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RIFM fragrance ingredient safety assessment, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol, CAS Registry Number 65113-99-7

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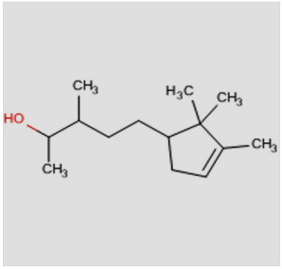


Name: 5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol
CAS Registry Number: 65113-99-7

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Safford et al., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species,

(*continued on next column*)

(*continued*)

most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is not genotoxic. Data on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol a No Expected Sensitization Induction Level (NESIL) of 2700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class II material, and the exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2001a; RIFM, 2010d)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(RIFM, 2010g)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2010g)
Skin Sensitization: NESIL = 2700 μg/cm^2.	RIFM (2002a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1981)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 81% (OECD 301F; 35 days)	RIFM (1995a)
Bioaccumulation: Screening-level: 1160 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day Chronic *Daphnia magna* NOEC (reproduction): 0.31 mg/L	RIFM (2006)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 7-Day Chronic *Daphnia magna* NOEC (reproduction): 0.31 mg/L	RIFM (2006)

RIFM PNEC is: 6.2 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe: <1

1. Identification

1. **Chemical Name:** 5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol
2. **CAS Registry Number:** 65113-99-7
3. **Synonyms:** 3-Cyclopentene-1-butanol, α,β,2,2,3-pentamethyl-; a,b,2,2,3-pentamethylcyclopent-3-ene-1-butanol; Sandalore; Sandal Series G; 3-methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol; 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol
4. **Molecular Formula:** $C_{14}H_{26}O$
5. **Molecular Weight:** 210.36
6. **RIFM Number:** 1311

7. **Stereoisomers:** Isomer not specified. Three chiral centers and a total of 8 enantiomers possible.

2. Physical data

1. **Boiling Point:** 273.81 °C (EPI Suite)
2. **Flash Point:** >100 °C (RIFM Database), >100 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.6 to 4.8 at 25 °C (RIFM, 1996), 5.15 (EPI Suite)
4. **Melting Point**: 47.63 °C (EPI Suite)
5. **Water Solubility:** 5.013 mg/L (EPI Suite)
6. **Specific Gravity:** 0.896–0.904 (RIFM Database)
7. **Vapor Pressure:** 0.000223 mm Hg at 20 °C (EPI Suite v4.0), 0.000443 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless to pale yellow liquid with woody, warm, mild odor

3. Volume of use (Worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.63% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.071 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0049 mg/kg/day (RIFM, 2018)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015; Safford, 2015; Safford, 2017; and Comiskey, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (RIFM, 2015; Safford, 2015; Safford, 2017; and Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 41.1%

RIFM, 1984**:** The dermal penetration of 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol in an *in vitro* system utilizing the excised skin of naked rats and pigs was determined under unoccluded conditions. The test material, dissolved in ethanol at a concentration of 30%, was applied to a skin area of 5 cm^2 at a dose of 6 μL/cm^2 (1800 μg active substance/cm^2). The specific activity used for labeling was 332.42 μCi/mL. Absorption was evaluated at 1, 6, and 16 h after application. Radioactivity was measured in skin washings (residual material), stratum corneum, skin strippings (horny layer), and receptor fluid. The test material penetrated into and through the rat and pig skin. The total skin absorption values were time- and species-dependent. On the naked rat skin, the total absorption values (amount in the horny layer [tape strippings], amount in the remaining skin, and amount in the chamber liquid combined) after 1 and 16 h were 213.6 and 738.5 μg/cm^2, respectively. On pig skin, the total skin absorption values were 52.5 and 59.9 μg/cm^2 after 1 and 16 h of exposure, respectively. This was significantly lower than the rat. It was assumed that approximately 10% of the test material was lost due to evaporation from the rat skin. For the naked rat, after 16 h of exposure, 7.4% of the applied dose was in the horny layer (tape strippings) and 33.1% in the remaining skin tissue layers. The amount of test material found in the chamber liquid was 0.6% of the total applied dose. The residual material on the skin surface was 49.9%. Thus, it was concluded that 41.1% of 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was absorbed by the naked rat skin; the total recovery accounted for 91%. For the pig, after 16 h of exposure, 1.6% of the applied dose was in the horny layer and 1.7% in the remaining skin tissue layers. The amount of test material found in the chamber liquid was negligible. The residual material on the skin surface was 75.6%. Thus, it was concluded that 3.3% of 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was absorbed by pig skin. The total recovery accounted for was 78.9%. It was assumed that approximately 22% of the test material had evaporated from the pig skin. The total skin absorption value for rats was much higher than the pigs, and the percent radioactivity recovery was much higher in the rats (approximately 91%) as compared to the pig (approximately 78%). Thus, the most conservative skin absorption value of 41.1% obtained from the rat skin was used for the safety assessment of 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol.

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1.0	OECD QSAR Toolbox v4.2
II*	II	I

*See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Weight of evidence (WoE): 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is not reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol has been pre-registered for 2010; no dossier available as of 11/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.21
2	Products applied to the axillae	0.062
3	Products applied to the face/body using fingertips	1.2
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.29
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.29
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.29
5D	Baby cream, oil, talc	0.097
6	Products with oral and lip exposure	0.36
7	Products applied to the hair with some hand contact	2.4
8	Products with significant ano-genital exposure (tampon)	0.097
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.3
10A	Household care products with mostly hand contact (hand dishwashing detergent)	8.1
10B	Aerosol air freshener	8.1
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.097
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol, the basis was the reference dose of 3.33 mg/kg/day, a skin absorption value of 41.1%, and a skin sensitization NESIL of 2700 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic potential of 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol was evaluated according to OECD TG 471/GLP using the plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA1535, TA100, TA102, and TA1537 were treated with 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol in dimethyl sulfoxide (DMSO) at doses of 33, 100, 333, 1000, 2500, and 5000 μg/plate for strains TA98 and TA100; at 3, 10, 33, 100, 333, and 1000 μg/plate for strains TA1535 and TA1537; and at 10, 33, 100, 333, 1000, and 2500 μg/plate for strain TA102. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of rat liver S9. It was concluded that 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol was not mutagenic under the conditions of this study (RIFM, 2001a).

The clastogenicity of 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol was assessed in a chromosome aberration (*in vitro* cytogenetics) study conducted according to OECD TG 473/GLP. Cultured human lymphocytes were treated with 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol in the presence and absence of S9 metabolic activation. In the first experiment, lymphocytes were treated in the presence or absence of S9 metabolic activation, with concentrations ranging from 15 to 90 μg/mL for 4 h followed by a 20-h recovery period. In the second experiment, cells received continuous treatment for 24 h, in the absence of S9 metabolic activation, with concentrations ranging from 10 to 70 μg/mL. In both experiments, no toxicologically significant increases in the frequency of chromosomal aberrations were observed with any dose of 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol, either with or without metabolic activation (RIFM, 2010d). Under the conditions of the study, 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol was considered not clastogenic in mammalian cells.

Based on the available data, 5-(2,2,3-trimethyl-3-cyclopentyl)-3-methylpentan-2-ol does not present a concern for genotoxic potential.

Additional References: RIFM, 2001b; RIFM, 2010e.

Literature Search and Risk Assessment Completed On: 12/07/20.

11.1.2. Repeated dose toxicity

The MOE for 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (Sandalore) to support the repeated dose toxicity endpoint. In a GLP and OECD 421-compliant study, 10 Crl:WI (Wistar Han) rats/sex/dose were administered Sandalore once daily via gavage at dose levels of 0, 100, 300, and 1000 mg/kg/day in a corn oil vehicle. Male rats were treated for 14 days before cohabitation, through the cohabitation period (maximum 13 days), and until the day before termination (14 days after the completion of cohabitation). Female rats were treated through day 4 of lactation. At 1000 mg/kg/day, 1 female was euthanized before the scheduled termination due to adverse clinical conditions resulting from difficulties during parturition (dystocia). Daily administration of the test material resulted in clinical signs such as excess salivation in both male and female rats at dosage levels of 300 and 1000 mg/kg/day and urine-stained abdominal fur in both male and female rats at dosage levels of 1000 mg/kg/day. Observations of salivation of this nature are commonly made following oral administration of an unpalatable test material formulation. Hence, it was not considered to be an adverse effect. Piloerection, ptosis, and a red perivaginal substance occurred in female rats in the 1000 mg/kg/day group during the gestation period. Reductions in mean body weight gains and feed consumption occurred early in the dosing periods and resulted in reductions in mean body-weight gain during the overall study period in male rats in the 300 and 1000 mg/kg/day groups. However, this effect was confined to 1 sex. There were no changes observed in the ability of the male and female rats to mate and produce viable litters at any dose level tested. No microscopic changes were observed in the testes of male rats up to the highest dose tested. There were no clinical signs or gross lesions observed in the offspring that could be attributed to maternal treatment with the test material. The NOAEL for general toxicity was determined to be 1000 mg/kg/day based on a no toxicologically relevant adverse effects seen up to the higher dose group (RIFM, 2010g).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 421 study (ECHA, 2012a). The safety factor has been

approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol NOAEL in mg/kg/day by the total systemic exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol, 333/0.0049, or 67959.

A dermal *in vitro* rat and pig skin absorption study was conducted on the test material 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol. The most conservative skin absorption value obtained was 41.1% (RIFM, 1984; see Section V). **When correcting for skin absorption (see** Section V**), the total systemic exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (4.9 μg/kg/day) is below the TTC (9 μg/kg/day;** Kroes, 2007**) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.**

3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1; see Section VI) has sufficient repeated dose toxicity data to use as WoE. An OECD 407 28-day subchronic toxicity study was conducted in Han Wistar rats. Groups of 5 rats/sex/dose were gavaged with test material 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol in a corn oil vehicle daily for 28 consecutive days at dose levels of 0, 35, 325, or 1000 mg/kg/day. Two recovery groups, 5 rats/sex/dose, were treated with the high dose (1000 mg/kg/day) or the vehicle alone for 28 consecutive days and then maintained without treatment for an additional 14 days. There was an increase in salivation among all animals of the mid- and high-dose groups. An increase in the absolute and relative liver weights was reported among all females and males in the mid- and high-dose groups. The effect on liver weight continued in recovery animals following 14 days without treatment. Histopathological alterations included centrilobular hepatocellular hypertrophy among animals of both sexes treated with 1000 mg/kg/day and in males treated with 325 mg/kg/day. Hyaline droplets/granules in the proximal tubules were noted in males treated with 1000 or 325 mg/kg/day. Thyroid follicular cell hypertrophy was noted in males from all treatment groups, females treated with 1000 and 325 mg/kg/day, and 1 female treated with 35 mg/kg/day. This effect was not observed following the completion of the treatment-free recovery period. Thyroid hormone assessments conducted at the end of the treatment period showed no treatment-related effects on the pituitary-thyroid axis. The study concluded that the oral administration of test material to rats by gavage resulted in non-adverse treatment-related effects in animals of either sex from all treatment groups. Kidney changes in males at 1000 mg/kg/day were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). Changes in thyroid cell microscopy were also considered to be a secondary change to an increase in hepatocellular cell size. Therefore, the NOAEL was determined to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010f).

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 3.33 mg/kg/day.

11.1.2.1.1. Derivation of reference dose (RfD). The reference dose for 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 1992b; RIFM, 1988; ECHA, 2010; ECHA, 2012b.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.3. Reproductive toxicity

The MOE for 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol to support the developmental toxicity endpoint. An OECD 421 reproductive and developmental screening study was conducted on Wistar rats with the test material 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol. Groups of 10 rats/sex/dose were administered the test material via gavage at dose levels of 0, 100, 300, and 1000 mg/kg/day in a corn oil vehicle. Mating, natural delivery, and litter observation parameters were unaffected by treatment up to 1000 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was determined to be 1000 mg/kg/day, based on the absence of any clinical signs or gross lesions observed in the offspring that could be attributed to maternal treatment with the test material (RIFM, 2010g). **Therefore, the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol MOE for the developmental toxicity endpoint can be calculated by dividing the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol NOAEL in mg/kg/day by the total systemic exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol, 1000/0.0049, or 204082.**

There are sufficient fertility data on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol to support the reproductive toxicity endpoint. An OECD 421 reproductive and developmental screening study was conducted on Wistar rats with the test material 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol. Groups of 10 rats/sex/dose were administered the test material via gavage at dose levels of 0, 100, 300, and 1000 mg/kg/day in a corn oil vehicle. There were no adverse effects reported in the animals treated up to the highest dose, both in mating ability and the reproductive organs of males and females and the female estrous cycles. Therefore, the NOAEL for reproductive toxicity was determined to be 1000 mg/kg/day (RIFM, 2010g). **Therefore, the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol MOE for the fertility endpoint can be calculated by dividing the 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol NOAEL in mg/kg/day by the total systemic exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol, 1000/0.0049, or 204082.**

When correcting for skin absorption (see Section V), the total systemic exposure to 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (4.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.4. Skin sensitization

Based on the existing data, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is considered a weak skin sensitizer with a defined NESIL of 2700 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is considered a weak skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In guinea pig studies, the material was classified as a non-sensitizer (RIFM, 1992a; RIFM, 1980; RIFM, 1977). In a Confirmation of No Induction in Humans test (CNIH), 1/95

subjects reacted to 5000 μg/cm^2 (RIFM, 2001c). However, the reaction was not confirmed with a re-challenge. Additionally, no reactions (0/108) were observed with 1111 μg/cm^2 and 2778 μg/cm^2 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpenta-2-ol in 3:1 alcohol SDA39C:diethyl phthalate (RIFM, 2002b; RIFM, 2002a).

Based on WoE from structural analysis as well as animal and human studies, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is a sensitizer with a WoE NESIL of 2700 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 3.33 mg/kg/day.

Additional References: RIFM, 1975; RIFM, 1979.

Literature Search and Risk Assessment Completed On: 11/13/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and *in vivo* experimental data, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a phototoxicity study conducted with albino guinea pigs, topical application of 10% 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol in ethanol, followed by UVA or UVB exposure did not result in phototoxic reactions (RIFM, 1981). Based on the *in vivo* experimental data and the lack of absorbance in the critical range, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/04/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.071 mg/day. This exposure is 6.6 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative

Table 1
5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol – Data summary.

LLNA Weighted Mean EC3 value (No. Studies) μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
NA	Weak	2778	NA	5000	2700

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2015), 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1995a**:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Sandalore 100 mg/L, as the nominal source of carbon, was incubated with activated sludge for 35 days. The test material underwent 81% biodegradation in 35 days (78% after 28 days).

RIFM, 1995b**:** The inherent biodegradability of the test material was determined by the respirometric method (modified MITI Test II) according to the OECD 302C method. The test material at 100 mg/L, as the nominal source of carbon, was incubated with activated sludge for 35 days. Biodegradation of 75% was observed after 35 days.

11.2.2.1.2. Ecotoxicity. RIFM, 2001d**:** A *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions. The calculated 48-h EC50 value was reported to be 2.3 mg/L (95% CI: 1.8–2.9 mg/L).

RIFM, 2010a**:** An algae inhibition test was conducted according to the OECD 201 method. Under the conditions of this study, the EC50 values based on nominal test concentration for yield, biomass, and growth rate at 72 h were reported to be 6.9, 7.1, and >17 mg/L, respectively.

RIFM, 2010b: A *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 1.3 mg/L (95% CI: 1.1–1.5 mg/L).

RIFM, 2010c: The acute toxicity of the test material to fathead minnows (*Pimephales promelas*) was evaluated according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 2.3 mg/L (95% CI: 1.7–3.1 m/L).

RIFM, 2006: A short-term *Daphnia magna* chronic toxicity study was conducted according to the EPA-821-R-02-013 method under static conditions. The 7-day NOEC values based on nominal test concentration were reported to be 0.31 mg/L and 1.25 mg/L for reproduction and survival, respectively.

RIFM, 2005: A 7-day chronic static renewal study was conducted using *Daphnia magna* according to EPA/600/4–90/027 method. The NOEC was 0.94 mg/L and <0.47 mg/L for survival and reproduction, respectively.

RIFM, 2005: A short-term, chronic, static renewal effluent toxicity test with immature fathead minnows (*Pimephales promelas*) was conducted according to the EPA/600/4–90/027 method. The 7-day NOEC values based on nominal test concentration were reported to be 0.94 mg/L and 1.88 mg/L for growth and survival, respectively.

11.2.2.1.3. Other available data. 5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>1.039</u>			1000000	0.001039	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.528	<u>0.388</u>	0.843	10000	0.0388	Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	2.3		0.94			
Daphnia		1.3	<u>0.31</u>	50	6.2	
Algae		6.9				

Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 6.2 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/08/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 11/10/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113030.

Appendix

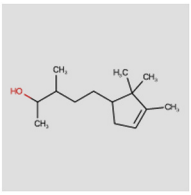
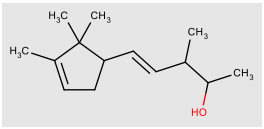
Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).

The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	WoE Material
Principal Name	5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol	3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol
CAS No.	65113-99-7	67801-20-1
Structure		
Similarity (Tanimoto Score)		0.60
Read-across Endpoint		• Repeated dose toxicity
Molecular Formula	$C_{14}H_{26}O$	$C_{14}H_{24}O$
Molecular Weight	210.36	208.45
Melting Point (°C, EPI SUITE)	47.63	46.53
Boiling Point (°C, EPI SUITE)	273.81	278.76
Vapor Pressure (Pa @ 25 °C, EPI SUITE)	0.0591	0.0442
Log K_{ow} (KOWWIN v1.68 in EPI SUITE)	4.6*	4.93
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI SUITE)	5.013	7.838
J_{max} (μg/cm^2/h, SAM)	14.202	14.610
Henry's Law (Pa·m^3/mol, Bond Method, EPI SUITE)	4.97E+000	4.37E+000
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Metabolism		
OECD QSAR Toolbox (v4.2)	See Supplemental Data 1	See Supplemental Data 2
Rat Liver S9 Metabolism Simulator		

*RIFM, 1996.

Summary

There are sufficient toxicity data on 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS # 65113-99-7). However, additional weight of evidence can be provided using an analog material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) could be used as a structurally similar WoE material for the target material 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS # 65113-99-7) for the repeated dose toxicity endpoint.
  - o The target material and the WoE analog are structurally similar and belong to a class of cyclic terpene alcohols.
  - o The target material and the WoE analog have a 2,2,3-trimethyl-3-cyclopenten-1-yl fragment common between them.
  - o The key difference between the target material and the WoE analog is that the target material has a saturated aliphatic chain, while the WoE has an unsaturated aliphatic chain connected to a cyclopentenyl ring.
  - o The target material and the WoE analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 2,2,3-trimethyl-3-cyclopenten-1-yl fragment. The differences in the structure that are responsible for a Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
  - o The target material and the WoE analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the WoE analog are estimated to be toxicologically insignificant for the repeated dose endpoint.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the repeated dose endpoint are consistent between the target material and the WoE analog.
  - o The target material and the WoE analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural differences between the target material and the WoE analog are deemed to be toxicologically insignificant for the repeated dose toxicity endpoint.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q16. Common terpene? **No**

Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open chain? **No**
Q23. Aromatic? **No**
Q24. Monocarbocyclic with simple substituents? **Yes**
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity)? **Yes**, Class Intermediate (Class II)

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