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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol, CAS Registry number 41199-19-3

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Version: 031918. This version replaces any previous versions.

Name: 1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol

CAS Registry Number: 41199-19-3

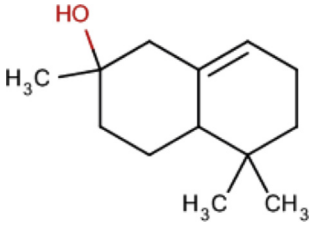
Additional CAS Numbers*:

670-24-6 β-Ambrinol

71832-76-3 Octahydro-2,5,5-trimethyl-2-naphthol

643-53-8 2,3,4,4a,5,6,7,8-Octahydro-2,5,5-trimethyl-2-naphtol (no reported use)

*These materials are included in this assessment because they are a commercial mixture.



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

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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., 2015b, 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
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
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 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 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 use of this material under current conditions is supported by existing information

1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material show that this material is not genotoxic. Based on existing data and the application of the non-reactive DST, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol does not present a concern for skin sensitization. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and available data. The environmental endpoints were evaluated; 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol 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, 1988; RIFM, 2015)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization. Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1981; RIFM, 2001)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.34 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 173.2 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.135 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.135 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.2135 μg/L	

- Revised PEC/PNECs (2015 IFRA Volume of Use): North America and Europe: < 1

1. Identification

Chemical Name: 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol	Chemical Name: β-Ambrinol	Chemical Name: Octahydro-2,5,5-trimethyl-2-naphthol	Chemical Name: 2,3,4,4a,5,6,7,8-Octahydro-2,5,5-trimethyl-2-naphtol
CAS Registry Number: 41199-19-3	**CAS Registry Number:** 670-24-6	**CAS Registry Number:** 71832-76-3	**CAS Registry Number:** 643-53-8
Synonyms: 2-Naphthalenol, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-; 1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthol; Ambrinol; 2,5,5-トリメチル-1,2,3,4,4a,5,6,7-オクタヒドロ-2-ナフトールと2,5,5-トリメチル-1,2,3,4,5,6,7,8-オクタヒドロ-2-ナフトールと2,5,5-トリメチル-2,3,4,4a,5,6,7,8-オクタヒドロ-2-ナフトールの混合物; 2,5,5-Trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol; Polyambrol; Ambrinol S; 1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol	**Synonyms:** (S)-1,2,3,4,5,6,7,8-Octahydro-2,5,5-trimethyl-2-naphtol; 2,5,5-Trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-ol; 2-Naphthalenol, 1,2,3,4,5,6,7,8-octahydro-2,5,5-trimethyl-, (S)-	**Synonyms:** 2-Naphthalenol, octahydro-2,5,5-trimethyl-; Ambrinol	**Synonyms:** gamma-Ambrinol; 2,5,5-Trimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-ol; 2-Naphthalenol, 2,3,4,4a,5,6,7,8-octahydro-2,5,5-trimethyl-
Molecular Formula: $C_{13}H_{22}O$	**Molecular Formula:** $C_{13}H_{22}O$	**Molecular Formula:** $C_{13}H_{22}O$	**Molecular Formula:** $C_{13}H_{22}O$
Molecular Weight: 194.32	**Molecular Weight:** 194.32	**Molecular Weight:** 194.32	**Molecular Weight:** 194.32
RIFM Number: 5125	**RIFM Number:** Not Available	**RIFM Number:** 5965	**RIFM Number:** 5965
Stereochemistry: Isomer not specified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

Boiling Point: 266.66 °C (US EPA, 2012a)	Boiling Point: 270.03 °C (US EPA, 2012a)	Boiling Point: 274.31 °C (US EPA, 2012a)	Boiling Point: 266.66 °C (US EPA, 2012a)
Flash Point: > 93 °C (GHS)	**Flash Point:** 239.00 °F TCC (115.00 °C)* *http://www.thegoodscentscompany.com/data/rw1378761.html, retrieved 08/16/17	**Flash Point:** > 212.00 °F TCC (> 100.00 °C)* *http://www.thegoodscentscompany.com/data/rw1024191.html#toorgano, retrieved 08/16/17	**Flash Point:** 240.00 °F TCC (115.30 °C)* *http://www.thegoodscentscompany.com/data/rw1378831.html, retrieved 08/16/17
Log K_{OW}: 3.9 (US EPA, 2012a)	**Log K_{OW}:** 4.37 (US EPA, 2012a)	**Log K_{OW}:** 3.6 (US EPA, 2012a)	**Log K_{OW}:** 3.9 (US EPA, 2012a)

Melting Point: 62.22 °C (US EPA, 2012a)	**Melting Point:** 69.12 °C (US EPA, 2012a)	**Melting Point:** 71.29 °C (US EPA, 2012a)	**Melting Point:** 62.22 °C (US EPA, 2012a)
Water Solubility: 71.04 mg/L (US EPA, 2012a)	**Water Solubility:** 28.09 mg/L (US EPA, 2012a)	**Water Solubility:** 134.3 mg/L (US EPA, 2012a)	**Water Solubility:** 71.04 mg/L (US EPA, 2012a)
Specific Gravity: 0.93600 to 0.94800 @ 20.00 °C* *http://www.thegoodscentscompany.com/data/rw1052421.html#toorgano, retrieved 12/3/2015	**Specific Gravity:** Not Available	**Specific Gravity:** 0.94000 to 0.95000 @ 25.00 °C* *http://www.thegoodscentscompany.com/data/rw1024191.html#toorgano, retrieved 08/16/17	**Specific Gravity:** Not Available
Vapor Pressure: 0.000253 mm Hg @ 20 °C (US EPA, 2012a), 0.000503 mm Hg @ 25 °C (US EPA, 2012a)	**Vapor Pressure:** 0.000348 mm Hg @ 25 °C (US EPA, 2012a)	**Vapor Pressure:** 0.000253 mm Hg @ 25 °C (US EPA, 2012a), 0.000125 mm Hg @ 20 °C (US EPA, 2012a)	**Vapor Pressure:** 0.000253 mmHg @ 20 °C (US EPA, 2012a), 0.000503 mm Hg @ 25 °C (US EPA, 2012a)
UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)	**UV Spectra:** No reported use in 2015	**UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)	**UV Spectra:** No reported use in 2015
Appearance/Organoleptic: A colorless to pale yellow clear liquid to solid with a high amber, natural, musk, animal odor while at 10% in dipropylene glycol (Luebke, William tgsc, 1993).* *http://www.thegoodscentscompany.com/data/rw1052421.html#toorgano, retrieved 12/3/15	**Appearance/Organoleptic:** Not Available	**Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a powerful, amber, natural, musk, animal odor* *http://www.thegoodscentscompany.com/data/rw1024191.html#toorgano, retrieved 08/16/17	**Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.015% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000016 mg/kg/day or 0.0012 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00021 mg/kg/day (RIFM, 2016)

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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*	III	I

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further detail.

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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol is not reported to occur in foods by the VCF* and is not found in natural complex substances (NCS).

*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. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 08/16/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol, however the mutagenic potential of a mixture containing octahydro-2,5,5-trimethyl-2-naphthol (CAS # 71832-76-3) was evaluated. The mutagenic activity of octahydro-2,5,5-trimethyl-2-naphthol has been evaluated in a bacterial reverse mutation assay conducted in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with octahydro-2,5,5-trimethyl-2-naphthol in solvent (not specified) 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, 1988). Under the conditions of the study, octahydro-2,5,5-trimethyl-2-naphthol was not mutagenic in the Ames test.

The clastogenic activity of a mixture containing 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol was evaluated in an in vitro micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol in dimethyl sulfoxide (DMSO) at concentrations up to 1940 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015). Under the conditions of the study, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol or any read-across materials. The total systemic exposure to 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol (0.21 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/17/17.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol or any read-across materials. The total systemic exposure to 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol or any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol (0.21 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/17/17.

10.1.4. Skin sensitization

Based on existing data and the application of DST, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol does not present a safety concern concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol. The chemical structures of this material indicate that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In 3 separate human repeat insult patch tests (HRIPTs), 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol was shown to be non-sensitizing (RIFM, 1975a; RIFM, 1975b; RIFM, 1981). Acting conservatively, due to limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford et al., 2015a). 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 acceptable concentration for 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: RIFM, 2001.

Literature Search and Risk Assessment Completed on: 07/26/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available study data, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. 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 et al., 2009). In a photo-HRIPT, 4% test material was not phototoxic or photoallergenic to human volunteers (RIFM, 1981). In an *in vivo* guinea pig phototoxicity test, the test material at concentrations up to 50% was not phototoxic

Table 1
Acceptable concentrations for 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.07%	0.00%[b]
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.02%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.00%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.09%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

(RIFM, 2001). Based on the lack of absorbance and study data, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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, $1000\,L\,mol^{-1}\cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/21/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol 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 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol. Based on the Creme RIFM Model, the inhalation exposure is 0.0012 mg/day. This exposure is 392 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: 08/17/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening level 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, 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol 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 (US EPA, 2012a) identified 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol 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 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, 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 v4.1). Data on persistence 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 Volume of Use (2015), 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1,2,3,4,4a,5,6,7-octahydro-2,5,5-trimethyl-2-naphthalenol has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	5.827			1,000,000	0.005827	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.155	2.135	3.281	10,000	0.2135	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} used	3.9	3.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

*Combined Regional Volumes for al CAS #

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

The RIFM PNEC is 0.2135 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 07/31/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix

Explanation of Cramer classification

Due to potential discrepancies between 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 (see explanation in Cramer et al., 1978)? **No**.

Q17. Readily hydrolyzed to a common terpene? **No**.

Q19. Open chain? **No**.

Q23. Aromatic? **No**.

Q24. Monocarbocyclic with simple substituents? **No**.

Q25. Cyclopropane (see explanation in Cramer et al., 1978)? **No**.

Q26. Monocycloalkanone or a bicyclo compound? **Yes**, Class Intermediate (Class II).

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