Essential oils, Australian sandalwood: Human health tier II assessment

12 December 2019

CAS Number: 8024-35-9

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	Santalum spicatum sandalwood oil, Western Australia Fusanus spicatus wood oil
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight (g/mol)	Unspecified
Appearance and Odour (where available)	Pale yellow slightly viscous oil with a woody odour.
SMILES	C1(C)(CCC=C(C)CO)C2(C)C3C2CC1C3

Import, Manufacture and Use

Australian

Based on NICNAS data, the Forest Products Commission Western Australia industry development plan and AgriFutures Australia, the essential oils, Australian sandalwood (hereafter referred to as 'oil') is manufactured locally and exported for use in

perfumery, incense products, and for the tobacco industry as a flavouring for chewing tobacco (RIRDC, 2006; FPC, 2008).

The oil has reported non-industrial use in therapeutics (TGA, 2007).

International

The following international uses have been identified through Galleria Chemica; 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 Household Products Database (HPD); and other sources (International Fragrance Association (IFRA) Transparency List; ScienceDirect; Forest Products Commission Western Australia).

The oil has reported cosmetic use as a fragrance ingredient in perfumes and a wide range of personal care products.

The oil has reported domestic use in detergents, incense products and insect repellents.

The oil has reported non-industrial use in therapeutic products.

Restrictions

Australian

Sandalwood oil (as *Santalum spicatum*) is approved in listable therapeutic goods only if the active ingredient oil is derived from the root or stem wood, and for topical or inhalational use, but not for oral use (TGA, 2000).

International

Sandalwood oil is not specifically restricted internationally.

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

The Australian sandalwood oil is obtained from solvent extraction and steam distillation of the heartwood of a tree native to Western Australia, *Santalum spicatum* or *Fusanus spicatus.* Although it is a close relative to the parent tree of East Indian sandalwood oil, the top notes are characteristically different and the oil cannot be used as a direct substitute (RIRDC, 2006; FPC, 2008).

The oil is widely used as a fragrance ingredient in various perfumery and personal care products. It is also used in therapeutic products and exported to Asia to be made into incense and joss sticks for religious purposes. The oil makes up a considerable part of the sandalwood oil market (Poucher, 1991; SCCS, 2012; ScienceDirect).

The international (ISO) standard for Australian sandalwood oil states that it contains 75 % santalols (a mixture of alpha- and beta-santalol) and 10 % farnesol (SCCS, 2012).

No data are available for the Australian sandalwood oil. Therefore, studies for the major constituents santalol and farnesol (CAS No. 4602-84-0) are considered as suitable analogues for local and systemic effects. In some studies for sandalwood oil, it is not clear whether the oil relates to sandalwood oil from *Santalum album* L (CAS No. 8006-87-9) or the Australian sandalwood oil. Therefore, this assessment should be read together with the Human Health Tier II assessment for ‘Santalol and related substances’ (NICNASa).

Toxicokinetics

Australian sandalwood oil is expected to be absorbed following oral, dermal and inhalation exposure. The major identified constituents, santalol and farnesol, are cyclic and non-cyclic terpene alcohols, which follow a major metabolic pathway of glucuronic acid conjugation.

Santalols, which constitute 75 % of the oil, are sesquiterpenoids, and are a mixture of alpha- and beta isomers. The chemicals are oxidised to yield carboxylic acid metabolites, conjugated with glucuronic acid then excreted in the urine (NICNASa).

In an in vitro study in human tissue microsomes, the metabolites of farnesol were identified as farnesyl glucuronide, hydroxyfarnesol and hydroxyfarnesyl glucuronide. Following oral administration in rats, the metabolites of farnesol were detected in the urine and faeces at 6.7 % and 12.6 %, respectively after 24 hours (NICNASb).

Acute Toxicity

Oral

No data are available.

Data for santalol and farnesol indicate low acute toxicity in animals following oral exposure (NICNASa; NICNASb).

Dermal

No data are available.

Data for santalol and farnesol indicate low acute toxicity in animals following dermal exposure (NICNASa; NICNASb).

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

Most essential oils may cause mucous membrane irritation following exposure, and there is risk of aspiration from both the essential oil and from hydrocarbons or emulsifiers added to the products (HSDB).

Skin Irritation

No specific skin irritation studies are available. Based on available studies for santalol and farnesol, the oil is not likely to be a strong skin irritant.

Sandalwood oil and its major constituent santalol are not likely to be strong skin irritants. Santalol was not irritating up to a concentration of 20 % in humans. Undiluted sandalwood oil was considered to be a skin irritant in an in vitro study, but not in humans (NICNASa).

Farnesol was irritating when applied undiluted to the skin of New Zealand White (NZW) rabbits. However, no skin irritation was observed in human studies up to concentrations of 12 %. Therefore, the available data was insufficient to warrant hazard classification (NICNASb).

Eye Irritation

No specific eye irritation studies are available. Based on available studies for its sandalwood extract and farnesol, the oil is not likely to be a strong eye irritant.

Sandalwood extract was not considered to be corrosive or a severe irritant in an in vitro eye irritation study (NICNASa).

Undiluted farnesol was irritating in two eye irritation tests in rabbits. In another primary eye irritation study in rabbits, the undiluted chemical was considered as ‘minimally irritating’. The available data for farnesol was insufficient to warrant hazard classification (NICNASb).

Observation in humans

Santalol was not irritating when tested at 20 % in petrolatum on 5 healthy male volunteers for 48 hours (NICNASa).

In several human studies, farnesol was not irritating at 10 % or 12 % in human maximisation study, and at 5 % in 3 human repeated insult patch tests (HRIPT) (NICNASb).

Sensitisation

Skin Sensitisation

Although no data are available for Australian sandalwood oil, it is considered to be a skin sensitiser based on the major components santalol and farnesol. Based on the widespread reports of skin sensitisation cases in humans for the constituents, the oil is recommended for hazard classification.

Alpha-santalol was 'mildly sensitising' in a guinea pig maximisation test at 10 % concentration, and not sensitising in two open epicutaneous tests (OET) at 20 % concentration (NICNASa).

Farnesol was considered to be a skin sensitiser based on positive results in several animal studies (NICNASb):

- in a local lymph node assays (LLNA), the chemical was tested up to 25 % concentrations in female CBA mice. The stimulation index (SI) values were 12.7 and 17.6 at the highest concentration, and the EC3 value was estimated as 5.5 %;

- in several guinea pig maximisation tests, negative skin sensitisation results were reported at induction concentrations ranging from 5–10 %, and challenge concentrations up to 100 %;
- in a modified Freund's complete adjuvant (FCA) test, the chemical was positive at 3 % or 10 % concentrations; and
- in a guinea pig OET, negative results were reported at 2 % concentration.

Observation in humans

The European Union Scientific Committee on Consumer Safety (SCCS) has categorised the Australian sandalwood oil as an 'established contact allergen in humans', based on the content of 'well-known allergenic compounds (santalols)' (SCCS, 2012).

Many clinical studies are available on the skin sensitisation of santalol in humans. In diagnostic patch tests, positive results were observed with incidences of 0.0071–1.53 % when santalol was tested up to 10 % concentration. However, no sensitisation was observed at 20 % concentration in 25 male volunteers in a human maximisation test. In a 6-year patch test study, patients with facial dermatoses were tested with a mixture of alpha and beta-santalol up to 10 % concentration and positive reactions were seen at an incidence of 1.5 %. No effects were observed when these patients were tested for phototoxicity and photoallergy (NICNASa).

Farnesol produced mixed results in several human maximisation tests at 10 or 12 % concentration. No sensitisation reactions were observed in a HRIPT at 5 % concentration. In patients with suspected cosmetic contact dermatitis, application of the chemical at up to 10 % resulted in positive reactions with incidences of 0 – 3.92 % (NICNASb).

Repeated Dose Toxicity

Oral

No data are available.

Santalol is predicted to metabolise to innocuous products, and is not likely to present a safety concern at estimated levels of intake from food sources (JECFA, 2003).

Farnesol is not considered to cause serious damage to health from repeated oral exposure. In a 28-day repeat dose toxicity study (non-guideline), no significant effects were observed in in CD rats when administered the chemical daily at doses of 0, 500, or 1000 mg/kg bw/day in corn oil. Observed effects included statistically significant dose-related changes in the liver and kidney weights, and increased drug metabolising activities of the liver and kidney. Following a 28-day recovery period, all effects for the treated group were reversible and comparable to the control group. No significant effects were reported in body weight, food consumption, clinical signs, or haematological or coagulation parameters (NICNASb). A dose level of 500 mg/kg bw/day was considered to be 'minimally toxic' based on slight changes in clinical chemistry parameters, and significant enzyme inducing changes in the liver and kidney. A No Observed Adverse Effect Level (NOAEL) was not proposed, although effects were reversible after 28 days (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on available data for sandalwood oil (*Santalum album*) and farnesol, the Australian sandalwood oil is not likely to be genotoxic.

No data are available for santalol. Sandalwood oil (*Santalum album*) was not mutagenic in a bacterial reverse mutation assay, and not genotoxic in a *Bacillus subtilis* Rec assay, with or without metabolic activation (NICNASa).

Farnesol was not genotoxic in two bacterial mutation assays or in an in vivo bone marrow micronucleus assay (NICNASb).

Carcinogenicity

Although no data are available, sandalwood oil is not known to be carcinogenic based on its long history and widespread use in consumer products.

Alpha-santalol is reported to show chemopreventive properties on tumour development in several strains of mice and in in vitro studies (NICNASa).

No data are available for farnesol. There were 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 (NICNASb).

Reproductive and Developmental Toxicity

No data are available for santalol. Farnesol was not considered to be a reproductive or developmental toxicant in animal studies (NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation for Australian sandalwood oil include:

- local effects (skin sensitisation).

Public Risk Characterisation

Considering the range of products that may contain the chemical, the main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products.

Australian sandalwood oil is considered to be a skin sensitiser based on its major constituent santalol, and; therefore, has potential to cause skin sensitisation especially to individuals with allergies or pre-sensitised to other allergens. When evaluated by the SCCS, the oil is not considered to be among the more common fragrance allergens. The oil was not included on the list of common allergens that require labelling in cosmetic products regardless of its widespread use (SCCS, 2012). Therefore, the risk of skin sensitisation following exposure to products containing Australian sandalwood oil as a fragrance ingredient is expected to be low.

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 oil 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 oil 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) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all 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 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. 1B (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.

References

Agrifutures Australia. Rural Industries Research and Development Corporation (RIRDC) (2006). Australia's Sandalwood Industry: An overview and analysis of research needs. Accessed August 2019 at https://www.agrifutures.com.au/wp-content/uploads/publications/06-131.pdf

ChemID Plus Advanced. Accessed July 2019 at https://chem.nlm.nih.gov/chemidplus/

Cosmetic Ingredients & Substances (CosIng) Database. European Commission. Accessed August 2019 at http://ec.europa.eu/consumers/cosmetics/cosing/

Galleria Chemica. Accessed August 2019 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed July 2019 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

International Fragrance Association (IFRA) Transparency List. Accessed August 2019 at https://ifrafragrance.org/initiatives/transparency/ifra-transparency-list

Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2003. WHO Food Additives Series 50: Alicyclic Primary Alcohols, Aldehydes, Acids, and Related Esters. Accessed July 2019 at: http://www.inchem.org/documents/jecfa/jecmono/v50je10.htm

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Human health Tier II assessment for Santalol and related substances. Australian Government Department of Health. Accessed at https://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Human health Tier II assessment for 2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl- (CAS No. 4602-84-0). Australian Government Department of Health. Accessed at https://www.nicnas.gov.au

Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed August 2019 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

Poucher WA. Jouhar AJ (ed). 1991. Poucher’s Perfumes, Cosmetics and Soaps — Volume 1: The Raw Materials of Perfumery. Chapman& Hall. London.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Farnesol (CAS No. 4602-84-0). Accessed October 2019 at https://echa.europa.eu/registration-dossier/-/registered-dossier/23466/1

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed July 2019 at http://hcis.safeworkaustralia.gov.au/

Scientific Committee on Consumer Safety (SCCS) 2012. Opinion on Fragrance Allergens in Cosmetic Products. Accessed July 2019 athttp://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf

The Forest Products Commission (FPC) Western Australia. WA Sandalwood industry development plan 2008-2020. Accessed August 2019 at http://www.fpc.wa.gov.au/about-us/publications/industry-development-plans

Therapeutic Goods Administration (TGA) (2000). Complementary Medicines Evaluation Committee (CMEC 22). Extracted Ratified Minutes: Twenty-second Meeting. Accessed at https://www.tga.gov.au/sites/default/files/cmec-minutes-22.pdf

Therapeutic Goods Administration (TGA). Substances that may be used in listed medicines in Australia. Accessed July 2019 at Therapeutic Goods Administration (2007).

US National Library of Medcicine's Hazardous Substances Database (HSDB). National Library of Medicine. Alpha-Santalol (CAS No. 115-71-9). Accessed July 2019 at http://toxnet.nlm.nih.gov.

US National Library of Medicine Household Products Database, Health and Safety Information on Household Products. Accessed August 2019 at http://householdproducts.nlm.nih.gov/

Last update 12 December 2019

Share this page