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Short review

RIFM fragrance ingredient safety assessment, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, CAS Registry Number 107898-54-4

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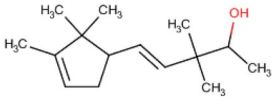

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development

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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
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 et al., 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, 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.

3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is not genotoxic. Data on 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data from read-across analogs 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) and 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (Sandlore) (CAS # 65113-99-7) provide a calculated MOE > 100 for the developmental and reproductive toxicity endpoints. Data provided 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol a NESIL of 2500 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1984b; RIFM, 1988)
Repeated Dose Toxicity: NOAEL = 33 mg/kg/day.	RIFM (1989b)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2010a; RIFM, 2010b)
Skin Sensitization: NESIL = 2500 μg/cm^2.	(RIFM, 2016; RIFM, 2005a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; RIFM, 1984a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 7% (OECD 301C)	RIFM (2014a)
Bioaccumulation: Critical Measured Value: 80 (-OECD 305)	(RIFM, 2014b)
Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day Fish Chronic NOEC: 0.25 mg/L	RIFM (2005b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 7-day Fish Chronic NOEC: 0.25 mg/L	RIFM (2005b)
RIFM PNEC is: 25 μg/L	
● Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1	

1. Identification

1. **Chemical Name:** 3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol
2. **CAS Registry Number:** 107898-54-4
3. **Synonyms:** 4-Penten-2-ol, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-; Polysantol; ３，３－ジメチル－５－(２，２，３－トリメチルシクロペンタ－３－エン－１－イル)ペンタ－４－エン－２－オール; Mysantol; (±) *trans*-3,3-Dimethyl-5-(2,2,3-trimethyl-cyclopent-3-en-1-yl)pent-4-en-2-ol; Nirvanol; 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol
4. **Molecular Formula:** $C_{15}H_{26}O$
5. **Molecular Weight:** 222.37
6. **RIFM Number:** 6325

2. Physical data

1. **Boiling Point:** 288.22 °C (EPI Suite)
2. **Flash Point:** > 100 °C (GHS)
3. **Log K_{OW}:** 4.33 (CV = 2.6) log10P (RIFM, 1991), 5.39 (EPI Suite)
4. **Melting Point**: 63.64 °C (EPI Suite)
5. **Water Solubility:** 2.711 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000125 mm Hg @ 25 °C (EPI Suite), 0.000061 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless, clear liquid with a medium woody, sandalwood, herbal, tropical odor while at 10% in dipropylene glycol (Luebke, William tgsc, 1997).*

*http://www.thegoodscentscompany.com/data/rw1032011.html, retrieved 5/21/2015.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.93% (RIFM, 2013a,b)
3. **Inhalation Exposure*:** 0.00022 mg/kg/day or 0.016 mg/day (RIFM, 2013a,b)
4. **Total Systemic Exposure**:** 0.0071 mg/kg/day (RIFM, 2013a,b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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; Safford et al., 2017; and Comiskey 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 I, Low

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

2. Analogs Selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1); 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (Sandlore) (CAS # 65113-99-7).
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is not reported to occur in food by the VCF*.

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

8. REACH dossier

Three dossiers available, accessed 11/04/16.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.019
2	Products applied to the axillae	0.057
3	Products applied to the face/body using fingertips	0.16
4	Products related to fine fragrances	1.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.27
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.27
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.27
5D	Baby cream, oil, talc	0.091
6	Products with oral and lip exposure	0.00023
7	Products applied to the hair with some hand contact	0.35
8	Products with significant ano-genital exposure (tampon)	0.091
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.1
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.1
10B	Aerosol air freshener	2.9
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.091
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	85

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, the basis was the reference dose of 0.33 mg/kg/day, a predicted skin absorption value of 10%, 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).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was assessed in an Ames assay conducted in compliance with GLP regulations. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No significant increase in the number of revertant colonies was observed in any of the strains at the conditions tested (RIFM, 1984b). Under the conditions of the study, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was considered not mutagenic in the Ames assay.

The clastogenic activity of 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was assessed in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations and in compliance with OECD TG 473. Human peripheral blood lymphocytes were treated with 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in DMSO at concentrations up to 625 μg/mL in the presence of metabolic activation and 1250 μg/mL in the absence of metabolic activation. An increase in the frequency of chromosome aberrations was observed at the maximum dose only. The increase was significant only in the absence of metabolic activation with little to no indication of a dose-response relationship. Furthermore, there were no exchange-type aberrations detected in any of the treatment groups, which supports the view that 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is non-clastogenic (RIFM, 1988). Under the

conditions of the study, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is non-clastogenic to human lymphocytes *in vitro*.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/01/16.

10.1.2. Repeated dose toxicity

The MOE for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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 for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol are sufficient for the repeated dose toxicity endpoint. A 28-day gavage study was conducted in groups of 10 Crl:CD(SD)BR rats/sex/dose treated with the test material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol at the dose levels of 0, 100, 500, and 2500 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day based on decreased bodyweight gain and increased liver weight among both sexes at the high-dose group and only in the males of the mid-dose group. These effects were accompanied by significantly altered blood chemistry parameters among the rats treated with the high dose of the test material, along with the presence of ketones in the urine of most males treated with the test material (RIFM, 1989b). The most conservative NOAEL of 100 mg/kg/day was selected for this safety assessment.

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

Thus, the derived NOEL for the repeated dose toxicity data is 100/3 or 33 mg/kg/day.

Therefore, the 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol NOEL in mg/kg/day by the total systemic exposure to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, 33/0.0071 or 4648.

In addition, the total systemic exposure to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (7.1 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section 9 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.33 mg/kg/day.

10.1.3. Derivation of reference dose (RfD)

The reference dose for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

*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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/26/16.

10.1.4. Developmental and reproductive toxicity

The MOE for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.4.1. Risk assessment. There are no developmental and reproductive toxicity data on 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol. Read-across material, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1; see section 5) has an OECD 421 reproductive and developmental screening study performed on Wistar rats. Groups of 10 rats/sex/dose were administered the test material 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (Ebanol) via gavage with doses of 0, 30, 300, or 1000 mg/kg/day in a corn oil vehicle. The NOAEL for parental growth, reproductive performance, and offspring growth was determined to be 1000 mg/kg/day, the highest dose tested (RIFM, 2010a).

In another OECD 421 reproductive and developmental screening study conducted on rats with read-across material 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS # 65113-99-7; see section 5), groups of 10 Crl:WI(Wistar Han) rats/sex/dose were administered the test material via gavage with doses of 0, 100, 300, and 1000 mg/kg/day in a corn oil vehicle. There was an increase in salivation among the mid- and high-dose treatment groups that persisted throughout the study, along with urine-stained abdominal fur in both male and female rats at 1000 mg/kg/day that was considered to be treatment-related. However, there were no adverse effects reported both in mating ability and reproductive organs among males and females and the estrous cycles in females treated up to the highest dose. The NOAEL for the developmental and reproductive toxicity was determined at 1000 mg/kg/day (RIFM, 2010b).

Therefore, the 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, 1000/0.0071 or 140845.

In addition, the total systemic exposure to 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (7.1 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: ECHA REACH Dossier: 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (ECHA, 2012b; accessed 09/08/2015).

Literature Search and Risk Assessment Completed On: 10/26/16.

10.1.5. Skin sensitization

Based on the existing data, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is considered a skin sensitizer with a defined NESIL of 2500 μg/cm^2.

10.1.5.1. Risk assessment. Based on animal and human studies, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.6; OECD Toolbox v3.3). In a murine local lymph node assay (LLNA), the maximum tested concentration of 20% v/v did not result in a Stimulation Index (SI) above 3 (RIFM, 2001b). In a guinea pig study using the Magnusson and Kligman maximization method, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was reported to be a non-sensitizer

Table 1
Data summary for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
> 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 2 significant figures.

(RIFM, 1989a). In a confirmatory human repeated insult patch test (HRIPT), 1 out of 109 subjects reacted at 10% or 5000 μg/cm^2 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol in diethyl phthalate (DEP) (RIFM, 2001a). However, in a subsequent HRIPT with 107 subjects at a higher dose, 20% or 10000 μg/cm^2 in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reaction indicative of sensitization was observed in any of the subjects tested (RIFM, 2005a). Similarly, no reactions were observed with 2.2% or 2598 μg/cm^2 in 1:3 ethanol:DEP (RIFM, 2016).

Based on the available data, summarized in Table 1, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is considered to be a weak skin sensitizer with a defined NESIL of 2500 μg/cm^2. Section 9 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.33 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/06/16.

10.1.6. Phototoxicity/photoallergenicity

Based on UV/Vis spectra and human study data, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.6.1. 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 et al., 2009). In a photo-HRIPT conducted on 20 volunteers with 4% 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, there were no observed effects, and the material was not considered phototoxic or photoallergenic (RIFM, 1984a). Based on UV/Vis spectra and human study data, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.6.2. 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, 1000 L mol^{-1} · cm^{-1}, for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/04/16.

10.1.7. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment. There are no inhalation data available on 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol. Based on the Creme RIFM Model, the inhalation exposure is 0.016 mg/day. This exposure is 87.5 times lower than the Cramer Class I TTC value of 1.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was performed following the RIFM Environmental Framework (Salvito et al., 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, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.1 identified 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol as possibly being 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative 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 v4.1). Specific key data on biodegradation and fate and bioaccumulation are reported

below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (2015), 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-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, 1989d**:** A biodegradation study was conducted according to the OECD 301C method. No biodegradation was reported after 28 days.

RIFM, 2014a**:** A study was conducted to evaluate the biodegradability of the test material according to the OECD 301C method. Under the conditions of the study, no biodegradation was observed after 28 days.

RIFM, 2014b**:** A fish (carp) bioaccumulation study was conducted according to the OECD 305 method under flow-through conditions. The bioconcentration factor (BCF) at a steady state was 79 and 80 for high (5 µg/L) and low (0.5 µg/L) concentrations, respectively.

RIFM, 2014c**:** A fish (carp) bioaccumulation study was conducted according to the OECD 305 method under flow-through conditions. Under the conditions of this study, a steady state was achieved on day 28 of exposure, and the BCF factor was determined to be 46 at 0.025 mg/L and 60 at 0.0025 mg/L.

10.2.3.2. Ecotoxicity. RIFM, 1989c**:** An acute toxicity study was conducted with rainbow trout under semi-static conditions. The 96-h LC50 calculated by probit analysis and based on nominal concentrations was 2.209 mg/L.

RIFM, 1992a**:** An acute toxicity study was conducted with rainbow trout according to the OECD 203 method under semi-static conditions. The 96-h LC50 was reported to be 1.2 mg/L (based on mean measured test concentrations).

RIFM, 2013a,b**:** A 48-h *Daphnia magna* acute test was conducted according to the OECD 202 guidelines under static conditions. The EC50 was reported to be 1.45 mg/L (based on mean measured test concentrations).

RIFM, 1992b**:** A 48-h *Daphnia magna* acute immobilization test was performed, and the 48-h EC50 was reported to be 1.0 mg/L (based on nominal concentrations).

RIFM, 1999**:** An algae growth inhibition test was conducted according to the OECD 201 method. The 96-h EbC50 was reported to be 0.62 mg/L, the ErC50 was reported to be 1.0 mg/L, and the NOEC was reported to be 0.45 mg/L (based on measured concentrations).

RIFM, 2005b**:** A 10-day chronic static renewal effluent toxicity test with *Daphnia magna* was conducted according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. The NOECs were reported to be 0.51 mg/L for reproduction and 2.03 mg/L for survival.

RIFM, 2005b**:** Short-term, 7-day, 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 NOECs were reported to be 0.25 mg/L for growth and 2.03 mg/L for survival.

RIFM, 2006**:** A short-term chronic toxicity test was conducted with fathead minnows (*Pimephales promelas*) following methods EPA/600/4–90/027 and ASTM E729, 1997. The 7-days NOEC for growth and survival were reported as 0.34 mg/L and 2.71 mg/L, respectively.

10.2.3.3. Other available data. 3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol has been registered under REACH with no additional data at this time.

10.2.4. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)(mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>2.992</u>			1000000	0.002992	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.166	<u>0.129</u>	0.349	10000	0.0129	Neutral Organic
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.2		<u>0.25</u>	10	25	
Daphnia		1.0	0.51			
Algae		0.62	0.45			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	433	4.33
Biodegradation Factor Used	0	0
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; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/15/19.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/13/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

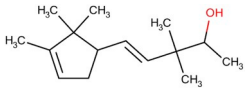
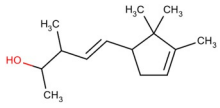
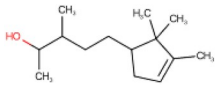
Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110715.

Appendix

Read-across Justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physical–chemical properties of the target material and read-across analogs were calculated using EPI Suite v4.11 developed by the US EPA (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (polysantol)	3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol	5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol
CAS No.	107898-54-4	67801-20-1	65113-99-7
Structure			
Similarity (Tanimoto Score)*		0.854	0.741
Read-across Endpoint		• Developmental and Reproductive	• Developmental and Reproductive
Molecular Formula	$C_{15}H_{26}O$	$C_{14}H_{24}O$	$C_{14}H_{26}O$
Molecular Weight	222.37	208.34	210.36
Melting Point (°C, EPI Suite)	63.64	46.53	47.63
Boiling Point (°C, EPI Suite)	288.22	278.76	273.81

Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.0166	0.0442	0.0591
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	5.39	4.93	4.6[1]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.711	7.838	5.013
J_{max} (μg/cm^2/h, SAM)	4.690	14.610	14.202
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.81E + 000	4.37E + 000	4.96E + 000
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (v3.4)	• Non-binder without OH or NH2 group	• Non-binder without OH or NH2 group	• Non-binder without OH or NH2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Toxicant (low reliability)	• Toxicant (low reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat Liver S9 Metabolism Simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

*RIFM, 1996.

Summary

There are insufficient toxicity data on 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (polysantol) (CAS # 107898-54-4). Hence, an *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) and 5-(2,2,3-trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS # 65113-99-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- 3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol (CAS # 67801-20-1) could be used as a structurally similar read-across analog for target material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (polysantol) (CAS # 107898-54-4) for the developmental and reproductive toxicity endpoint.
  - 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 material and the read-across analog have a 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol fragment common between them.
  - o The key difference between the target material and the read-across analog is that the target material has an additional branching of the methyl group at the β-carbon which the read-across analog lacks.
  - o The target material and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicology endpoint perspective.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the developmental and reproductive toxicity endpoint.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the developmental and reproductive toxicity endpoint are consistent between the target material and the read-across analog.
  - o According to the CAESAR model, both the read-across analog and the target material are predicted to be toxicants for the developmental toxicity endpoint. The data described in the developmental toxicity section above shows that the read-across substance presents no concern. Therefore, the alert will be superseded by the availability of 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 developmental and reproductive toxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant for the developmental and reproductive toxicity endpoint.
- 5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol (CAS # 65113-99-7) could be used as a structurally similar read-across analog for the target material 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (polysantol) (CAS # 107898-54-4) for the developmental and reproductive toxicity endpoint.
  - 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 material and the read-across analog have a 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pentan-2-ol fragment common between them.
  - o The key difference between the target material and the read-across analog is that the target has an additional vinyl group in the aliphatic chain which the read-across analog lacks.
  - o The target material and the read-across analog have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pentan-2-ol fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicology endpoint perspective.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the developmental and reproductive toxicity endpoint.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the developmental and reproductive toxicity endpoint are consistent between the target material and the read-across analog.
  - o According to the CAESAR model, both the read-across analog and the target material are predicted to be toxicants for the developmental toxicity endpoint. The data described in the developmental toxicity section above shows that the read-across substance presents no concern.

Therefore, the alert will be superseded by the availability of 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 developmental and reproductive toxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
- o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant for the developmental and reproductive toxicity endpoint.

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