2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl-: Human health tier II assessment

25 November 2016

CAS Number: 4602-84-0

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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	3,7,11-trimethyldodeca-2,6,10-trienol farnesol farnesyl alcohol 3,7,11-trimethyl-2,6,10-dodecatrienol 3,7,11-trimethyl-2,6,10-dodecatrien-1-ol
Structural Formula	
Molecular Formula	C15H26O
Molecular Weight (g/mol)	222.37
Appearance and Odour (where available)	Colourless liquid with a delicate odour
SMILES	C(C)(={c}CCCC(C)={c}CCO)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 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 (EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the International Fragrance Association (IFRA) Transparency List (IFRA, 2011); and various international assessments [the US EPA Biopesticide Registration Action Document (US EPA, 2009); the World Health Organization (WHO) Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluation of certain food additives and contaminants (WHO, 2004); the European Food Safety Authority (EFSA) Scientific Opinion o some flavouring groups (EFSA, 2013); and the European Commission's Scientific Committee on Consumer Products (SCCP) Opinion on Dermal Sensitisation Quantitative Risk Assessment (SCCP, 2008)].

The chemical has reported cosmetic uses as:

- a fragrance compound;
- a deodorising agent;
- a masking agent; and
- a solvent.

The chemical is reported to be a component of several personal care products (e.g. shampoo and conditioner, shaving and other grooming preparations, bar and liquid soaps, eau de toilette, bath salts, facial and body cleansing products, lipsticks, makeup preparations, dusting and talcum powder). The maximum concentrations recommended by IFRA are 5 % in liquid soaps and shampoos, 2.5 % for baby diapers and hand washing, 0.11 % in deodorants, and 1.2 % in hydroalcoholic products for unshaven skin (SCCP, 2008).

The chemical has reported domestic uses, including in:

- detergents;
- air fresheners; and
- household cleaning products.

The chemical has reported non-industrial uses including as:

- a biochemical pesticide;
- an insect attractant; and
- a flavouring agent in food and beverages.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetics Directive 76/768/EEC Annex III Part 1—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down: the presence of the substance must be indicated in the list of ingredients referred to in the Article 19(1)g when its concentration exceeds 0.001% in leave-on products and exceeds 0.01% in rinse-off products;
- New Zealand Cosmetic Products Group Standard—Schedule 5 - Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: the presence of the substance must be indicated in the list of ingredients referred to in Part 2(2A) of Schedule 1 when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products; and
- Europe Directive 2009/48/EC of the European Parliament (the 'Toy Directive')—List of allergenic fragrances that shall be listed on toys if exceeding 100 mg/kg.

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

No specific exposure standards are available.

Health Hazard Information

The chemical, also referred to as farnesol in this assessment, is a non-cyclic terpene alcohol that is a colourless, oily liquid with delicate sweet-oily odour (Belsito et al., 2008). It is naturally found in and extracted from several aromatic plants (Staines et al., 2004; HSDB).

Toxicokinetics

The main metabolic pathways for cyclic and non-cyclic terpenes include glucuronic acid conjugation, side-chain oxidation yielding polar metabolites, and endocyclic double bond conjugation. The polar metabolites can be easily eliminated in the urine and faeces (WHO, 2004; Belsito et al., 2008).

Following injection of one eye of rats (3/group; strain not specified) with [^{3}H]-farnesol (in DMSO), 90 % of the non-saponifiable radioactivity was recovered as the parent chemical (Lapczynski et al., 2008). An in vitro study in human tissue microsomes reported the potential metabolites of the chemical as farnesyl glucuronide, hydroxyfarnesol and hydroxyfarnesyl glucuronide (Staines et al., 2004).

Metabolites of the chemical were detected in urine and faeces at levels of 6.7 and 12.7 %, respectively, of the total applied radioactivity 24 hours after gavage administration of radiolabelled chemical in rats (strain, number, and sex not specified). Distribution of the chemical to the liver and small intestines was reported (Lapczynski et al., 2008).

Acute Toxicity

Oral

The chemical has low acute oral toxicity based on the available data.

The median lethal doses (LD50) in rats and mice are all > 2000 mg/kg bw (US EPA, 1989; Lapczynski et al., 2008; US EPA, 2009; HSDB).

Dermal

The chemical has low acute dermal toxicity based on the available data.

The LD50s in rats are > 2010 mg/kg bw (US EPA, 2009) and > 15 mg/kg bw (Lapczynski et al., 2008), and > 5000 mg/kg bw in rabbits (Lapczynski et al., 2008).

Inhalation

The chemical has low to moderate acute inhalation toxicity based on the available data.

The median lethal concentration (LC50) in rats is 0.917 mg/L. The form of the test substance, duration of exposure, and sub-lethal effects are not specified.

Corrosion / Irritation

Skin Irritation

The chemical has the potential to irritate skin in animal studies. The minimal reporting of the data, including skin irritation scores, is not sufficient to determine whether hazard classification for the chemical is warranted.

The neat chemical was applied to the shaved back skin of New Zealand White (NZW) rabbits under a semi-occlusive dressing for 4 hours. Very slight to severe erythema, including scale formation, and oedema was seen in the 15-day observation period (Belsito et al., 2008; Lapczynski et al., 2008).

In an occluded application, the neat chemical was applied to shaved and intact skin of NZW rabbits for 24 hours. Irritation was reported following observations at 1, 25, 48, and 72 hours after patch removal. No other details were specified (Belsito et al., 2008; Lapczynski et al., 2008).

Neat farnesol was 'practically non-irritating' in a primary dermal irritation study in rabbits (US EPA, 2009).

Eye Irritation

The chemical has the potential to irritate eyes in animal studies. The minimal reporting of the data, including eye irritation scores, is not sufficient to determine whether hazard classification for the chemical is warranted.

In two eye irritation tests, one eye of albino rabbits (3 or 6 animals per dose) was treated with the neat chemical or 0.3 % of the chemical in soybean oil. The untreated eye served as the control. Effects of the treatment with the neat chemical included hyperaemia and moderate redness. At 0.3 %, slight redness, distinct swelling of conjunctivae and distinct hypersecretion were reported. The effects cleared by the fifth day of observation (Belsito et al., 2008; Lapczynski et al., 2008). Moderate eye irritation was observed in six NZW rabbits applied the chemical using the similar treatment regime (Belsito et al., 2008; Lapczynski et al., 2008).

Neat farnesol was 'minimally irritating' in a primary eye irritation study in rabbits (US EPA, 2009).

Observation in humans

No skin irritation was observed in the following human studies (Belsito et al., 2008; Lapczynski et al., 2008):

- a series of 11 pre-testing applications for a human maximisation study which consisted of 48-hour closed patch tests on the back of male and female individuals using 10 or 12 % farnesol;
- induction phase of two human repeated insult patch tests (HRIPT) which consisted of nine 24-hour applications using 5 % farnesol in petrolatum applied under semi-occlusion; and
- another HRIPT which consisted of nine 24-hour applications of 5 % farnesol in 3:1 diethyl phthalate/ethanol vehicle applied under occlusion.

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results in local lymph nose assays (LLNA) (EC3 is 5.5 % or less) and in human studies (see **Sensitisation: Observation in Humans**).

A LLNA was conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 429 and in compliance with the principles of good laboratory practice (GLP). Female CBA mice (n=4) received farnesol at 5, 10, or 25 % in 3:1 actenone/olive oil vehicle. The stimulation index (SI) values were reported as 3.8, 6.7, and 12.7 at 5, 10, and 25 % concentrations, respectively. The EC3 value could not be determined as all SI values were above 3 (Belsito et al., 2008; Lapczynski et al., 2008). In another LLNA conducted using the same method and concentrations as above, the SI values were 2.8, 4.7, and 17.6 at 5, 10, and 25 % concentrations, respectively. The EC3 was estimated as 5.5 % (Belsito et al., 2008; Lapczynski et al., 2008).

The following maximisation tests, conducted according to the Magnusson and Kligman method (test guideline information not specified), reported negative skin sensitisation results (Belsito et al., 2008; Lapczynski et al., 2008):

- in Pirbright guinea pigs (sex and number not specified) with induction concentration of 10 % in Vaseline applied intradermally and 10 % in petrolatum occluded application, and challenge concentrations of 25, 50, or 100 % in Vaseline;
- in guinea pigs (sex, strain, and number not specified) with induction concentration of 5 % in peanut oil applied intradermally or neat chemical occluded application, and challenge concentration of 25 % in peanut oil;
- in guinea pigs (sex, strain, and number not specified) with induction and challenge concentration of 10 %; and
- in guinea pigs (n=10; sex and strain not specified) using 0.16 % of the chemical in acetone.

Skin sensitisation was reported in a modified Freund's complete adjuvant (FCA) test with the chemical at concentrations of 3 or 10 % in acetone. No skin reactions were observed in a guinea pig open epicutaneous test (OET) with 2 % of the chemical in unspecified vehicle (Belsito et al., 2008; Lapczynski et al., 2008).

Data submitted to the US EPA for the registration of the chemical as a biopesticide indicated that the neat chemical is negative for skin sensitisation in guinea pigs (US EPA, 2009).

Observation in humans

There were no skin sensitisation reactions seen in HRIPT at concentrations of 5 % farnesol in 3:1 diethyl phthalate/ethanol (108 individuals) and 5 % farnesol in petrolatum (one group of 103 individuals and one group of 101 individuals) (Belsito et al., 2008; Lapczynski et al., 2008).

Mixed results were reported in human maximisation studies. Sensitisation was observed at concentrations of 10 % farnesol in petrolatum (4/25 and 6/25 individuals) and 12 % farnesol in petrolatum (2/25, 4/25, and 7/25 individuals). No sensitisation was observed at concentrations of 10 % farnesol in petrolatum (25 individuals) and 12 % farnesol in petrolatum (three groups of 25 individuals, one group of 26 individuals, and one group of 35 individuals) (Belsito et al., 2008; Lapczynski et al., 2008).

In several diagnostic studies on patients suspected of having cosmetic contact dermatitis, the patch tests of 2 to 10 % farnesol in petrolatum showed skin sensitisation reactions with incidences ranging from 0 to 3.92 % (Belsito et al., 2008; Lapczynski et al., 2008).

Repeated Dose Toxicity

Oral

The chemical is not considered to cause serious damage to health from repeated oral exposure.

There were no effects on the total or high density lipoprotein (HDL) serum cholesterol levels in Fischer 344 (F/344) rats (6/dose; sex not specified) administered 0 or 1.5 % farnesol in the diet for eight weeks (Belsito et al., 2008; Lapczynski et al., 2008).

The effects of the chemical on the activity of hepatic and renal drug metabolising enzymes were investigated in CD rats (10/sex/dose) administered farnesol (corn oil vehicle) daily by gavage at doses of 0, 500, or 1000 mg/kg bw/day for 28 days. Effects included changes in the liver and kidney weights, and increased drug metabolising activities of the liver (CYP2E1, glutathione reductase, NADPH quinone reductase) and kidneys (glutathione-S-transferase). The treatment effects on the dosed group were reversible and comparable to the control group following the 28-day recovery period. No significant effects were reported in bodyweight, food consumption, clinical signs, or haematology/coagulation parameters (Belsito et al., 2008; Lapczynski et al., 2008; HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

The JECFA and EFSA evaluations of groups of food additives and flavourings including farnesol indicated that there is no safety concern for the chemical at low intake levels (WHO, 2004; EFSA, 2013).

Genotoxicity

Based on the available information, the chemical is not considered to be genotoxic.

The chemical is negative in two bacterial mutation assays in *Salmonella typhimurium* strains with and without metabolic activation at concentrations up to 5000 µg/plate, and one chromosomal aberration test in Chinese hamster ovary (CHO) cells (concentration not specified) with and without metabolic activation (Belsito et al., 2008; Lapczynski et al., 2008; HSDB).

The chemical is not genotoxic in an in vivo mouse bone marrow micronucleus assay. No other details were provided (Belsito et al., 2008).

Carcinogenicity

No animal data are available. Based on the available information, the chemical is not considered to be carcinogenic.

The chemical has no structural alerts for binding to DNA based on the mechanistic profilers of the OECD Quantitative Structure-Activity Relationship (QSAR) Application Toolbox v.3.4.

Data available for cyclic and non-cyclic terpene alcohols indicate that these chemicals are unlikely to be carcinogenic (Belsito et al., 2008).

Reproductive and Developmental Toxicity

The chemical is not considered to be a reproductive or developmental toxicant.

In previously described studies (see **Repeat Dose Toxicity: Oral**), no adverse effects on the histopathology of reproductive organs of male and female rats were reported following the administration of the chemical.

Farnesol (0.75 mg) was injected into the amniotic fluid of foetal rats (strain and number not specified) on gestation day (GD) 17 and the barrier function was examined on GD 19 following caesarian extraction. The effect reported was increase in skin barrier ontogenesis. The significance of this effect is not known and no other details were provided (Belsito et al., 2008; Lapczynski et al., 2008).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin sensitisation.

Public Risk Characterisation

Although use in cosmetic and domestic products in Australia is not known, the chemical is reported to be used in cosmetic and domestic products overseas.

The chemical is readily available, and is expected to be widely distributed for use as a raw fragrance material. However, 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 is expected to sufficiently manage the public risks associated with chemical exposure through fragrances (e.g. concentration limit in finished products of 0.2 – 5 % of the chemical (IFRA, 2016)).

Occupational Risk Characterisation

Given the critical health effect, the risk to workers from these chemicals is considered high unless adequate control measures to minimise occupational exposure to these chemicals 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.

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	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 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 (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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