Damascones: Human health tier II assessment

02 March 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
2-Buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-	23696-85-7
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (E)-	23726-91-2
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (Z)-	23726-92-3
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (Z)-	23726-94-5
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (E)-	24720-09-0
2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-	33673-71-1
2-Buten-1-one, 1-(2,2-dimethyl-6-methylenecyclohexyl)-	35087-49-1
2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-, (E)-	39872-57-6

Chemical Name in the Inventory	CAS Number
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-	43052-87-5
2-Buten-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-	57378-68-4
2-Buten-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-, [1.alpha.(E),2.beta.]-	71048-82-3

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of chemicals are the damascones, which are fragrance chemicals with similar chemical structures. The structural features common to the group consist of a cyclohexene or cyclohexadiene ring, with a pendant 1,3-butenone side chain and a dimethyl functionality. 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). All of the chemicals in the group have the same molecular weight, with the exception of damascenone (2-buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-; CAS No. 23696-85-7), which has an extra carbon-carbon double bond.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information for the chemicals has been identified.

Online database searches have indicated that several of the chemicals (identified by the CAS Nos. 23726-91-2, 24720-09-0 and 57378-68-4) are available for wholesale supply as raw fragrance or flavouring ingredients.

The chemical alpha-damascone (2-buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-; CAS No. 43052-87-5) 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; 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 Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat) database; the US EPA Aggregated Computer Toxicology Resource (ACToR); and various international assessments (EFSA, 2016; SCCS, 2012; SCENIHR, 2016).

All chemicals in this group have reported cosmetic uses as fragrance compounds in perfumes, soaps and other personal care products.

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

- air care products such as masking agents, air fresheners and candles (chemicals identified by the CAS Nos. 57378-68-4, 43052-87-5, 24720-09-0, 23726-94-5, 23726-92-3, 23696-85-7, 71048-82-3 and 23726-91-2);
- cleaning and washing agents (chemicals identified by the CAS Nos. 57378-68-4, 43052-87-5, 24720-09-0, 23726-94-5, 23726-92-3, 23726-91-2, 23696-85-7 and 71048-82-3);
- polishes and wax blends (chemicals identified by the CAS Nos. 24720-09-0, 23726-91-2 and 71048-82-3);
- paints, lacquers and varnishes (chemicals identified by the CAS Nos. 39872-57-6 and 23726-91-2); and
- absorbents and adsorbents (chemical identified by the CAS No. 57378-68-4).

Some of the chemicals have reported site-limited uses as intermediates in manufacturing (chemicals identified by the CAS Nos. 57378-68-4, 43052-87-5, 24720-09-0, 23726-92-3 and 23696-85-7).

The chemical damascenone (identified by the CAS No. 23696-85-7) has a reported use as flavouring in tobacco products.

The chemicals have reported non-industrial uses as flavouring or fragrance ingredients, including in:

- food and beverages (chemicals identified by the CAS Nos. 71048-82-3, 57378-68-4, 43052-87-5, 35087-49-1, 24720-09-0, 23726-94-5, 23726-92-3, 23726-91-2 and 23696-85-7);
- animal feed (chemicals identified by the CAS Nos. 23696-85-7, 23726-91-2 and 23726-92-3); and
- pesticides and biocides (chemicals identified by the CAS Nos. 23696-85-7, 24720-09-0 and 71048-82-3).

Restrictions

Australian

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

The α-damascone isomers (CAS Nos. 23726-94-5, 24720-09-0 and 43052-87-5) have restrictions for their non-industrial use as excipients in medicines (TGA, 2017) at certain concentrations depending on their use as a flavour or a fragrance:

- 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 %.

International

The chemicals are 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 (all chemicals except CAS No. 35087-49-1). These chemicals may be used in cosmetics and personal care products at a maximum concentration of 0.02 %, individually or in combination. The restriction is based on test data showing sensitising potential for the chemicals and evidence of cross-reactivity (CosIng); and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products may contain with restrictions (all chemicals except CAS Nos. 35087-49-1 and 43052-87-5). These chemicals may be used in oral products at a maximum authorised concentration in the finished cosmetic product of 0.02 %. The sum of those substances used in combination should not exceed the authorised concentration.

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 100 µg/cm^2 for the rose ketones (IFRA, 2009).

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

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

Health Hazard Information

These chemicals, α-damascones, β-damascones and damascenone, are found naturally as flavours and fragrance chemicals in substances such as tea, tobacco, wine and rose oils/extracts. The chemical δ-damascone is synthetically produced for use as fragrances. The chemical structures of all damascones and damascenone all 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 the structurally similar chemicals called the ionones. The ionones possess an α,β-unsaturated ketone side chain bonded to the cyclohexene core, but with the relative positions of the carbon-carbon double bond and the keto group reversed compared with damascones.

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

Toxicokinetics

Absorption

The damascones 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. Systemic availability through dermal absorption is expected to be low, based on results obtained for the structurally-similar compound, methyl ionone. In an in vitro dermal penetration/permeability study using rat and pig skin, 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).

Distribution

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 ring methyl groups;
- reduction of the exocyclic double bond in γ-damascone;
- 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 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).

Excretion

No excretion data is available for the damascones. 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 unconjugated forms. Only a small amount (~1 % of applied dose) 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 animal test results for several chemicals within the group, the chemicals are expected to have low to moderate acute toxicity following oral exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bodyweight (bw) for damascenone, trans-β-damascone and γ-damascone. The LD50 in rats for α-damascone (isomer unspecified) is 1670 mg/kg bw, and the LD50 for δ-damascone (isomer unspecified) in mice is 1821 mg/kg bw. Sub-lethal effects were not reported (Belsito et al., 2007). Hazard classification is warranted for α-damascone, δ-damascone and their geometric isomers (chemicals identified by the CAS Nos. 23726-94-5, 24720-09-0, 43052-87-5, 57378-68-4, and 71048-82-3) (see **Recommendation** section).

Dermal

The chemicals are expected to have low acute toxicity based on results from animal tests following dermal exposure. The LD50s of damascenone, α-damascone, γ-damascone and trans-β-damascone in rabbits and rats are >2000 mg/kg bw. Details on sub-lethal effects are not available (Belsito et al., 2007).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the results from animal studies for several chemicals in the group, the damascones are not expected to cause skin irritation at the concentrations used in consumer products. Hazard classification is not warranted.

These chemicals, cis-β-damascone and α-damascone, produced irritation in guinea pigs at 1.5 % and 1.8 % in ethanol, respectively, when tested as part of a delayed contact hypersensitivity study. The chemical γ-damascone produced irritation reactions in guinea pigs at 20 and 50 % when tested prior to a Buehler sensitisation study. No other irritation reactions were observed with these chemicals when tested using vehicles other than ethanol, or with other damascones when tested at concentrations ranging from 0.0025–50 % (Belsito et al., 2007).

Eye Irritation

Several of the damascones tested (damascenone, α-isodamascone, isodamascone, cis-β-damascone and α-damascone) have shown no evidence of eye irritation at concentrations of 0.5–100 % (Belsito et al., 2007).

Observation in humans

Mild to moderate cumulative skin irritation was observed in human studies with cis-β-damascone at concentrations as low as 0.05 %, α-isodamascone at 2 % and α-damascone at 0.1 % (vehicle not specified). No other irritation reactions were observed with these chemicals when tested using other vehicles, or with other damascones when tested at concentrations ranging from 0.05–3 % (Belsito et al., 2007).

Sensitisation

Skin Sensitisation

The chemicals are considered to be moderate to strong skin sensitisers based on the positive results seen in several local lymph node assays (LLNA) for five chemicals in the group (damascenone, α-damascone, δ-damascone, γ-damascone and trans-β-damascone). The EC3 values (concentration required to produce a three-fold increase in lymphocyte proliferation compared with controls) for the chemicals were reported to be in the range of 0.9–9.6 %. The effects observed in human patch test studies also indicate that several damascones have the potential to cause skin sensitisation (see **Observation in humans** section), warranting hazard classification (see **Recommendation** section).

Damascenone (10 % in propylene glycol) was negative in a Buehler test carried out with 11 male Hartley guinea pigs. In a maximisation test carried out on 10 Hartley-Dunkin guinea pigs (sex not specified) at concentrations of 0, 0.25, 0.5, 1.5 and 3 % in distilled water, reactions were seen in 0, 1/10, 1/10, 1/10 and 2/10 animals per dose, respectively. In two separate LLNAs in CBA/J Hsd female mice, with the chemical at concentrations of 0, 0.25, 0.5, 1.0, 2.5 and 5.0 % in 4:1 acetone/olive oil, EC3 values of 1.22 % and 1.24 % were produced, indicating moderate potential for sensitisation (Belsito et al., 2007).

In two separate LLNAs with δ-damascone at concentrations of 0, 0.25, 0.5, 1.0, 2.5 and 5.0 % in 4:1 acetone/olive oil, EC3 values of 0.9 % and 5.19 % were found. In an additional LLNA carried out using CBA/J female mice (five/dose) at concentrations of 0, 7.5, 15 or 30 % in 3:1 ethanol/diethyl phthalate, an EC3 value of 9.6 % was obtained (Lalko et al., 2007). These studies indicate a weak-to-strong sensitisation potential for the chemical depending on the vehicle.

Sensitisation was also evaluated in several LLNAs conducted using α-damascone, γ-damascone and trans-β-damascone at concentrations of 0, 0.25, 0.5, 1, 2.5 and 5 % in 4:1 acetone/olive oil. Moderate sensitisation potential was observed, with EC3 values of 3.3, 4.6 and 2.4 calculated for α-damascone, γ-damascone and trans-β-damascone, respectively (Belsito et al., 2007).

The chemicals damascenone, trans-β-damascone, cis-β-damascone and α-damascone are reported to induce sensitisation reactions at concentrations of 0.5–10 % using several different guinea pig sensitisation test methods (maximisation, Buehler and delayed hypersensitivity tests). No sensitisation was observed in a maximisation test with isodamascone at a concentration of 50 % in peanut oil (Belsito et al., 2007).

Observation in humans

Several of the damascones are well known contact allergens (SCCS, 2012), which has contributed to the restriction of the chemicals to maximum combined concentrations of 0.02 % in cosmetic products in a number of countries (see **Restrictions: International** section). This is supported by the relatively high number of positive responses in human repeated insult patch tests (HRIPT) mostly conducted in the late 1970's in relation to the estimated low exposure to the chemicals from cosmetic and domestic products.

Seven damascone isomers have been tested in two maximisation tests, and 18 earlier HRIPT studies in 992 volunteers. Sensitisation reactions were observed when damascone, trans-β-damascone, α-isodamascone, cis-β-damascone, α-damascone, isodamascone and γ-damascone were evaluated at concentrations ranging from 0.5 % to 10 % in a number of vehicles (not specified in the tests). No effects were observed at concentrations of 0.2 % or lower (Belsito et al., 2007).

Cross-sensitisation reactions were also observed in human subjects who were induced with 1 % γ-damascone, then challenged with 0.1 % α-damascone or cis-β-damascone (Belsito et al., 2007).

Repeated Dose Toxicity

Oral

The chemicals are not expected to pose serious damage to health from repeated oral exposure.

A 13-week study using trans-β-damascone demonstrated a low order of toxicity, suggesting that the chemicals are not expected to cause adverse effects at low doses. In addition, several of the damascones are present at low levels in many common foods and beverages for human consumption. This points to a low level of concern regarding the potential of the damascones for long-term toxicity via the oral route. This is supported by the low order of toxicity demonstrated in subchronic oral toxicity studies for the structurally-similar chemicals, α-ionone and β-ionone.

In a 13-week study, trans-β-damascone was administered in feed to Wistar CF/Gif rats (16/sex/dose) at 0 and ~2.3 mg/kg bw/day (dose calculated to represent likely daily intake for human consumption). No adverse toxic effects were observed. Non-specific inflammatory changes were seen in the livers and kidneys of a few animals; however, these changes were not considered to be treatment-related (Belsito et al., 2007; WHO, 1999).

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 subchronic 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).

Dermal

No data are available. Based on their expected low dermal absorption (see **Toxicokinetics** section), the chemicals are not likely to be toxic through repeated dermal exposure at the concentrations expected in consumer products.

Inhalation

No data are available.

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 after receiving equivocal in vitro data from industry submissions that α-damascone and four structurally-related substances (cis- and trans-α-damascone, α-damascenone and δ-damascone) could not be ruled out as having genotoxic potential, requiring additional genotoxicity data (EFSA, 2015). The EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that β-damascone was safe for use in tobacco products if it did not contain traces of α-damascone and δ-damascone (SCENIHR, 2016).

In vitro

In the bacterial reverse mutation test, damascenone, α-damascone, δ-damascone (CAS No. 57378-68-4) and γ-damascone did not show any mutagenic activity in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 or *Escherichia coli* WP2uvrA, with or without metabolic activation (Belsito et al., 2007; EFSA, 2015; EFSA, 2016). The chemical cis-β-Damascone did not induce mutations in five strains of *S. typhimurium* (strains and doses unspecified) (SCENIHR, 2016).

Micronucleus experiments performed in human peripheral blood lymphocytes to detect induction of chromosomal damage or aneuploidy were carried out using α-damascone, with or without metabolic activation. The chemical gave equivocal results, with weak induction of micronuclei observed at cytotoxic concentrations of the chemical (EFSA, 2015).

In an in vitro micronucleus assay in human peripheral blood lymphocytes, cis-β-damascone was found to induce chromosomal damage with metabolic activation, while equivocal results were obtained for the chemical without metabolic activation. No further study details were reported (SCENIHR, 2016).

In vivo

A combined in vivo micronucleus assay/liver comet assay was carried out following oral administration of cis-β-damascone to rats (species unspecified). The chemical did not induce micronucleated erythrocytes in harvested rat bone marrow or evidence of genotoxicity in the liver or duodenum. No further study details were provided (SCENIHR, 2016).

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 damascones 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 indicate that the chemicals are not likely to be genotoxic at the low concentrations of the chemicals expected in consumer products.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemicals in this group. Based on the available genotoxicity data (see **Genotoxicity** section) and a negative tumour promotion study for a structurally similar compound, the chemicals do not have the potential to be carcinogenic. Any potentially reactive metabolites that may arise from epoxidation or Michael addition of damascones 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.

In a dermal tumour promotion study, ICR Swiss mice (30) were administered once with 0.125 mg of a tumour-initiating 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

No data are available for the damascones. The chemicals are not expected to cause reproductive or developmental toxicity based on the negative results reported from studies carried out on several ionones.

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 sensitisation for all chemicals. Several of the chemicals may also cause systemic acute effects following oral exposure.

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 (α-damascone, β-damascone, δ-damascone) 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 0.003 % – 0.07 % of the chemicals) (IFRA, 2009).

These conclusions do not apply to the readily available commercial products rose water and rose oils. This will be considered in a further assessment of these commercial products.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) indicated that the use of ionones and related substances such as damascones as flavouring agents would not present a safety concern at the current estimated intake levels (WHO, 1999).

Daily dermal exposure to damascones was calculated using the following assumptions:

- calculated relative daily exposure from a range of personal care products such as those used for bathing/showering, hair care, skin care, make-up, and deodorant is 246.72 mg/kg bw/day (SCCS, 2015);
- maximum concentration of damascones in personal care products is 0.07 % (IFRA, 2009); and
- dermal absorption is 100 %.

Although the assumptions used above were conservative and could be considered worst-case, the calculated dermal exposure still indicate that the levels of damascones that could become systemically-available following dermal application are within the human dietary exposure threshold following oral exposure used by JECFA.

In the absence of further information, daily dermal exposure to the damascones at concentrations consistent with the IFRA Standard concentrations will present no unreasonable risk to the public and are generally regarded as safe.

Occupational Risk Characterisation

During product formulation, oral, 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 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) (refer to **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 damascones becomes available. The assessment of these chemicals will also inform the forthcoming assessments of the more commercially available rose oil and certain extracts of the *Rosa* species.

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 Harmonised 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 acute toxicity classification is recommended for the chemicals identified by the CAS Nos. 23726-94-5, 24720-09-0, 43052-87-5, 57378-68-4, and 71048-82-3. The skin sensitisation classification applies to all the chemicals in this group.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (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

Formulations containing these chemicals should always comply with the relevant IFRA standards.

Control measures to minimise the risk from oral, 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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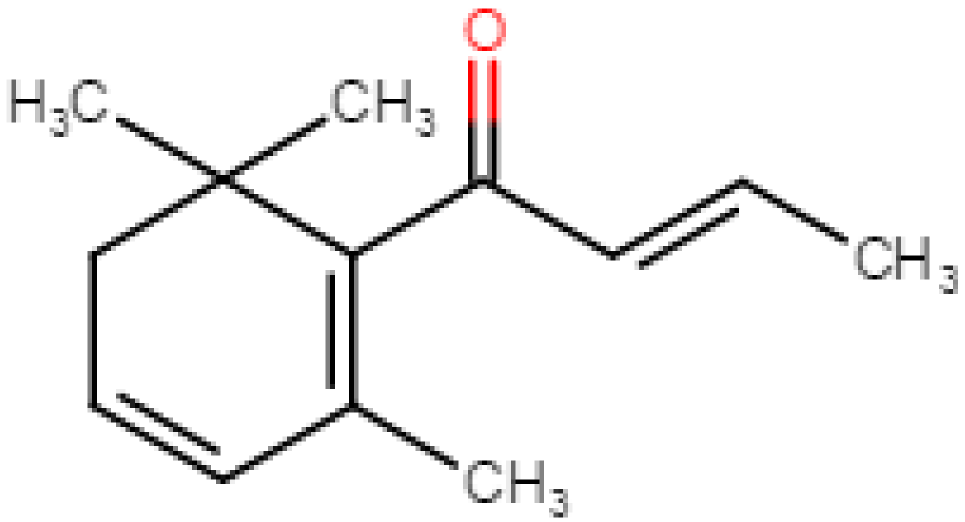
Last Update 02 March 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**2-Buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-** damascenone beta-damascenone rose ketone-4
CAS Number	23696-85-7
Structural Formula	
Molecular Formula	C13H18O
Molecular Weight	190.3

Chemical Name in the Inventory and Synonyms	**2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (E)-** 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-one, (E)- (E)-beta-damascone trans-beta-damascone rose dihydroketone
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	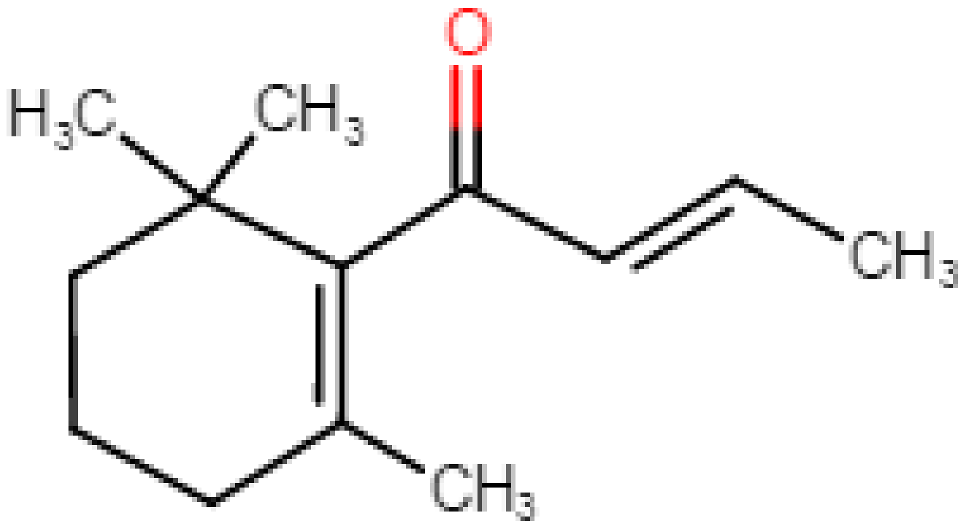
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	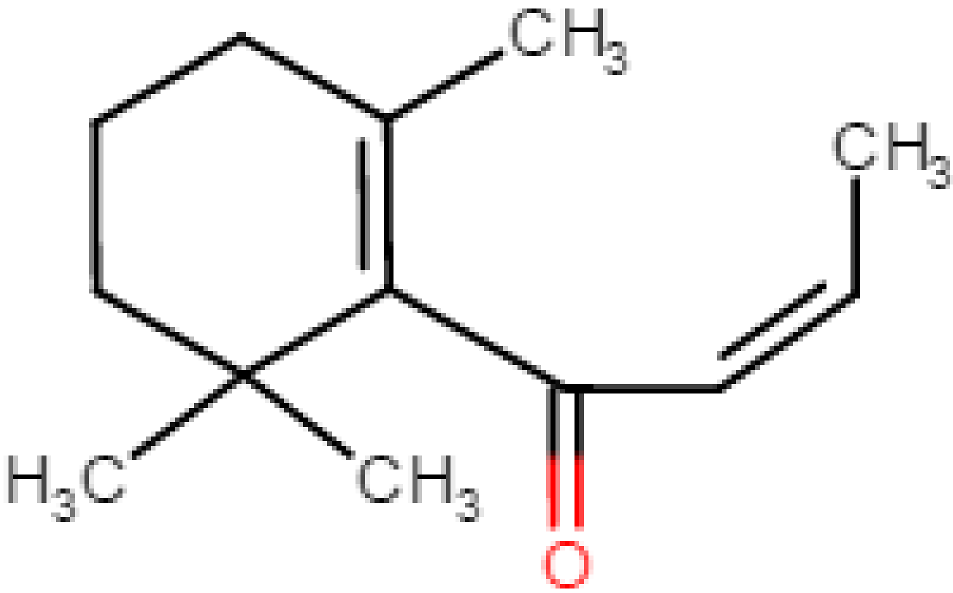
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	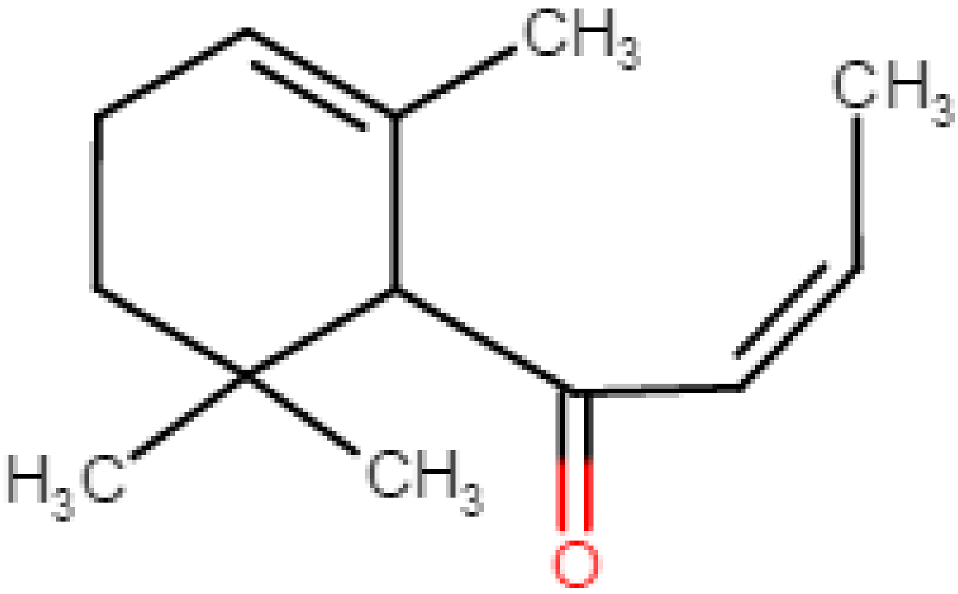
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	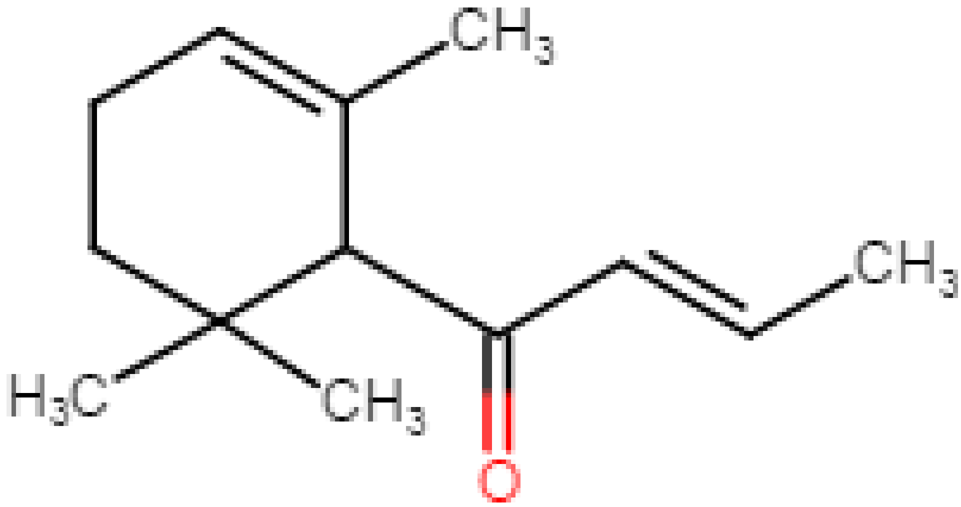
Molecular Formula	C13H20O
Molecular Weight	192.3

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	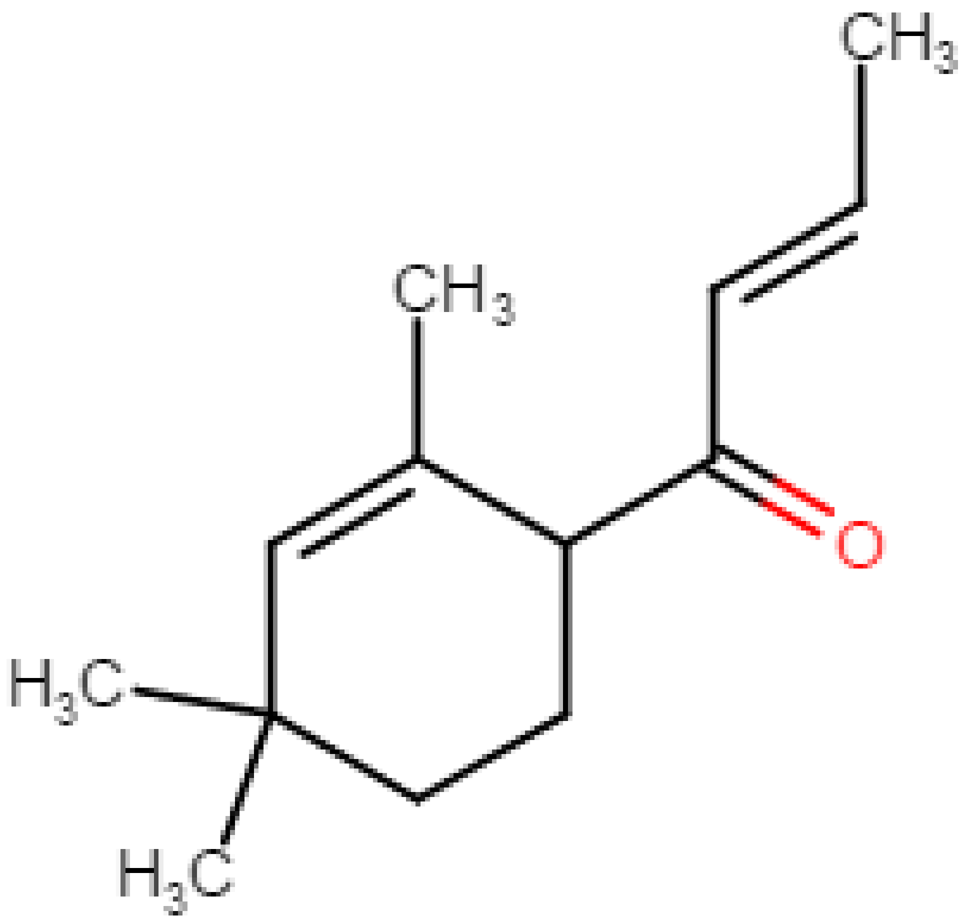
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Molecular Weight	192.3

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	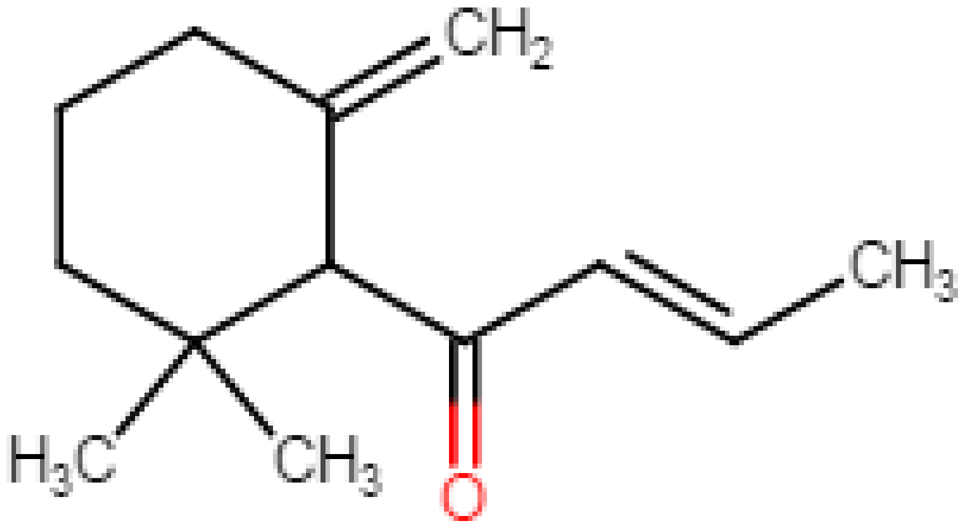
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Molecular Weight	192.3

Chemical Name in the Inventory and Synonyms	**2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-, (E)-** (2,4,4-trimethyl-2-cyclohexenyl)-2-butenone, trans- trans-(2,4,4-trimethyl-2-cyclohexenyl)-2-butenone (E)-1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (E)-isodamascone
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	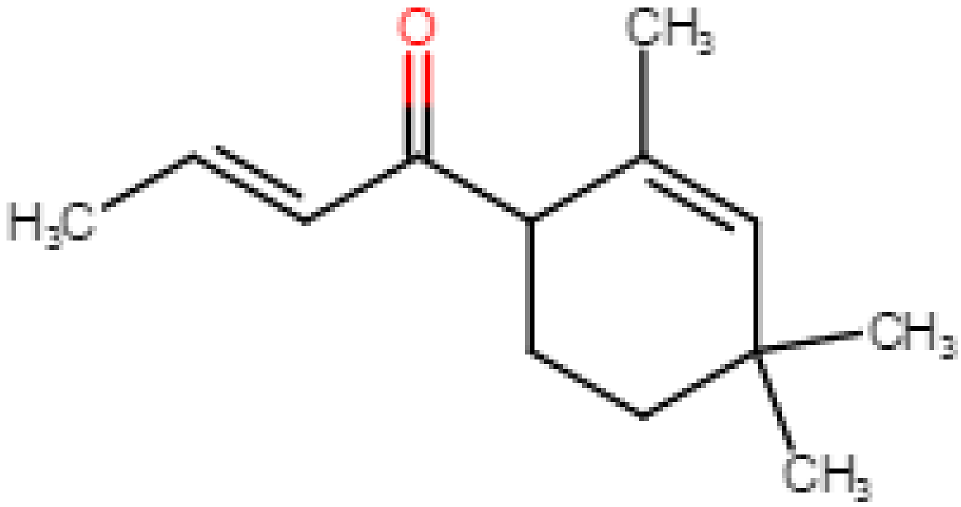
Molecular Formula	C13H20O
Molecular Weight	192.3

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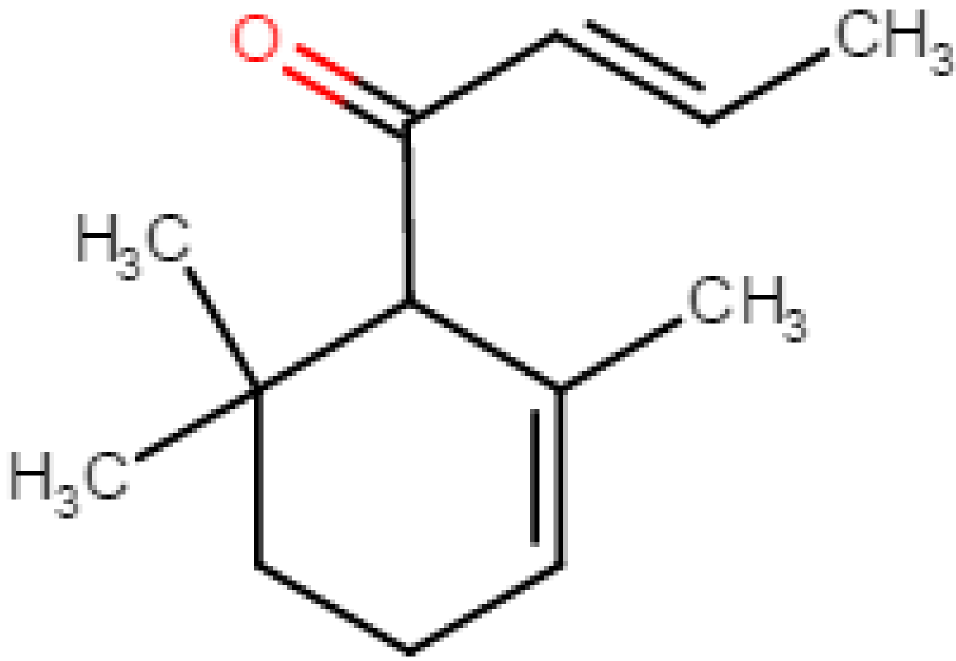
Structural Formula	



Molecular Formula	C13H20O
Molecular Weight	192.3

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	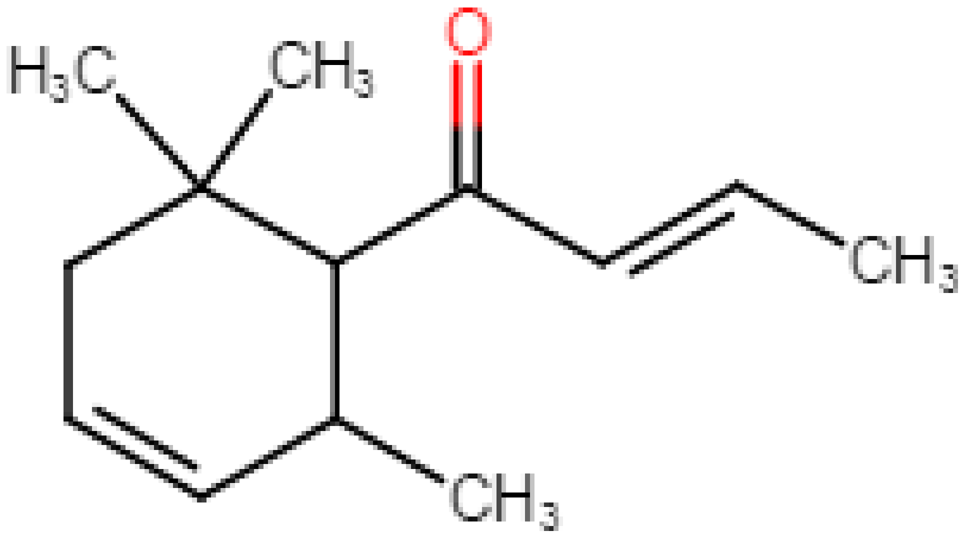
Molecular Formula	C13H20O
Molecular Weight	192.3

Chemical Name in the Inventory and Synonyms	**2-Buten-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-, [1.alpha.(E),2.beta.]-** 1-(2-beta,6,6-trimethyl-3-cyclohexen-1.alpha.-yl)-2-butene-1-one, (E)- (E)-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-butene-1-one (E)-delta-damascone trans,trans-delta-damascone
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	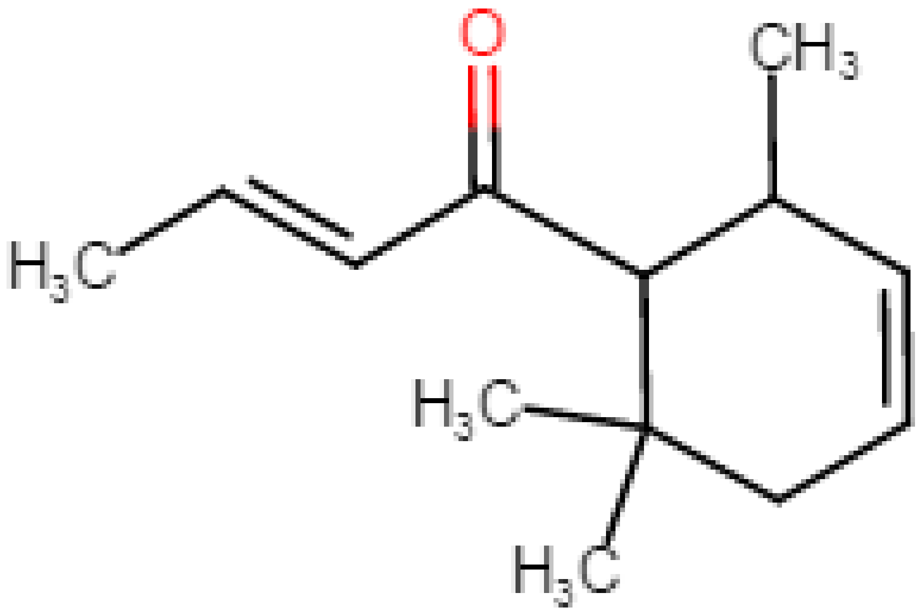
Molecular Formula	C13H20O
Molecular Weight	192.3

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