Alkyl ethers of geraniol: Human health tier II assessment

27 October 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
2,6-Octadiene, 1-methoxy-3,7-dimethyl-, (E)-	2565-82-4
2,6-Octadiene, 1-methoxy-3,7-dimethyl-, (Z)-	2565-83-5
2,6-Octadiene, 1-ethoxy-3,7-dimethyl-	40267-72-9
2,6-Octadiene, 1-ethoxy-3,7-dimethyl-, (Z)-	22882-89-9
2,6-Octadiene, 1-ethoxy-3,7-dimethyl-, (E)-	22882-91-3

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

Grouping Rationale

Derivatives of geraniol including methyl and ethyl ethers are assessed together in this report because of their similarities in chemical structure and metabolic profile (see **Toxicokinetics** section).

The following synonyms and their corresponding CAS numbers will be used in this assessment:

- geranyl methyl ether: CAS No. 2565-82-4
- neryl methyl ether: CAS No. 2565-83-5
- geranyl ethyl ether: CAS No. 40267-72-9
- neryl ethyl ether: CAS No. 22882-89-9
- (E)-geranyl ethyl ether: CAS No. 22882-91-3

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; European Food Safety Authority (EFSA) the International Fragrance Agency (IFRA); and the Good Scent Company (GSC).

The chemicals have reported cosmetic use in perfumes at concentrations of 3–10 %.

Restrictions

Australian

No known restrictions have been identified.

International

Geranyl methyl ether (CAS No. 2565-82-4) and neryl methyl ether (CAS No. 2565-83-5) are listed in Annex III of the REACH regulation based on suspected skin sensitisation (REACH).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are 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

This group of chemicals have similar properties and metabolic profile to geranyl acetate (NICNAS), which includes cleavage to geraniol and in these cases, the corresponding alcohols, ethanol and methanol. However, the metabolism of this group of chemicals is expected to be slower than geranyl acetate due to the slow reactivity of ether moieties (EFSA, 2011).

It is also expected that geranyl methyl ether (CAS No. 2565-82-4) and neryl methyl ether (CAS No. 2565-83-5) may release formaldehyde during metabolism; and geranyl ethyl ether (CAS No. 40267-72-9), neryl ethyl ether (CAS No. 22882-89-9) and (E)-geranyl ethyl ether (22882-91-3) may release acetaldehyde. These aldehydes are produced in the body by normal metabolic processes and can be detoxified at low levels. Considering the low concentrations used in cosmetic and the expected slow

metabolism, these chemicals are not expected to produce aldehydes beyond the capacity of cellular metabolism to detoxify them.

Where data are unavailable for this group of chemicals, the health hazard information for geranyl acetate (CAS No 105-87-3) will be used as read across in this assessment.

Toxicokinetics

Simple aliphatic ethers are expected to be rapidly absorbed from the gastrointestinal tract and excreted via the urine and breath. Aliphatic ethers undergo O-dealkylation to the corresponding alcohols and aldehydes. The alcohol may undergo oxidation and conjugation, while the aldehydes may be oxidised to the corresponding carboxylic acid (EFSA, 2011).

Acute Toxicity

Oral

The available information indicates that the chemicals in this group have low acute oral toxicity.

The reported median lethal dose (LD50) for geranyl ethyl ether was >5000 mg/kg bw (EFSA, 2011) and the LD50 for geranyl acetate was 6330 mg/kg (NICNAS).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

No data are available for the chemicals in this group.

Observation in humans

No data are available for the chemicals in this group. Geranyl acetate was not considered sensitising based on a maximisation test conducted in 25 human volunteers at a concentration of 4 % in petrolatum; however, hypersensitivity reactions were reported in certain individuals (NICNAS).

Repeated Dose Toxicity

Oral

No data are available for the chemicals in this group. Based on the available data on geranyl acetate, the chemicals in this group are not expected to cause systemic effects following repeated oral exposure.

Fischer 344 (F344) rats and B6C3F1 mice (n=5/sex/dose) were administered geranyl acetate by gavage at doses of 0, 62, 125, 250, 500 or 1000 mg/kg bw/day in rats and 0, 125, 250, 500, 1000 or 2000 mg/kg bw/day for 14 days. No effects were reported to be seen in rats. At the highest dose in mice, three females at the highest dose died and one male and three females had thickened duodenal and cardia stomach walls, respectively. A no observed adverse effect level (NOAEL) was not determined (NICNAS).

No toxic effects were observed when geranyl acetate was administered in diet of rats (species; number not specified) at concentrations up to 10000 ppm (NICNAS).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

No data are available for the chemicals in this group.

Based on the negative results in in vitro and in vivo data, geranyl acetate is not considered to be genotoxic.

In vitro tests using geranyl acetate including (NICNAS):

- Ames test in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100; with and without metabolic activation;
- Rec-assay test in *Bacillus subtilis*;
- hypoxanthine phosphoribosyl transferase (HGPRT) gene mutation assay and chromosomal aberration assay in Chinese hamster ovary (CHO) cells; and
- unscheduled DNA synthesis in rat primary hepatocytes.

In vivo tests using geranyl acetate including (NICNAS):

- micronucleus and chromosomal aberration assays in mouse bone marrow;

- unscheduled DNA synthesis in male F344 rats; and
- sex-linked recessive lethal assay in *Drosophila melanogaster*;

Carcinogenicity

No data are available for the chemicals in this group.

In a study, F344/N rats (n=50/sex/dose) were administered geranyl acetate by gavage at doses of 0, 1000 or 2000 mg/kg bw/day, 5 days/week for two-years. At 1000 mg/kg bw/day, squamous cell papillomas and carcinomas were observed on the skin; however, incidence of epidermal tumours were not significant in any group (NICNAS).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

Based on the available hazard information, the chemicals in this group do not have any critical health effects for risk characterisation.

Public Risk Characterisation

Although the public could be exposed to the chemicals through potential cosmetic uses, the chemicals are not considered to pose an unreasonable risk to public health on the basis of their low hazard profile.

Occupational Risk Characterisation

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

The chemicals in this group have low hazard; therefore, the risks to workers from these chemicals are not considered to be unreasonable.

NICNAS Recommendation

Current chemical regulatory 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

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation.

Work Health and Safety

The chemicals in this group currently have no hazard classification for worker health and safety; this is considered appropriate based on the available data.

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise any risks from oral, ocular, inhalation and dermal exposure to the chemicals 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 chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Annex III inventory of Registration, Evaluation, Authorisation and Restriction of Chemicals (Annex III). Accessed September 2017 at **https://echa.europa.eu/information-on-chemicals/annex-iii-inventory**

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed August 2017 at **http://ec.europa.eu/growth/tools-databases/cosing/**

European Food Safety Authority (EFSA) 2011. Scientific Opinion on Flavouring Group Evaluation 23, Revision 3: Aliphatic, alicyclic, and aromatic ethers including anisole derivatives from chemical groups 15, 16, 22, 26 and 30. EFSA Journal: 9(10), 2398.

Galleria Chemica. Accessed August 2017 at **http://jr.chemwatch.net/galleria/**

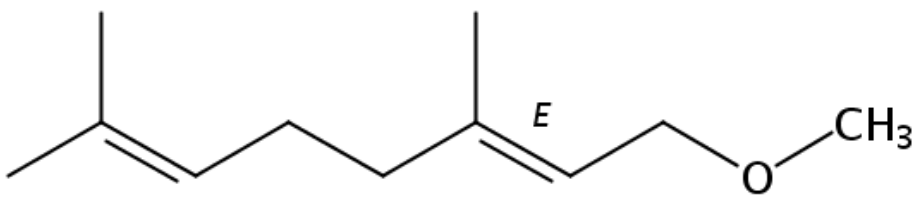
International Fragrance Association (IFRA) Survey: Transparency List. Accessed August 2017 at **http://www.ifraorg.org/en/ingredients**

Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed August 2017 at **http://hcis.safeworkaustralia.gov.au/HazardousChemical**

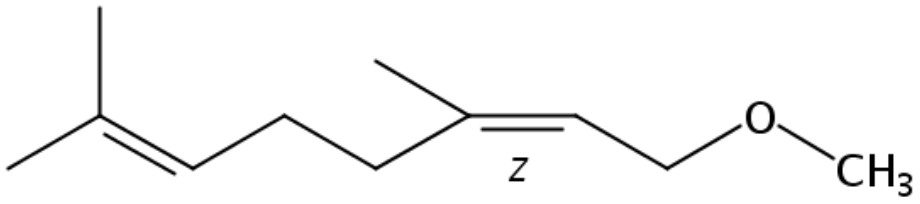
The Good Scent Company. Accessed August 2017 at **http://www.thegoodscentscompany.com/**

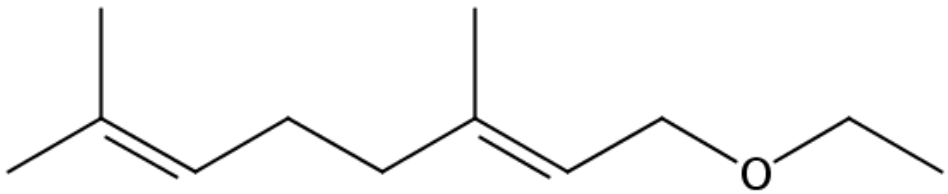
Last Update 27 October 2017

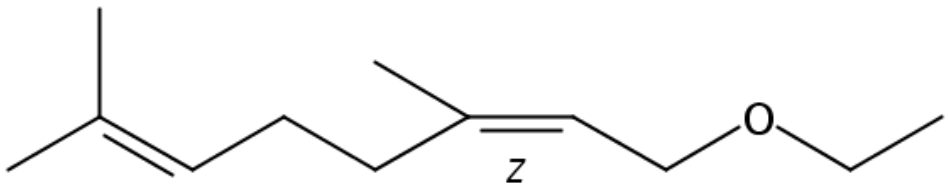
Chemical Identities

Chemical Name in the Inventory and Synonyms	**2,6-Octadiene, 1-methoxy-3,7-dimethyl-, (E)-** Geraniol, methoxy Geranyl methyl ether trans-methoxy-dimethyloctadiene
CAS Number	2565-82-4
Structural Formula	
Molecular Formula	C11H20O
Molecular Weight	168.28

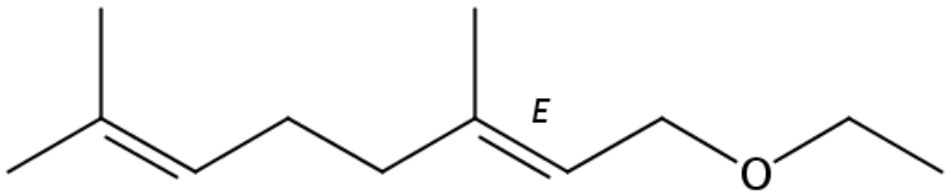
Chemical Name in the Inventory and Synonyms	**2,6-Octadiene, 1-methoxy-3,7-dimethyl-, (Z)-** Neryl methyl ether cis-methoxy-dimethyloctadiene

CAS Number	2565-83-5
Structural Formula	
Molecular Formula	C11H20O
Molecular Weight	168.28

Chemical Name in the Inventory and Synonyms	**2,6-Octadiene, 1-ethoxy-3,7-dimethyl-** ether, 3,7-dimethyl-2,6-octadienyl ethyl geranyl ethyl ether
CAS Number	40267-72-9
Structural Formula	
Molecular Formula	C12H22O
Molecular Weight	182.30

Chemical Name in the Inventory and Synonyms	**2,6-Octadiene, 1-ethoxy-3,7-dimethyl-, (Z)-** ether, 3,7-dimethyl-2,6-octadienyl ethyl, (Z)- neryl ethyl ether
CAS Number	22882-89-9
Structural Formula	

Molecular Formula	C12H22O
Molecular Weight	182.30

Chemical Name in the Inventory and Synonyms	**2,6-Octadiene, 1-ethoxy-3,7-dimethyl-, (E)-** 3,7-Dimethyl-2,6-octadienyl ethyl ether, trans- (E)-geranyl ethyl ether
CAS Number	22882-91-3
Structural Formula	
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