2-Propenoic acid, 3-phenyl-, 2-propenyl ester: Human health tier II assessment

26 October 2018

CAS Number: 1866-31-5

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.

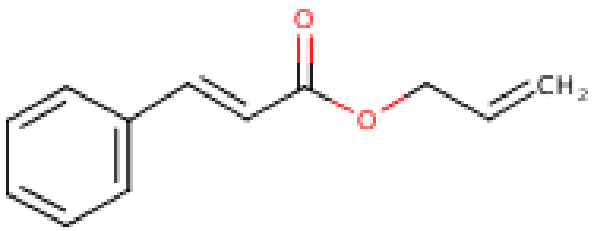
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	cinnamic acid, allyl ester allyl cinnamate allyl 3-phenylacrylate propenyl cinnamate vinyl carbinyl cinnamate
Structural Formula	
Molecular Formula	C12H12O2
Molecular Weight (g/mol)	188.23
Appearance and Odour (where available)	Colourless to light yellow liquid with a fruity scent
SMILES	C(=O)(C={t}Cc1ccccc1)OCC=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; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US Food & Drug Administration's Substances Added to Food; the International Fragrance Association (IFRA) transparency list; Health Canada's Natural Health Products Ingredients Database (NHPID); and Bhatia et al., 2007.

The chemical has reported cosmetic use as a fragrance ingredient in decorative cosmetics, fine fragrances, shampoos, and toilet soaps.

The chemical has reported domestic use as a fragrance ingredient in household cleaners and detergents.

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

Restrictions

Australian

Specific allyl esters are listed in Schedule 6 of the Poison Standard — the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2019) as follows:

Schedule 6:

'ALLYL ESTERS (excluding derivatives) being:

ALLYL CYCLOHEXANEACETATE (CAS No. 4728-82-9)

ALLYL CYCLOHEXANEPROPIONATE (CAS No. 2705-87-5)

ALLYL HEPTANOATE/ALLYL HEPTYLATE (CAS No. 142-19-8)

ALLYL HEXANOATE (CAS No. 123-68-2)

ALLYL ISOVALERATE (CAS No. 2835-39-4)

ALLYL NONANOATE (CAS No. 7493-72-3)

ALLYL OCTANOATE (CAS No. 4230-97-1)

ALLYL PHENYLACETATE (CAS No. 1797-74-6)

ALLYL TRIMETHYLHEXANOATE (CAS No. 68132-80-9)

in preparations containing 0.1 per cent or less of free allyl alcohol by weight of allyl ester except in preparations containing 5 per cent of less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl esters' (SUSMP, 2019).'

Schedule 7:

'ALLYL ALCOHOL **except**

a. in preparations containing 5 per cent or less of allyl esters with 0.1 per cent or less of free allyl alcohol by weight of allyl ester; or

b. when separately specified in these Schedules.'

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply (SUSMP, 2019).

International

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

- EU Cosmetic Regulation No 344/2013 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions 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.

In both cases, the chemical has the following restriction: 'level of free allyl alcohol in the ester shall be less than 0.1 %'.

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

The chemical can be absorbed by the oral route, followed by metabolism. Male Holtzman rats showed increased plasma alanine-α-ketoglutarate transaminase (AKT) activity when administered the chemical via gavage at doses of up to 600 mg/kg bw (Bhatia et al., 2007).

An in vitro study with liver homogenates from male Holtzman rats demonstrated that the chemical was metabolised mainly by nonspecific esterases (Bhatia et al., 2007). Based on this study, it is expected that this chemical will be metabolised, by hydrolysis of the ester linkage, to produce the parent acid (cinnamic acid) and the corresponding alcohol (allyl alcohol). Both primary metabolites have been assessed by NICNAS under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNASa; NICNASb). In the absence of data for the chemical, the data for cinnamic acid and allyl alcohol, together with other allyl esters, will be considered relevant to evaluate the systemic hazards of the chemical to human health.

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on results from an animal test following oral exposure. The median lethal dose (LD50) in rats is 1520 mg/kg bw, warranting hazard classification (see **Recommendation** section).

In an acute oral toxicity study, Osborne-Mendel rats (n=5/sex) were administered the chemical by gavage (doses not specified). Mortality was observed between 4 hours and 8 days. The only reported sublethal effect was scrawny appearance (Bhatia et al., 2007).

Dermal

Only limited information is available on the chemical.

In an acute dermal toxicity study in rabbits (n=4 animals; sex and strain not specified) that received dermal application of the neat chemical at 5000 mg/kg bw, the LD50 value was reported to be less than 5000 mg/kg bw based on 3/4 deaths. Deaths occurred within 24 hours post-application. No clinical effects were reported (Bhatia et al., 2007).

Inhalation

No data are available for the chemical.

NICNAS has assessed that cinnamic acid is not expected to have acute toxicity via inhalation (NICNASa). However, there are present concerns for allyl alcohol with a recommended HCIS classification as a Category 2 hazardous chemical for this endpoint (NICNASb). Allyl acetate, which is an example of an allyl ester, had a reported median lethal concentration (LC50) value of 1000 ppm (approximately 1.02 mg/L) in rat after a one hour exposure (NICNASc). However, in the absence of more comprehensive information, a recommendation to classify the chemical as hazardous for this endpoint is not warranted.

Corrosion / Irritation

Skin Irritation

Based on the available human studies, the chemical is irritating to the skin at concentrations as low as 0.25 % (see **Observation in Humans**). Therefore, the chemical is recommended to be classified as hazardous with the following hazard statement in HCIS: ‘Causes skin irritation’ (H315) (see **Recommendation** section).

In an acute dermal toxicity study conducted in rabbits (see **Acute Toxicity—Dermal** section), no irritation was reported upon dermal exposure to the chemical (Bhatia et al., 2007).

Eye Irritation

No data are available for the chemical.

Observation in humans

The available human data on the chemical show that concentrations as low as 0.25 % can cause irritation, and concentrations as low as 0.1 % are potentially irritating to the skin.

In a pre-test for a human maximisation study, application of the chemical at 4% in petrolatum in a closed patch for 48 hours to the back of 22 volunteers caused irritation in 20 individuals (Bhatia et al., 2007).

In a primary irritation screen, the chemical was applied via a closed patch to the back of 11 healthy male volunteers for 48 hours at doses of 0.1 %, 0.25 %, 0.50 % or 4.0 %. Volunteers applied with 0.10 % of the chemical displayed 'questionable reactions' at the 42-h reading; however, these effects resolved by the 72-h reading. Volunteers treated with the chemical at doses of 0.25 % and above displayed irritation reactions from the 48-hour reading. By the 72-hour reading, the following number of irritation reactions per dose were observed: 5 reactions at 0.25 %; 9 reactions at 0.50 %; and, 10 reactions at 4.0 % (Bhatia et al., 2007).

Sensitisation

Skin Sensitisation

No animal studies are available for the chemical. Based on the human maximisation study and the metabolite information, the chemical is not expected to have skin sensitisation potential.

Cinnamic acid and allyl alcohol were both found to not cause skin sensitising effects based on various studies on guinea pigs and mice (NICNASa; NICNASb). Other allyl esters are not expected to have skin sensitisation potential except for allyl cyclohexanepropionate which was shown to be a moderate skin sensitiser in guinea pigs (NICNASc). In the absence of more comprehensive information, a recommendation to classify the chemical as hazardous for this endpoint is not warranted.

Observation in humans

No sensitising effects were observed in a human maximisation study conducted in 22 healthy male volunteers (Bhatia et al., 2007).

Repeated Dose Toxicity

Oral

No data are available for this chemical.

Although no concern for this particular endpoint exists for cinnamic acid (NICNASa), allyl alcohol is considered to cause serious damage to health from repeated oral exposure (NICNASb). Allyl alcohol is known to cause hepatotoxicity and hyperplasia of the squamous epithelial cells of the forestomach based on studies in rats and mice (NICNASb). Hepatotoxicity and effects on the stomach were also observed following repeated oral exposure to various allyl esters (NICNASc). Of these allyl esters, allyl acetate caused severe effects in rats and mice (hepatotoxicity was observed at doses of ≥25 mg/kg bw/d) and was classified for this particular endpoint. It was noted that the toxicity of allyl acetate was likely due to the allyl alcohol component of the ester; the weight equivalent of which decreases for larger carboxylates compared with acetic acid (NICNASc).

Dermal

No data are available for the chemical or the metabolites (NICNASa; NICNASb).

Inhalation

No data are available for the chemical.

Cinnamic acid is not considered to cause serious damage to health following repeated exposure through inhalation (NICNASa). However, different mammalian species exposed to allyl alcohol via inhalation caused effects in the lung and liver which includes slight congestion and necrosis (NICNASb).

Genotoxicity

Based on the available data, the chemical is not expected to be genotoxic. This is supported by the negative genotoxicity results from cinnamic acid (NICNASa) and allyl alcohol (NICNASb).

In vitro

The chemical gave negative results in an Ames test using *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA1538 and TA98; with or without metabolic activation at doses of up to 3600 µg/plate (Bhatia et al., 2007).

In vivo

The chemical gave negative results in the following studies (Bhatia et al., 2007):

- micronucleus test in NMRI mice at doses of up to 282 mg/kg where the mean number of micronucleated polychromatic erythrocytes (PE) were similar to controls;
- Basc test on *Drosophilia melonogaster* where no significant sex-linked recessive lethal (SRL) mutations were observed at dietary doses of 1 mM in 5 % saccarose.

Carcinogenicity

No data are available for the chemical. Based on the lack of carcinogenic potential for cinnamic acid and allyl alcohol (NICNASa; NICNASb), the chemical is not expected to cause carcinogenic effects.

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on animal studies, neither cinnamic acid or allyl alcohol exhibit significant toxic effects to reproduction or development (NICNASa; NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects from oral exposure and skin irritation.

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. It was reported that the majority of cosmetic formulations contains the chemical at 0.5 % with a

maximum daily skin exposure of 0.0127 mg/kg for high end product users (Bhatia et al., 2007).

At present, as a derivative, the chemical falls within the scope of the listing of ‘allyl alcohol' in Schedule 7 of the SUSMP. It is recommended that the chemical is exempted from the Schedule 7 entry, considering the acute toxicity value which is consistent with inclusion in a lower schedule, and dermal exposure to the chemical will be at low concentrations. A concentration cut-off for free allyl alcohol consistent with IFRA controls and the current entry in the Poison Standard for allyl esters is recommended for the chemical.

Occupational Risk Characterisation

During product formulation, oral and dermal 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 and 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 a new hazard classification entry in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Changes to risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of this chemical in cosmetics and domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

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

The following amendments to the SUSMP are recommended:

- inclusion of this chemical into Schedule 6 'ALLYL ESTERS'.

While this ester is not expected to be used at concentrations >5 %, it is recommended that regulatory control of the chemical be aligned with the other allyl esters by inclusion to the Schedule 6 entry for allyl esters.

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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)

[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:

- 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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