2-Propenoic acid, 3-phenyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester: Human health tier II assessment

28 June 2019

CAS Number: 78-37-5

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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.

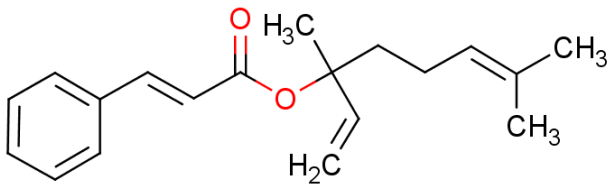
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	linalyl cinnamate cinnamic acid, linalyl ester 3,7-dimethyl-1,6-octadien-3-yl cinnamate
Structural Formula	
Molecular Formula	C19H24O2
Molecular Weight (g/mol)	284.4
Appearance and Odour (where available)	Colourless to yellow clear liquid with a sweet fruity odour.
SMILES	C(=O)(C={t}Cc1ccccc1)OC(C)(C=C)CCC=C(C)C

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 European Commission Cosmetic Ingredients and Substances (CosIng) database; and the International Fragrance Association (IFRA) Transparency List.

The chemical has reported cosmetic use in perfumes or as a fragrance ingredient.

The chemical has reported non-industrial use as a food additive (Adams et al., 2004).

The estimated dermal systemic exposure for linalyl cinnamate in cosmetic products is 0.03 mg/kg bw/day. For skin sensitisation, the calculated exposure concentration to linalyl cinnamate used in fine fragrance products is 0.42 % (Bickers et al., 2003).

Restrictions

Australian

No known restrictions have been identified.

International

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

- 'Terpenes and terpenoids' in the EU Cosmetic Directive 76/768/EEC Annex III—List of substances which Cosmetic Products must not contain except subject to the restrictions and conditions laid down: Peroxide value less than 10 mmoles/L; and
- 'Terpene hydrocarbons' in the New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: Peroxide value less than 10 mmoles/L.

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

Limited data are available for linalyl cinnamate (CAS No. 78-37-5). As the chemical is expected to be hydrolysed in vivo to form linalool and cinnamic acid, data for these metabolites are considered suitable analogues for systemic effects.

Toxicokinetics

Although no toxicokinetic studies are available for linalyl cinnamate, the chemical is expected to hydrolyse to linalool and cinnamic acid. Following oral exposure, linalyl esters readily hydrolyse in vivo by carboxylesterases or tissue esterases to linalool and the corresponding carboxylic acids. The hydrolysis products then conjugate with glucuronic acid and are excreted in urine. Studies for linalyl acetate indicate that linalool is available for systemic circulation following absorption (NICNASa).

The metabolite cinnamic acid is not considered to pose an unreasonable risk to public health. The major urinary metabolites identified in humans and in animals following metabolism of cinnamic acid are hippuric acid and glucuronic acid conjugates of benzoic acid (NICNASb).

Acute Toxicity

Oral

Based on available data, the chemical has low acute toxicity following oral exposure.

The median lethal dose (LD50) is 9960 mg/kg bw in rats and >39040 mg/kg bw in mice. No details on sub-lethal effects are available (Belsito et al., 2007; Bickers et al., 2003).

Dermal

Based on available data, the chemical has low acute toxicity following dermal exposure.

The dermal LD50 is >5000 mg/kg bw in rabbits. No details on sub-lethal toxic effects are available (Galleria Chemica).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Limited data are available. The chemical is not a strong skin irritant and; therefore, hazard classification is not warranted.

The undiluted chemical caused mild to moderate irritation in a 24-hour acute toxicity study in 10 rabbits, and very mild irritation in 3 rabbits following single application (duration not stated) to intact or abraded skin (Bickers et. al., 2003; Opdyke, 1979). The chemical tested at 5 % in diethyl phthalate was slightly irritating in rabbits but effects were reversible within 72 hours (Bickers et. al., 2003).

Eye Irritation

Based on available data, the chemical was reported to be a slight eye irritant in animal studies. However, available data are insufficient to warrant hazard classification.

In 2 eye irritation studies, the chemical caused very slight to well-defined irritation in rabbits (n=3) when applied undiluted, or at 5 % in diethyl phthalate. No further details are available (Bickers et. al., 2003).

Observation in humans

In a 48-hour closed-patch test study, the chemical was tested at 8 % in petrolatum on 5 male volunteers. No skin irritation was observed (Bickers et. al., 2003).

Sensitisation

Skin Sensitisation

No data are available. Based on the human maximisation study and information on the metabolites and analogues, the chemical is not considered to be a potent skin sensitiser. In the absence of more comprehensive information, hazard classification is not warranted.

The chemical could hydrolyse in skin to linalool which is a known contact allergen following auto-oxidation. Available data for linalyl acetate indicate auto-oxidation into a potent contact allergen. However, other linalyl esters (linalyl isobutyrate and linalyl propionate) were not sensitising when tested at 8 % in guinea pigs (NICNASa).

Quantitative Structure Activity Relationship (QSAR) modelling for the chemical using OECD Toolbox (version 4.2) gave a structural alert for protein binding based on the Michael Addition mechanism.

Observation in humans

In a human maximisation test, the chemical at 8 % in petrolatum was not sensitising on 25 male volunteers (Bickers et. al., 2003).

Repeated Dose Toxicity

Oral

Based on the available study for the chemical and information on the metabolites, the chemical is not likely to cause serious damage to health from repeated oral exposure.

In a repeat dose oral toxicity study, Osborne-Mendel rats (n=10/sex/dose) were administered the chemical in the diet at 0, 50, 125 or 500 mg/kg bw/day for 17–18 weeks. Detailed microscopic examination was performed on the high dose group only. No deaths or adverse clinical signs were observed. There were no effects on haematology parameters or growth, and no observed changes in the tissues. The no observed adverse effect level (NOAEL) was 500 mg/kg bw/day (Belsito et al., 2007; Bickers et. al., 2003)

The metabolite linalool was not considered to cause serious damage to health from repeated oral exposure. In a 28-day repeat dose oral toxicity study using coriander oil (72.9 % linalool), Sprague Dawley (SD) rats were treated at doses of 160, 400 or 1000 mg/kg bw/day. The NOAEL was 160 mg/kg bw/day based on histological effects in the liver and kidney at 400 mg/kg bw/day (NICNASa). Cinnamic acid is not considered to cause serious damage to health following repeated oral exposure (NICNASb).

Dermal

No data are available.

The metabolite linalool did not cause systemic toxicity effects at doses up to 1000 mg/kg bw/day in a 91-day repeat dose dermal toxicity study in SD rats. The NOAEL was 250 mg/kg bw/day for local effects (NICNASc).

Inhalation

No data are available.

Genotoxicity

Based on available in vitro data for the chemical and data for the metabolites, the chemical is not expected to be genotoxic.

The following in vitro results were reported for the chemical (Api et al., 2016; Belsito et al., 2007):

- Negative in bacterial reverse mutation assay (OECD TG 471) with several strains of *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100, and TA102) up to 5000 µg/plate, with or without metabolic activation.
- No increase in the frequency of binucleated cells with micronuclei (BNMN) in a micronucleus assay (OECD TG 487) in human peripheral blood lymphocytes at doses up to 172 µg/mL for 24 hours, up to 138 µg/mL for 3 hours without metabolic activation, and up to 400 µg/mL for 3 hours with metabolic activation.

Available in vitro data for linalool did not indicate mutagenic potential. Linalool was not clastogenic in an in vivo mouse micronucleus test (NICNASc). Cinnamic acid was generally negative in bacterial systems but positive in in vitro mammalian studies. Several in vitro studies indicated antimutagenic activity for cinnamic acid (NICNASb).

Carcinogenicity

No data are available.

The metabolite linalool is not considered to be a carcinogen (NICNASc). Although there are no data for cinnamic acid, animal studies with cinnamaldehyde, which metabolises to cinnamic acid, do not indicate carcinogenic activity (Belsito et al., 2007).

Reproductive and Developmental Toxicity

No data are available.

The metabolites linalool and cinnamic acid are not considered to be reproductive or developmental toxicants (NICNASb; NICNASc).

Risk Characterisation

Critical Health Effects

No critical health effects for risk characterisation were identified for the chemical.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products overseas as a fragrance compound at concentrations up to 0.42 %.

The public could be exposed to the chemical through potential cosmetic use. However given the low hazard identified for this chemical and low concentrations in consumer products, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the lack of critical health effects, the chemical is unlikely to pose an unreasonable risk to workers when adequate control measures to minimise exposure are implemented.

Based on the available data, the lack of hazard classification in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia) is considered appropriate.

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

Work Health and Safety

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

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

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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Last update 28 June 2019

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