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Short review

RIFM fragrance ingredient safety assessment, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol, CAS Registry Number 67801-20-1

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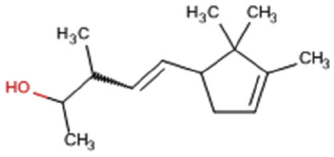

Abbreviation list:

2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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; Safford et al., 2015; Safford et al., 2017) compared to a deterministic aggregate approach.
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold

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ECHA - European Chemicals Agency
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
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
QRA - quantitative risk assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/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 under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic and also provided a MOE >100 for the repeated dose, developmental and reproductive toxicity endpoints. Data from the read across analog 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS# 107898-54-4) provided a NESIL of 2500 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.47 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoints were evaluated and the material was not found to be a PBT; its risk quotients, based on current volume of use in Europe and North America, were acceptable (PEC/PNEC < 1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(RIFM, 2006b; RIFM, 2010d)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day	(RIFM, 2010b)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day	(RIFM, 2010c)
Skin Sensitization: NESIL = 2500 μg/cm^2	(RIFM, 2016)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB; RIFM, 1984b; RIFM, 1984d)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 66% (OECD 301F)	(RIFM, 1994)
Bioaccumulation: Screening Level: 836.7 l/kg	(EPI SUITE v4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day *Daphnia magna* NOEC (repro) 0.25 mg/l	(RIFM, 2006a)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 7-day *Daphnia magna* NOEC (repro): 0.25 mg/l	(RIFM, 2006a)
RIFM PNEC is: 25 μg/L	
•**Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl) pent-4-en-2-ol
2. **CAS Registry Number**: 67801-20-1
3. **Synonyms:** 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol; 4-Penten-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-; Ebanol; 3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pent-4-en-2-ol
4. **Molecular Formula**: $C_{14}H_{24}O$
5. **Molecular Weight**: 208.45
6. **RIFM Number**: 5844

2. Physical data

1. **Boiling Point:** 278.76 °C [EPI Suite]
2. **Flash Point:** > 212.00 °F TCC (>100.00 °C)*
3. **Log K_{OW}**: 4.93 [EPI Suite]
4. **Melting Point**: 46.53 °C [EPI Suite]
5. **Water Solubility:** 3.41e-2 g/l at 20 ± 0.5 °C [RIFM, 2010g, (calculated) 7.838 mg/L [EPI Suite]
6. **Specific Gravity:** 0.89800 to 0.90400 @ 25.00 °C*
7. **Vapor Pressure:** 0.89 Pa at 25 °C [RIFM, 2010g, (calculated) 0.000166 mm Hg @ 20 °C [EPI Suite 4.0], 0.000332 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 $L\,mol^{-1}\cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a medium, sandalwood, woody, and musk like odor when in a 10.00% solution or less.*

*http://www.thegoodscentscompany.com/data/rw1061371.html, retrieved 6/27/14.

3. Exposure to fragrance ingredient

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA , 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.17% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00030 mg/kg/day or 0.022 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.0032 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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 et al., 2015; Safford et al., 2015 and Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	II	I

*See Appendix below for explanation.

2. **Analogs Selected**:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** 3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS# 107898-54-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justifications**: None

6. Metabolism

Not considered for this risk assessment (data not available at this time).

7. Natural occurrence (discrete chemical) or composition (NCS)

3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

This material will have an IFRA Standard (see Skin Sensitization section).

9. REACH dossier

Available; accessed on 12/14/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol has been assessed in an Ames assay in compliance with GLP regulations and in accordance with OECD TG 471 using both the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Eshcerchia Coli* strain WP2uvrA were treated with 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol in DMSO (dimethyl sulfoxide) at concentrations up to 5000 µg/plate in the presence and absence of S9 metabolic mix. No increase in the number of revertant colonies was observed in any of the tester strains at any concentrations (RIFM, 2006b). Under the conditions of the study, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was considered non-mutagenic.

The clastogenic activity of 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was assessed in an *in vitro* chromosome

aberration assay conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes *in vitro* were treated with 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol in DMSO at concentrations up to 90 μg/mL with and without metabolic activation. The test material did not induce a statistically significant increase in the frequency of cells with chromosome aberrations in either the absence or presence of a liver enzyme metabolizing system (RIFM, 2010d). The test material was therefore considered to be non-clastogenic.

Based on the available data, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol does not present a concern for genotoxic potential.

Additional References: RIFM, 1984c; RIFM, 2010f.

Literature Search and Risk Assessment Completed on: 09/13/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The repeated dose toxicity data on 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol are sufficient for the repeated dose toxicity endpoint. An OECD 407 gavage 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 fourteen 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 was 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 one 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 alpha-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 and Caudill, 1992; Lehman-McKeeman et al., 1990). Changes in thyroid cell microscopy was 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, 2010h, i).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day OECD 407 study. 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.

There are no repeated dose toxicity studies on ebanol via the dermal and inhalation routes.

The 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol, 333/0.0032 or 104063.

In addition, the total systemic exposure to 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (3.2 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

The RIFM criteria document (Api,2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10X) and intraspecies (10X) differences. The RfD for 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was calculated by dividing the NOAEL 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, 2010a.

Literature Search and Risk Assessment Completed on: 10/25/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. The developmental and reproductive toxicity data on 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol are sufficient for the developmental and reproductive toxicity endpoints. An OECD 421 gavage reproductive and developmental toxicity screening test was conducted in Han Wistar rats. Groups of 10 rats/sex/dose were administered via gavage test material, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (ebanol) with doses of 0, 30, 300 or 1000 mg/kg/day in a corn oil vehicle. There were no adverse effects reported due to treatment with 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol, up to the highest dose tested (RIFM, 2010a). In another study, groups of 10 rats/sex/dosage were gavaged daily for 28 consecutive days, at dose levels of 0, 35, 325 or 1000 mg/kg/day of test material, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol in a corn oil vehicle. 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. The study was conducted according to the OECD 407 guidelines. In addition to the systemic toxicity parameters, the estrous cycle was also monitored for the females. There was no effect of treatment on the estrous cycle of females up to the highest dose tested (RIFM, 2010b). Thus, the NOAEL for developmental and reproductive toxicity was determined to be 1000 mg/kg/day, the highest dosage tested.

The 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol, 1000/0.0032 or 312500.

In addition, the total systemic exposure to 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (3.2 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: RIFM, 2010h, i.

Literature Search and Risk Assessment Completed on: 10/25/2016.

Table 1
Data Summary for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol as read across for 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol.

LLNA weighted mean EC3 value [No. Studies] μg/cm[b]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
>5000 [1]	Weak	2598	NA	5000	2500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.
[c] WoE NESIL limited to two significant figures.

10.1.4. Skin sensitization

Based on the available data and read across to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS# 107898-54-4), 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol is considered a skin sensitizer with a defined NESIL of 2500 μg/cm^2.

10.1.4.1. Risk assessment. Based on the available data and read across to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS # 107898-54-4; see Section V), 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol is considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was reported to be a non-sensitizer (RIFM, 1984a). Similarly, in guinea pig test method, read across material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was reported to be a non-sensitizer (RIFM, 1989). Moreover, in a murine local lymph node assay (LLNA), the maximum tested concentration of 20% v/v read across material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol did not result in stimulation index above 3 (RIFM, 2001a). In a human confirmatory study no sensitization reactions were observed to 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (RIFM, 1985). In a confirmatory human repeat insult patch test (HRIPT) one out of 109 subjects reacted at 10% or 5000 μg/cm^2 read across material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in diethyl phthalate (RIFM, 2001b). However, in a subsequent HRIPT with 107 subjects at a higher dose of 20% or 10000μg/cm^2 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in 1:3 ethanol:DEP no reaction indicative of sensitization was observed in any of the subject tested (RIFM, 2005b). Similarly, no reactions were observed with 2.2% or 2598μg/cm^2 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in 1:3 ethanol:DEP (RIFM,2016).

Based on the weight of evidence from available data and data on read across 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, summarized in Table 1, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol is considered to be a weak skin sensitizer with a defined NESIL of 2500 μg/cm^2. Table 2 provides the recommended limits in finished products based on skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2008; IDEA project (International Dialogue for the Evaluation of Allergens) Final Report on the QRA2: Skin Sensitisation Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016 (http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf).).

Additional References: RIFM, 1984a,b,c,d

Literature Search and Risk Assessment Completed on: 04/25/14.

10.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra and the existing experimental study data, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV absorption spectra indicate no absorption between 290 and 500 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In guinea pig phototoxicity and photoallergenicity studies, responses indicative of phototoxicity or photoallergenicity were not observed (RIFM, 1984a; RIFM, 1984b). Based on lack of absorbance and the existing *in vivo* data, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/14/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol. Based on the Creme RIFM model, the inhalation exposure is 0.022 mg/day. This exposure is 21.4 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 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.

Additional References: None.

Literature Search and Risk Assessment Completed on: 7/20/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty

Table 2
Recommended limits[a] in the finished products– 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol.

IFRA Category[b]	Description of Product Type	Recommended Limits[a] in Finished Products
1	Products applied to the lips	0.19%
2	Products applied to the axillae	0.06%
3	Products applied to the face using finger tips	1.15%
4	Fine Fragrance products	1.07%
5	Products applied to the face and body using the hands (palms), primarily leave-on	
	5A: Body Lotion	0.27%
	5B: Face Moisturizer	0.27%
	5C: Hand Cream	0.27%
	5D: Baby Products	0.09%
6	Products with oral and lip exposure	0.63%
7	Products applied to the hair with some hand contact	2.19%
8	Products with significant ano-genital exposure	0.09%
9	Products with body and hand exposure, primarily rinse off	2.09%
10	Household care products with mostly hand contact	
	10A: Household care products	7.51%
	10B: Aerosol Air Fresheners	7.51%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.09%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted

[a] Recommended limits for each product category are based on the lowest maximum acceptable exposure level (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol the basis was the reference dose of 3.33 mg/kg/day and a skin sensitization NESIL of 2500 μg/cm^2.

[b] For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was identified as a fragrance material with potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE v4.1 identified 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol as not persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.*, OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.,* USEPA's BIOWIN and BCFBAF found in EPISUITE v4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 1994**: A modified MITI Test was conducted according to OECD Guideline 301 F. Flasks containing mineral salt medium inoculated with activated sludge were used. Following the addition of 100 mg/l of 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol to the inoculated medium, the closed flasks were incubated for 28 days. The biodegradation rate was 58% and 66% after 10 and 28 days, respectively.

10.2.3.2. Ecotoxicity. **RIFM, 2010e**: A 48-h *Daphnia magna* acute toxicity test was conducted according to the OECD 202 method under static conditions. The 48 h EC50 of the test material to *Daphnia magna* based on nominal concentrations was 1.9 mg/l.

RIFM, 2010b: A 96-h acute toxicity test was conducted with juvenile fathead minnow (*Pimephales promelas*) following the OECD 203 guidelines. Under the conditions of this study, the 96 h LC50 value was 2.3 mg/l.

RIFM, 2006a: Short-term chronic static renewal effluent toxicity tests with *Daphnia magna* were conducted according to EPA/600/4–90/027 and ASTM E729, 1997 methods. The calculated LC50 was 1.96 mg/l. The 7-day NOEC was reported to be 0.25 mg/l and 0.98 mg/l for reproduction and survival, respectively.

RIFM, 2005a: Short-term chronic static renewal effluent toxicity tests with *Daphnia magna* were conducted according to EPA/600/4–90/027 and ASTM E729, 1997 methods. The calculated LC50 was 1.47 mg/l the 7 day NOEC was reported to be 0.74 mg/l for both reproduction and survival.

RIFM, 2005a: Short-term chronic static renewal effluent toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. The 7-day LC50 of 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol was reported to be (*Pimephales promelas*) was 5.32 mg/L and the NOEC was 0.74 mg/l and 2.94 mg/l for growth and survival, respectively.

RIFM, 2010c: An Algae growth inhibition test was conducted according to the OECD 201 guidelines. Under the conditions of this study, the EC50 for growth rate, yield and biomass at 72 h were 24, 13 and 13 mg/l, respectively and at 96 h were 26, 13 and 13 mg/l, respectively. The 72-h NOEC for growth rate and biomass was reported to be 3.1 mg/l.

10.2.3.3. Other available data. 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol has been registered under REACH but no additional data is available.

10.2.3.4. Risk assessment refinement. REACH PNEC has been reported as 1.9 μg/l (*Daphnia magna* EC50), however since additional studies are available in RIFM database a lower NOEC has 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.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	3.427 mg/l			1,000,000	0.003427 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** Ver 1.11	0.396 mg/l	0.295 mg/l	0.674 mg/l	10,000	0.0295 µg/l	Neutral Organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.96 mg/l		0.74 mg/l			
Daphnia		1.47 mg/l	0.25 mg/l	10	25 µg/l	
Algae		13 mg/l	3.1 mg/l			

Exposure information and PEC calculation (following RIFM Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.2	4.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 25 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 04/22/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

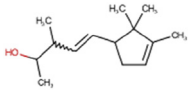
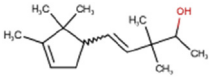
Appendix

Read across justification

Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al. 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012)

	Target material	Read across material
Principal Name	3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol	3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol
CAS No.	67801-20-1	107898-54-4
Structure		
Similarity (Tanimoto score)[1]		0.925
Read across endpoint		• Skin sensitization
Molecular Formula	$C_{14}H_{24}O$	$C_{15}H_{26}O$
Molecular Weight	208.45	222.37
Melting Point (°C, EPISUITE)	46.53	63.64
Boiling Point (°C, EPISUITE)	278.76	288.22
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.0442	0.0166
Log Kow (KOWWIN v1.68 in EPISUITE)	4.93	5.39
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	7.838	12.9[1]
J_{max} (mg/cm^2/h, SAM)	14.610	1.112
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.31E-005	5.73E-005
*Skin Sensitization*rowhead		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolismrowhead		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	67801-20-1 pdf	107898-54-4 pdf

1. RIFM, 1991.

Summary

There are insufficient toxicity data on 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analog 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS # 107898-54-4) was identified as a read across material with data for its respective toxicological endpoints.

Conclusion/Rationale

- 3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (CAS # 107898-54-4) could be used as a structurally similar read across analog for target material 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) for the skin sensitization endpoint.
  - o The target substance and the read across analog are structurally similar and belong to a class of alcohols.
  - o The target substance and the read across analog have a 2,2,3-trimethyl-3-cyclopenten-1-yl fragment common among them.
  - o The key difference between the target substance and the read across analog is that the target substance has a single methyl substitution on the 3rd position of the aliphatic chain while the read across analog has two methyl substitutions on the 3rd position of the aliphatic chain.
  - o The target substance and the read across 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 which are responsible for a Tanimoto score <1 are not relevent from a toxicological endpoint perspective.
  - o The target substance and the read across analog have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analog are estimated to be toxicologically insignificant for the skin sensitization endpoint.
  - o Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 80\%$ for the target substance and $\leq 40\%$ for the read across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.

- o According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read across analog. The read across analog and the target substance are predicted to be sensitizers by the CAESAR model for skin sensitization. The data described in the skin sensitization section above show that the read across analog is a sensitizer.
- o The target substance and the read across analog are expected to be metabolized similarly as shown by the metabolism simulator.
- o The structural alerts for the skin sensitization endpoint are consistent between the metabolites of the read across analog and the target substance.
- o The structural differences between the target substance and the read across analog are deemed to be toxicologically insignificant for the skin sensitization 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 hydrolysed 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)

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.12.065.

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