Chemicals with limited data availability that are used in fragrances: Human health tier II assessment

26 October 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1-Heptanol, 2-(phenylmethylene)-	101-85-9
2-Propenoic acid, 3-phenyl-, phenylmethyl ester	103-41-3
2-Butanone, 4-(4-methoxyphenyl)-	104-20-1
2-Octynoic acid, methyl ester	111-12-6
Ethanone, 1-(naphthalenyl)-	1333-52-4
Phenol, 2-methoxy-4-methyl-, acetate	879-67-4
Benzene, (2-isothiocyanatoethyl)-	2257-09-2
Octanal, 7-methoxy-3,7-dimethyl-	3613-30-7
Benzene, 2-methoxy-1-methyl-4-(1-methylethyl)-	6379-73-3
2-Tridecenal	7774-82-5

Chemical Name in the Inventory	CAS Number
Propanoic acid, 2-oxo-, 3-methylbutyl ester	7779-72-8
2-Buten-1-ol, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-	28219-60-5
2-Hepten-1-ol, (E)-	33467-76-4
Bicyclo[3.1.1]hept-2-ene-2-propanal, 6,6-dimethyl-	33885-51-7
Cyclohexenecarboxaldehyde, 2,6,6-trimethyl-	52844-21-0
Benzenepropanoic acid, .beta.-oxo-, 4-methylphenyl ester	67801-43-8
1-Penten-3-one, 4-methyl-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	68459-99-4
Cyclohexaneacetaldehyde, 4-(1-methylethyl)-	93981-63-6

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

The chemicals in this group have reported uses in fragrances. Based on a review of publicly available information in accordance with the IMAP Framework (NICNAS, 2013), limited empirical toxicological data were identified for all of the chemicals in this group.

For chemicals with limited data, NICNAS uses the principles of 'read across' in accordance with the Organisation for Economic Co-operation and Development (OECD) *Guidance on grouping of chemicals* (OECD, 2014) based on the known properties of similar chemicals (analogues). The quality of the data used is dependent on the similarity of the analogues to the chemicals. However, the relevant analogues identified for the chemicals in this group also have limited toxicological information from which to characterise the hazards and, therefore, are not considered suitable. Consequently, other approaches such as the analysis of Quantitative Structure–Activity Relationship (QSAR) modelling information is required to characterise the hazards of the chemicals.

Import, Manufacture and Use

Australian

No specific Australian industrial use, import, or manufacturing information has been identified for all of the chemicals in this group.

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 Compilation of Ingredients Used in Cosmetics in the US (CIUCUS) (Personal Care Products Council, 2011); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US Household Products Database (HHPD).

All of the chemicals have reported cosmetic use as fragrance compounds, with the majority of the chemicals listed on the International Fragrance Association (IFRA) transparency list (IFRA, 2011).

Benzyl cinnamate (CAS No. 103-41-3), methyl 2-octynoate (CAS No. 111-12-6), methyl naphthyl ketone (CAS No. 1333-52-4), methoxydihydrocitronellal (CAS No. 3613-30-7), methylcarvacrol (CAS No. 6379-73-3), and santalinol (CAS No. 28219-60-5) have reported domestic use in cleaning/washing products.

4-Methoxybenzylacetone (CAS No. 104-20-1), phenethyl isothiocyanate (CAS No. 2257-09-2), and methoxydihydrocitronellal (CAS No. 3613-30-7) have reported site-limited use as intermediates.

The following chemicals have reported non-industrial use as food flavourings and/or food additives: (alpha-amylcinnamyl alcohol, CAS No. 101-85-9; benzyl cinnamate, CAS No. 103-41-3; 4-methoxybenzylacetone, CAS No. 104-20-1; methyl 2-octynoate, CAS No. 111-12-6; phenethyl isothiocyanate, CAS No. 2257-09-2; methylcarvacrol, CAS No. 6379-73-3; 2-tridecenal, CAS No. 7774-82-5, isopentyl pyruvate, CAS No. 7779-72-8; and 2-heptenol, CAS No. 33467-76-4).

Restrictions

Australian

No known Australian restrictions have been identified for any of the chemicals in this group.

International

Alpha-amylcinnamyl alcohol (CAS No. 101-85-9) is listed in the following (Galleria Chemica):

- European Union (EU) Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products'; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down stated as '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'.

Benzyl cinnamate (CAS No. 103-41-3) is listed in the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products'; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down stated as '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'.

Methyl 2-octynoate (CAS No. 111-12-6) is listed in the following (Galleria Chemica):

- EU Cosmetics Regulation 344/2013 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'when present in combination with methyl octine carbonate, the combined level in the finished product should not exceed 0.01% (of which methyl octine carbonate should not be more than 0.002 %)' and 'the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products'; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: 'when present in combination with methyl octine carbonate, the combined level in the finished product should not exceed 0.01 % (of which methyl octine carbonate should not be more than 0.002 %)' and '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'.

No known international restrictions have been identified for the other chemicals in this group.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are not listed in 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

Limited or no toxicological data are available for the chemicals in this group.

The critical concern for fragrance chemicals relates to their potential skin sensitisation, mutagenicity and carcinogenicity. As such, these health hazards will be the focus of this assessment, with other hazards not considered.

Genotoxicity and carcinogenicity

The following tools were used to ascertain the mutagenicity and carcinogenicity potential of the chemicals:

- OECD QSAR Toolbox v3.2 profiling functionalities; and
- Optimized Approach based on Structural Indices Set–TIssue MEtabolism Simulator (OASIS–TIMES) v2.27.14 QSAR modelling for which predictions were obtained from the following models: in vitro Ames, in vitro chromosomal aberration, in vivo micronucleus test, and in vivo liver genotoxicity.

All the chemicals in this group either have functional groups that present alerts for mutagenicity and carcinogenicity potential based on their molecular structures as profiled by the OECD QSAR Toolbox, or were predicted to be positive for mutagenicity in one or more of the OASIS–TIMES genotoxicity models.

Skin sensitisation

Structural alerts for binding to proteins were identified for the majority of the chemicals in this group. Although skin sensitisation predictions using OASIS–TIMES were negative for most of the chemicals, possible metabolites, based on the metabolism simulators of OASIS–TIMES, were predicted to be strong skin sensitisers.

The Research Institute for Fragrance Materials (RIFM), in its submission to the US National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), indicated the following skin sensitisation potency, estimated as the concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3), of some of the chemicals (US National Institutes of Health, 2011):

- 18 % (geometric mean) for benzyl cinnamate (CAS No. 103-41-3); and
- 0.5 % (geometric mean) for methyl 2-octynoate (CAS No. 111-12-6).

Additionally, the European Commission's (EC) Scientific Committee on Consumer Safety (SCCS), formerly known as the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP), identified that alpha-amylcinnamyl alcohol (CAS No. 101-85-9), benzyl cinnamate (CAS No. 103-41-3), and methyl 2-octynoate (CAS No. 111-12-6) are consumer allergens (SCCNFP, 1999).

QSAR applicability domain

Some of the predictions were out of the applicability domain of the OASIS–TIMES models for skin sensitisation and genotoxicity, which indicates greater uncertainty about the reliability of the models since the performance statistics from the training set may not be applicable to the chemicals in this group. However, in the absence of any other information, the results from the QSAR model predictions will be considered in the weight of evidence analysis of the chemicals' health effects.

Risk Characterisation

Critical Health Effects

Based on the limited data available, the chemicals have been identified as possibly being able to cause systemic long-term effects (genotoxicity and carcinogenicity). The majority of the chemicals in this group have also been identified as having the potential to cause skin sensitisation. Other health hazards have not been considered.

Public Risk Characterisation

The public could be exposed to the chemicals in this group if they are used as ingredients in fragrances or in other cosmetic products in Australia. The extent of current usage in Australia is unknown, as the chemicals in this group were not notified as being used in fragrances.

The concerns about skin sensitisation, genotoxicity and carcinogenicity, if validated, are expected to be the dominant drivers for appropriate risk management measures.

Some of the chemicals are restricted internationally, particularly for use in cosmetics (see **Restrictions: International**).

Overall, there is uncertainty regarding the safety of these chemicals in cosmetic products; therefore a Tier III assessment may be required, depending on the outcomes of industry consultations (see **Recommendation**), to determine the extent of use and the availability of further skin sensitisation, genotoxicity and carcinogenicity data.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and/or inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations may 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.

Overall, there is uncertainty regarding the hazards of these chemicals in the workplace; therefore, a Tier III assessment may be required, depending on the outcomes of industry consultations (see **Recommendation**), to determine the appropriate occupational controls.

NICNAS Recommendation

The chemicals in this group are recommended for Tier III assessment to determine:

- whether the chemicals are being used in fragrances in Australia;
- if there are any other uses of the chemicals in Australia;
- the availability of toxicological information that is not accessible in the publicly-available literature to better characterise the hazards of the chemicals; and
- whether risk management controls are required.

Regulatory Control

References

CosIng. Cosmetic Ingredients and Substances. Accessed May 2015 at **http://ec.europa.eu/consumers/cosmetics/cosing/**.

Galleria Chemica. Accessed May 2015 at **http://jr.chemwatch.net/galeria/**

Hazardous Substances Information System (HSIS) Safe Work Australia. Accessed May 2015 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

International Fragrance Association (IFRA). List of fragrance ingredients used in consumer goods. Accessed May 2015 at **http://www.ifraorg.org/en/ingredients**

NICNAS 2013. Inventory Multi-tiered Assessment and Priorisation (IMAP) Factsheet 4: Leveraging international information. Accessed April 2015 at **http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-factsheets**

OECD (2014). Guidance on Grouping of Chemicals, Second Edition. Environment Directorate. Joint meeting of the Chemicals Committee and the Working party on Chemicals, Pesticides and Biotechnology. Series on Testing& Assessment No. 194. Accessed April 2015 at **http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en**

Personal Care Products Council 2011. Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition.

Substances in Preparations in Nordic Countries (SPIN). Accessed May 2015 at **http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx**

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) 1999. Opinion concerning fragrance allergy in consumers, a review of the problem – analysis of the need for appropriate consumer information and identification of consumer allergens. SCCNFP/0017/98. Accessed May 2015 at **http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out98_en.pdf**

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed April 2015 at **http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp**

US Department of Health and Human Services, Household Products Database (HHPD), Health and safety information on household products. Accessed May 2015 at **http://householdproducts.nlm.nih.gov/**

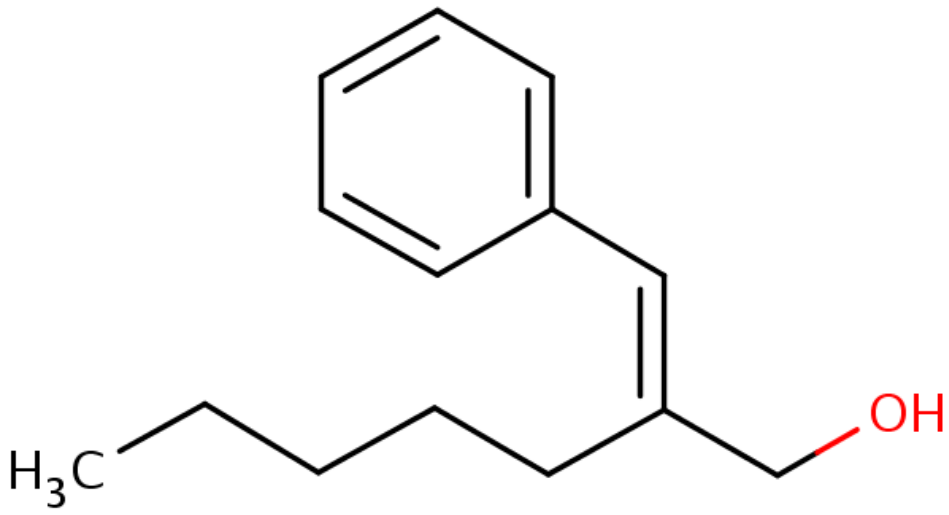
US Environmental Protection Agency's (EPA) Aggregated Computational Toxicology Resource (ACToR). Accessed May 2015 at **http://actor.epa.gov/actor/faces/ACToRHome.jsp**

US National Institutes of Health 2011. ICCVAM test method evaluation report: usefulness and limitations of the murine local lymph node assay for potency categorization of chemicals causing allergic contact dermatitis in humans. NIH Publication Number 11-7709. Accessed May 2015 at **http://ntp.niehs.nih.gov/iccvam/docs/immunotox_docs/llna-pot/tmer.pdf**

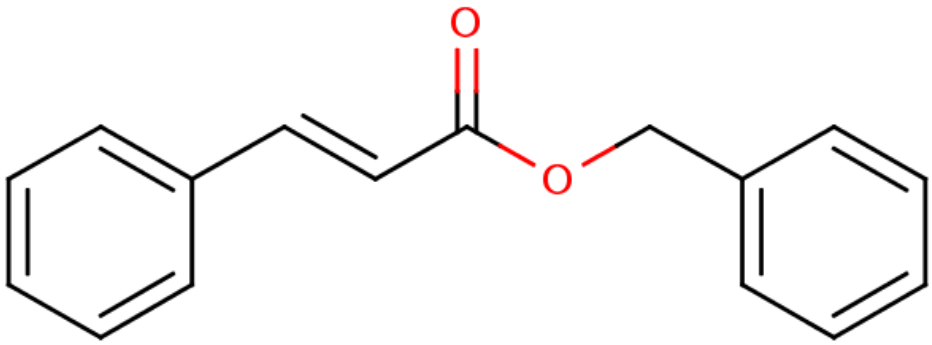
Last Update 26 October 2018

Chemical Identities

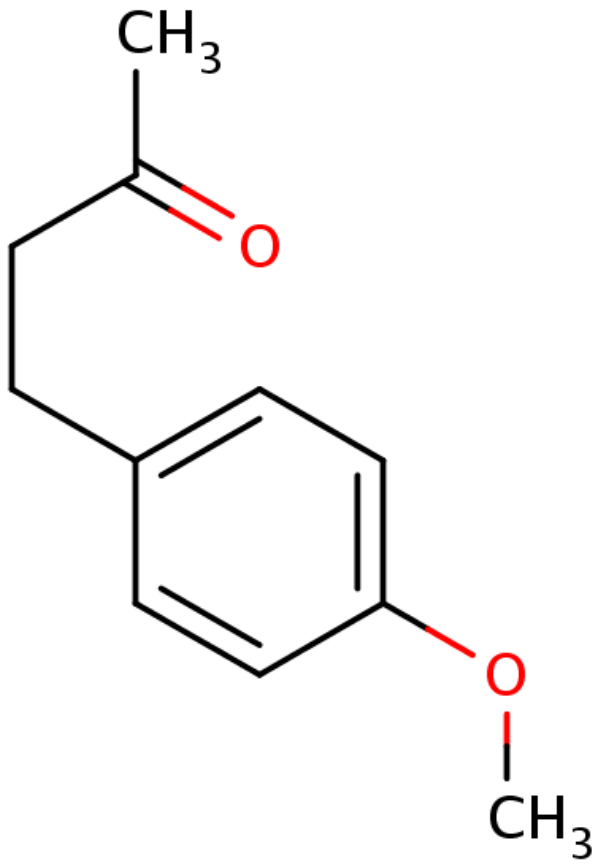
Chemical Name in the Inventory and Synonyms	**1-Heptanol, 2-(phenylmethylene)-** alpha-amylcinnamyl alcohol 2-pentylcinnamic alcohol 1-heptanol, 2-benzylidine
CAS Number	101-85-9

Structural Formula	
Molecular Formula	C14H20O
Molecular Weight	204.311

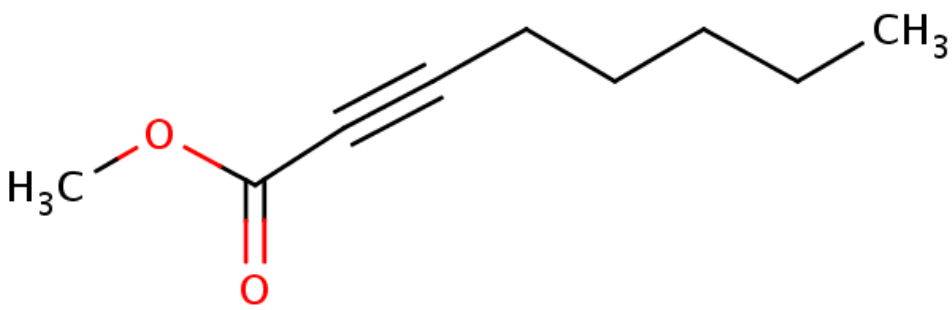
Chemical Name in the Inventory and Synonyms	**2-Propenoic acid, 3-phenyl-, phenylmethyl ester** benzyl cinnamate cinnamein cinnamic acid, benzyl ester
CAS Number	103-41-3
Structural Formula	

	
Molecular Formula	C16H14O2
Molecular Weight	238.2846

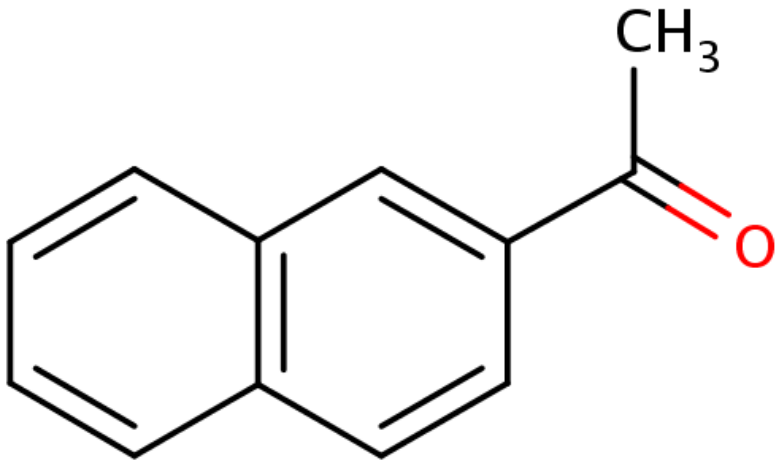
Chemical Name in the Inventory and Synonyms	**2-Butanone, 4-(4-methoxyphenyl)-** 4-methoxybenzylacetone 4-(4-methoxyphenyl)-2-butanone
CAS Number	104-20-1
Structural Formula	

	
Molecular Formula	C11H14O2
Molecular Weight	178.23

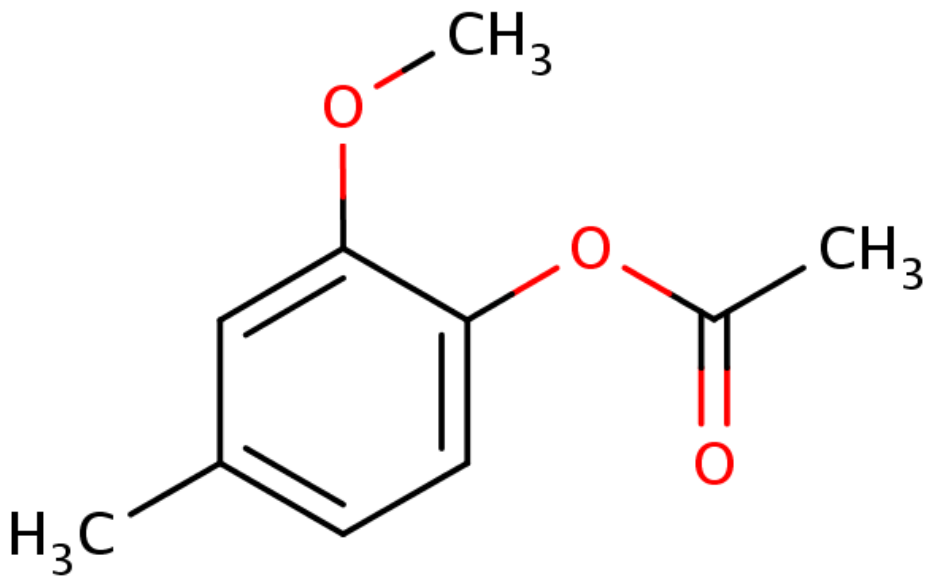
Chemical Name in the Inventory and Synonyms	**2-Octynoic acid, methyl ester** methyl heptine carbonate folione methyl 2-octynoate
CAS Number	111-12-6
Structural Formula	

	
Molecular Formula	C9H14O2
Molecular Weight	154.208

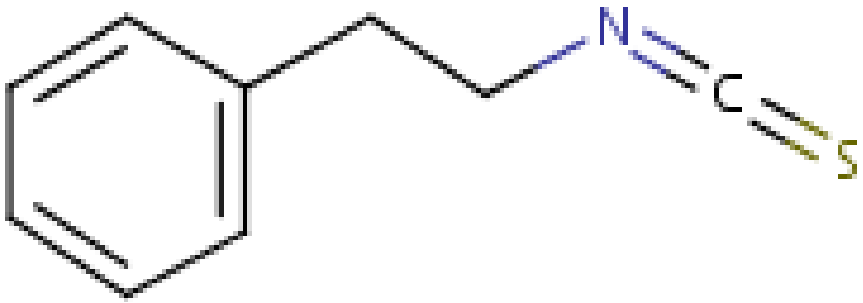
Chemical Name in the Inventory and Synonyms	**Ethanone, 1-(naphthalenyl)-** methyl naphthyl ketone acetonaphthone acetylnaphthalene
CAS Number	1333-52-4
Structural Formula	

	
Molecular Formula	C12H10O
Molecular Weight	170.21

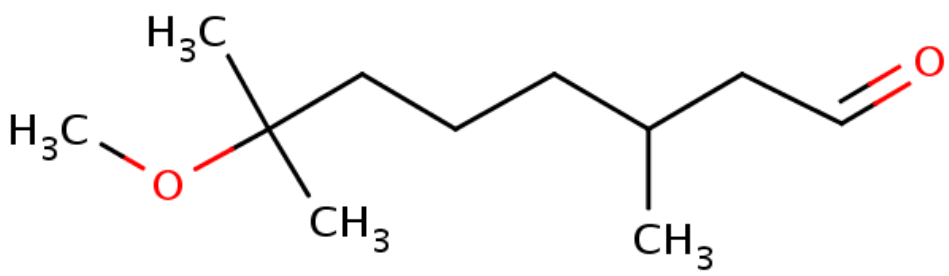
Chemical Name in the Inventory and Synonyms	**Phenol, 2-methoxy-4-methyl-, acetate** phenol, 2-methoxy-4-methyl-, 1-acetate 2-methoxy-p-cresol acetate 2-methoxy-p-tolyl acetate
CAS Number	879-67-4
Structural Formula	

	
Molecular Formula	C10H12O3
Molecular Weight	180.202

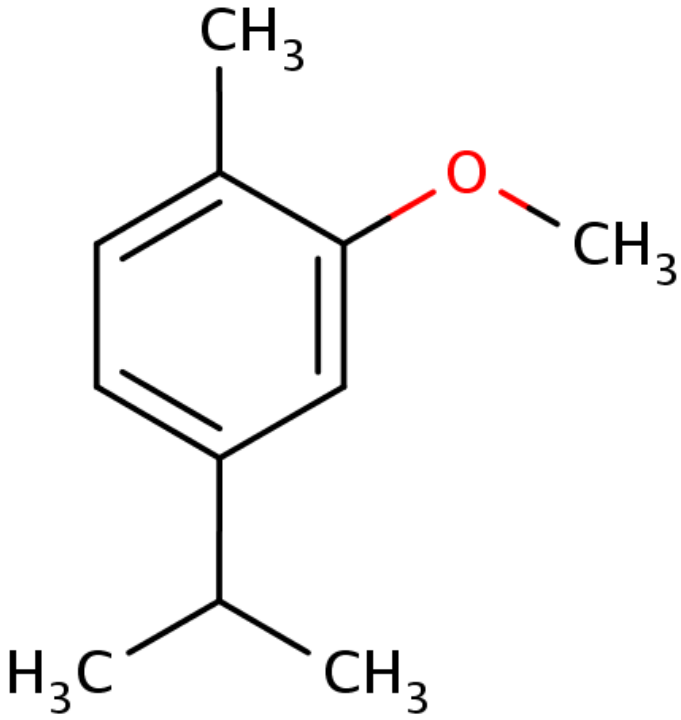
Chemical Name in the Inventory and Synonyms	**Benzene, (2-isothiocyanatoethyl)-** phenethyl isothiocyanate isothiocyanic acid, phenethyl ester 1-(2-isothiocyanatoethyl)benzene
CAS Number	2257-09-2
Structural Formula	

	
Molecular Formula	C9H9NS
Molecular Weight	163.243

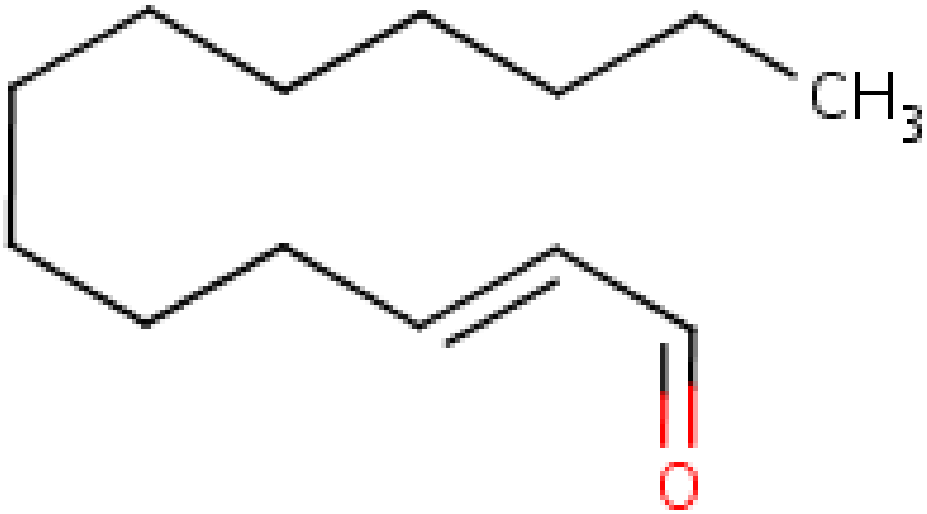
Chemical Name in the Inventory and Synonyms	**Octanal, 7-methoxy-3,7-dimethyl-** methoxydihydrocitronellal 7-methoxy-3,7-dimethyloctanal
CAS Number	3613-30-7
Structural Formula	

	
Molecular Formula	C11H22O2
Molecular Weight	186.293

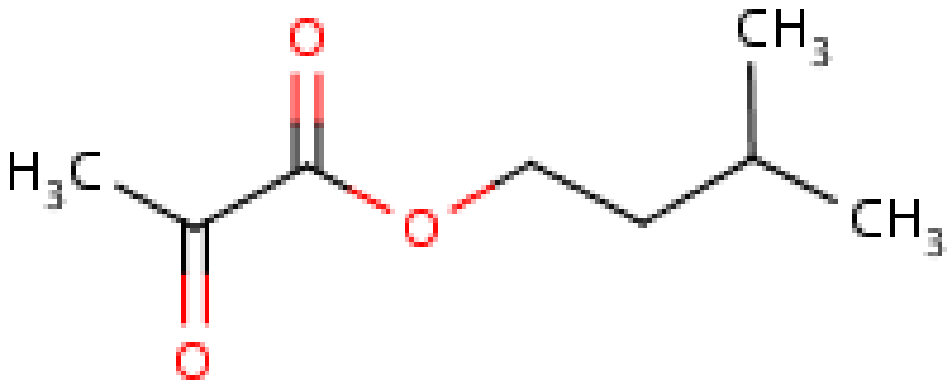
Chemical Name in the Inventory and Synonyms	**Benzene, 2-methoxy-1-methyl-4-(1-methylethyl)-** 5-isopropyl-2-methylanisole methylcarvacrol carvacryl methyl ether
CAS Number	6379-73-3
Structural Formula	

	
Molecular Formula	C11H16O
Molecular Weight	164.246

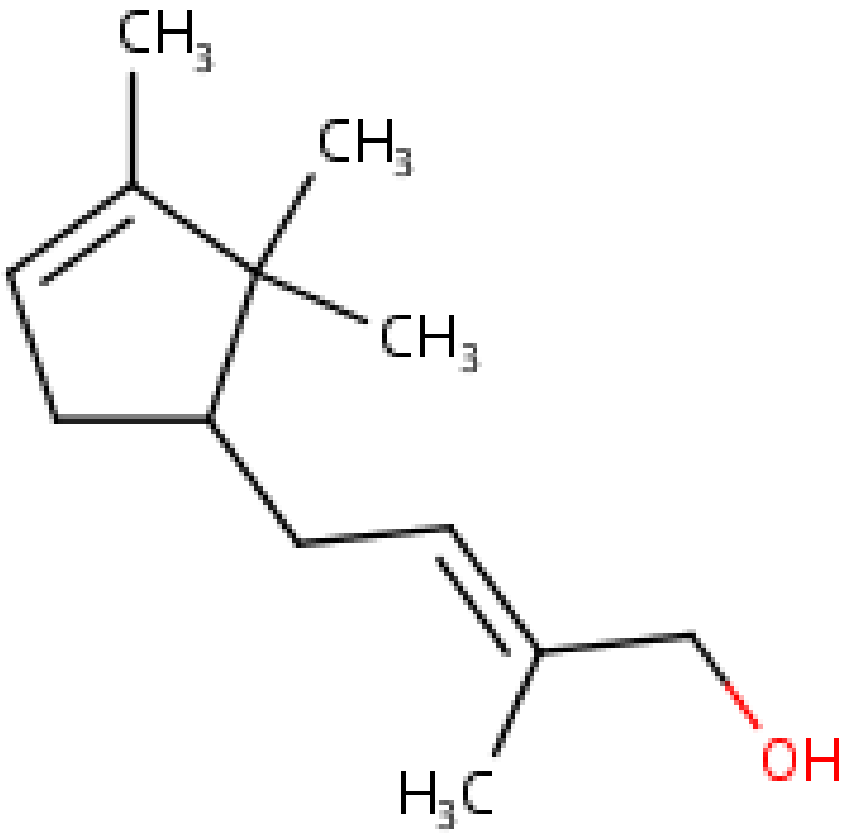
Chemical Name in the Inventory and Synonyms	**2-Tridecenal** tridec-2-enal 3-decylacrolein
CAS Number	7774-82-5
Structural Formula	

	
Molecular Formula	C13H24O
Molecular Weight	196.332

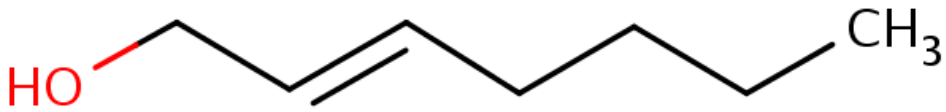
Chemical Name in the Inventory and Synonyms	**Propanoic acid, 2-oxo-, 3-methylbutyl ester** isopentyl pyruvate pyruvic acid, isopentyl ester isoamyl pyruvate
CAS Number	7779-72-8
Structural Formula	

	
Molecular Formula	C8H14O3
Molecular Weight	158.1

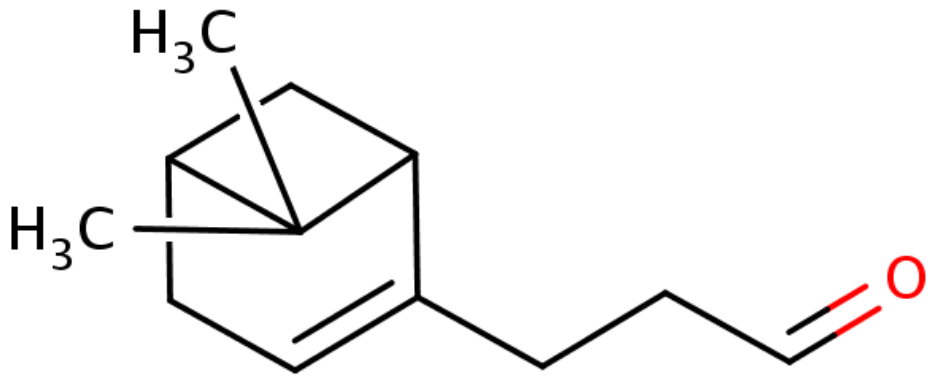
Chemical Name in the Inventory and Synonyms	**2-Buten-1-ol, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-** 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol santalinol
CAS Number	28219-60-5
Structural Formula	

	
Molecular Formula	C13H22O
Molecular Weight	194.316

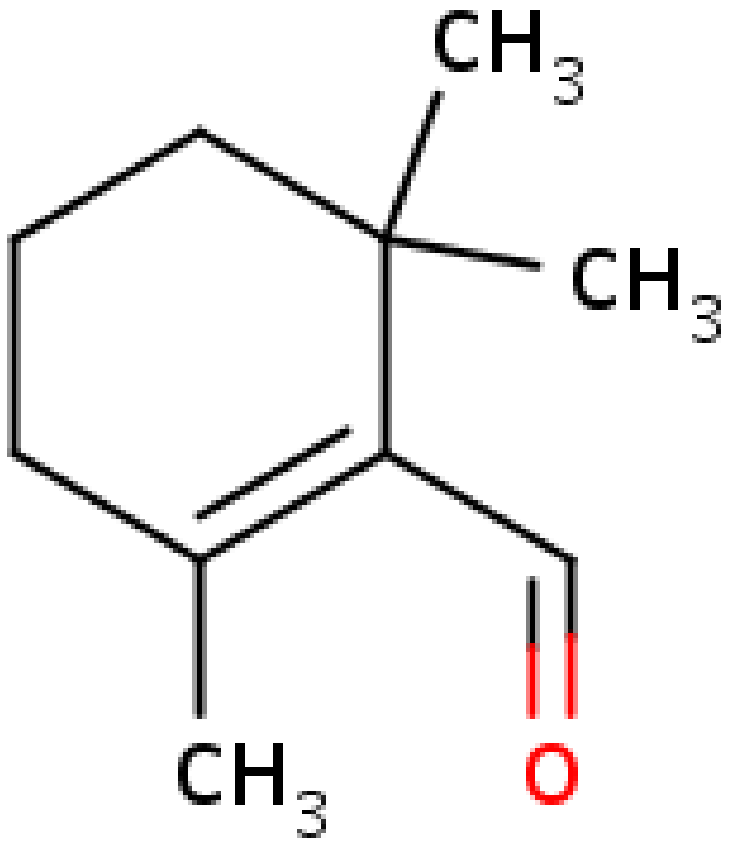
Chemical Name in the Inventory and Synonyms	**2-Hepten-1-ol, (E)-** 2-hepten-1-ol, trans- 2-heptenol
CAS Number	33467-76-4
Structural Formula	

	
Molecular Formula	C7H14O
Molecular Weight	114.187

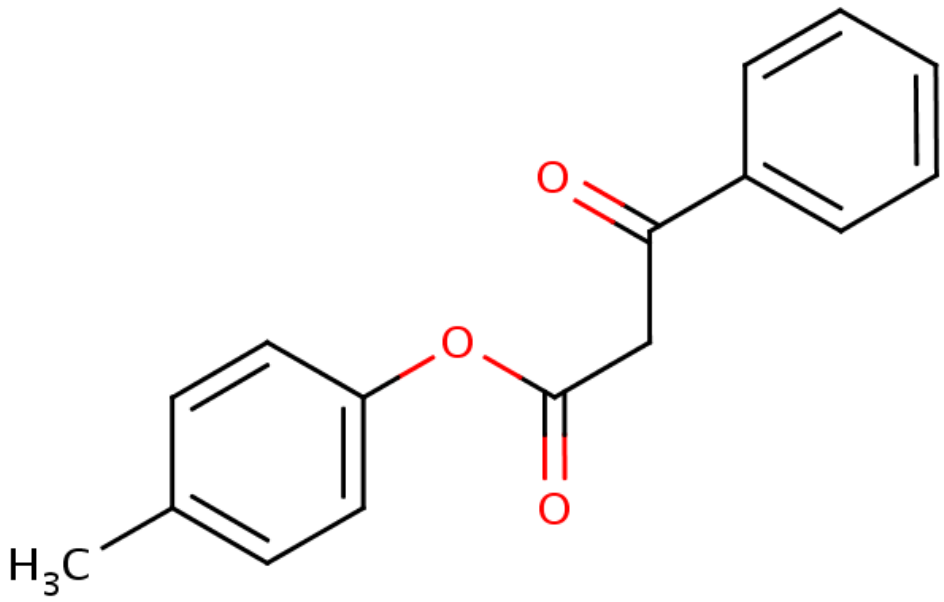
Chemical Name in the Inventory and Synonyms	**Bicyclo[3.1.1]hept-2-ene-2-propanal, 6,6-dimethyl-** 2-norpinine-2-propionaldehyde, 6,6-dimethyl 6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde
CAS Number	33885-51-7
Structural Formula	

	
Molecular Formula	C12H18O
Molecular Weight	178.273

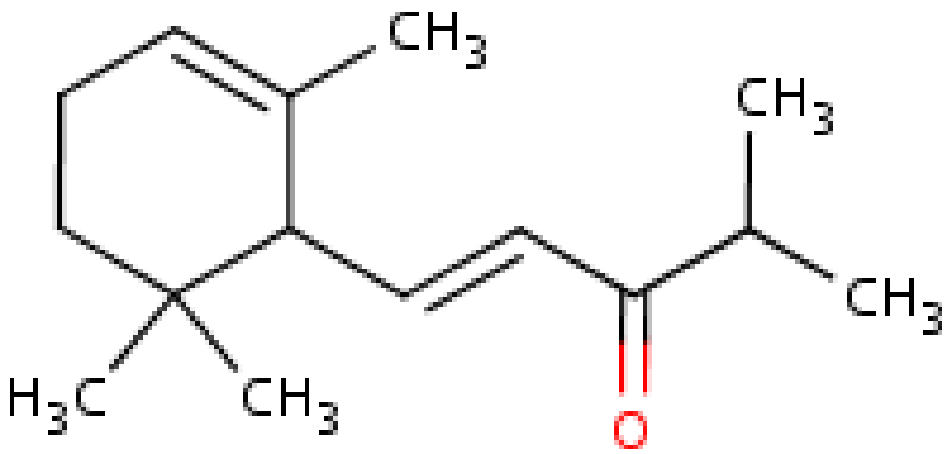
Chemical Name in the Inventory and Synonyms	**Cyclohexenecarboxaldehyde, 2,6,6-trimethyl-** alpha(beta)-cyclocitral 2,6,6-trimethylcyclohexenecarbaldehyde
CAS Number	52844-21-0
Structural Formula	

	
Molecular Formula	C10H16O
Molecular Weight	152.2354

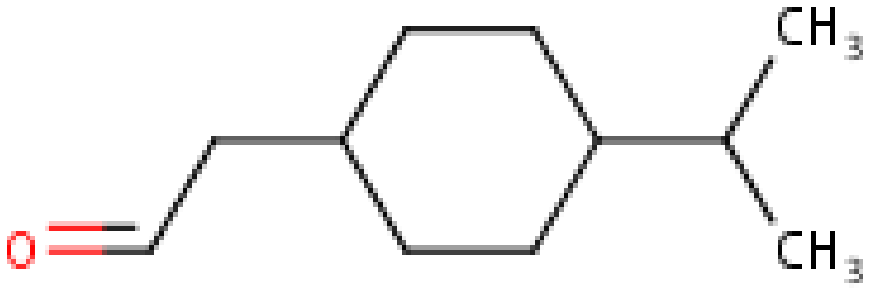
Chemical Name in the Inventory and Synonyms	**Benzenepropanoic acid, .beta.-oxo-, 4-methylphenyl ester** hydrocinnamic acid, .beta.-oxo, p-tolyl ester p-tolyl 3-oxo-3-phenylpropionate
CAS Number	67801-43-8
Structural Formula	

	
Molecular Formula	C16H14O3
Molecular Weight	254.284

Chemical Name in the Inventory and Synonyms	**1-Penten-3-one, 4-methyl-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-** alpha-dimethylionone dimethylionone
CAS Number	68459-99-4
Structural Formula	

	
Molecular Formula	C15H24O
Molecular Weight	220.354

Chemical Name in the Inventory and Synonyms	**Cyclohexaneacetaldehyde, 4-(1-methylethyl)-** p-menthane, 7-formyl- 4-(isopropyl)cyclohexaneacetaldehyde
CAS Number	93981-63-6
Structural Formula	

	
Molecular Formula	C11H20O
Molecular Weight	168.278

Share this page