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

08 March 2019

CAS Number: 2111-75-3

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

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

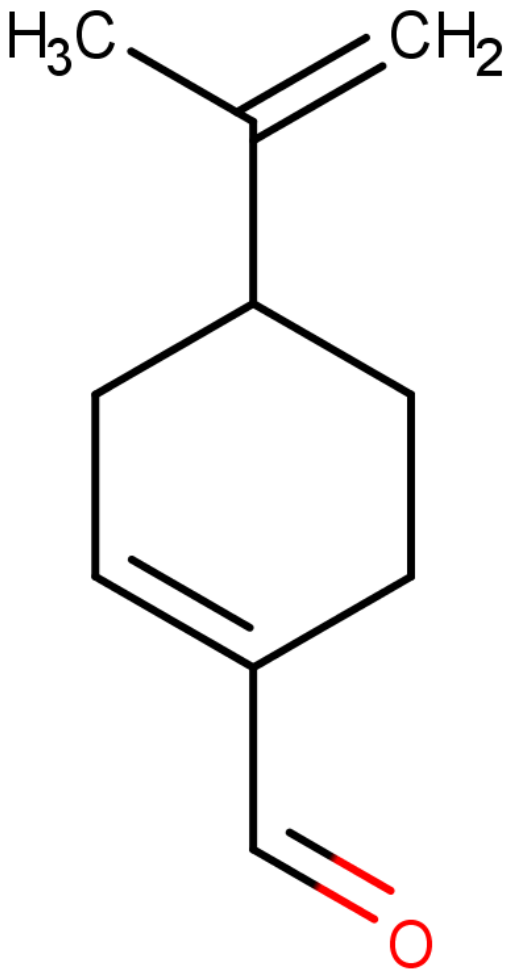
For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	p-mentha-1,8-dien-7-al perillaldehyde perilla aldehyde FEMA no. 3557
Structural Formula	

	
Molecular Formula	C10H14O
Molecular Weight (g/mol)	150.00
Appearance and Odour (where available)	pale yellowish oily liquid with a powerful, fatty-spicy, herbaceous odour
SMILES	C(=C)(C)C1CC=C(C=O)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: 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); US Food And Drug administration (US FDA); the European Food Safety Authority Scientific opinion of flavouring group evaluation reports (EFSA, 2015; EFSA, 2017); Expert Panel of the US Flavour and Extract Manufacturers Association (FEMA) report (Cohen et al, 2016); International Fragrance Association (IFRA) list; and the World health Organisation (WHO) Joint Expert Committee on Food Additives report (INCHEM, 2003).

The chemical has reported cosmetic uses as a:

- fragrance ingredient; and
- skin conditioning agent.

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

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- International Fragrance Association (IFRA) Standards Restricted—48th Amendment with restrictions.

Under the EU restrictions, the chemical must not be used in finished oral and cosmetic products at levels exceeding 0.1 % (SCCNFP, 2001; CosIng, Galleria Chemica).

According to the IFRA Standards, the restricted levels for the chemical in cosmetic products range from 0.02 to 0.1 %, and in oral hygiene products at up to 0.5 % (IFRA).

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

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Following intravenous administration of 12 mg/kg bw of the chemical to male Wistar rats, 46 % of the administered dose was eliminated in the bile and 10 % in urine as acyl and ether glucuronides, respectively. The chemical was readily absorbed and metabolised, mainly by oxidation to a carboxylic acid, perillic acid, excreted unchanged and as conjugates. The chemical underwent further reduction in the gastrointestinal tract (INCHEM, 2003; EFSA, 2015).

In an oral study, the chemical was administered to male rabbits (n=6) at 2000 mg/kg bw as a single dose by gavage. Perillic alcohol (46 %) and (-)-cis-shisool (p-menth-8-en-7-ol) (39 %) were the two major neutral metabolites detected in urine. Perillic acid (57 %), an acidic metabolite, was also detected in the urine. The chemical was readily oxidised to perillic acid and to a lower extent, reduced to perillyl alcohol (INCHEM, 2003; EFSA, 2015; Hobbs et al, 2016).

Acute Toxicity

Oral

Based on limited information available, the chemical has low to moderate acute oral toxicity.

The median lethal dose (LD50) was reported to be between 1000–1700 mg/kg bw for mice and 2100 mg/kg bw for rats. No other details were provided (INCHEM, 2003; Tisserand & Young, 2014).

Dermal

Based on the limited data available, the chemical is not expected to be toxic via dermal exposure.

The LD50 for dermal toxicity in guinea pigs (number of animals and sex not specified) was reported as >5000 mg/kg bw (Tisserand & Young, 2014).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on very limited data, the chemical (undiluted) was moderately irritating to guinea pig skin, but not irritating at 1–4 % concentrations in human volunteers (Tisserand & Young, 2014). The potential for the chemical to cause skin irritation cannot be inferred from the limited data available.

Eye Irritation

No data are available.

Observation in humans

In three separate panels of volunteers, perillaldehyde was not irritating when tested at 1 % and 4 % (Tisserand & Young, 2014).

Sensitisation

Skin Sensitisation

The available data in humans (see **Observation in humans** section) and animals indicate that the chemical is moderately sensitising to the skin, warranting hazard classification.

In a local lymph node assay (LLNA) (OECD TG 429), the chemical mixed with ethanol:diethyl phthalate was administered to mice (5 animals/dose) at concentrations of 0.5, 1, 2.5, 5 or 10 %. The estimated concentration to produce a three-fold increase in lymphocyte proliferation (EC3) was 9.3 %, equivalent to 2325 ug/cm^2 (0.62 M) (RIFM, 2009; ECHA Annex II).

In a summary of LLNA data on 66 fragrance substances, perillaldehyde was reported to have an EC3 value of 8.1 % with a mean of 0.54 at 2025 µg/cm^2 (SCCS, 2011).

The no-expected-sensitisation-induction-level (NESIL) based on a weight of evidence (WoE) was determined to be 700 µg/cm^2 (RIFM, 2009).

Observation in humans

Positive skin reactions in a human repeat insult patch test (HRIPT) and human maximisation test (HMT) were reported and no observed effect levels (NOEL) were determined to be 709 µg/cm^2 and 690 µg/cm^2, respectively (RIFM, 2009).

In a maximisation test, the chemical at 4 % produced 2/29 positive reactions. No positive reactions were reported at 1 % (Tisserand & Young, 2014).

Repeated Dose Toxicity

Oral

No specific repeated dose toxicity data are available for the chemical.

In a combined micronucleus and comet assay (see **Genotoxicity** section), Han Wistar (Crl:WI(Han)) male rats (6 animals/dose) were administered the chemical by gavage at doses of 175, 350 or 700 mg/kg bw/day for three consecutive days. Dose-related decreases in body weight were observed at all doses. At the highest dose, clinical signs of toxicity including reduced activity (5/6), ataxia (1/6) and piloerection (2/6) were observed. Slight increases in enzyme activity (aspartate aminotransferase and alanine aminotransferase) were also reported. Hepatocyte vacuolation was observed in 5/6 animals. The observed effects on hepatocytes were regarded as early stages of apoptosis/necrosis (EFSA, 2015; FEMA, 2016).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Various studies are available to assess the genotoxic potential of the chemical, although most of the studies were not performed according to test guidelines. Mixed results have been reported from in vitro studies, although in vivo studies were largely negative. There are differing views on the ability of the chemical to cause DNA damage in the liver (EFSA, 2015; Cohen et al, 2016; Hobbs et al, 2016). Based on the limitations and lack of consistencies in the study results, the overall potential for the chemical to cause genotoxic effects cannot be inferred.

In vitro

Negative results were reported in the following studies (INCHEM, 2003; EFSA, 2015; FEMA, 2016; Hobbs et al., 2016):

- Ames test (OECD TG 471) conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA153 and TA102 with and without metabolic activation at concentrations up to 5000 µg/plate;
- in a micronucleus assay (OECD TG 487), the chemical did not induce micronuclei in cultured human peripheral blood lymphocytes with and without metabolic activation;
- in an SOS-chromotest in *Escherichia coli*, the chemical gave negative results;
- hypoxanthine-guanine phosphoribosyl transferase (HPRT) assay (OECD TG 476) in mouse L5178Y cells with metabolic activation at concentrations up to 180 µg/mL;
- sister chromatid exchange (SCE) assay, in CHO-K1 cells without metabolic activation at concentrations up to 300 µg/plate.

Positive results were reported in the following studies (INCHEM, 2003; EFSA, 2015; FEMA, 2016; Hobbs et al., 2016):

- Ames test (OECD TG 471) conducted in *S. typhimurium* strain TA98;
- *rec*-assay with *Bacillus subtilis* strains M45 and H17 at 2500 µg/plate;
- standard chromosomal aberration assay in Chinese hamster lung fibroblasts without metabolic activation;
- sister chromatid exchange (SCE) assay in CHO-K1 cells with metabolic activation at concentrations up to 300 µg/plate; and
- HPRT assay (OECD TG 476) in mouse L5178Y cells without metabolic activation at concentrations up to 180 µg/mL.

In vivo

In a non-guideline micronucleus assay, the chemical was administered to ddY mice (6/group) via a single intraperitoneal injection at doses of 75, 150, 300 or 600 mg/kg bw. Bone marrow cells were collected after 24 hours. There was no evidence of micronucleus induction (FEMA, 2016; INCHEM, 2003).

In a combined comet assay (OECD TG 489)/ micronucleus test (OECD TG 474), Han Wistar (Crl:WI(Han) male rats (6/dose) were administered the chemical by gavage at doses of 175, 350 or 700 mg/kg bw/day for three consecutive days. Liver and duodenum tissues were collected for the comet assay, and bone marrow samples were collected for the micronucleus test. Toxicity was reported at the highest dose tested (700 mg/kg bw/day). There was no DNA damage in the duodenum as evidenced by no statistically significant increases in the mean % tail intensity. A small but statistically significant increase in % tail intensity was observed at the highest dose in the liver; however, the % tail intensity for all six animals were within the laboratory's historical vehicle control 95th percentile range. These animals were also affected by liver toxicity (see **Repeated**

dose toxicity section); therefore, the increased in % tail intensity may have been associated with liver toxicity rather than damage to DNA. There was no dose-related increase in % hedgehogs or % cells with halos in liver cells. There were no statistically significant increases in micronucleus frequencies reported (Cohen et al, 2016; Hobbs et al, 2016).

Carcinogenicity

Limited data are available.

The chemical may induce apoptosis in cancer cells (Tisserand & Young, 2014).

The chemical inhibited the proliferation of mouse B16(F10) melanoma cells with an inhibitory concentration (IC50) of 120 μM (18.0 mg/L). The chemical dose- and time- dependently inhibited cell proliferation in human BroTo (head and neck cancer) and A549 lung cancer cells (INCHEM, 2003; Tisserand & Young, 2014).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (skin 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 indicate cosmetic and domestic uses (see **Import, manufacture and use** section). Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products.

Considering the range of domestic, cosmetic and personal care products that could contain the chemical, the main route of public exposure is expected to be through the skin, inhaled from products applied as aerosols, and potential oral exposure from lip products (0.02 %) and oral hygiene products (0.5 %).

The distribution of the chemical for fragrance purposes is expected to be controlled by members of IFRA. The restriction of the chemical under the IFRA Standard (see **Restrictions** section) is expected to sufficiently address the public risks associated with chemical exposure through the uses as fragrance (i.e. the lowest concentration allowed is 0.02 % in all types of lip products) (IFRA). The chemical is not reported by SCCS as one of the commonly reported human fragrance allergens (SCCS, 2011). Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation 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.

Given the critical local health effect, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	Not Applicable	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 and dermal 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:

- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;

- 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 safety data sheets (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 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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