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RIFM fragrance ingredient safety assessment, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol, CAS Registry Number 28219-60-5

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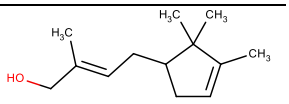

Name: 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol CAS Registry Number: 28219-60-5

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 (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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 Observed 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.

2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) show that 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is not expected to be genotoxic. Data on read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint and show that there are no safety concerns for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol for skin sensitization under the current declared levels of use. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-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, 2007a; RIFM, 2014a)
Repeated Dose Toxicity: NOAEL = 300 mg/kg/day. (RIFM, 2014b)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not a concern for skin sensitization under the current, declared use levels.
(RIFM, 1987a; RIFM, 1991b)
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.
(UV/Vis Spectra; RIFM Database; RIFM, 2005)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 84% (BODIS) (RIFM, 1994a)
Bioaccumulation:
Screening-level: 540.3 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: 48-h *Daphnia magna* EC50: 0.262 mg/L (ECOSAR; US EPA, 2012b)
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: 48-h *Daphnia magna* EC50: 0.262 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0262 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol
2. **CAS Registry Number:** 28219-60-5
3. **Synonyms:** 2-Buten-1-ol, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-; Santalinol; Sandal Mysore Core; Hindinol; Santaliff (Santalaire Dlair); 2-ﾒﾁﾙ-4-(2，2，3-ﾄﾘﾒﾁﾙ-3-ｼｸﾛﾍﾟﾝﾃﾝ-1-ｲﾙ)-2-ﾌﾞﾃﾝ-1-ｵｰﾙ; 2-Methyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-en-1-ol; Nor radjanol; 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol

4. **Molecular Formula:** $C_{13}H_{22}O$
5. **Molecular Weight:** 194.31
6. **RIFM Number:** 5640
7. **Stereochemistry:** Isomer not specified. One chiral center and 1 geometric center present. Total of 2 structural and 2 optical isomers possible.

2. Physical data

1. **Boiling Point:** 282.81 °C (EPI Suite), 268 °C (541 K) (RIFM, 2014c)
2. **Flash Point:** >93 °C (Globally Harmonized System), 120.5 °C (mean rounded off to the nearest 0.5 °C) (RIFM, 2014d)
3. **Log K_{OW}:** 4.65 (EPI Suite), 3.8 (RIFM, 2015b)
4. **Melting Point**: 50.1 °C (EPI Suite)
5. **Water Solubility:** 16.29 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000118 mm Hg at 20 °C (EPI Suite v4.0), 0.000238 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:** Not Available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.36% (RIFM, 2019b)
2. **Inhalation Exposure*:** 0.00079 mg/kg/day or 0.055 mg/day (RIFM, 2019b)
3. **Total Systemic Exposure**:** 0.0073 mg/kg/day (RIFM, 2019b)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
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2. Analogs Selected:
   a. **Genotoxicity:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
   b. **Repeated Dose Toxicity:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6)
   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 501-52-0 specific endpoint sections as discussed below.

Additional References: None.

8. Natural occurrence

2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is not reported to occur in foods 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

Available; accessed 11/06/20 (ECHA, 2017b).

10. Conclusion

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

11. Summary

Human health endpoint summaries

Genotoxicity

Based on the current existing data, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol does not present a concern for genotoxicity.

Risk assessment. 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenicity of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol; however, read-across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section VI). The mutagenicity of read-across

material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2uvrA were treated with 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2007a). These results indicate that 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is non-mut agenic in the Ames test when tested up to 5000 μg/plate under the conditions of the study.

There are no studies assessing the clastogenic activity of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol; however, read-across can be made to 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section VI). The clastogenicity of 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung fibroblasts were treated with 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in DMSO at concentrations up to 190 μg/mL in the presence and absence of exogenous metabolically active microsomal mixture. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test material, either with or without metabolic activation (RIFM, 2014a). Under the conditions of the study, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol does not present a concern for genotoxic potential and this can be extended to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol.

Additional References: RIFM, 1985; RIFM, 1998; RIFM, 1990; RIFM, 1987b; RIFM, 2007b.

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

Repeated dose toxicity

The MOE for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

Risk assessment. There are no repeated dose toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Read-across material, 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section VI) has sufficient repeated dose toxicity data. In a subchronic study, groups of 5 Crl:CD(SD) rats/sex/dose were administered test material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (Bacdanol) via gavage at dose levels of 0, 100, 350, and 1000 mg/kg/day dissolved in corn oil for 28 days. Control and high-dose recovery groups were set for the control and 1000 mg/kg/day groups to investigate reversibility of the effect of the treatment for 14 days. Effects on the liver and kidneys and irritating effects on the digestive tracts such as the forestomach attributable to the test material were detected but only at the highest dose tested. Liver effects included increased absolute and relative liver weights and diffuse hypertrophy of hepatocytes in both sexes; focal necrosis of hepatocytes in males; and granuloma in females, all at a high dose (statistically significant). Kidney effects included increased absolute and relative kidney weights, dilation and regeneration of collecting ducts, cell infiltration, single cell necrosis of proximal tubules, and regeneration of tubules of kidneys and turbidity of urine in females; there was also occult blood and protein in urine in males, all at a high dose (statistically significant). Microscopic alterations observed at the highest dose included the above-described treatment-related alterations in the hepatocytes and kidney tubules, as well as the stomach. All these effects were seen to be reversible, except for incidences of granulomas of the female hepatocytes. Hence, the NOAEL was determined to be 350 mg/kg/day (RIFM, 2014b).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 350/3 or 116.7 mg/kg/day.

Therefore, the 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol, 116.7/0.0073, or 15986.

In addition, the total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (7.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: None.

Literature Search and Risk Assessment Completed On: 11/09/20.

Reproductive toxicity

There are insufficient reproductive toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol or any read-across materials. The total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Risk assessment. There are no reproductive toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (7.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.
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Additional References: None.

Literature Search and Risk Assessment Completed On: 12/10/20.

Skin sensitization

Based on the existing data and read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6), 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Based on the existing data and read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6; see Section VI), 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is not considered a skin sensitizer. The chemical structure

of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0). However, both the target and the read-across materials were found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) (RIFM, 2019a). In a guinea pig maximization test, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol did not present reactions indicative of sensitization when 10% in liquid paraffin was used for the topical induction (RIFM, 2005). Similarly, in multiple guinea pig maximization tests, read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol did not present reactions indicative of sensitization (RIFM, 1987a; RIFM, 1991b; RIFM, 1986a; RIFM, 1986b; RIFM, 1986c). In a guinea pig Buehler test, the read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol was not determined to be a sensitizer when 1% in ethanol SDA39C was used (RIFM, 1979a). In a Confirmation of No Induction in Humans test (CNIH) with 5% or 2066 μg/cm^2 of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in 3:1 alcohol SD39C:diethyl phthalate (DEP), no reactions indicative of sensitization were observed in any of the 47 volunteers (ECHA, 2017b; RIFM, 1996b). Additionally, in A CNIH with 12.5% or 6250 μg/cm^2 of read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in 3:1 alcohol:DEP, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2002).

Based on weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies, and the data on the read-across material 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1979b; RIFM, 1980; RIFM, 1991a; RIFM, 1994b; RIFM, 1995a; RIFM, 1996c; RIFM, 2015b; RIFM, 1995b; European Centre for Ecotoxicology and Toxicology of Chemicals, 2003.

Literature Search and Risk Assessment Completed On: 11/27/20.

Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra and *in vivo* experimental data, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

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 3%, 10%, or 30% 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol in ethanol, followed by UV exposure, did not result in phototoxic reactions (RIFM, 2005). Based on *in vivo* experimental data and the lack of absorbance in the critical range, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

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.

Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol is below the Cramer Class I TTC value for inhalation exposure local effects.

Risk assessment. There are no inhalation data available on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.055 mg/day. This exposure is 25.5 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/19/20.

Environmental endpoint summary

Screening-level assessment

A screening-level risk assessment of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-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 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, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-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 is > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-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, 2012). 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 if the EPI Suite model BCFBAF predicts a fish BCF $\geq$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.

Risk assessment. Based on the current Volume of Use (2015), 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol presents a risk to the aquatic compartment in the screening-level assessment.

Key studies

Biodegradation. **RIFM, 1994a:** Biodegradation was evaluated during a biological oxygen demand for insoluble substances (BODIS) test. Biodegradation of 84% was observed after 28 days.

RIFM, 2015a: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 79% was observed after 28 days.

Ecotoxicity. **RIFM, 1996a:** A 96-h fish (*Brachydanio rerio*) acute toxicity study was conducted according to the EU 92/69 EWG method, under semi-static conditions. Under the conditions of the study, the LC50 was reported to be 6.3 mg/L (analytically corrected value).

Other available data. 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol has been registered for REACH with no additional data available at this time.

Risk assessment refinement. Since 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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 Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.8	3.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 0.0262 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 VoU.

Literature Search and Risk Assessment Completed On: 12/01/20.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	7.12			1000000	0.00712	
ECOSAR Acute Endpoints (Tier 2) v1.11	1.512	0.262	0.830	10000	0.0262	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints (Tier 2) v1.11	0.671	0.486	0.995			Neutral Organic SAR (Baseline toxicity)

- **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 09/30/21.

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.2021.112683.

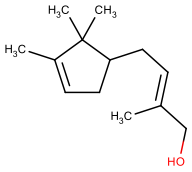
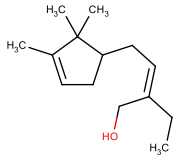
Appendix

Read-across justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow 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, 2017a).

- 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 v4.11 (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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol
CAS No.	28219-60-5	28219-61-6
Structure		
Similarity (Tanimoto Score)		0.98
Endpoint		• Genotoxicity • Skin sensitization • Repeated dose toxicity
Molecular Formula	$C_{13}H_{22}O$	$C_{14}H_{24}O$
Molecular Weight	194.318	208.345
Melting Point (°C, EPI Suite)	50.10	60.19
Boiling Point (°C, EPI Suite)	282.81	298.07
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.17E-02	9.57E-03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.63E+01	5.26E+00
Log K_{OW}	4.65	5.14

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
J_{max} (μg/cm^2/h, SAM)	2.44	0.83
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.89E+00	5.16E+00
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	Not categorized	Not categorized
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified	Alert for Schiff base formation identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There is insufficient toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-60-5). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical−chemical properties, and expert judgment, analog 2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) was identified as a read-across material with sufficient data.

Conclusion

- 2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-61-6) could be used as a structurally similar read-across analog for the target material 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol (CAS # 28219-60-5) for the genotoxicity, skin sensitization, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of unsaturated cyclic terpene alcohols.
  - o The target and read-across material have 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol substructure common among them.
  - o The key difference between the target material and the read-across is that the read-across has an ethyl substitution on the vinylene group on the aliphatic chain and the target has methyl substitution at the same place.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox, structural alerts for genotoxicity, skin sensitization, and repeated dose toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog both have an alert of Schiff base former and protein binding potency for skin sensitization endpoint. The existing data confirm that the read-across analog does not present a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog, and data for the read-across analog, the alerts are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the genotoxicity, skin sensitization, and repeated dose toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.

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