Ionones: Human health tier II assessment

02 March 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
3-Buten-2-one, 4-(2,5,6,6-tetramethyl-2-cyclohexen-1-yl)-	79-69-6
3-Buten-2-one, 4-(2,5,6,6-tetramethyl-1-cyclohexen-1-yl)-	79-70-9
3-Buten-2-one, 4-(2,2-dimethyl-6-methylenecyclohexyl)-	79-76-5
3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (E)-	79-77-6
1,6-Heptadien-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	79-78-7
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	79-89-0
Ionone, methyl-	1335-46-2
Irone	1335-94-0
3-Buten-2-one, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (E)-	127-41-3

Chemical Name in the Inventory	CAS Number
1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, [R-(E)]-	127-42-4
1-Penten-3-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	127-43-5
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	127-51-5
1-Penten-3-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-	7784-98-7
1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	7779-30-8
Ionone	8013-90-9
3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	14901-07-6
3-Buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]-	54992-91-5
3-Buten-2-one, 3-methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-	67801-29-0
4-Penten-3-one, 5-(2,4,6-trimethyl-3-cyclohexen-1-yl)-	67801-30-3
3-Buten-2-one, 3-methyl-4-(3,5,6-trimethyl-3-cyclohexen-1-yl)-	67801-31-4
4-Penten-3-one, 5-(3,5,6-trimethyl-3-cyclohexen-1-yl)-	67801-32-5
3-Buten-2-one, 4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-	67801-38-1
3-Buten-2-one, 4-(3,5,6-trimethyl-3-cyclohexen-1-yl)-	67801-39-2
1-Hexen-3-one, 5-methyl-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	70092-23-8

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 are the ionones, which are fragrance chemicals with similar chemical structures. The structural features common to the group consist of a cyclohexene ring, with a pendant α,β-unsaturated ketone side chain tethered through the carbon-carbon double bond. They exist as individual geometric isomers or a mixture of both (based on the cis or trans configuration of the double bond in the butenone side chain). In the case of commercial methyl ionone (ionone, methyl-; CAS No. 1335-46-2) and commerical ionone (ionone; CAS No. 8013-90-9), several different ionones are present as a mixture.

The chemicals in the group possess similar molecular weights. Slight structural differences, such as the positioning of double bonds and methyl groups around the cyclohexene ring and differences in length of the α,β-unsaturated ketone side chains, are not expected to significantly alter the toxicological profile of the chemicals.

Import, Manufacture and Use

Australian

Online database searches have indicated that several of these chemicals are ingredients in a number of consumer products available in Australia. Several chemicals are also widely available online as pure fragrance ingredients for cosmetic and domestic uses.

The chemical α-isomethyl ionone (3-buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; CAS No. 127-51-5) has reported cosmetic use as a fragrance ingredient in perfumes and personal care products, including lip products. The chemical has also reported domestic use as automotive aftermarket cleaner and polish, and car wash soap.

The chemical α-cyclocitrylidenacetone (3-buten-2-one, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; CAS No. 127-41-3) has reported use as an industrial cleaner.

The chemical methyl ionone (CAS No. 1335-46-2) has reported non-industrial use as a rubbing compound in marine applications.

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 (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the International Fragrance Association (IFRA) Transparency List (IFRA, 2017); 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 OECD High Production Volume chemical program (HPV); the United States (US) Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR); the US EPA Chemical and Product Categories (CPCat) database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments and online database sources (Belsito et al., 2007; EFSA, 2015; EFSA, 2016; Good Scents Company; SCCS, 2012; SCENIHR, 2016).

All of the chemicals have reported cosmetic use as fragrance ingredients in cosmetics and personal care products.

Some of the chemicals have reported domestic uses, including as fragrances in:

- cleaning/washing agents (chemicals identified by the CAS Nos. 79-69-6, 79-70-9, 79-77-6, 79-78-7, 79-89-0, 1335-46-2, 127-41-3, 127-42-4, 127-43-5, 127-51-5, 7784-98-7, 7779-30-8, 8013-90-9 and 14901-07-6);
- odour agents (chemicals identified by the CAS Nos. 79-77-6, 1335-46-2, 127-41-3, 7779-30-8, 8013-90-9 and 14901-07-6);
- absorbents and adsorbents (chemicals identified by the CAS Nos. 1335-46-2, 127-41-3, 127-51-5 and 14901-07-6);
- paints, lacquers and varnishes (chemicals identified by the CAS Nos. 1335-46-2 and 127-41-3)
- dehumidifier/dehydrating agents (chemical identified by the CAS No. 127-41-3);
- bleaching agents (chemical identified by the CAS No. 127-51-5); and
- aerosol propellants (chemical identified by the CAS No. 14901-07-6).

Some of the chemicals have reported commercial uses, including as:

- surface treatments (chemicals identified by the CAS Nos. 1335-46-2, 127-51-5, 8013-90-9 and 14901-07-6); and
- softeners (chemical identified by the CAS No. 127-51-5).

Some of the chemicals have reported site-limited uses, including as:

- intermediates (chemicals identified by the CAS Nos. 79-77-6 and 127-51-5);

- impregnation materials (chemical identified by the CAS No. 1335-46-2);
- fuel additives (chemical identified by the CAS No. 127-41-3); and
- hydraulic fluids (chemical identified by the CAS No. 127-41-3).

The chemicals identified by the CAS Nos. 127-41-3 and 8013-90-9 have reported use as flavourings in tobacco products.

Some of the chemicals have reported non-industrial uses as flavouring and fragrance ingredients in:

- food, feed, and beverages (chemicals identified by the CAS Nos. 79-77-6, 79-76-5, 127-41-3, 7784-98-7 and 8013-90-9);
- non-agricultural pesticides and preservatives (chemicals identified by the CAS Nos. 1335-46-2, 127-41-3, 127-51-5 and 14901-07-6).

Restrictions

Australian

No restrictions for industrial use have been identified for the chemicals in Australia.

The chemicals allyl-α-ionone, α-ionone, α-irone, β-ionone, γ-ionone, methyl ionone, α-methyl ionone, γ-methyl ionone, β-methyl ionone and α-isomethyl ionone have restrictions for their non-industrial use as an excipient in medicines (TGA, 2017) at certain concentrations depending on the following uses as flavour or fragrance ingredients:

- Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.
- If used in a flavour the total flavour concentration in a medicine, must be no more than 5 %.
- If used in a fragrance the total fragrance concentration in a medicine, must be no more than 1 %.

Ionone has restrictions for its non-industrial use as an excipient in medicines (TGA, 2017), where it is permitted for use only:

- in topical medicines for dermal application; and
- in oral medicines in combination with other permitted ingredients as part of a flavour proprietary excipient formulation. When ionone is used in a flavour, the total flavour proprietary excipient formulation in a medicine must be no more than 5 %.

Irone is permissible for use as an excipient in medicines in Australia (TGA, 2017).

Isomethyl ionone and β-isomethyl ionone have restrictions for their non-industrial use as excipients in medicines (TGA, 2017), where they are permitted for use only in combination with other permitted ingredients as fragrance ingredients. If used in a fragrance the total fragrance concentration in a medicine must be no more than 1 %.

International

The chemical α-isomethyl ionone (CAS No. 127-51-5) is listed on 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. (CosIng); and
- New Zealand Cosmetic Products Group Standard (NZ EPA)—Components cosmetic products may contain with restrictions.

Under these restrictions, the presence of α-isomethyl ionone must be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products, and 0.01 % in rinse-off products.

Several of the chemicals are also included in the International Fragrance Association (IFRA) Standards. The Research Institute for Fragrance Materials (RIFM) Expert Panel established a No Expected Sensitisation Induction Level (NESIL) of 70000 µg/cm^2 for methyl ionone, mixed isomers (chemicals identified by the CAS Nos. 1335-46-2, 127-42-4, 127-43-5, 127-51-5, 7779-30-8 and 79-89-0) (IFRA, 2015).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for the chemicals methyl ionone, α-isomethyl ionone, ionone, and β-ionone (Galleria Chemica).

Exposure limits of 111–150 mg/m^3 (20–25 ppm) time weighted average (TWA) and 300 mg/m^3 (50 ppm) short-term exposure limit (STEL) in different countries such as Canada (Alberta), Denmark, Estonia and Sweden.

Health Hazard Information

The ionones exist naturally as flavours and fragrance chemicals in substances such as raspberries, carrots, roasted almonds and herbs. The chemical structures of the ionones contain activated carbon-carbon double bonds that can potentially undergo Michael-type addition reactions with proteins and nucleosides; and therefore, raise concerns for human health endpoints such as sensitisation and genotoxicity. This group of chemicals is part of the "rose ketone" category of fragrance chemicals, which also includes a group of structurally similar chemicals called the damascones. The damascones possess a pendant α,β-unsaturated ketone side chain with the keto group adjacent to the ring (reverse compared with the ionones).

There are limited toxicological data available for the ionones, with little to no data available for endpoints such as carcinogenicity and genotoxicity. Where there are data gaps, information from the damascones are considered suitable for read across to the ionones due to their similar structural features and likely similar modes of action.

Toxicokinetics

There are limited toxicokinetic data available for the ionones.

Absorption

Systemic availability through dermal absorption is low for all the chemicals in this group. In a dermal absorption study in the skin of rats and pigs (no other details specified), 74 and 60 % of the applied dose was recovered from the skin after 6 and 16 hours, respectively, following administration of radiolabelled methyl ionone at 10 % in ethanol (REACHc). In an in vitro dermal penetration/permeability study using rat and pig skin (no other details specified), only 0.7 % of methyl ionone was recovered in

the receptor fluid following application. About 50 % of methyl ionone was absorbed into the rat skin, with a further 30 % lost to evaporation (Belsito et al., 2007).

The ionones are lipophilic substances that are expected to be orally available, with oil/water partition coefficient (log Kow) values in the range of 3.85–5.20. The chemical β-ionone is readily absorbed via the oral route, as evidenced by the yield of urinary metabolites following gavage administration in male albino rabbits (REACHf).

Distribution

There are no distribution data available for the ionones. The chemicals are expected to be systemically available following absorption due to their lipophilicity.

Metabolism

A number of metabolic processes in various combinations are expected for these chemicals, producing a variety of similar metabolites. These processes include:

- hydroxylation/oxygenation of the cyclohexene ring;
- reduction of the butenone group to a secondary alcohol;
- oxidation of the angular methyl groups;
- reduction of the exocyclic double bond;
- conjugation of the hydroxylated metabolites with glucuronic acid; and
- conjugation with glutathione.

Other metabolic routes such as epoxidation of the carbon-carbon double bond groups may also be possible, with the potential to produce highly reactive intermediates. However, epoxidation of the ring double bonds is expected to be unlikely due to steric hindrance from directly attached substituents (methyl groups) and neighbouring functional groups. These chemicals have been shown to possess comparatively low electrophilicity in studies with glutathione compared to less sterically-hindered α,β-unsaturated ketones (Portoghese et al., 1989).

The chemical β-ionone is metabolised into a number of polar metabolites by hydroxylation of the ring system at the carbon atom a to the ring double bond, followed by oxidation of the hydroxyl group to 3-oxo derivatives, as well as other cyclohexenyl compounds. The main urinary metabolites found in urine 96 hours after oral administration of β-ionone to rabbits were 3-oxo-β-ionone, 3-oxo-β-ionol, dihydro-3-oxo-β-ionol, 3-hydroxy-β-ionol and unchanged β-ionone (REACHf). It is expected that all the chemicals in this group are metabolised. The metabolites are either excreted unchanged in the urine or conjugated with glucuronic acids.

Excretion

Due to the number of metabolic processes available for these chemicals that lead to polar metabolites, the chemicals are expected to be excreted in the urine in both free and conjugated forms. A minimal amount (~1 %) of unchanged β-ionone was recovered in the urine in rabbits. Recovery levels of the metabolites were not specified (Belsito et al., 2007).

Acute Toxicity

Oral

Based on results from animal tests following oral exposure to several chemicals within the group, the ionones are expected to have low acute oral toxicity. The median lethal dose (LD50) in rats is reported to be 2000–10000 mg/kg bodyweight (bw) for the chemicals allyl α-ionone, α-irone, trans-β-ionone, methyl ionone (mixed isomers), ionone (mixed isomers), a-isomethyl ionone, iritone, and β-ionone. Reported sub-lethal effects include cyanosis, somnolescence, dehydration and heavy breathing (Belsito et al., 2007; REACHa–f). Hazard classification is not warranted.

Dermal

Based on results from animal tests following dermal exposure to several chemicals within the group, the chemicals are expected to have low acute dermal toxicity. The LD50 in rats in each case is >2000 mg/kg bw. Hazard classification is not warranted.

The chemical ionone (mixed α- and β-isomers) has a reported dermal LD50 of >2000 mg/kg bw in rats. No signs of treatment-related systemic effects or skin irritation were observed (REACHb). The chemicals methyl ionone and a-isomethyl ionone have a reported dermal LD50 of >5000 mg/kg bw in rabbits. Sublethal effects such as diarrhoea, anorexia, lethargy and severe skin irritation were reported for a-isomethyl ionone. No sub-lethal effects were reported for methyl ionone (REACHc; REACHd).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemicals are irritating to the skin, warranting hazard classification (see **Recommendation** section). Minimal to no skin effects were observed at low concentrations in animal and human studies for several chemicals in the group (see **Observation in Humans**). However, moderate to severe skin irritation was observed in animal studies when the chemicals are used undiluted or following repeated exposure. However, there is limited reporting of the study details available.

Most of the chemicals in the group are suspected of being irritating to the skin based on a number of notifications to the Classification and Labelling Inventory by industry in the European Union (ECHA C&L).

In an acute dermal irritation study equivalent to OECD Test Guideline (TG) 404, α-irone produced slight to moderate erythema and oedema 24 hours after application of the undiluted chemical under semi-occlusive conditions in New Zealand White (NZW) rabbits (REACHa). The chemical also produced slight irritation at concentrations of 1 % and 5 % (REACHa).

The chemical a-isomethyl ionone was tested for skin irritation in NZW rabbits. A 0.5 mL aliquot of undiluted chemical was applied under semi-occlusive conditions for four hours. Slight erythema and slight to moderate oedema were observed in all animals. The chemical was concluded to be a skin irritant when applied undiluted. This was confirmed in an additional study where undiluted α-isomethyl ionone was applied to rabbit skin, resulting in well-defined erythema on abraded and intact rabbit skin 72 hours post-application. Slight to well-defined oedema in 2/3 rabbits was seen at 24 hours, and disappeared by 72 hours. Application of 5 % α-isomethyl ionone showed no evidence of skin irritation under the same test conditions (REACHe).

Severe dermal irritation was observed in a 90-day dermal repeat dose study using α-isomethyl ionone (see **Repeat Dose Toxicity: Dermal**).

The chemical methyl ionone applied undiluted to intact rabbit skin under semiocclusive conditions produced marginal to distinct erythema and oedema after 4 hours in most rabbits. These effects increased after 24 hours, with marginal skin cracking also observed in 5/8 animals. After 72 hours, 7/8 animals had marginal to distinct erythema and oedema with cracking and scaling (REACHc).

The chemical β-ionone was found to be only slightly irritating when applied at 5 % in diethyl phthalate (DEP) to abraded and intact skin of NZW rabbits. Slight to well-defined erythema and slight oedema were observed at 24 hours in 2/3 animals; however, these effects were fully reversible at 72 hours after application. Slight to well-defined erythema was observed 72 hours after application of neat β-ionone; however, slight oedema that was observed after 24 hours was not seen after 72 hours (REACHf).

The chemical α-ionone was not found to be irritating to skin of miniature swine when applied undiluted under occluded conditions to the dorsal surface for 48 hours. No skin reactions were observed (REACHd). In a preliminary irritation screen, the

chemical was applied at a concentration of 30 % (vehicle unreported) to shaved skin of guinea pigs for 24 hours. No skin irritation was observed under the test conditions (REACHd).

The chemical trans-β-ionone was found to be non-irritating when applied undiluted to rabbit skin under semi-occlusive conditions for four hours (REACHb).

The undiluted chemical ionone (CAS No. 8013-90-9) was found to be non-irritating in a 24-hour closed patch test (REACHf).

Eye Irritation

The chemical α-isomethyl ionone and its geometric isomers are found to be irritating to the eyes, warranting hazard classification (see **Recommendation** section). The other chemicals in the group are not expected to cause serious effects to the eyes. There is limited reporting of the study details available.

The chemicals in this group are suspected of being irritating to the eyes based on a number of notifications to the Classification and Labelling Inventory by industry in the European Union (ECHA C&L).

In an eye irritation study conducted similarly to OECD TG 405, α-isomethyl ionone was found to be irritating to the eyes of NZW rabbits at concentrations of 12.5 % (vehicle unreported) and 100 %. Intense conjunctivitis involving chemosis and discharge were observed at 24, 48 and 72 hours after application. No corneal opacity of iris congestion was observed. Effects were fully reversible within seven days (REACHe).

The chemical α-irone applied undiluted to the eyes of NZW rabbits caused slight irritation in one animal after 24 hours; however, all eye reactions were clear after one week (REACHa). In another study conducted according to OECD TG 405, the chemical was applied undiluted and at a concentration of 5 % in diethyl phthalate—in both instances no irritating effects were observed (REACH).

The chemical trans-β-ionone produced weak effects when applied undiluted to rabbit eyes. All observed effects were fully reversed within 72 hours (REACHb).

The chemical β-ionone produced very slight conjunctival irritation in 3/3 animals when applied undiluted to rabbit eyes. These effects were reversible within 24 hours (REACHf). Slight conjunctival redness was also observed in rabbits treated with 5 % β-ionone in the eye (REACHf).

The chemical a-ionone did not cause eye irritation in NZW rabbits after 72 hours of observation when applied undiluted or at a concentration of 5 % in diethyl phthalate (REACHd). Very slight conjunctival irritation was observed; with effects reversible within 24 hours.

Observation in humans

The chemical ionone (mixed isomers) was patch tested in healthy volunteers and dermatology patients at concentrations of 0.2, 2 and 20 % using different vehicles. No irritation effects were observed (REACHd).

The chemical α-isomethyl ionone was tested for skin irritation in 28 volunteers. The chemical was applied under occlusive conditions for 24 hours as a 10 % solution in ethanol. No skin irritation effects were observed (REACHe). In the induction phase of a human repeat insult patch test (HRIPT), the chemical was found to be non-irritating at a concentration of 12.5 % (vehicle unspecified). In another HRIPT, skin irritation was observed in 1/106 volunteers following application of 60 % α-isomethyl ionone in 3:1 DEP:ethanol nine times for 24 hours over a three week period (REACHe).

In a modified dermal primary irritation study, 12 volunteers were treated with 60 % α-isomethyl ionone in either 3:1 DEP:ethanol or 3:1 ethanol:DEP twice for 24 hours. Reactions were scored at patch removal and 24 hours after patch removal. No skin irritation was observed (REACHe).

Sensitisation

Respiratory Sensitisation

No data are available. A number of chemicals within the group are suspected of being respiratory sensitisers based on a number of notifications to the Classification and Labelling Inventory by industry in the European Union (ECHA C&L). In the absence of further information, no conclusion can be made on the respiratory sensitisation potential of the chemicals.

Skin Sensitisation

The chemicals are considered to be weak skin sensitisers based on the results seen in a single local lymph node assay (LLNA) and a number of animal studies for several chemicals in the group. The EC3 value (concentration required to produce a three-fold increase in lymphocyte proliferation compared with controls) for the chemical α-isomethyl ionone was reported to be 21 %. The effects observed in human patch tests also indicate that several ionones have weak sensitisation potential (see **Observation in humans**). Concerns for a number of the chemicals as potential fragrance allergens in cosmetic products (SCCS, 2012), has also led to a number of international restrictions based on their sensitisation potential (see **Restrictions: International**; IFRA, 2017). Based on these concerns, hazard classification is warranted (see **Recommendation** section).

Many of the chemicals in the group are suspected of being skin sensitisers based on a number of notifications to the Classification and Labelling Inventory by industry in the European Union (ECHA C&L).

In a LLNA study in female CBA/Ca mice, concentrations of up to 50 % α-isomethyl ionone in 3:1 DEP:ethanol were tested. The EC3 was reported to be 21.8 %. No other details are available (Belsito et al., 2007).

The ionones appear to have a weaker sensitisation potential compared to the damascones (Belsito et al., 2007), possibly due to the greater steric hindrance created by the internal configuration of the α,β-unsaturated ketone side chain, which would prevent protein interactions from readily occuring compared to the damascones.

The chemical α-irone was found to be non-sensitising when applied undiluted to guinea pig skin in an open epicutaneous test. The chemical was also non-sensitising in a KeratinoSens™ assay or direct peptide reactivity assay, as it did not induce the luciferase gene (responsible for induction) above the 1.5-fold threshold at any concentrations tested. (more explanation of method) (REACHa).

In a GPMT, topical induction of 10 % β-ionone was carried out in guinea pigs (5/dose). No details on intradermal induction were specified. The animals were then topically challenged with 5, 10, 20 or 40 % β-ionone in acetone. No evidence of sensitisation was observed (REACHf).

The chemical methyl ionone was non-sensitising in two GPMTs, two open epicutaneous tests, Freund's complete adjuvant test and a Draize test (REACHc). The chemical was sensitising in a Vitamin A enhanced ear swelling test, but not sensitising when animals were not fed Vitamin A beforehand (REACHc).

In a modified Draize test, α-ionone was administered to ten inbred Hartley strain guinea pigs (10 animals), with an induction challenge concentration of 0.1 % and an application challenge concentration of 30 %. Although some irritation was observed, no sensitisation effects were observed.

Observation in humans

Several of the chemicals are 'established contact allergens' in the European Union (SCCS, 2012).

The chemical α-isomethyl ionone was tested for its sensitisation potential in 179 patients, including patients suffering from dermatitis in which cosmetic allergy was suspected. The chemical was tested at 10 % in petrolatum, and produced positive patch test reactions in 2/179 patients. The chemical was concluded to be a skin sensitiser (REACHe). In a HRIPT carried out on 37 subjects, the chemical was applied nine times for 3 successive weeks for an exposure period of 24 hours. Two weeks after the induction period, the chemical was applied to a previously unexposed area of skin. No skin reactions were observed in any of the volunteers (REACHe). In another patch test carried out on 28 healthy volunteers, patches of 10 % α-isomethyl ionone in ethanol were applied to the volunteers. Following the induction period, the challenge patch was applied. No skin reactions were observed. In another patch test study, 119 volunteers presenting with cosmetic-related contact dermatitis, 1/119 volunteers

presented with skin sensitisation using 5 % α-isomethyl ionone in petrolatum. The chemical was concluded not to be skin sensitising (REACHe).

The chemical α-ionone was tested for its sensitisation potential in 86 male and 119 female volunteers (REACHd). No skin reactions were observed following application of the chemical at a concentration of 1 % in petrolatum to the skin of the back, even after 4 days of observations (REACHd).

The chemical β-ionone (CAS No. 14901-07-6), at concentrations of 1 and 5 % in petrolatum, was used in patch testing of 205 volunteers. No patients demonstrated any skin effects at 2–4 days following application of 1 % solution. Skin irritation effects were observed for 2/205 patients following application of 5 % solution; however, no sensitisation reactions were observed (REACHe).

Repeated Dose Toxicity

Oral

The chemicals are not expected to pose serious damage to health from repeated oral exposure. Several of the ionones are generally regarded as safe (GRAS) for use as flavour ingredients by the US Food and Drug Administration, reflecting the low level of concern regarding their potential for long-term toxicity via the oral route.

In a 90-day oral toxicity study, α-ionone (~11 mg/kg bw/day) and β-ionone (~12 mg/kg bw/day) in cottonseed oil were administered in the diet of FDRL rats (15/sex). No effects were observed on body weight gain, food consumption, liver and kidney weights or haematology/blood chemistry parameters. No adverse effects on the gross or microscopic appearance of the organs at necroscopy were observed (Belsito et al., 2007). In another study, α-ionone and β-ionone were administered separately in the diet to groups of Sprague Dawley (SD) rats (15/sex) at doses of 10 or 100 mg/kg bw/day. The only significant effect observed for either chemical was a modest but significant increase in absolute and/or relative liver weights; however, no histopathological effects in the liver were found (Belsito et al., 2007).

The chemical a-isomethyl ionone was administered to FDRL rats (15/sex) via diet at doses of 3.55 and 4.10 mg/kg bw/day in male and female rats, respectively (REACHe) for 90 days. These doses were roughly 100 times the maximum estimated human dietary levels. No treatment-related gross pathological changes were observed. In another study, the chemical was admistered to SD rats at doses of 0, 5, 30 or 500 mg/kg bw/day. The no observed adverse effect level (NOAEL) was determined to be 30 mg/kg bw/day for male rats based on histopathological effects in the kidneys, and 500 mg/kg bw/day for female rats based on relative kidney weight changes.

In another 90-day oral toxicity study, male and female FDRL rats (15/sex/dose) dosed in diet at 0, 11.6 or 13.1 mg/kg bw/day β-ionone in males and females, respectively. No treatment-related effects were reported based on evaluations of body weight, food intake, haematology, blood chemistry, liver and kidney weights and histopathology. The NOAEL for male FDRL rats was 11.6 mg/kg bw/day, while the NOAEL for female FDRL rats was 13.1 mg/kg bw/day (REACHf).

Dermal

The chemicals are not expected to cause serious damage to health by repeated dermal exposure based on the limited available data. This is supported by the expected low dermal absorption (see **Toxicokinetics** section) of the chemicals.

The chemical α-isomethyl ionone was applied daily, unoccluded, to Sprague Dawley (SD) rats (15/dose) in a dermal 90-day subchronic toxicity study. Doses of 0, 50, 170, 580 or 2000 mg/kg bw/day were applied to the skin on clipped backs. Erythema and oedema with eschar formation were observed at all dose levels and were dose dependent. The chemical was found to be a severe dermal irritant on repeated exposure. A lowest observed adverse effect level (LOAEL) of 50 mg/kg bw/day was determined based on local skin irritation effects observed at all dose levels (REACHe).

Inhalation

Sprague-Dawley rats (10/sex) were exposed (nose only) to cigarette smoke containing α-ionone, 5 days per week for 13 weeks. Effects observed included increase in body weight and some smoke treatment related effect. No statistically significant differences in any of the mean histopathological parameters were noted (REACHd).

Genotoxicity

Limited animal and human data are available. In the absence of further information, hazard classification is not warranted.

The European Food Safety Authority (EFSA) concluded that the genotoxicity potential of the chemicals cannot be ruled out due to insufficient data evaluated (EFSA, 2015).

In vitro

The chemical α-irone was found to be negative for inducing gene mutations in a bacterial reverse mutation assay carried out using *Salmonella typhimurium* strains TA1535, 1537, 98, 100 and 102, with and without metabolic activation (S9) at concentrations of 33, 100, 333, 1000, 2500 and 5000 µg/plate (REACHa).

The chemical α-ionone was found to be negative for inducing gene mutations in a bacterial reverse mutation assay carried out using *S. typhimurium* strains TA1535, 1537, 98, 100 and 102, with and without metabolic activation (S9) at concentrations of 0.01–50 µg/plate (REACHd). Significant increases in chromosomal aberrations were observed in Chinese hamster B241 cells, with or without metabolic activation (REACHd).

In a bacterial gene mutation study, α-isomethyl ionone was found to be negative up to a concentration of 3600 µg/plate in *S. typhimurium* strains TA1535, TA1537, TA98 and TA100, with and without metabolic activation (REACHe).

In a bacterial gene mutation study, β-ionone was found to be negative at concentrations of 3.3–180 µg/plate with metabolic activation, and 1–50 µg/plate without metabolic activation in *S. typhimurium* strains TA100, TA98, TA1535 and TA1537 (REACHf).

In a mammalian cell gene mutation assay, Chinese Hamster ovary (CHO) cells were exposed to ionone at concentrations of 0, 1, 2.5, 5 or 10 mM in ethanol, with and without metabolic activation (REACHe). No signs of genotoxicity were observed.

In vivo

The chemical trans-β-ionone was found to be non-mutagenic in a micronucleus test in NMRI mice (male) following single adminstration of the chemical via ip in olive oil at doses of 0, 250, 500 and 750 mg/kg bw/day. It was found that the test substance did not lead to any statistically significant increase in the number of polychromatic erythrocytes containing either small or large micronuclei (REACHb).

Quantitative Structure-Activity Relationship (QSAR) information

All the chemicals in this group present alerts for mutagenicity based on their molecular structures as profiled by the OECD QSAR Toolbox v3.3. The presence of one or more α,β-unsaturated ketone groups in each of the ionones presents an opportunity for potential binding to proteins and DNA molecules through Michael addition. However, the mostly negative results from the available in vitro and in vivo studies indicating that the chemicals are not likely to be genotoxic at the low concentrations of the chemicals expected in consumer products.

Carcinogenicity

Limited data are available. Based on the available genotoxicity data (see **Genotoxicity** section) and a negative tumour promotion study, the chemicals are not likely to have the potential for carcinogenicity. Any potentially reactive metabolites that may arise from epoxidation or Michael addition of ionones and their metabolites are not expected to occur at levels that will cause damage at the concentrations in consumer products. In the absence of further information, hazard classification is not warranted.

The European Food Safety Authority (EFSA) concluded that the genotoxicity potential of the chemicals cannot be ruled out due to insufficient data evaluated (EFSA, 2015).

In a dermal tumour promotion study, ICR Swiss mice (30) were administered once with 0.125 mg of a tumourinitiating agent (7,12-dimethylbenz[a]anthracene (DMBA)) in acetone applied to the skin, followed by application of β-ionone (3 mg/kg bw/day) five times a week for 18 weeks. Treatment with the chemical did not

increase the incidence of tumours. No tumours were seen with DMBA or β-ionone controls (Belsito et al., 2007).

Reproductive and Developmental Toxicity

The chemicals are not expected to cause reproductive or developmental toxicity.

The following results were reported for several ionones (Belsito et al., 2007):

- no treatment-related effects were observed on reproductive organs, oestrous cycles or sperm parameters following dietary administration of trans-β-ionone to Wistar rats at doses of approximately 7, 72 or 720 mg/kg bw/day for three months;
- no developmental abnormalities were observed following a two-week dietary administration of trans-β-ionone to pregnant Wistar rats at doses of 25, 100 or 400 mg/kg bw/day;
- no embryotoxic effects were observed in rabbits administered 50 mg/kg bw/day of trans-β-ionone;
- no reproductive toxicity effects were seen in Syrian hamsters administered β-ionone by gavage at 0, 48, 240 or 480 mg/kg bw/day;
- no overt signs of maternal toxicity and no dose-related reduction of pregnancy weight gain were observed in a one-generation study in pregnant Wistar rats exposed to a single dose of β-ionone (0, 250, 500, 750 or 1000 mg/kg bw/day) in corn oil by oral gavage;
- no significant gross pathological and histopathological changes were observed in the reproductive organs in FDRL rats administered 11 mg/kg bw/day α-ionone in the diet; and
- no treatment-related changes in reproductive parameters were seen in pregnant SD rats administered α-isomethyl ionone at doses of 0, 3, 10 or 30 mg/kg bw/day.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include skin irritation and skin sensitisation for all chemicals. Some chemicals may also cause eye irritation.

Public Risk Characterisation

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

Several of the chemicals are readily available, and are expected to be widely distributed for use as raw fragrance materials. However, the distribution of the chemicals for fragrance purposes is expected to be controlled by members of IFRA. The restriction of these chemicals under the IFRA Standard is expected to sufficiently manage the public risks associated with chemical exposure through fragrances (e.g. concentration limits in finished products of 2.00 % – 50.72 % of the chemicals) (IFRA, 2015).

The Joint Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) indicated that the use of ionones as flavouring agents would not present a safety concern at the current estimated intake levels. The acceptable daily intake (ADI) of 0-0.1 mg/kg is established for α-ionone and β-ionone (WHO, 1999).

In the absence of further information, daily dermal exposure to the ionones at concentrations consistent with the IFRA Standard concentrations will present no unreasonable risk to the public. Additionally, several of the chemicals are listed in the US Food and Drug Administration (FDA) generally recognised as safe (GRAS) list. The list establishes safety of chemicals through their long history of use in food.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation 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.

Given the critical systemic acute and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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 Hazardous Chemical Information System (HCIS) (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Use of these chemicals will mostly be proprietary limited for fragrance purposes, and will likely adhere to the IFRA standard. No further risk management is required other than changes to the hazard classification of these chemicals. Further assessment may be warranted if additional information regarding genotoxic effects of the ionones becomes available.

Assessment of these chemicals are 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

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.

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.

The eye irritation classification is recommended only for the chemicals identified by the CAS Nos. 127-51-5, 79-89-0, 67801-29-0 and 67801-31-4. The skin irritation and skin sensitisation classifications apply to all the chemicals in this group.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319) 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 industry

Control measures

Control measures to minimise the risk from dermal, ocular 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:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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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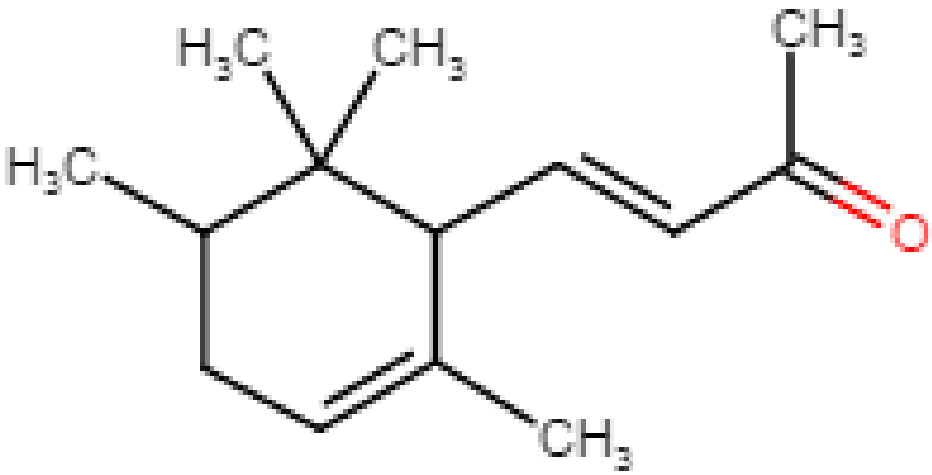
Last Update 02 March 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(2,5,6,6-tetramethyl-2-cyclohexen-1-yl)-** alpha-irone 6-alpha-methyl ionone 6-methyl-alpha-ionone 5-methyl-alpha-ionone
CAS Number	79-69-6
Structural Formula	
Molecular Formula	C14H22O

Molecular Weight	206.3

Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(2,5,6,6-tetramethyl-1-cyclohexen-1-yl)-** 6-beta-methyl ionone 6-methyl-beta-ionone
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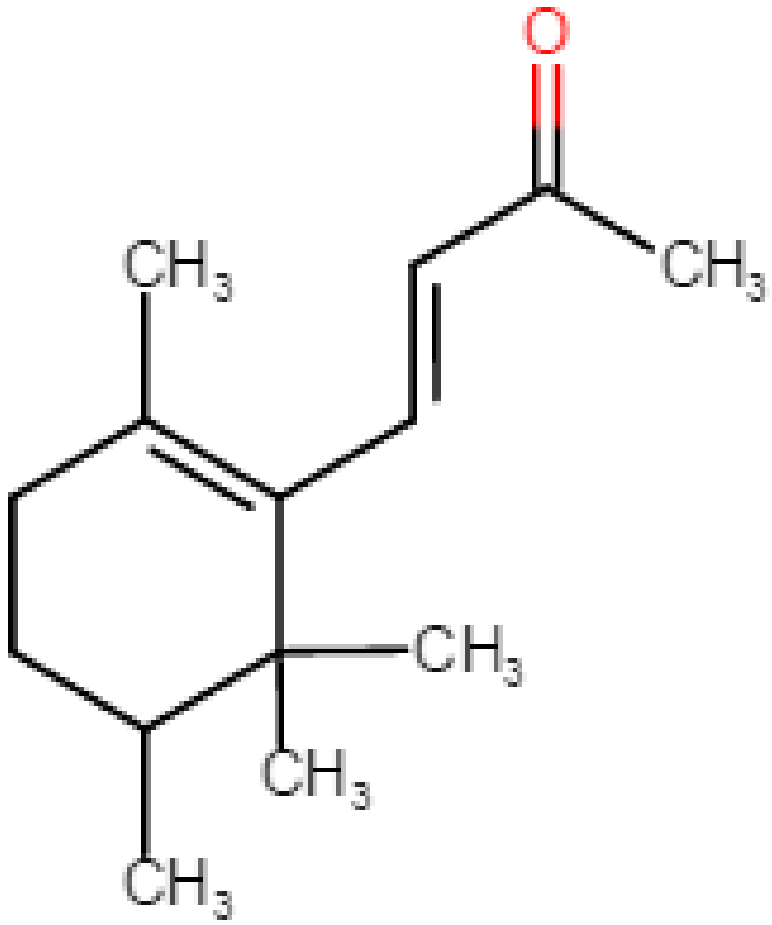
Structural Formula	
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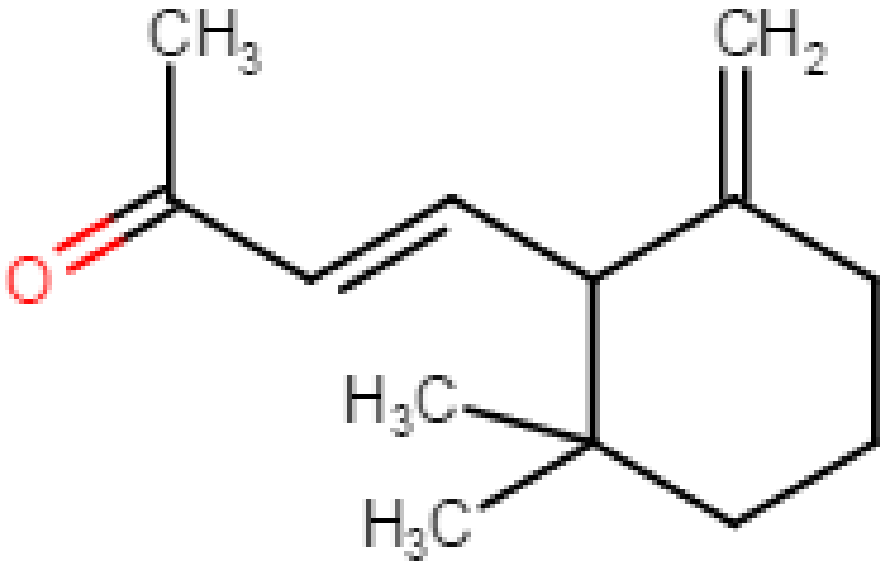
Structural Formula	
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	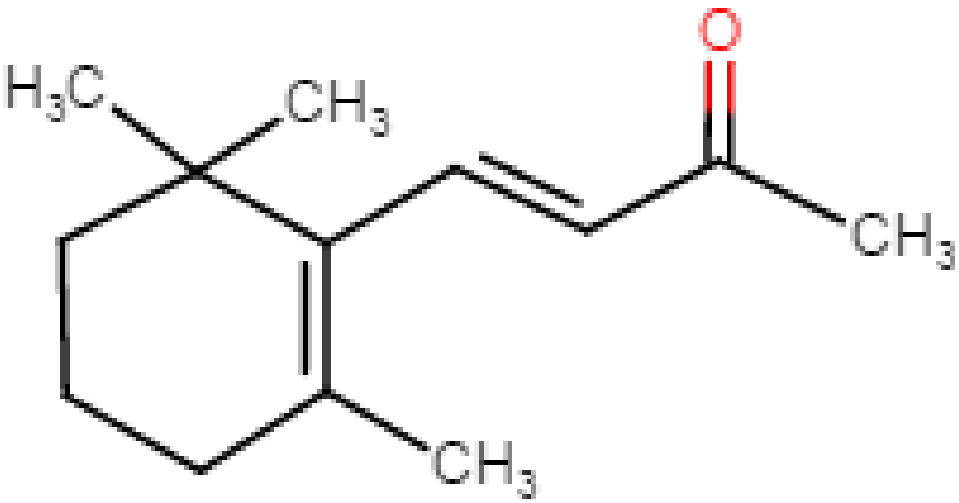
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	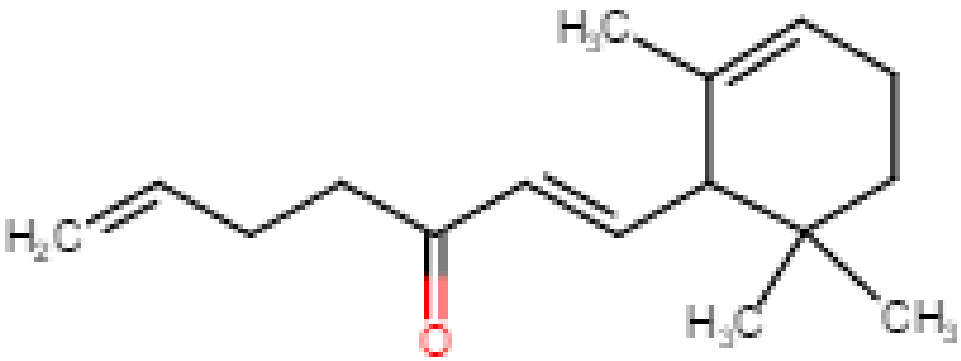
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	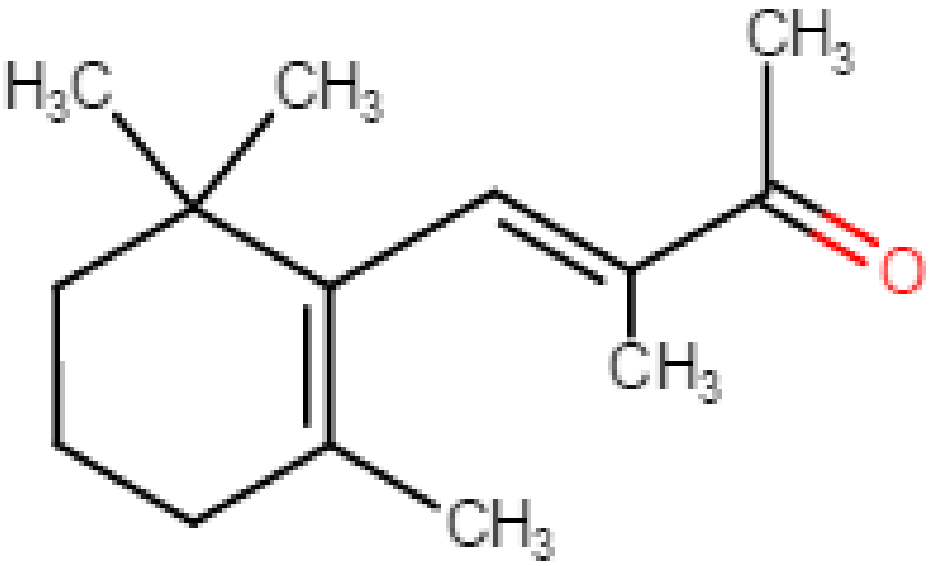
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	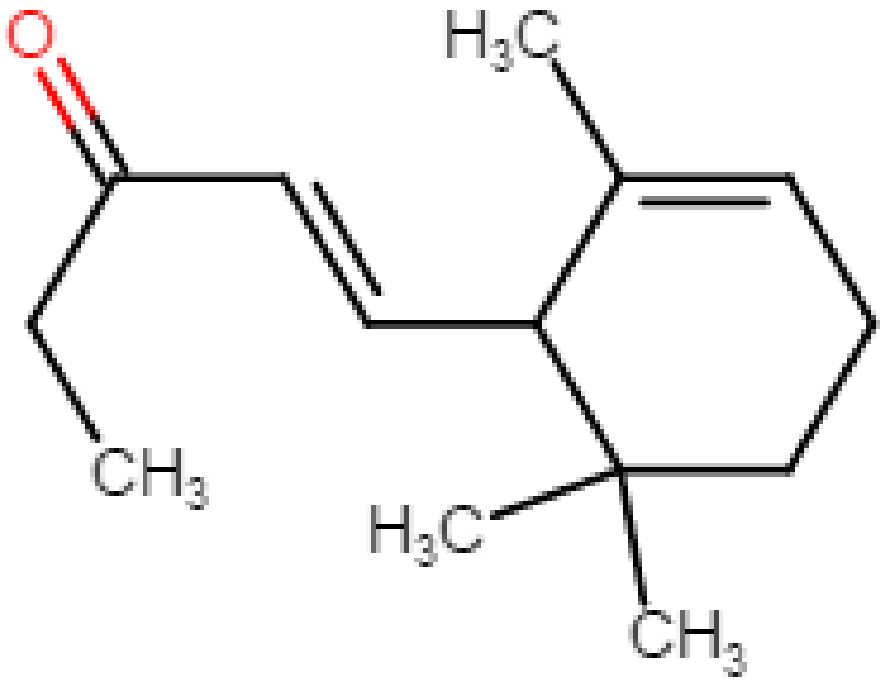
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	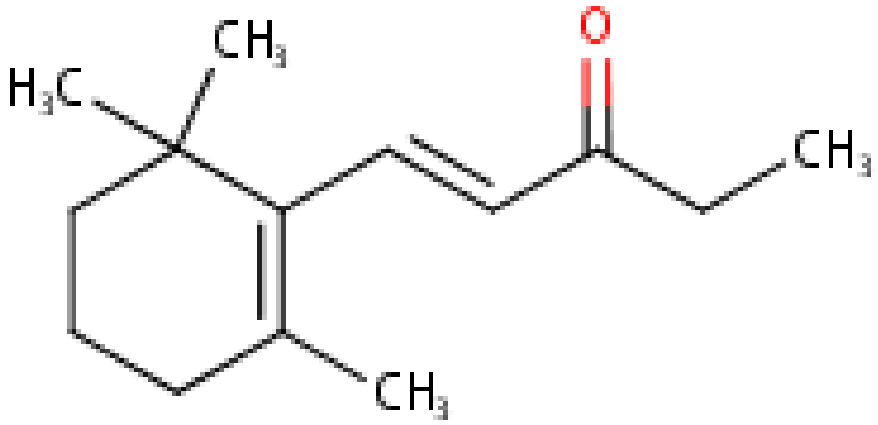
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Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (E)-** alpha-cyclocitrylidenacetone alpha-ionone alpha-irisone E-alpha ionone
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	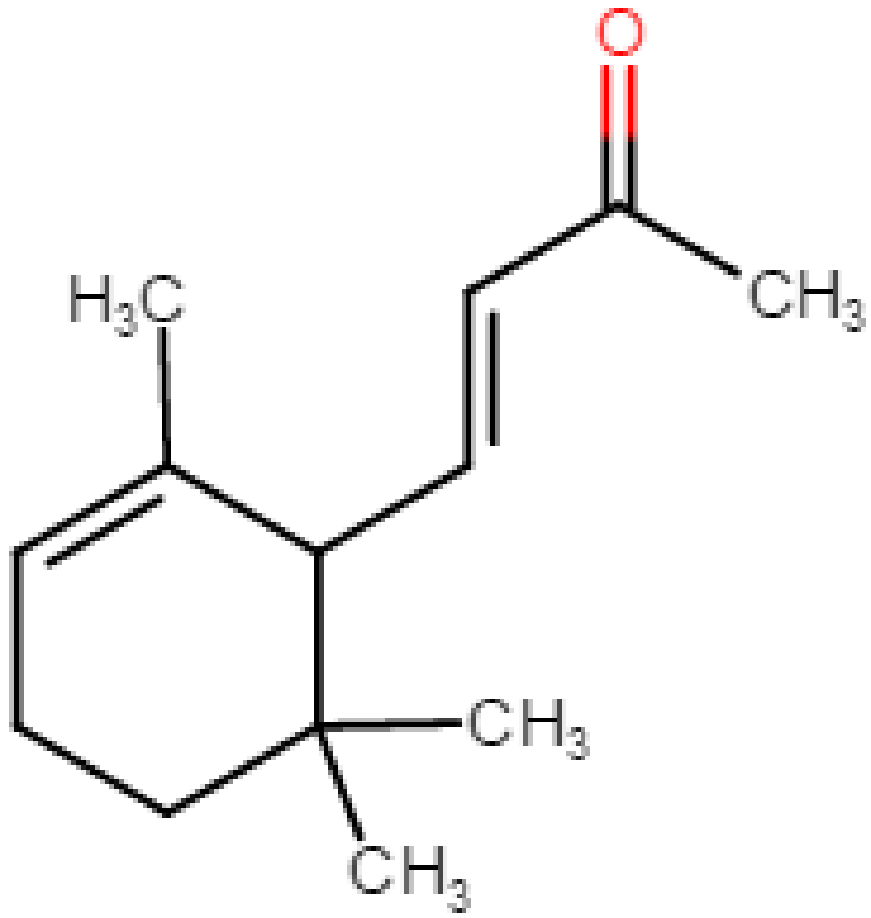
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Chemical Name in the Inventory and Synonyms	**1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, [R-(E)]-** alpha-methyl ionone methyl-alpha ionone
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	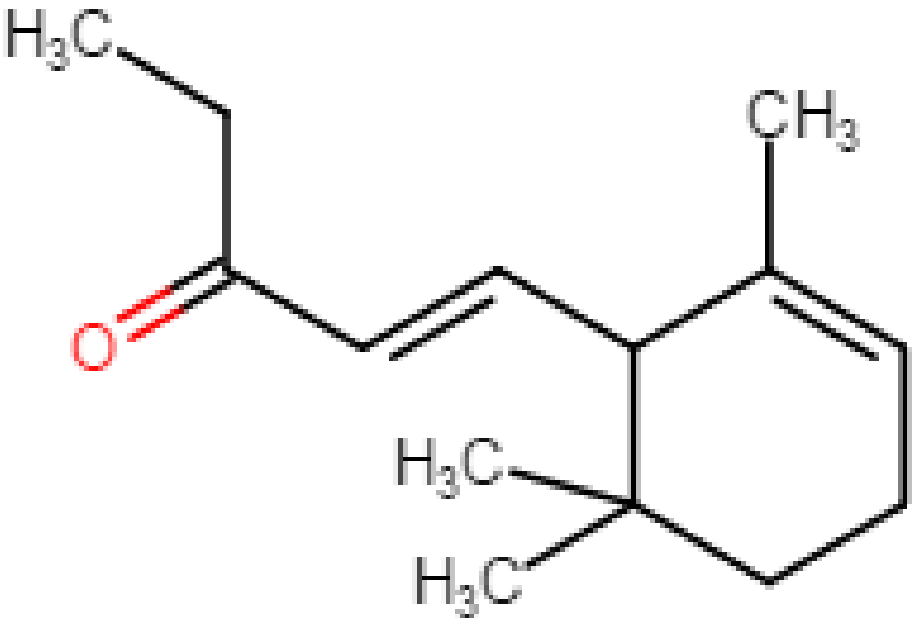
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Chemical Name in the Inventory and Synonyms	**1-Penten-3-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-** beta-iraldeine 5-(2,6,6-trimethyl-1-cyclohexenyl)-4-penten-3-one
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	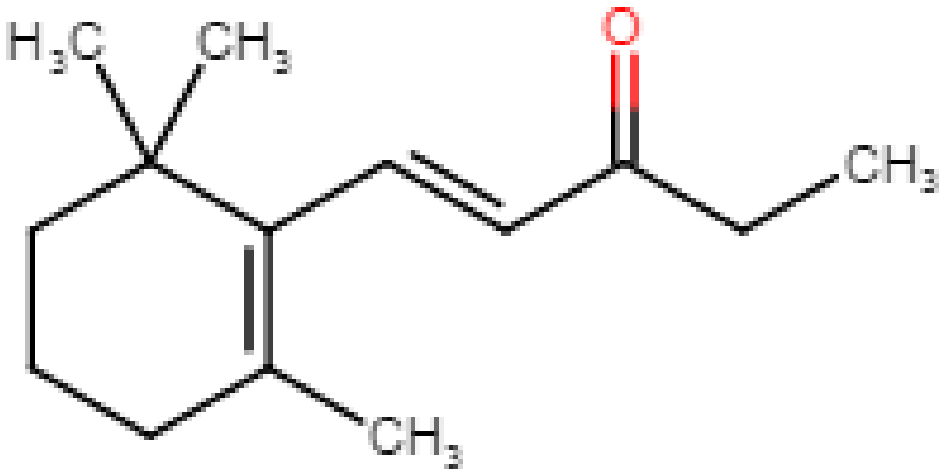
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	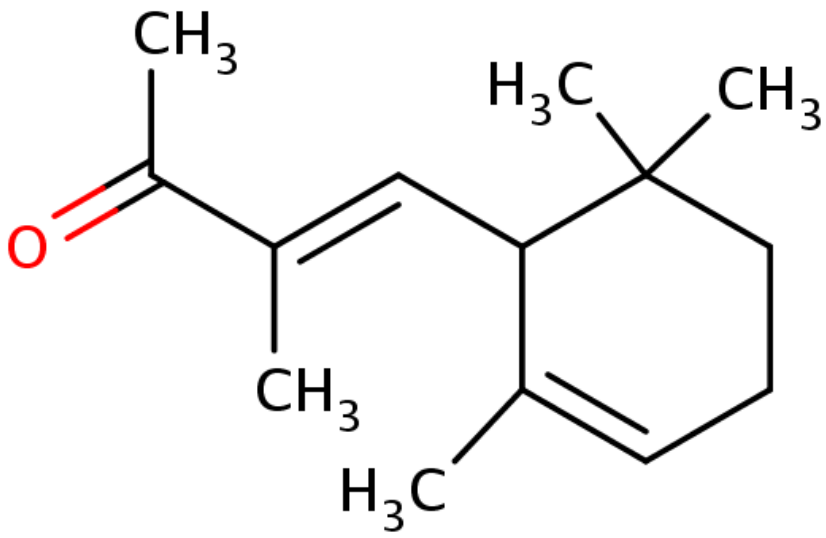
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	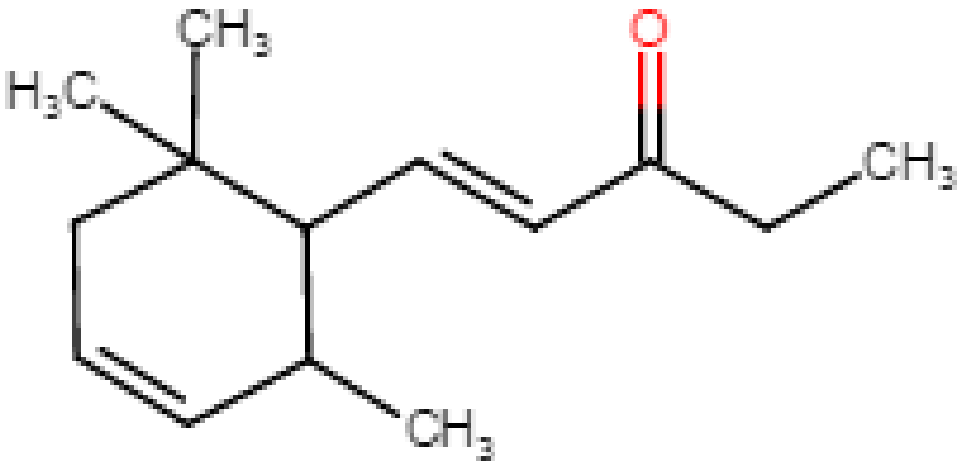
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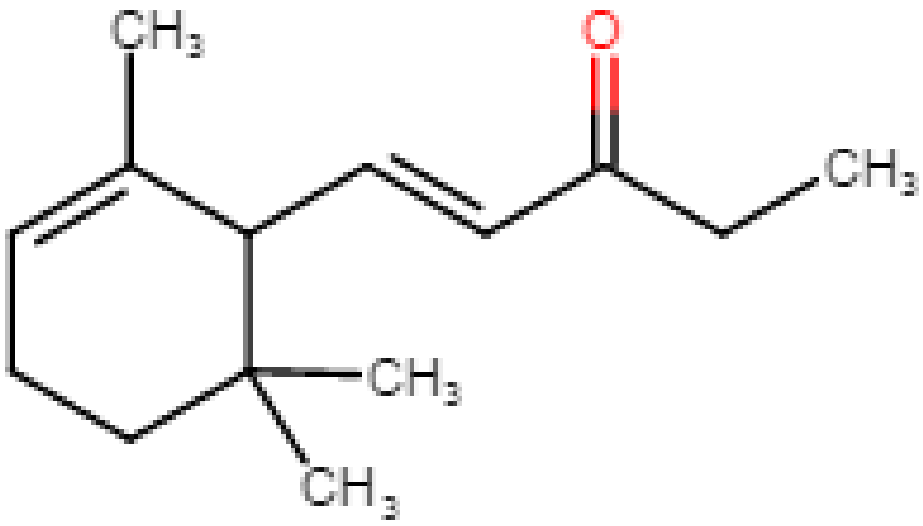
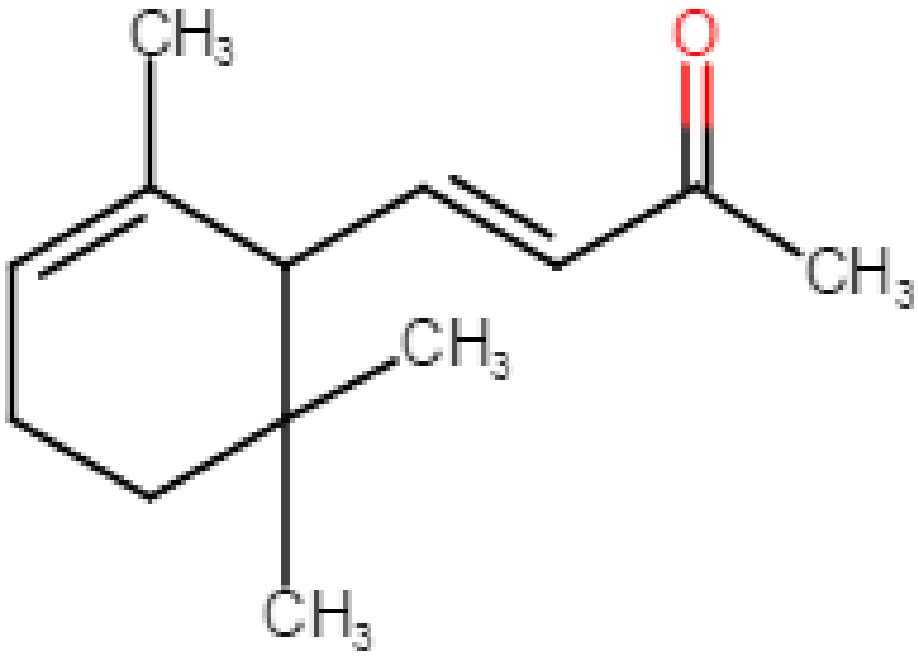
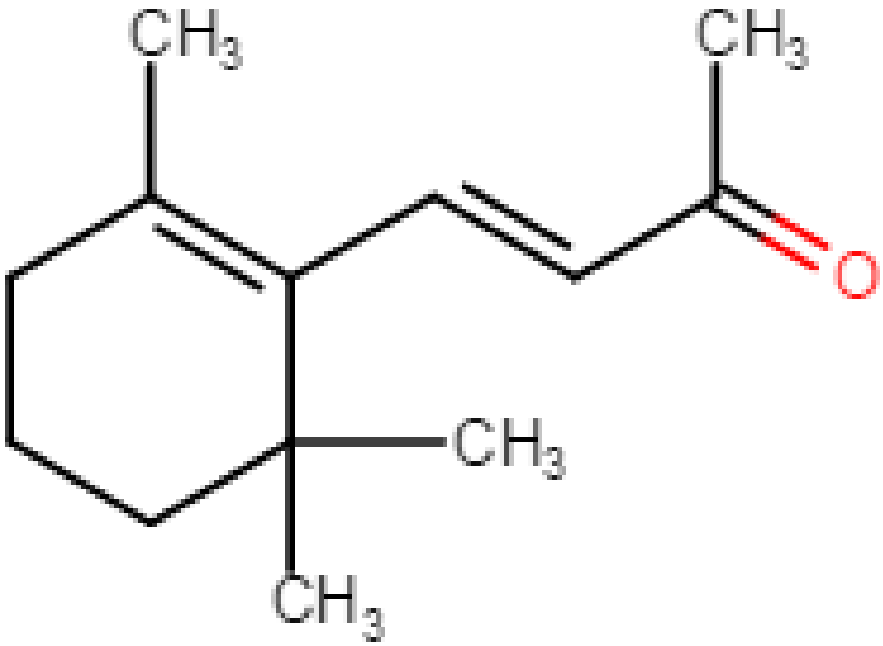
Chemical Name in the Inventory and Synonyms	**1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-** methyl ionone 1-trimethyl-2-cyclohexenyl-1-penten-3-one
CAS Number	7779-30-8
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

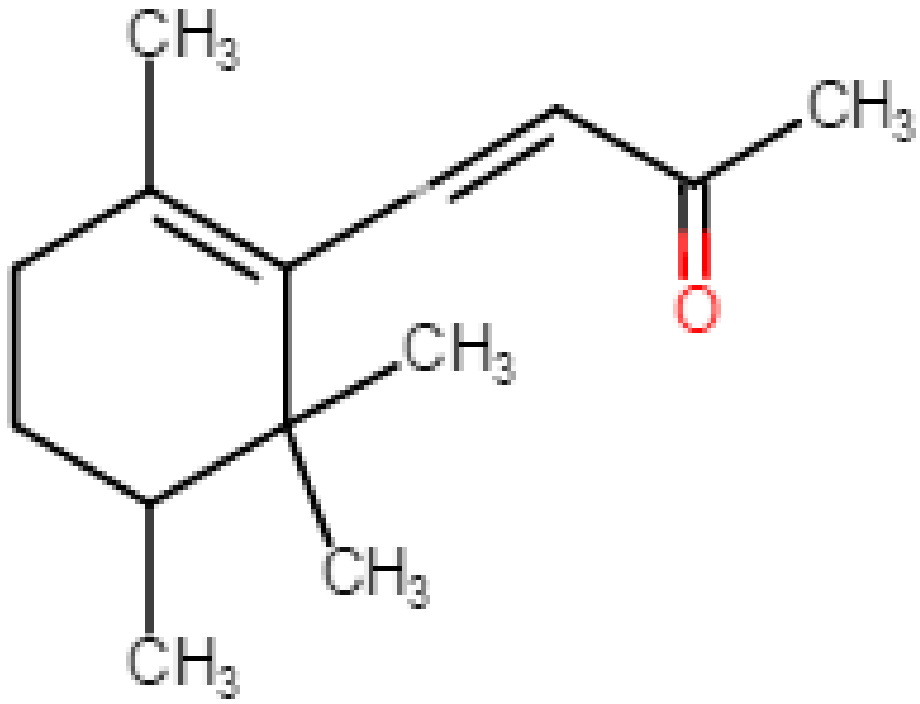
Chemical Name in the Inventory and Synonyms	**Ionone** irisone ionone (mixed isomers) alpha- and beta-ionone
CAS Number	8013-90-9
Structural Formula	

	
Molecular Formula	C13H20O
Molecular Weight	192.3

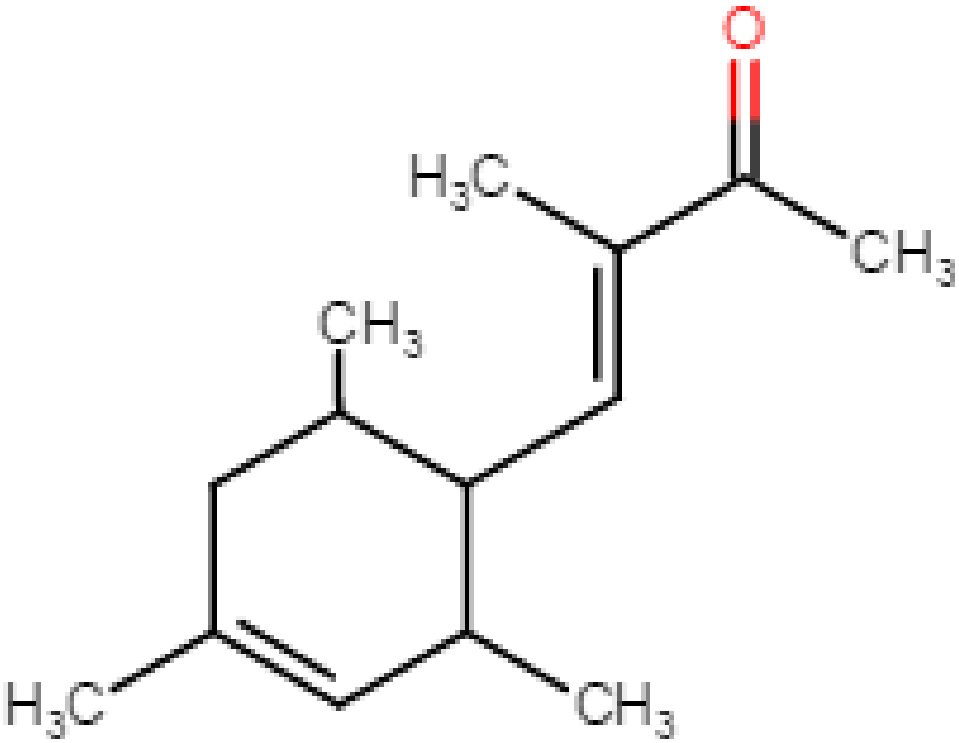
Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-** beta-ionone 4-(2,6,6-trimethyl-1-cyclohexenyl)-3-buten-2-one
CAS Number	14901-07-6
Structural Formula	

	
Molecular Formula	C13H20O
Molecular Weight	192.3

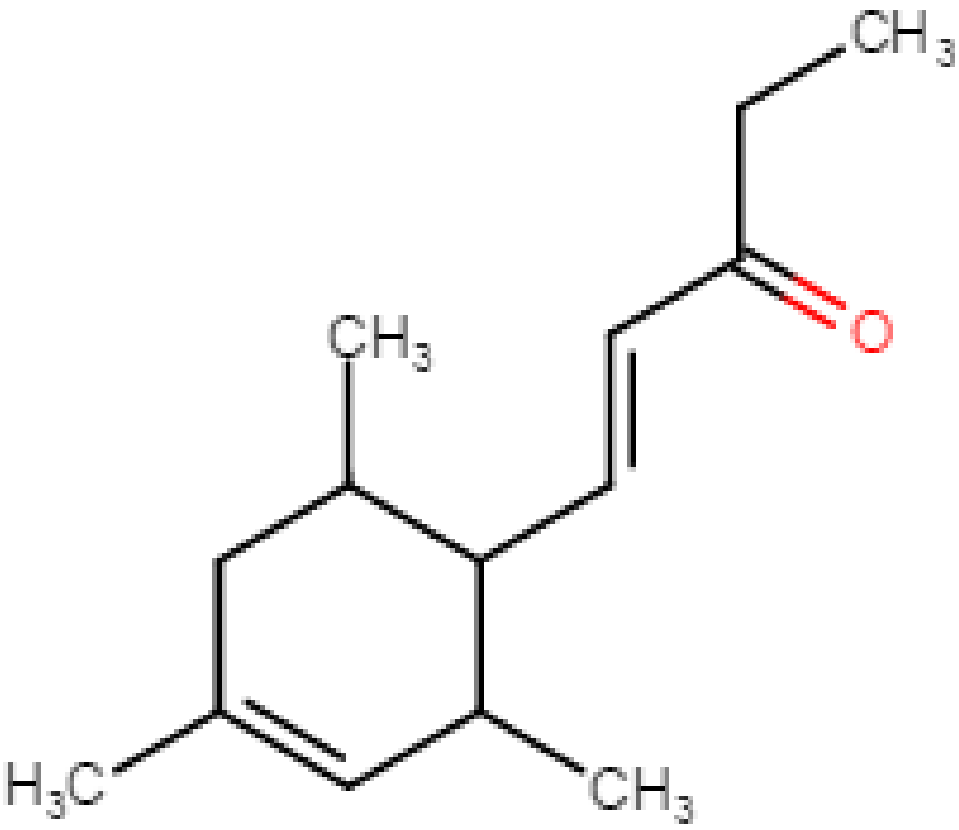
Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-[2,5,6,6-tetramethyl-1(or 2)-cyclohexen-1-yl]-** irone
CAS Number	54992-91-5
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

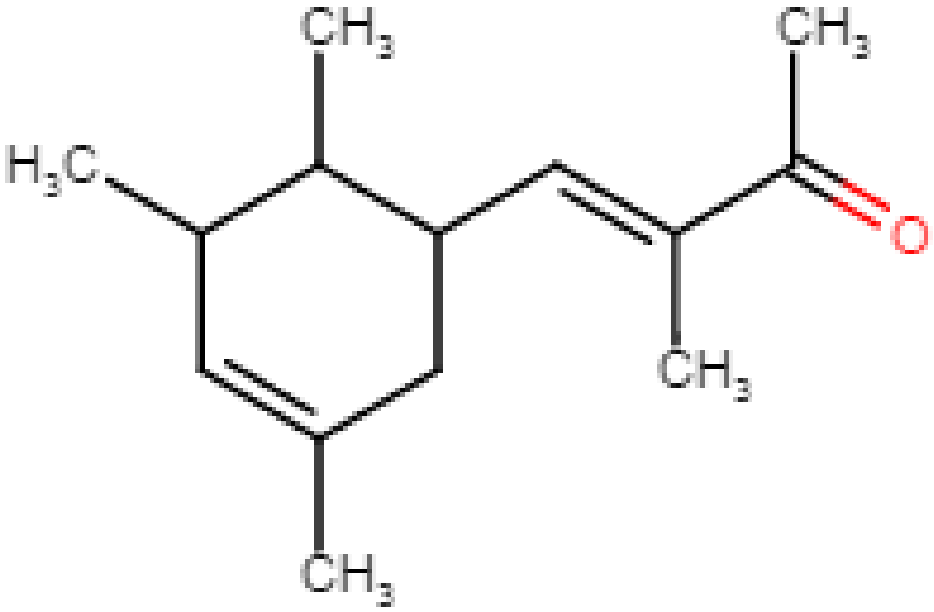
Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 3-methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-** 3-methyl-4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one
CAS Number	67801-29-0
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

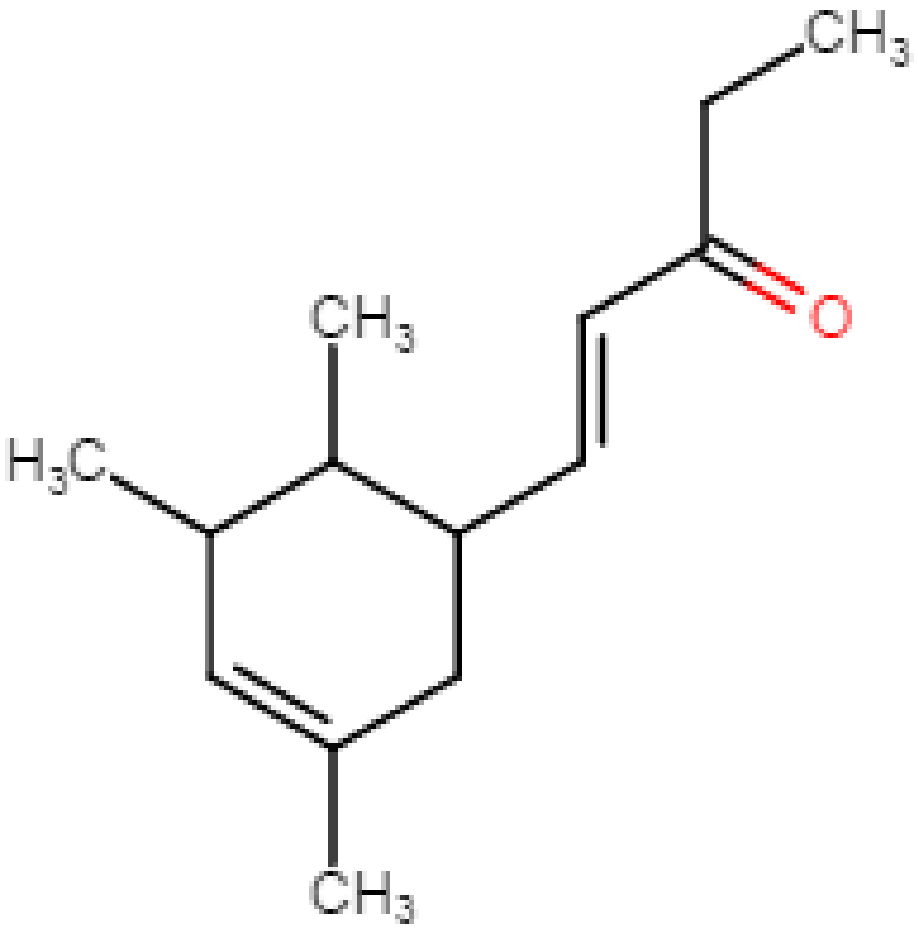
Chemical Name in the Inventory and Synonyms	**4-Penten-3-one, 5-(2,4,6-trimethyl-3-cyclohexen-1-yl)-** 1-(2,4,6-trimethyl-3-cyclohexen-1-yl)-1-penten-3-one
CAS Number	67801-30-3
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

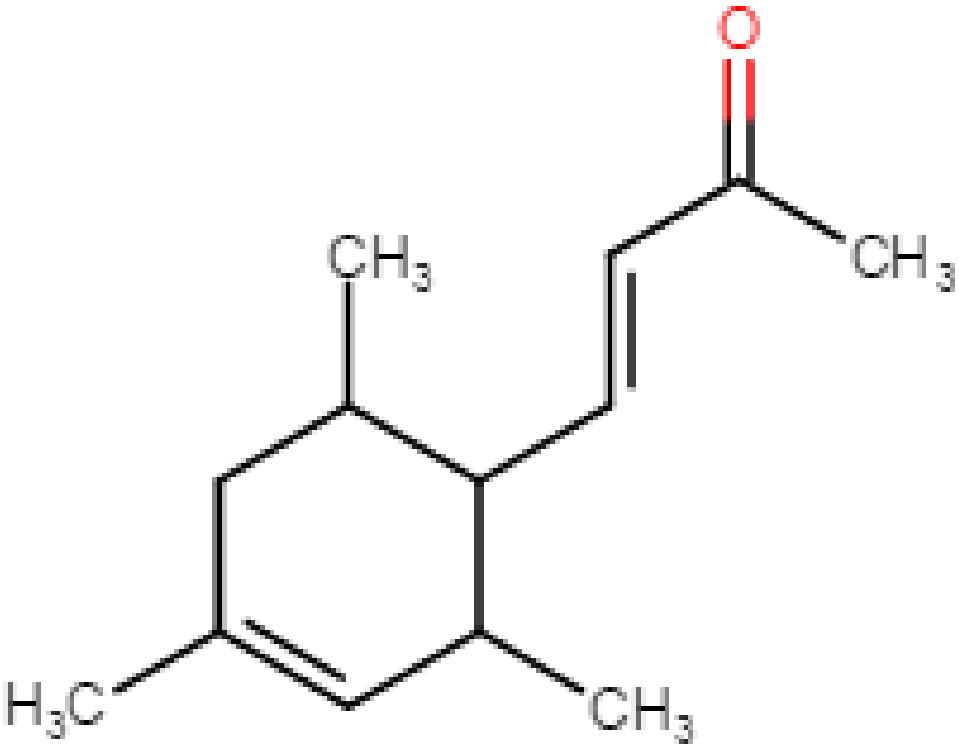
Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 3-methyl-4-(3,5,6-trimethyl-3-cyclohexen-1-yl)-** 3-methyl-4-(2,3,5-trimethyl-4-cyclohexen-1-yl)-3-buten-2-one
CAS Number	67801-31-4
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

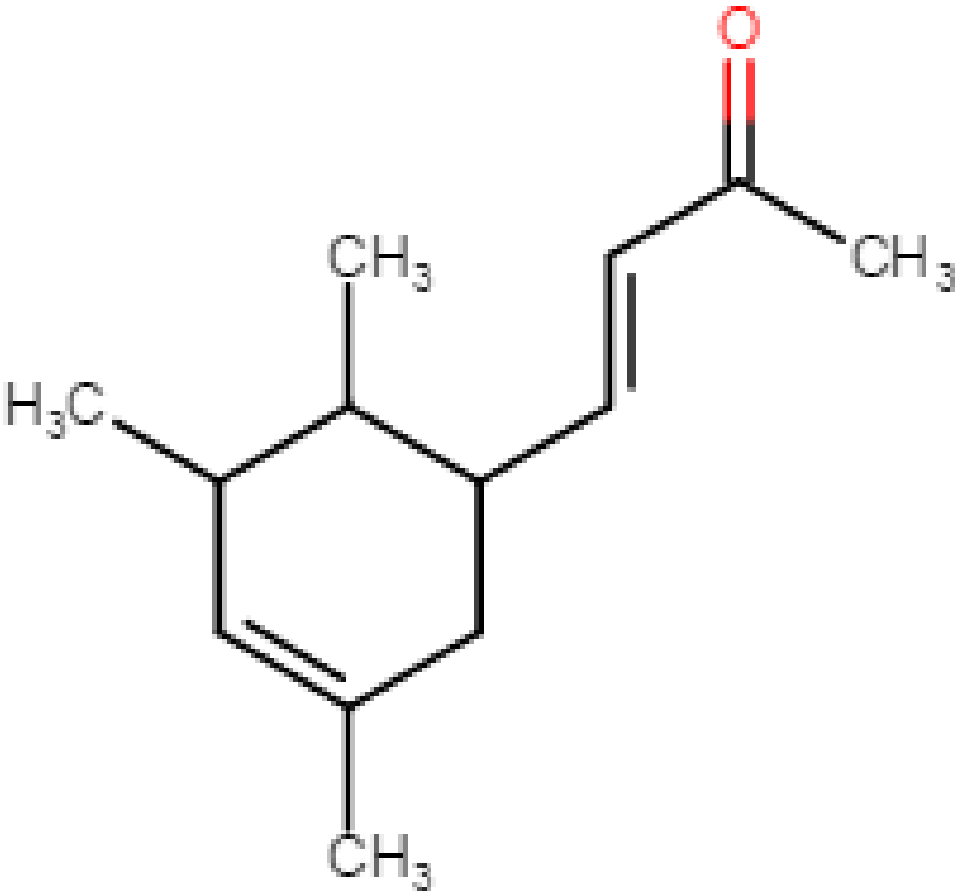
Chemical Name in the Inventory and Synonyms	**4-Penten-3-one, 5-(3,5,6-trimethyl-3-cyclohexen-1-yl)-** 1-(3,5,6-trimethyl-3-cyclohexen-1-yl)-1-penten-3-one
CAS Number	67801-32-5
Structural Formula	

	
Molecular Formula	C14H22O
Molecular Weight	206.3

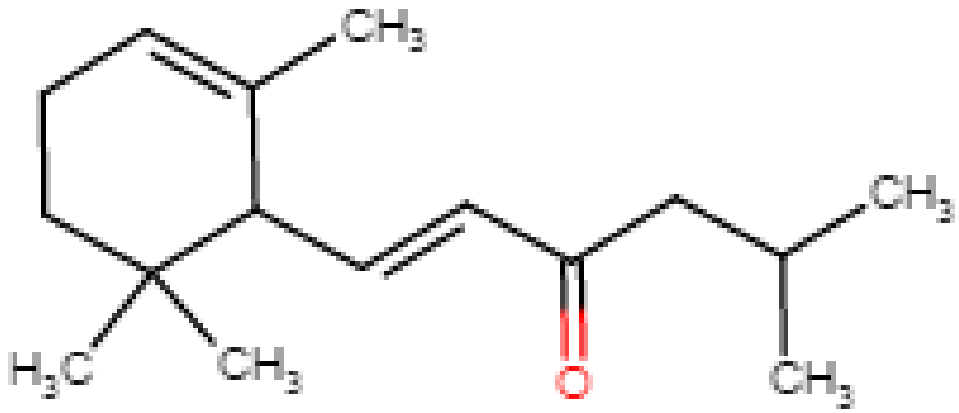
Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-** 4-(2,4,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one iritone
CAS Number	67801-38-1
Structural Formula	

	
Molecular Formula	C13H20O
Molecular Weight	192.3

Chemical Name in the Inventory and Synonyms	**3-Buten-2-one, 4-(3,5,6-trimethyl-3-cyclohexen-1-yl)-** 4-(3,5,6-trimethyl-3-cyclohexen-1-yl)-3-buten-2-one
CAS Number	67801-39-2
Structural Formula	

	
Molecular Formula	C13H20O
Molecular Weight	192.3

Chemical Name in the Inventory and Synonyms	**1-Hexen-3-one, 5-methyl-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-** 6-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-methyl-5-hexen-4-one
CAS Number	70092-23-8
Structural Formula	

	
Molecular Formula	C16H26O
Molecular Weight	234.4

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