheral blood lymphocytes were treated with the chemical in dimethyl sulfoxide (DMSO) at concentrations up to 1520 µg/mL in the presence and absence of metabolic activation. No increases in the number of micronucleated cells were reported and the chemical was considered to be non-clastogenic (Api et al, 2018; EFSA, 2017).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The chemical is not considered to have high toxicity, although no data are available to address the critical toxicological endpoint of potential eye irritation. The chemical is susceptible to auto-oxidation leading to formation of hydroperoxide species. These oxidised species may induce sensitisation.

Public Risk Characterisation

Information on Australian use of the chemical has not been made available. International information is considered representative for Australian use and indicates that it has cosmetic and domestic uses as a fragrance ingredient (see **Import, manufacture and use** section).

Considering the range of domestic and cosmetic products that may contain the chemical, the main route of public exposure is expected to be through the direct application of cosmetic products onto the skin and inhalation from products sprayed as an aerosol, such as perfume and personal care products.

The chemical is expected to be present in cosmetic and domestic products at very low concentrations due to its identified use as fragrance ingredient. This mitigates the risk of local effects including potential for sensitisation caused by the chemical oxidising over time. Therefore the chemical is not considered to pose an unreasonable risk and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, dermal exposure might 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.

Whilst the chemical is not recommended for classification as a hazardous chemical, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure to high concentrations are implemented.

NICNAS Recommendation

The risk to workers and public from this chemical is not considered to be unreasonable. The chemical is not recommended for classification and labelling under the adopted GHS. This report does not consider classification of physical hazards and environmental hazards. No recommendatons or further assessment is required.

Regulatory Control

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 that could minimise the risk include, but are not limited to:

- 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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