Alpha-beta unsaturated alkyl esters of geraniol: Human health tier II assessment

27 October 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
2-Butenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E,E)-	7785-33-3
2-Butenoic acid, 2,3-dimethyl-, 3,7-dimethyl-2,6-octadienylester, (E)-	10402-48-9
2-Butenoic acid, 3-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E)-	55066-43-8
2-Butenoic acid, 3,7-dimethyl-2,6-octadienyl ester, (?,E)-	56172-46-4
2-Butenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E,Z)-	93981-55-6
2-Propenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester	94070-95-8

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

This group of chemicals is composed of various alpha-beta unsaturated alkyl esters of geraniol and its isomeric forms: nerol and citrol (a mix of geraniol and nerol).

Although limited use data are available, the chemicals in this group are known to be used in perfumes (see **Use** section). Upon exposure, it is expected that the chemicals will be hydrolysed into geraniol and the appropriate alpha,beta-unsaturated carboxylic anion. The activated double bond at the alpha,beta-unsaturated esters and carboxylate salts will contribute to the toxicological profiles of these chemicals. On the basis of similar uses and the expected similarity in toxicity effects, the assessment of these chemicals as a group is considered appropriate.

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 US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and various international assessments (Opdyke, 1974; European Food Safety Authority (EFSA), 2009; PubChem; the Good Scents Company).

The use information below relates to both geranyl tiglate (CAS No. 7785-33-3) and geranyl crotonate (CAS No. 56172-46-4).

The chemicals have cosmetic uses in fragrances and perfumes.

The chemicals have domestic uses in soaps and detergents.

The chemicals have commercial uses in paints, lacquers and varnishes.

The chemicals have non-industrial use as flavourings.

Restrictions

Australian

No known restrictions have been identified.

International

Geranyl tiglate (CAS No. 7785-33-3), geranyl methyltiglate (CAS No. 10402-48-9), geranyl beta, beta-dimethylacrylate (CAS No. 55066-43-8), geranyl crotonate (CAS No. 56172-46-4) and neryl tiglate (CAS No. 93981-55-6) are listed in Annex III of the REACH regulation based on suspected skin sensitisation (REACH).

The citryl methacrylate, CAS No. 94070-95-8, is listed in Annex III of the REACH regulation based on suspected mutagenicity and sensitisation (respiratory and skin) (REACH).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group 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

Limited hazard information is available for the chemicals in this group. In the absence of hazard data, the information on geraniol esters, in particular, geranyl acetate (CAS No. 105-87-3) is considered relevant and will be used as read across for the hazard assessment of the hydrolysis component of the chemicals in this group.

There is also limited information available on an alpha, beta unsaturated carboxylic acid derivative for this group of chemicals. The chemical isodecyl methacrylate (CAS No. 29964-84-9) is a methacrylic acid ester similar in structure and expected physicochemical properties to the chemicals in this group, the long chain esters of alpha, beta-unsaturated acids. In the absence of information on the chemicals in this group, data on isodecyl methacrylate will be used as read across for local and systemic effects.

The metabolic profile and hazards for geraniol and its esters have been discussed in previous NICNAS Tier II assessments (NICNAS). Esters of geraniol and nerol were not considered hazardous.

Toxicokinetics

Aliphatic esters are expected to hydrolyse to form the corresponding alcohol and carboxylate anion (WHO, 2003); therefore, alpha,beta unsaturated alkyl esters of geraniol are expected to metabolise to geraniol and the component carboxylic acid anion.

No other information is available on the chemicals in this group.

Acute Toxicity

Oral

Based on the available information, the chemicals in this group are expected to have low acute oral toxicity.

The reported oral median lethal dose (LD50) values for the following chemicals were reported (Opdyke, 1974) as:

- geranyl tiglate in rats >5000 mg/kg; and
- geranyl crotonate in rats: >5000 mg/kg.

Dermal

Based on the available information, the chemicals in this group are expected to have low acute dermal toxicity.

The dermal LD50 values for the following chemicals were reported (Opdyke, 1974) as:

- geranyl tiglate in rats >5000 mg/kg; and
- geranyl crotonate in rats: >5000 mg/kg.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available animal and human data, the chemicals in this group are not expected to cause more than slight skin irritation.

Geranyl crotonate (100 %) and geranyl tiglate (100 %) caused slight skin irritation when applied to intact or abraded rabbit skin for 24 hours under occlusive conditions (Opdyke, 1974).

Eye Irritation

No data are available for the chemicals.

Observation in humans

In a 48-hour closed patch test, geranyl crotonate (10 % in petrolatum) and geranyl tiglate (6 % in petrolatum) produced no skin reactions in human volunteers (Opdyke, 1974).

Sensitisation

Skin Sensitisation

Based on the available data, the chemicals in this group are not expected to cause skin sensitisation.

In a local lymph node assay conducted according to OECD TG 429, CBA mice (4/sex/dose) were administered isodecyl methacrylate (CAS No. 29964-84-9) (in acetone/olive oil, 4:1) at concentrations of 25, 50 or 100 %. Stimulation indices were calculated to be 1.43, 1.22 and 0.97, respectively. The chemical was determined to be non-sensitising to the skin (REACH).

No data are available for geranyl acetate (CAS No. 105-87-3).

Observation in humans

Geranyl crotonate (10 % in petrolatum) and geranyl tiglate (6 % in petrolatum) did not produce skin sentitisation reactions when applied to 25 subjects in a human maximisation test (Opdyke, 1974).

Repeated Dose Toxicity

Oral

No data are available for the chemicals in this group; however, data for geranyl acetate (CAS No. 105-87-3) indicate that this group of chemicals are not expected to cause serious damage to health from repeated oral exposure.

Geranyl acetate was administered to Fischer 344 (F344)/N rats and B6C3F1 mice (5/sex/dose) by gavage at doses of 0–1000 and 0–2000 mg/kg bw/day, respectively for 14 days. At 2000 mg/kg bw/day, three mice died, and one male showed thickened

duodenal wall while three females showed 'thickened wall of the cardia stomach'. Mice dosed at 1000 mg/kg bw/day were inactive but returned to normal 24 hours post-administration. These effects were determined to be treatment-related. No deaths or treatment related effects were observed in rats. A no observed adverse effect level (NOAEL) was not determined in this study (NICNAS).

No data are available for isodecyl methacrylate (CAS No. 29964-84-9).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available information, geranyl acetate (CAS No. 105-87-3) is not considered to be genotoxic (NICNAS). Geranyl tiglate has been evaluated as having no safety concern for genotoxicity (EFSA, 2009). Overall, the available data are limited and considered insufficient to determine the genotoxic potential of the chemicals in this group.

Negative results were reported in several in vitro tests using isodecyl methacrylate (CAS No. 29964-84-9) (REACH).

In vitro:

- Ames test in *Salmonella typhmurium* strains TA1535, TA1537, TA98, TA100 and TA102, with and without metabolic activation at concentrations up to 5000 µg/plate;
- mammalian chromosome aberration test in human lymphocytes with and without metabolic activation; and
- mammalian cell gene mutation test in Chinese hamster lung fibroblasts with and without metabolic activation at concentrations up to 1200 µg/mL.

Negative results were reported in several in vitro and in vivo tests using geranyl acetate (NICNAS).

In vitro

- Ames test in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100; with and without metabolic activation;
- rec assay test in *Bacillus subtilis*;
- hypoxanthine-guanine 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

- micronucleus and chromosomal aberration assays in mouse bone marrow;
- unscheduled DNA synthesis in male F344 rats; and
- sex-linked recessive lethal assay in *D. melanogaster*.

Carcinogenicity

Based on the available data for geranyl tiglate (CAS No. 7785-33-3) and geranyl acetate (CAS No. 105-87-3), the chemicals in this group are not expected to have carcinogenic potential.

Geranyl tiglate has been evaluated as having no safety concern for carcinogenicity (EFSA, 2009).

In a study, F344/N rats (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. Squamous cell papillomas and carcinomas were observed on the skin of rats dosed 1000 mg/kg bw/day; however, the overall incidence of epidermal tumours was not different among groups (NICNAS).

Reproductive and Developmental Toxicity

No data are available for the chemicals in this group.

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

While Australian use information is not available, the chemicals in this group have reported international use in domestic and cosmetic products. Considering the range of products that may contain the chemicals, the public could be exposed to the chemicals through the skin and inhalation from products applied as aerosols. On the basis of their low hazard profile, the chemicals are not considered to pose an unreasonable risk to public health. In addition, the use for geranyl tiglate (CAS No. 7785-33-3) and geranyl crotonate (CAS No. 56172-46-4) are expected to be at very low concentrations, ranging from 0.005–0.2% in various cosmetic and domestic products (Opdyke, 1974). The other members of the group would be expected to have similar use concentrations.

Occupational Risk Characterisation

During product formulation, oral, 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, they are not considered to pose unreasonable risk to workers.

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, occular, dermal and inhalation 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:

- 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 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 August 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) 2009. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF): Flavouring Group Evaluation 202. The EFSA Journal 1081, 1-27.

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

National Center for Biotechnology Information. PubChem Compound Database. Accessed August 2017 at **https://pubchem.ncbi.nlm.nih.gov/compound/**

National Industrial Chemical Notification and Assessment Scheme (NICNAS). Human health Tier II assessment for Esters of geraniol and nerol. Australian Government Department of Health. Available at **https://www.nicnas.gov.au**

Opdyke DL 1979. Monographs on fragrance raw materials. Food Cosmet Toxicol. 1979 Aug;17(4):357-90.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier for isodecyl methacrylate (CAS No. 29964-84-9). Accessed September 2017 at **https://echa.europa.eu/registration-dossier/-/registered-dossier/14316/**

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

Safety evaluation of certain food additives. World Health Organisation (WHO) Food Additives Series, No. 50, 2003, pp. 1053-1071. Accessed August 2017 at **http://www.inchem.org/documents/jecfa/jecmono/v52je14.htm#int**

SPIN (Substances in Preparations in Nordic Countries) Database. Available: **http://195.215.202.233/DotNetNuke/default.aspx**

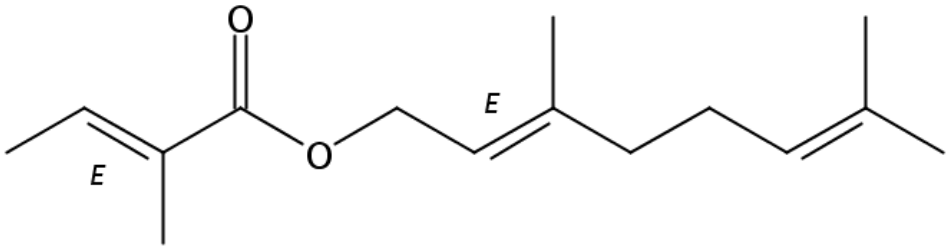
The Good Scent Company. Accessed August 2017 at **http://www.thegoodscentscompany.com/**

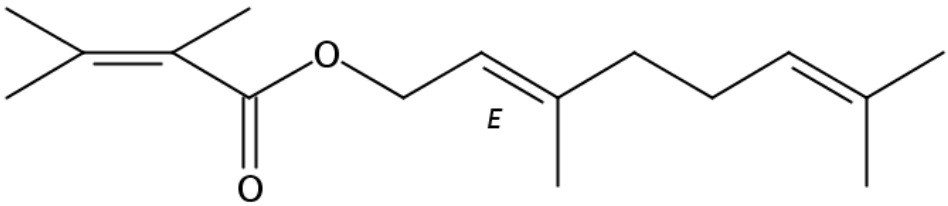
The United States (US) Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR). Accessed August 2017 at **https://actor.epa.gov/actor/searchidentifier.xhtml**

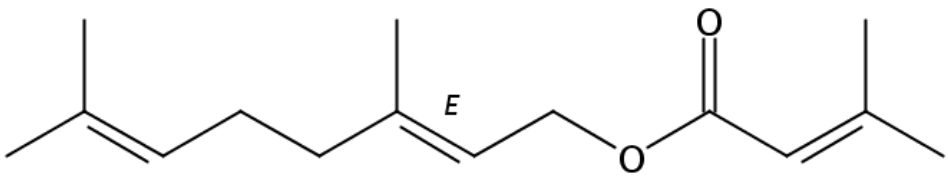
Last Update 27 October 2017

Chemical Identities

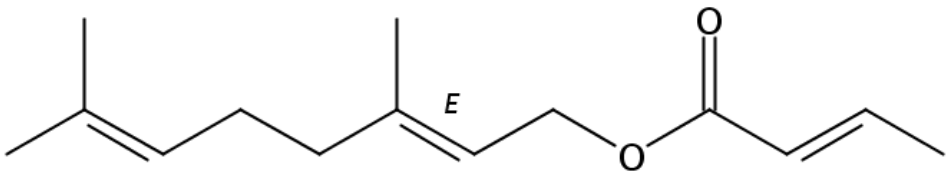
Chemical Name in the Inventory and Synonyms	**2-Butenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E,E)-** geranyl tiglate (E)-3,7-dimethyl-2,6-octadienyl 2-methylcrotonate tiglic acid, geranyl ester
CAS Number	7785-33-3
Structural Formula	

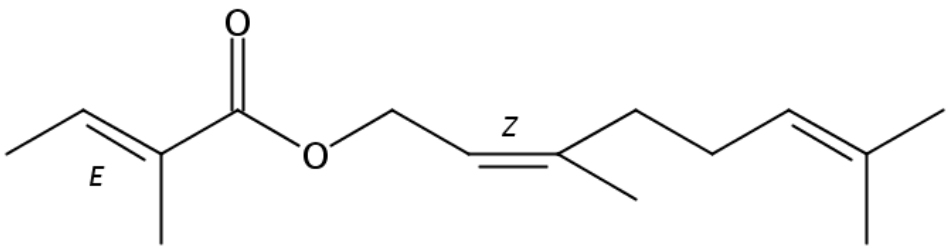
	
Molecular Formula	C15H24O2
Molecular Weight	236.35

Chemical Name in the Inventory and Synonyms	**2-Butenoic acid, 2,3-dimethyl-, 3,7-dimethyl-2,6-octadienylester, (E)-** geranyl methyltiglate crotonic acid, 2,3-dimethyl-, 3,7-dimethyl-2,6-octadienyl ester, (E)- 3,7-dimethyl-2,6-octadienyl 2,3-dimethylcrotonate
CAS Number	10402-48-9
Structural Formula	
Molecular Formula	C16H26O2
Molecular Weight	250.38

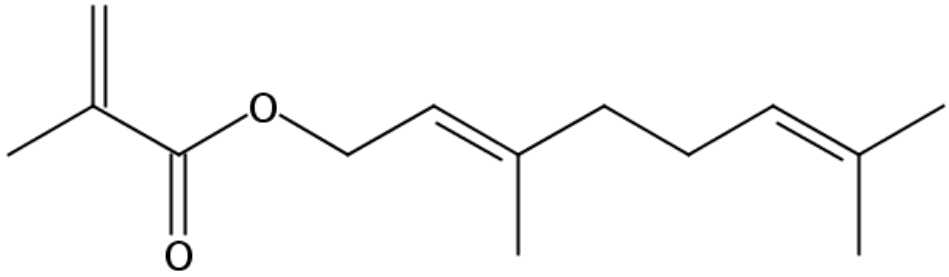
Chemical Name in the Inventory and Synonyms	**2-Butenoic acid, 3-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E)-** geranyl beta,beta-dimethylacrylate 3,7-dimethyl-2,6-octadienyl 3-methylcrotonate
CAS Number	55066-43-8
Structural Formula	
Molecular Formula	C15H24O2

Molecular Weight	236.35

Chemical Name in the Inventory and Synonyms	**2-Butenoic acid, 3,7-dimethyl-2,6-octadienyl ester, (?,E)-** geranyl crotonate crotonic acid, geraniol ester geranyl-2-butenoate
CAS Number	56172-46-4
Structural Formula	
Molecular Formula	C14H22O2
Molecular Weight	222.32

Chemical Name in the Inventory and Synonyms	**2-Butenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester, (E,Z)-** 2-methyl-2-butenoic acid, neryl ester, trans- neryl tiglate (Z)-3,7-dimethyl-2,6-octadienyl 2-methylcrotonate
CAS Number	93981-55-6
Structural Formula	
Molecular Formula	C15H24O2
Molecular Weight	236.35

Chemical Name in the Inventory and Synonyms	**2-Propenoic acid, 2-methyl-, 3,7-dimethyl-2,6-octadienyl ester** 3,7-dimethylocta-2,6-dienyl methacrylate

CAS Number	94070-95-8
Structural Formula	
Molecular Formula	C14H22O2
Molecular Weight	222.32

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