Simple esters of linalool: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Propanoic acid, 2-methyl-, 1-ethenyl-1,5-dimethyl-4-hexenylester	78-35-3
Butanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester	78-36-4
1,6-Octadien-3-ol, 3,7-dimethyl-, acetate	115-95-7
1,6-Octadien-3-ol, 3,7-dimethyl-, formate	115-99-1
1,6-Octadien-3-ol, 3,7-dimethyl-, benzoate	126-64-7
1,6-Octadien-3-ol, 3,7-dimethyl-, propanoate	144-39-8
Butanoic acid, 3-methyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester	1118-27-0
Benzeneacetic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester	7143-69-3
Hexanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester	7779-23-9

Chemical Name in the Inventory	CAS Number
Octanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester	10024-64-3
1,6-Octadien-3-ol, 3,7-dimethyl-, acetate, (R)-	16509-46-9

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**

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are esters of linalool (CAS No. 78-70-6), known as linalyl esters. Most of the chemicals in this group have similar uses; they are used in food flavouring or as a fragrance component (see **Use** section). The favoured configuration in genuine lavender oils is the (*R*)-isomer of linalyl acetate (Mosandl, 2004).

Following absorption, linalyl esters are expected to hydrolyse to linalool and the corresponding acids in the gastrointestinal tract and by tissue hydrolases. Among the esters, linalyl acetate (CAS No. 115-95-7) is the main component of lavender and bergamot oils, and is the most widely used (SCCS, 2012). Given the close structural similarities of the chemicals in this group and common hydrolysis product (linalool), they are expected to have similar toxicological effects.

Limited data is available for some of the esters in this group. Therefore, where toxicological data are lacking for specific endpoints in this assessment, data available for linalyl acetate and the metabolite linalool (NICNAS) are considered applicable to these chemicals, particularly for systemic long-term toxicity.

The corresponding carboxylate ions produced by ester hydrolysis in vivo of the chemicals in this group are all expected to have low toxicity.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the majority of the chemicals in this group. However, linalyl acetate (CAS No 115-95-7) has reported domestic use in automotive aftermarket products including car wash soaps, boat wash soaps, polishes and rubbing compounds.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US Household Products Database and the International Fragrance Association (IFRA) Transparency List.

All chemicals in this group, except for (*R*)-linalyl acetate (CAS No. 16509-46-9) and linalyl octanoate (CAS No. 10024-64-3), have reported cosmetic use in perfumes or as fragrance ingredients.

Linalyl acetate (CAS No. 115-95-7) has been reported as being used in a number of cosmetic products in the Compilation of Ingredients used in Cosmetics in the United States (CIUCUS, 2011).

The chemicals have reported domestic/commercial uses, including in:

- adhesives and sealants;
- cleaning and maintenance products;
- paints, lacquers and varnishes;
- process regulators;
- welding and soldering agents; and
- odour agents.

The chemicals have reported non-industrial uses including:

- as food additives; and
- in non-agricultural pesticides and preservatives.

Linalyl acetate is a substitute for pettigrain oil (HSDB).

Restrictions

Australian

No known restrictions have been identified.

International

The chemicals are listed on the following (Galleria Chemica):

- as 'Terpenes and terpenoids' in the EU Cosmetic Directive 76/768/EEC Annex III—List of substances which Cosmetic Products must not contain except subject to the restrictions and conditions laid down: Peroxide value less than 10 mmoles/L; and
- as 'Terpene hydrocarbons' in the New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: Peroxide value less than 10 mmoles/L.

The acceptable daily intake (ADI) for linalyl acetate and linalyl formate is 0.5 mg/kg bw (EFSA, 2012).

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 known restrictions are identified.

International

The following exposure standards are identified for terpenes (Galleria Chemica).

A time weighted average (TWA) of 111–150 mg/m^3 (20–25 ppm) in Canada (Alberta), Estonia and Sweden.

Short-term exposure limits (STEL) of 300 mg/m^3 (50 ppm) in Estonia and Sweden.

Health Hazard Information

Toxicokinetics

Linalyl esters readily hydrolyse to linalool and the corresponding carboxylic acids following oral exposure. Hydrolysis is catalysed by carboxylesterases or esterases, in particular beta-esterases in the liver. The hydrolysis products then conjugate with glucuronic acid and are excreted in urine. Based on studies for linalyl acetate, it is expected that linalool is available for systemic circulation following oral administration of linalyl esters (OECD, 2002; Bickers et al., 2003a).

Following an inhalation exposure to linalyl acetate at 5 mg/L for 1 hour in mice, serum levels of linalyl acetate and linalool were reported to be 1–2 ng/mL and 4–5 ng/mL, respectively. In another inhalation study, mice exposed to linalyl acetate for 1 hour had serum levels of 1 ng/mL linalyl acetate and 4 ng/mL linalool. When the mice were exposed to 5 mg/mL lavender oil (37 % linalool and 42 % linalyl acetate), the serum levels were 3 ng/mL for linalool and 11 ng/mL for linalyl acetate (Bickers et al., 2003a).

In vitro studies of linalyl acetate have shown hydrolysis to linalool then, to some extent, rapid rearrangement to the ring-closed form alpha-terpineol. Linalyl acetate hydrolyses rapidly (half-life (t1/2) < 5 min) at the low pH (acidic) of gastric fluids to form linalool and acetic acid. The hydrolysis rate of this chemical is slow in neutral gastric juice (t1/2 = 121 min) and in intestinal fluid with or without pancreatin (t1/2 = 153–198 min). Hydrolysis of this chemical in homogenates of rat intestinal mucosa, blood and liver is slower than in acidic gastric juice (Bickers et al., 2003a; HSDB).

In a percutaneous absorption case study, a massage oil containing lavender oil and peanut oil (2:98 ratio) was applied to the skin of a male subject (age 34 years). The lavender oil contained linalool and linalyl acetate at 24.79 % and 29.59 %, respectively. Following application within 5 minutes, linalool and linalyl acetate were found in trace amounts in the blood. Peak plasma concentrations of 121 ng/mL linalyl acetate and 100 ng/mL linalool were reached after 20 minutes. Most of the lavender oil had disappeared from the blood within 90 minutes with a biological half-life of 14.3 minutes. The authors concluded that lavender oil is rapidly absorbed through the skin and excreted within 90 minutes (Bickers et al., 2003a; HSDB).

The dermal permeability constants are reported to be 0.0746 cm/hour for linalyl acetate (CAS No. 115-95-7), 0.711 cm/hour for linalyl benzoate (CAS No. 126-64-7), 0.860 cm/hour for linalyl isovalerate (CAS No. 1118-27-0), and 0.882 cm/hour for linalyl phenylacetate (CAS No. 7143-69-3) (Galleria Chemica).

Linalyl acetate auto-oxidises when exposed to air in a manner similar to linalool, forming allergenic hydroperoxides. A non-sensitising epoxide was identified as a secondary oxidation product for linalyl acetate. The corresponding epoxide was not found in the oxidation products of linalool (Skold et. al., 2008).

Acute Toxicity

Oral

Based on animal test results, the chemicals have low acute oral toxicity following oral exposure.

The reported median lethal dose (LD50) values are (Bickers et al., 2003b; Galleria Chemica):

- linalyl acetate (CAS No. 115-95-7), 10000 mg/kg bw in rats and 13360 mg/kg bw in mice;
- linalyl formate (CAS No. 115-99-1), >5000 mg/kg bw in rats and in rabbits, and 5490 mg/kg bw in male mice;
- linalyl propionate (CAS No. 144-39-8), >5000 mg/kg bw in rats and in rabbits, and 13870 mg/kg bw in male mice;
- linalyl benzoate (CAS No. 126-64-7), >5000 mg/kg bw in rats and 9400 mg/kg bw in male mice;
- linalyl butyrate (CAS No. 78-36-4), >5000 mg/kg bw in rats and in rabbits, and >8900 mg/kg bw in male mice;
- linalyl hexanoate (CAS No. 7779-23-9), 39040 mg/kg bw in mice;
- linalyl octanoate (CAS No. 10024-64-3), 48850 mg/kg bw in mice;

- linalyl isobutyrate (CAS No. 78-35-3), >36500 mg/kg bw in rats and 15100 mg/kg bw in mice;
- linalyl isovalerate (CAS No. 1118-27-0), >5000 mg/kg bw in rats and 25170 mg/kg bw in mice;
- linalyl phenylacetate (CAS No. 7143-69-3), >5000 mg/kg in rats and 15480 mg/kg bw in mice.

Dermal

Based on animal test results, the chemicals have low acute toxicity following dermal exposure.

The reported dermal LD50 values in rabbits are (Bickers et al., 2003b; Galleria Chemica):

- linalyl acetate (CAS No. 115-95-7), >5000 mg/kg bw;
- linalyl formate (CAS No. 115-99-1), >5000 mg/kg bw;
- linalyl propionate (CAS No. 144-39-8), >2000 mg/kg bw;
- linalyl benzoate (CAS No. 126-64-7), >5000 mg/kg bw;
- linalyl butyrate (CAS No. 78-36-4), >2000 mg/kg bw;
- linalyl hexanoate (CAS No. 7779-23-9), >2000 mg/kg bw;
- linalyl isobutyrate (CAS No. 78-35-3), >5000 mg/kg bw;
- linalyl isovalerate (CAS No. 1118-27-0), >2000 mg/kg bw; and
- linalyl phenylacetate (CAS No. 7143-69-3), >5000 mg/kg bw.

No data are available for linalyl octanoate (CAS No. 10024-64-3).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Results for linalyl acetate appeared to be species-specific. Moderate skin irritation effects were reported in a rabbit study but not observed in miniature swine (pig) study. No effects were observed in humans up to a concentration of 32 %. However, it should be noted that concentrations less than 100 % of linalyl acetate were used for human patch test studies. The metabolite linalool is a skin irritant (NICNAS). Therefore, based on the available information, classification is warranted for linalyl acetate (see **Recommendation** section). This classification does not apply to the other chemicals in the group.

In a skin irritation study conducted according to the OECD Test Guideline (TG) 404, 0.5 mL of undiluted linalyl acetate was applied (semi-occlusively) on the skin of rabbits for 4 hours, with observation up to 7 days. Two test runs were conducted, using a total of 7 rabbits (3 in the first test, 4 in the second test). The mean erythema scores (24, 48, 72 hours) for test 1 and test 2 were 1.88 and 1.91, respectively. The mean oedema scores were 1.78 and 1.00, respectively. Slight to marked desquamation was observed in 6/7 animals at the end of the observation period. In another skin irritation study (BASF test), 2 rabbits were applied undiluted linalyl acetate under occlusive patches for 5 minutes, 15 minutes and 20 hours, with observation period up to 8 days. Desquamation was observed and the mean erythema score (24, 48 hours) was ≥2. Based on the above studies, the chemical was determined to be a skin irritant (REACHa).

In several skin irritation studies in rabbits, reactions to linalyl acetate (undiluted) ranged from slight to severe. Severe irritation was observed in a 24-hour open patch test on the dorsal skin of albino Angora rabbits (n = 6). Minimal irritation was observed in a 24-hour closed patch test on New Zealand female rabbits (n = 9). Undiluted linalyl acetate was moderately irritating on male Hartley guinea pigs and not irritating when applied at 0.05 g on miniature swines for 48 hours (OECD, 2002; Bickers et al., 2003a).

Linalyl esters (acetate, benzoate, butyrate, formate, isobutyrate, isovalerate, phenylacetate and propionate) tested at 5 % in diethyl phthalate were slightly irritating in rabbits. Effects generally cleared by 72 hours. Effects for linalyl propionate were reported not to be fully reversible within 72 hours; however, they were not considered severe enough to warrant classification (Bickers et al., 2003a; REACHb).

When tested undiluted, results for linalyl esters (benzoate, butyrate, formate, isobutyrate, isovalerate, phenylacetate and propionate) ranged from very slight to well defined irritation in rabbits (Bickers et al., 2003a).

Linalyl esters were tested in guinea pigs and rats for photoirritation or photoallergy and showed no potential to elicit these effects (Bickers et al., 2003a).

Eye Irritation

Based on the available information, the chemicals are not considered to be eye irritants.

In several eye irritation studies, the results for six undiluted linalyl esters (acetate, benzoate, butyrate, formate, isobutyrate, and propionate) ranged from very slight to slight irritation effects in rabbits. Two linalyl esters (isovalerate and phenylacetate) were reported to cause very slight to well defined irritation in rabbits (Bickers et al., 2003a). When tested at a concentration of 5 % in diethyl phthalate, linalyl esters (acetate, benzoate, butyrate, formate, isobutyrate, isovalerate, phenylacetate and propionate) caused very slight irritation in rabbits (Bickers et al., 2003a).

In an eye irritation study, 0.05 mL of linalyl acetate was administered to one eye of each of 2 Vienna White rabbits, with observation for 8 days. Slight conjunctival redness was observed in both animals, but this was reversible by day 2 (REACHa).

Observation in humans

In human patch-test studies in approximately 380 healthy male and female volunteers, no irritation was observed with linalyl esters tested up to a concentration of 32 % (Bickers et al., 2003a). No signs of irritation were observed up to 120 hours after exposure (OECD, 2002).

In several skin irritation tests on human volunteers, no effects were observed when linalyl esters (benzoate, butyrate, formate, isobutyrate, isovalerate, phenylacetate and propionate) at 8 % in petrolatum were applied (Bickers et al., 2003b).

Sensitisation

Skin Sensitisation

Based on the available data, linalyl acetate in its highly purified form is a weak skin sensitiser. However when exposed to air, the chemical is auto-oxidised into a potent contact allergen. Exposure to linalyl acetate will primarily be as a constituent in natural oils (lavender oil), which also involves co-exposure to linalool, a known skin sensitiser. Given that public exposure to linalyl acetate will be through products exposed to air, linalyl acetate is expected to undergo auto-oxidation. Overall, the above information warrants classification for linalyl acetate as a skin sensitiser (see **Recommendation** section). This classification does not apply to the other esters in this group.

In a skin painting study, female white guinea pigs were topically induced with linalyl acetate (95–99% purity) at concentrations of 10 and 50 %. The animals were challenged at day 28 and day 31 at concentrations of 5 and 10 % linalyl acetate, respectively. No positive responses were reported. However, when repeatedly applied to the clipped flank skin, strong desquamation was observed within the area of application (REACHa).

The skin sensitising effects for auto-oxidised linalyl acetate were investigated in a local lymph node assay (LLNA) (OECD TG 429) with female CBA/Ca mice. The hydroperoxide oxidation products of linalyl acetate were also tested (see **Toxicokinetics** section). The EC3 values for linalyl acetate as unchanged (97 % purity), distilled, or air-exposed over 10 weeks were reported to be 20 %, 25.4 % and 3.6 %, respectively. For the air-exposed sample, 74 % of the original test substance remained after 10 weeks. The EC3 value for the identified hydroperoxide derivatives was 3.6 %, similar to that of air-exposed linalyl acetate. The authors concluded that the hydroperoxides were responsible for the sensitising potency of the chemical (Skold et. al., 2008; REACHa).

In guinea pig maximisation tests, linalyl acetate was weak to moderately sensitising at a concentration of 10 %, and non-sensitising when tested at 5 %. The purity of linalyl acetate was not stated. In a Freund's complete adjuvant test (FCAT), female albino Dunkin-Hartley guinea pigs (n = 30) were intradermally induced with linalyl acetate at 10 % in Freund’s complete adjuvant and topically at 10 % in acetone. The animals were challenged topically with 5, 10 and 20 % in acetone. Skin reactions were observed in 0/10, 2/10 and 4/10 animals, respectively (Bickers et al., 2003a; REACHa).

No reactions were observed for linalyl isobutyrate and linalyl propionate tested at 8 % in guinea pigs (Bickers et al., 2003a).

The Scientific Committee on Consumer Safety (SCCS) has categorised linalyl acetate as an ‘established contact allergen in humans’. This is based on up to 10 positive test reactions reported in humans (SCCS, 2012).

Observation in humans

In a study in Sweden (2008–2011), 1717 subjects were assessed for eczema related to a contact allergy. The patients were patch-tested with oxidised linalyl acetate at 6 % in petrolatum for 48 hours. Around 37 (2.2 %) showed positive reactions to oxidised linalyl acetate. Among these positive reactions, 76 % were weakly positive and 24 % were strongly positive. No irritant reactions were recorded. For patients with positive reactions to oxidised linalyl acetate, 13 (41 %) were positive to oxidised linalool, and 37 % had no other positive reactions to other fragrance markers. The patients were also patch-tested with oxidised linalool and 3.4 % were positive.This study also investigated the auto-oxidation of linalyl acetate and reported that the concentration of hydroperoxides after 42 weeks of air exposure (with stirring) was 37 %. Linalyl acetate hydroperoxides were also found to be relatively stable compared with linalool hydroperoxides which indicated accumulation with time (Hagvall et. al., 2015).

In a number of human maximisation tests, linalyl acetate was tested at concentrations of 10 or 20 % in petrolatum, or at 12 % in an unspecified vehicle. Reactions were observed in a total of 3 out of 131 subjects. No reactions were observed when the same samples were retested, or purified then retested (Bickers et al., 2003a).

No reactions were observed for the rest of the linalyl esters (benzoate, butyrate, formate, isobutyrate, isovalerate, phenylacetate and propionate) tested at concentrations 4–20% in perolatum in 25 volunteers (Bickers et al., 2003a).

In a multicentre study, a total of 1855 patients with a history of allergy to fragrances were patch-tested with 10 % linalyl acetate (95–99 % purity) in petrolatum for 48 hours. Positive reactions were reported in 4 patients, and ‘doubtful positive reactions’ (only erythema) were observed in 8 patients (REACHa).

Repeated Dose Toxicity

Oral

There are no reliable repeat dose oral toxicity studies for linalyl acetate. Based on the limited data for the esters and data for linalool, the chemicals in this group are not likely to cause serious damage to health from repeated oral exposure.

In a repeated dose oral toxicity study, a total dose level of 100 mg/kg bw/day of a mixture consisting of linalyl acetate (24.2 mg/kg bw/day), linalyl isobutyrate (27.5 mg/kg bw/day) and geranyl acetate (48.8 mg/kg bw/day) was administered to the diet of rats (n = 10/sex) for 12 weeks. Slight growth retardation was observed in the females only, which were attributed to poor palatability. There were no significant differences between the treated and control groups for haematology, clinical chemistry and urinalysis measurements at weeks 6 and 12. Histopathology revealed no dose-related lesions (Bickers et al., 2003a).

In another repeated dose oral toxicity study, linalyl isobutyrate was administered in the diet to Osborne-Mendel rats (n = 10/sex/dose) at dose levels of 0, 1000, 2500 or 10000 ppm for 17–18 weeks. The estimated daily intakes were 0, 50, 120 or 500 mg/kg bw/day. There were no deaths, and no adverse effects were observed. The no observed adverse effect level (NOAEL) was determined as 500 mg/kg bw/day (Bickers et al., 2003a).

Linalool was not considered to cause serious damage to health from repeated oral exposure. In a 28-day repeated dose oral toxicity study using coriander oil (72.9 % linalool), SD rats (n = 10/sex/dose) were treated by gavage at doses of 160, 400 or 1000 mg/kg bw/day. A NOAEL of 160 mg/kg bw/day was established based on histological effects in the liver and kidney at 400 mg/kg bw/day (NICNAS).

Dermal

There are no repeat dose dermal toxicity studies for linalyl esters. Based on studies on linalool, the chemicals in this group are not likely to cause serious damage to health from repeated dermal exposure.

In a 91-day repeated dose dermal toxicity study (OECD TG 411) in SD rats, a NOAEL of 250 mg/kg bw/day for local effects was established for linalool. No systemic toxicity effects were reported at doses up to 1000 mg/kg bw/day. Depressed motor activity was significant at 4000 mg/kg bw/day (NICNAS).

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro data for the linalyl esters, and the data available for linalool, the chemicals in this group are not considered genotoxic.

In vitro

The following results were reported for linalyl acetate (OECD, 2002; HSDB; REACHa):

- negative in bacterial reverse mutation assay (OECD TG 471) with several strains of *Salmonella (S.) typhimurium* (TA97, TA98, TA100, TA1535, TA1537, TA1538 and TA102) up to 25000 µg/plate, with or without metabolic activation;
- negative in *Escherichia coli* strain WP2uvrA (trp-) at doses of 125–1000 µg/plate, with or without metabolic activation; but positive at doses of 9 mg/plate and above. The authors concluded that linalyl acetate was cytotoxic at doses >9 mg/plate, and exceeded the regulatory requirement of 5 mg/plate;
- negative in *Bacillus subtilis* H17 (rec+) and M45 (rec-) at 18 µg/plate (Marnett et. al., 2014);
- no induction of chromosome aberrations (OECD TG 473) in human peripheral blood lymphocytes at doses up to 130 µg/mL without metabolic activation, and up to 180 µg/mL with metabolic activation; and
- negative in unscheduled DNA synthesis (UDS) assays in primary rat (Fischer or SD) hepatocytes at doses up to 300 µg/mL, without metabolic activation.

The following result was reported for linalyl propionate (REACHb) and linalyl isobutyrate (RIFM, 2015):

- negative in bacterial reverse mutation assay with several strains of *S. typhimurium* (TA1535, TA1537, TA98, TA100 and TA102) up to 5000 µg/plate, with or without metabolic activation.

The following result was reported for linalyl benzoate (Api et. al., 2016):

- negative in bacterial reverse mutation assay with several strains of *S. typhimurium* (TA1537, TA98 and TA102) up to 5000 µg/plate, with or without metabolic activation; and

- no increase in the frequency of binucleated cells with micronuclei (BNMN) in a micronucleus assay (OECD TG 487) in human peripheral blood lymphocytes at doses up to 640 µg/mL (without metabolic activation), and up to 960 µg/mL (with metabolic activation).

Linalool was generally negative in vitro: negative in bacterial reverse mutation assays (*S. typhimurium* and *E. coli*) and recombination assays with *Bacillus subtilis*; no induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells and Chinese hamster lung V79 fibroblast cells; and negative in mouse lymphoma cell forward mutation assay. Linalool was not clastogenic in an in vivo mouse micronucleus test (NICNAS).

No data are available for the other chemicals in this group.

Carcinogenicity

Limited information available for linalyl acetate does not indicate carcinogenic potential. The metabolite linalool is not considered to be a carcinogen (NICNAS). Therefore, the chemicals in this group are not likely to have carcinogenic effects.

In a carcinogenicity assay, linalyl acetate (purity ≥85 %) was administered (intraperitoneally) in mice (A/He) at 200 or 1000 mg/kg bw, 3 times/week for 8 weeks, with observation up to 24 weeks. Histopathological examinations were conducted on the lungs. The other organs (liver, kidney, spleen, thymus, intestine and salivary and endocrine glands) were subjected to macroscopic investigation. There was no evidence of carcinogenic activity (OECD, 2002). It is stated that the duration for this test was too short to develop into possible carcinogenic effects; however, the positive control (urethane) showed a 100 % response.

In a tumour induction dermal study, distilled linalyl acetate was applied topically alone or with a co-carcinogen benzo[a]pyrene (BaP) (at 1 or 5 µg) on female ICR/Ha Swiss mice, 3 times/week for 67 weeks. No carcinogenicity was observed when the chemical was administered alone, or with 1 µg BaP. Weak co-carcinogenic activity (slight increase in the number of skin papillomas and carcinomas compared with BaP alone) was observed when co-administered with 5 µg BaP (OECD, 2002; Bickers et al., 2003a).

No animal carcinogenicity studies for the metabolite linalool are available with relevant routes of exposure. Linalool was negative for pulmonary tumour response when intraperitoneally (i.p.) injected into A/He mice. No significant effect on the incidence of tumours was observed in rats or mice when linalool was administered orally or dermally in tumour-promotion studies (NICNAS).

Reproductive and Developmental Toxicity

There are no toxicity studies for linalyl esters. The metabolite linalool is not considered a reproductive or developmental toxicant. Therefore, the chemicals in this group are not likely to be reproductive or developmental toxicants.

In a combined study (OECD TG 421), female rats administered coriander oil (containing 72.9 % linalool) displayed urine-stained abdominal fur and neurotoxic effects at the highest dose (1000 mg/kg bw/day). Adverse effects on the offspring were only observed at the highest dose, and did not occur at the absence of significant maternal toxicity. The maternal and developmental NOAELs were both established as 500 mg/kg bw/day (NICNAS). The equivalent dose calculated for linalyl acetate is ~464 mg/kg bw/day (OECD, 2002).

In a developmental toxicity study for linalool, maternal toxicity was only observed at the highest gavage dose (1000 mg/kg bw/day) in female SD rats. Changes in developmental parameters were considered to be secondary to maternal toxicity (NICNAS).

Other Health Effects

Neurotoxicity

Linalyl acetate is one of the primary constituents of lavender oil, which is known as a relaxant.

When the sedative properties of lavender essential oil were studied in mice, the mobility of the animals was observed to decrease significantly and for which this effect was closely dependent on the exposure time. After the animals were injected with caffeine, they exhibited hyperactivity which was reduced to almost normal levels following inhalation of this fragrance (HSDB). In an inhalation study, a decrease in motor activity was observed in Swiss mice exposed to 2.74 mg linalyl acetate/L air for 90 minutes. A 100 % reduction in motor activity was reported in mice aged 6–8 weeks, and up to 81 % reduction in mice aged 6 months old (HSDB).

Linalyl butyrate was reported to strongly decrease the spontaneous mobility of mice at a dose of 100 mg/kg bw (Opdyke, 1979)

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation for linalyl acetate (CAS No. 115-95-7 and CAS No. 16509-46-9) include potential local effects (skin sensitisation in its oxidised form; and at high concentrations, skin irritation).

The other chemicals in this group do not have any critical health effects for risk characterisation.

Public Risk Characterisation

Based on the international uses identified, the chemicals may be used in cosmetics and domestic products in Australia as a fragrance ingredient. The general public could be exposed to the chemicals when using cosmetics or domestic products containing the chemicals. The estimated consumer dermal systemic exposure for linalyl esters in cosmetic products are reported as: 0.03 mg/kg bw/day for linalyl butyrate, formate, hexanoate, isobutyrate, isovalerate and phenylacetate; 0.05 mg/kg bw/day for linalyl propionate; 0.1 mg/kg bw/day for linalyl benzoate and 0.331 mg/kg bw/day for linalyl acetate. For skin sensitisation, the calculated exposure concentrations to linalyl esters used in fine fragrance products are reported as 0.4 % for linalyl isovalerate and at a maximum of 4.6 % for linalyl acetate, based on the use in consumer products at 20 % (Bickers et al., 2003a).

There were no Australian uses identified for the majority of the chemicals except for linalyl acetate (CAS No 115-95-7) which was reported to be used in domestic products including car wash soaps, boat wash soaps, polishes and rubbing compounds. The chemicals were also reported to be used overseas in cosmetics and domestic products, particularly perfumery. Except for linalyl acetate, only low hazards are identified for these chemicals. However, this group of chemicals are expected to be present in domestic and/or cosmetic products at low concentrations due to their known use as fragrance ingredients. Therefore, the general public could be exposed through the skin when using domestic and/or cosmetic products containing these chemicals.

Consumer products containing these chemicals can oxidise over time. While the oxidation products are potentially hazardous (skin sensitisation), these will be present at low concentrations. Products that contain relatively high concentrations but which are used infrequently and have long shelf-lives could contain oxidation products that could pose a sensitisation risk for sensitive individuals. This oxidation potential in consumer products could be reduced by incorporating an anti-oxidant. Stabilised or fresh products are not likely to be a risk to public health.

Overall, the risk to public health from this group of chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

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

Given the critical health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure are implemented. The chemicals 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) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2018).

Work Health and Safety

The chemicals are 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.

Note: The recommended classification applies to linalyl acetate (CAS No. 115-95-7 and CAS No. 16509-46-9) only.

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]
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)
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 these chemicals should be used according to the instructions on the label.

Advice for industry

Control measures to minimise the risk from dermal exposure to these 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:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, 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 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 (material) safety data sheets ((M)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 (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 these chemicals has not been undertaken as part of this assessment.

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Last Update 29 June 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Propanoic acid, 2-methyl-, 1-ethenyl-1,5-dimethyl-4-hexenylester** 3,7-dimethyl-1,6-octadienyl isobutyrate linalyl isobutyrate
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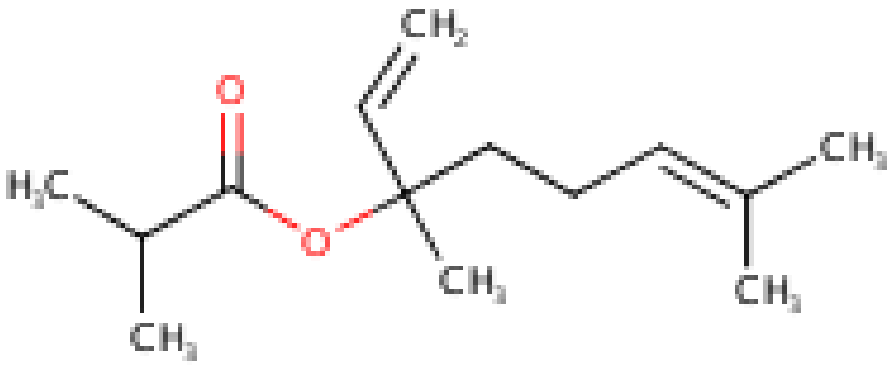
Structural Formula	
Molecular Formula	C14H24O2
Molecular Weight	224.13

Chemical Name in the Inventory and Synonyms	**Butanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester** linalyl butyrate 1,6-octadien-3-ol, 3,7-dimethyl-, butyrate
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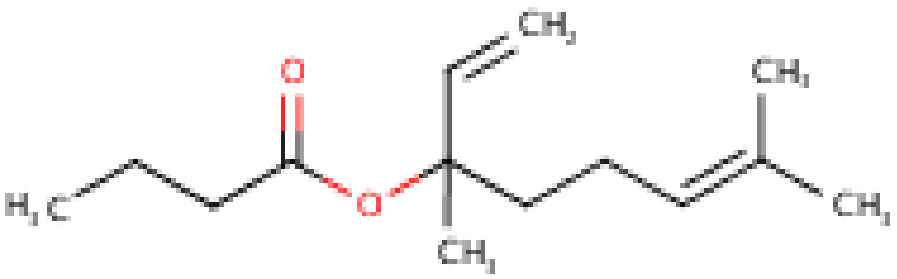
Structural Formula	
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	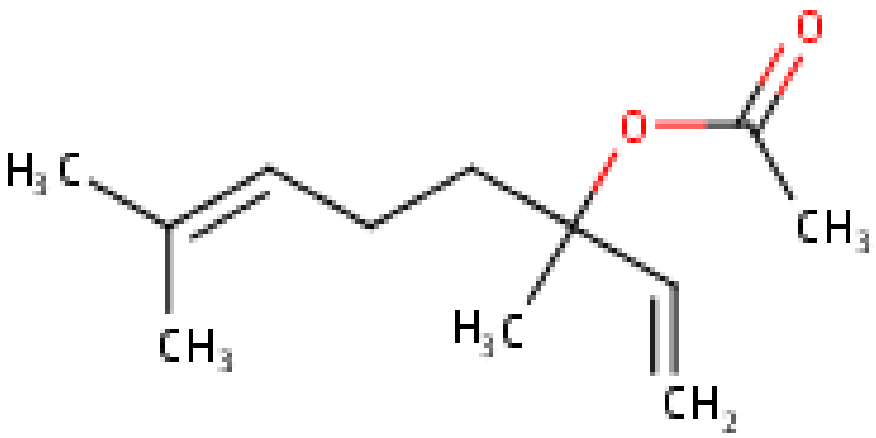
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	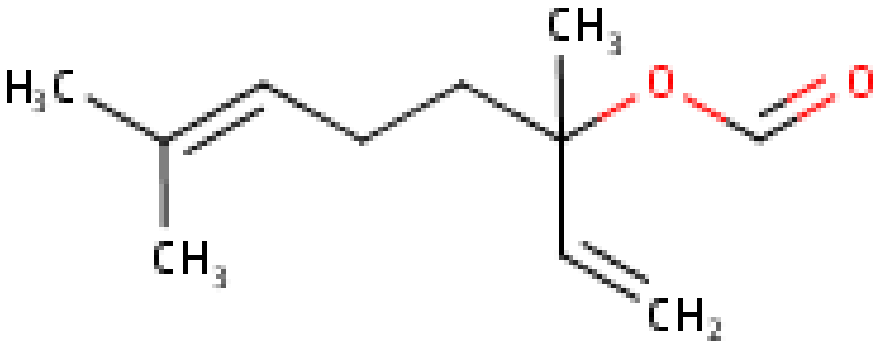
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	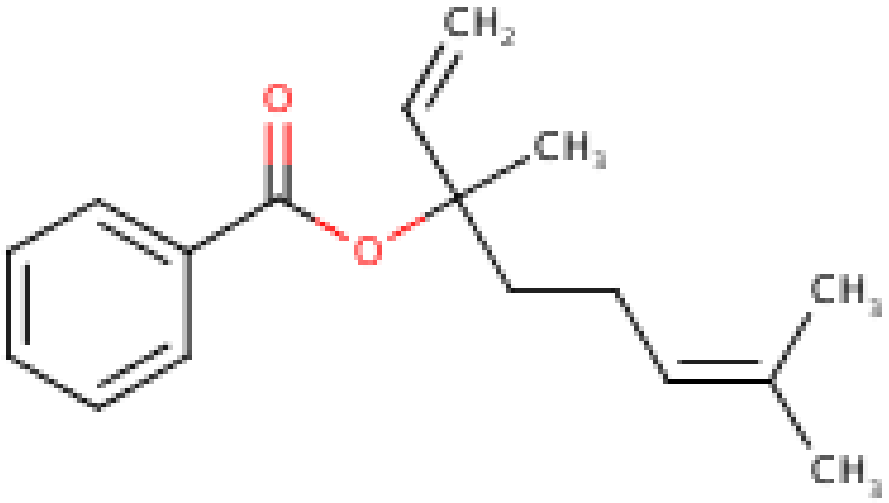
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	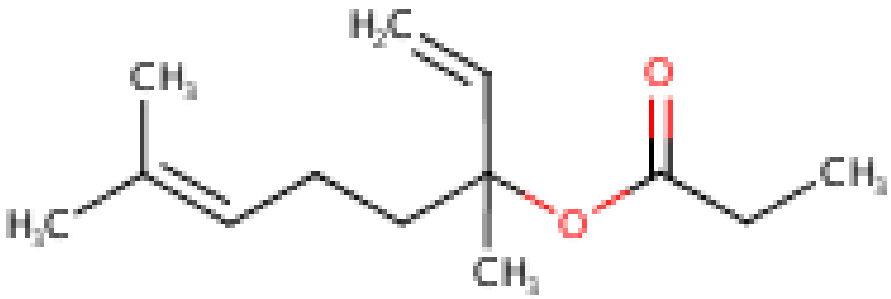
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	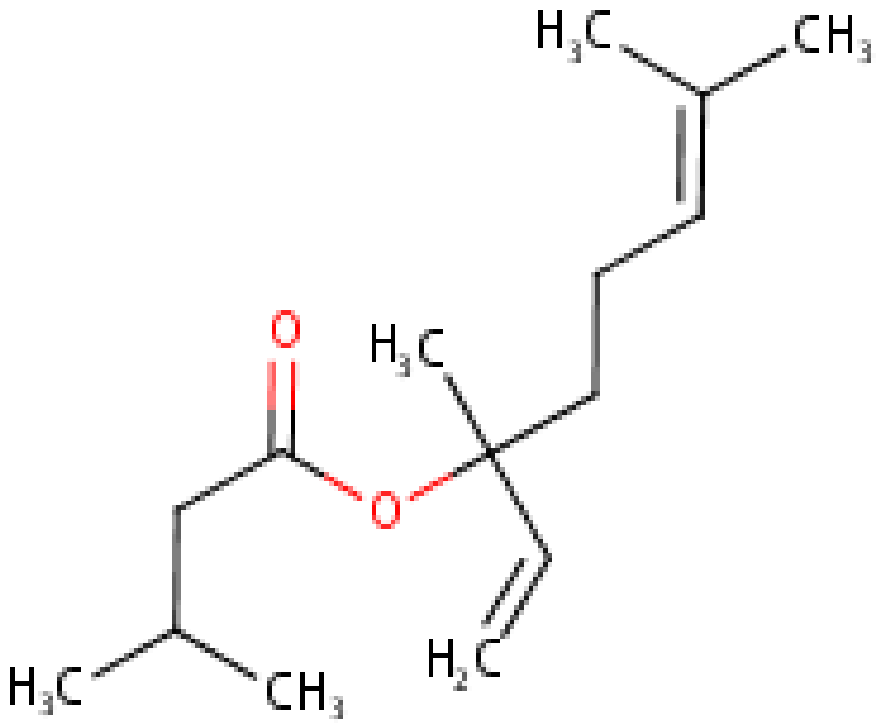
Molecular Formula	C15H26O2
Molecular Weight	238.37

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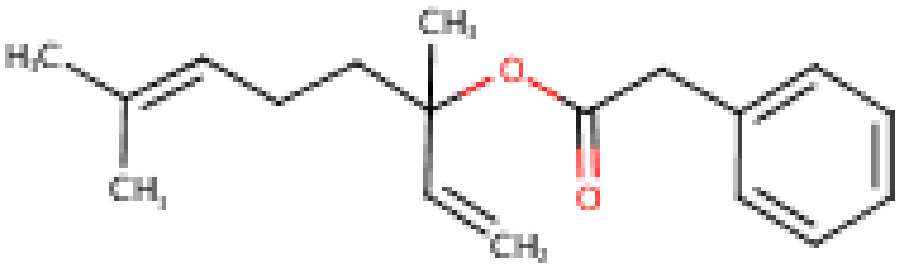

Molecular Formula	C18H24O2
Molecular Weight	272.39

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	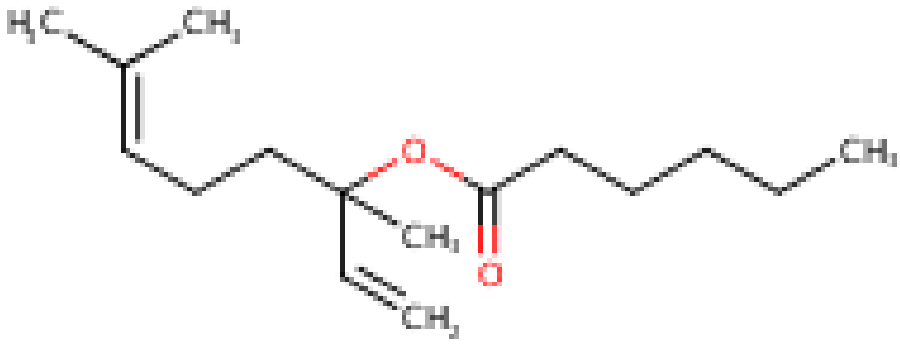
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Chemical Name in the Inventory and Synonyms	**Octanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester** linalyl octanoate linalyl caprylate octanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester 3,7-dimethyl-1,6-octadien-3-yl octanoate
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	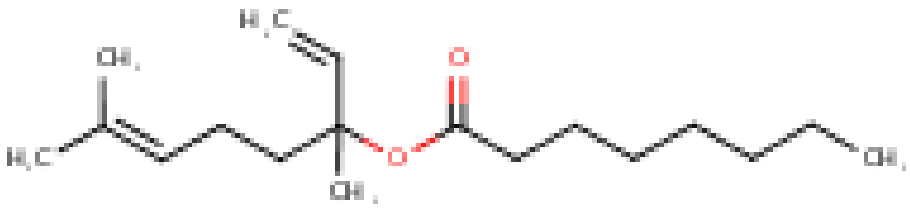
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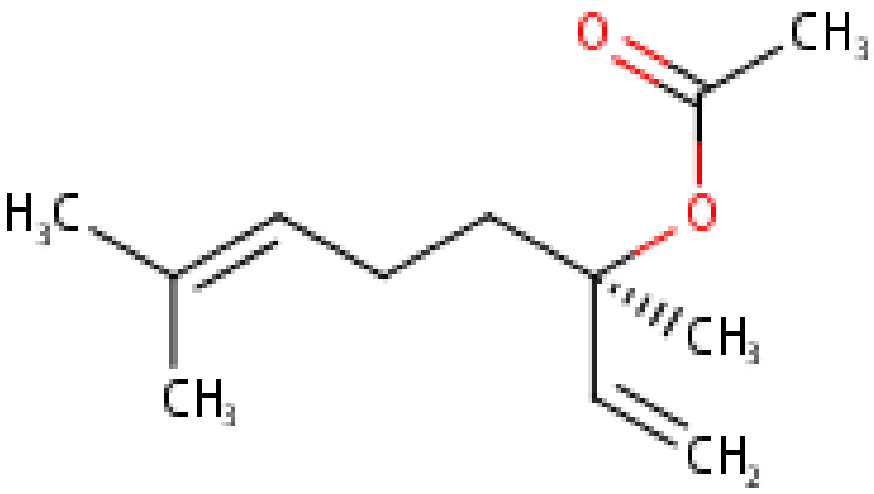
Chemical Name in the Inventory and Synonyms	**1,6-Octadien-3-ol, 3,7-dimethyl-, acetate, (R)-** linalyl acetate, (-)- (R)-linalyl acetate
CAS Number	16509-46-9
Structural Formula	

	
Molecular Formula	C12H20O2
Molecular Weight	196.29

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