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RIFM fragrance ingredient safety assessment, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol, CAS Registry Number 104864-90-6

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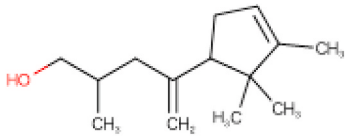

Abbreviation/Definition List:

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

(*continued on next column*)

(*continued*)

(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, 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)-4-penten-1-ol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol is not genotoxic and provides a margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The reproductive and local respiratory toxicity endpoints were completed using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxic/photoallergenic endpoints was evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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)-4-penten-1-ol was not found to be persistent, bioaccumulative, and toxic (PBT) as per 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, 2006; RIFM, 1999e)
Repeated Dose Toxicity: 333 mg/kg/day. RIFM (1999d)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Phototoxicity/ Photoallergenicity: Not phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1984)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 14% (OECD 301B) RIFM (1999i)
Bioaccumulation:
Screening-level: 1148 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.6 mg/L RIFM (1999g)
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 RIFM (1999g)
Endpoint: 48-h *Daphnia magna* EC50: 0.6 mg/L
RIFM PNEC is: 0.6 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)-4-penten-1-ol
2. **CAS Registry Number:** 104864-90-6

3. **Synonyms:** 3-Cyclopentene-1-butanol,.β.,2,2,3-tetramethyl-.δ.-methylene-; 4-Penten-1-ol, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-; Firsantol; 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol
4. **Molecular Formula:** $C_{14}H_{24}O$
5. **Molecular Weight:** 208.34
6. **RIFM Number:** 6362
7. **Stereochemistry:** Isomer not specified. Two chiral centers present and a total of 4 enantiomers possible.

2. Physical data

1. **Boiling Point:** 544±0.5 K at 99.50 kPa (RIFM, 1999a)
2. **Flash Point:** 133±2 °C (RIFM, 1999b)
3. **Log K_{OW}:** 4.71 (RIFM, 1999a)
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** Not Available
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 v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.21% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.00018 mg/kg/day or 0.013 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0020 mg/kg/day (RIFM, 2016)

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

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   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:** None

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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

Not pre-registered; no dossier available as of 04/12/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP and OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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, 2006). Under the conditions of the study, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol was not mutagenic in the Ames test.

The clastogenicity of 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol in DMSO at concentrations of/up to 2080 μg/mL in the presence and absence of exogenous metabolic activation. No statistically 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 S9 metabolic activation (RIFM, 1999e). Under the conditions of the study, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol was considered to be non-clastogenic to

human cells.

Based on the data available, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol does not present a concern for genotoxic potential.

Additional References: RIFM, 1985; RIFM, 2001.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol. An OECD/GLP 407 gavage 28-day subchronic toxicity study was conducted in Sprague Dawley Crl:CD BR strain rats. Groups of 5 rats/sex/dose were administered 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol via gavage at doses of 0, 15, 150, or 1000 mg/kg/day in an arachis oil BP vehicle. There were no treatment-related alterations in body weight, hematology, and clinical chemistry parameters. Males in the 150 and 1000 mg/kg/day groups showed a statistically significant increase in the absolute and relative kidney weights when compared to the controls. A statistically significant increase in the relative liver weights was observed among males and females of the highest-dose group when compared to the controls. All males treated with 1000 mg/kg/day showed speckled kidneys and enlarged livers at necropsy. Males treated with 1000 mg/kg/day showed an increase in the incidence and severity of globular accumulations of eosinophilic material in the renal proximal tubular epithelium. These kidney changes in males 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). Enlargement of centrilobular hepatocytes was also observed among these male animals of the highest-dose group and extended to 2 males of the 150 mg/kg/day group. Alterations in liver weight (in both sexes) and associated incidences of centrilobular hepatocyte hypertrophy (in males) were considered to be of adaptive nature since there was a lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and related clinical chemistry alterations (Hall, 2012). The liver effects were likely related to induction of microsomal metabolizing enzymes. Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1999d).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

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

Therefore, the 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol NOAEL in mg/kg/day by the total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol, 333/0.002, or 166500.

In addition, the total systemic exposure to 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol (2.0 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: 08/13/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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)-4-penten-1-ol (2.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for reproductive toxicity of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/29/20.

11.1.4. Skin sensitization

Based on existing data and the application of DST, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) (RIFM, 2019). In a guinea pig maximization test, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol did not present reactions indicative of sensitization (RIFM, 1999c). In 2 separate Confirmation of No Induction in Humans tests (CNIHs) with 10% 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4--penten-1-ol (5000 μg/cm^2) in diethyl phthalate and 4% 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol (unknown patch size) in petrolatum, no reactions indicative of sensitization were observed in any of the 106 or 50 volunteers, respectively (RIFM, 2000; RIFM, 1984). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/02/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and available human data, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-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 well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In a study conducted in human volunteers, 4% 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol in petrolatum was not phototoxic or

Table 1
Maximum acceptable concentrations for 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	0.015%
3	Products applied to the face using fingertips	0.41%	0.0058%
4	Fine fragrance products	0.39%	0.29%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.013%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	0.0025%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0063%
10	Household care products with mostly hand contact	2.7%	0.029%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.80%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

photoallergenic (RIFM, 1984). Based on the human study data and the lack of absorbance, 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4--penten-1-ol does not 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: 09/21/20.

11.1.6. 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)-4-penten-1-ol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.013 mg/day. This exposure is 107.7 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: 09/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

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

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4--penten-1-ol as possibly persistent but not 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 ≥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 Volume of Use (2015), 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol presents a risk to the aquatic

compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation**

RIFM, 1999i: Ready biodegradability of the test material was evaluated according to the OECD 301B guideline. The test material achieved 14% biological degradation after 28 days calculated from the results of the inorganic carbon analyses.

Ecotoxicity

RIFM, 1999f: A 96-h fish (Rainbow trout) acute toxicity study was conducted according to the OECD 203 method under flow-through conditions. The 96-h LC50 value, based on nominal test concentrations, was reported to be greater than 1.0 mg/L.

RIFM, 1999g: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 0.6 mg/L (95% CI: 0.52–0.70 mg/L).

RIFM, 1999h: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 value based on time-weighted mean measured test concentration for growth rate was reported to be greater than 0.61 mg/L.

Other available data

2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol has been pre-registered for REACH with no additional information 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 Framework: Salvito, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.71	4.71
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.6 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: 09/28/20.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.23			1000000	0.00123	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.258	0.196	0.484	10000	0.0196	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.0					
Daphnia		0.6		1000	0.6	
Algae		0.61				

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- **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 04/12/21.

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.

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