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Short Review

# RIFM fragrance ingredient safety assessment, *dl*-citronellol, CAS Registry Number 106-22-9

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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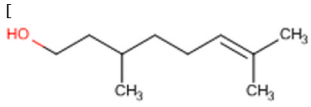
Name: *dl*-Citronellol
CAS Registry Number: 106-22-9
Additional CAS Numbers*: 6812-78-8 Rhodinol 26489-01-0 6 -Octen-1-ol, 3,7-dimethyl-,(+/−)- (no reported use) 1117-61-9 (+)-(R)-Citronellol (no reported use) 141-25-3 3,7-Dimethyloct-7-en-1-ol 7540-51-4 l-Citronellol
*Included because the materials are isomers

[  ]

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* Corresponding author.
*E-mail address:* gsullivan@rifm.org (G. Sullivan).

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**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**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
**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.**

*dl*-Citronellol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that *dl*-citronellol is not genotoxic. Data on read-across materials geraniol (CAS # 106-24-1) and nerol (CAS # 106-25-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. Data on *dl*-citronellol provide a calculated MOE >100 for the developmental toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 29 000 μg/cm$^2$ for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; *dl*-citronellol is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure to *dl*-citronellol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *dl*-citronellol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

**Human Health Safety Assessment**

| | |
|---|---|
| **Genotoxicity**: Not genotoxic. | (ECHA Reach Dossier: Citronellol; ECHA, 2010) |
| **Repeated Dose Toxicity:** NOAEL = 60.2 mg/kg/day. | (RIFM, 2010a) |
| **Developmental and Reproductive Toxicity:** | |
| Developmental Toxicity NOAEL = 750 mg/kg/day. Reproductive Toxicity NOAEL = 1000 mg/kg/day. | (ECHA Dossier: Citronellol; ECHA, 2010; RIFM, 2010) |
| **Skin Sensitization:** NESIL = 29 000 μg/cm$^2$. | (RIFM, 2005a) |
| **Photoirritation/Photoallergenicity:** Not photoirritating/not expected to be photoallergenic. | (UV/Vis Spectra, RIFM Database; RIFM, 1983) |
| **Local Respiratory Toxicity:** No NOAEC available. Exposure is below TTC. | |

**Environmental Safety Assessment**

| | |
|---|---|
| **Hazard Assessment:** | |
| **Persistence:** Critical Measured Value: 99.1 % (301B) | (RIFM, 1994) |
| **Bioaccumulation:** Screening-level: 176.5 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** Critical Ecotoxicity Endpoint: 96-h algae acute: 5.6 mg/L | RIFM (2021b) |

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(*continued*)

| | |
|---|---|
| **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards | |
| **Risk Assessment:** | |
| **Screening-level:** PEC/PNEC (North America and Europe) > 1 | (RIFM Framework; Salvito, 2002) |
| **Critical Ecotoxicity Endpoint:** 96-h algae acute: 5.6 mg/L | RIFM (2021b) |
| **RIFM PNEC is:** 5.6 μg/L | |
| • Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1 | |

## 1. Identification

8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Organoleptic:** A colorless liquid which has a fresh rosy odor, variable according to its purity

| Chemical Name: *dl*-Citronellol | Chemical Name: *l*-Citronellol | Chemical Name: 3,7-Dimethyloct-7-en-1-ol | Chemical Name: (+)-(R)-Citronellol | Chemical Name: 6-Octen-1-ol, 3,7-dimethyl-,(+/−)- | Chemical Name: Rhodinol |
|---|---|---|---|---|---|
| **CAS Registry Number:** 106-22-9 | **CAS Registry Number:** 7540-51-4 | **CAS Registry Number:** 141-25-3 | **CAS Registry Number:** 1117-61-9 | **CAS Registry Number:** 26 489-01-0 | **CAS Registry Number:** 6812-78-8 |
| **Synonyms:** Citronellol; 3,7-Dimethyl-6-octen-1-ol; 6-Octen-1-ol, 3,7-dimethyl-; 脂肪族不飽和アルコール(C = 9 ~ 14); 3,7-Dimethyloct-6-en-1-ol; Rhodinol pure; *dl*-Citronellol | **Synonyms:** (−)-3,7-Dimethyloct-6-en-1-ol; (S)-3,7-Dimethyl-6-octen-1-ol; 3,7-Dimethyloct-6-en-1-ol; 6-Octen-1-ol, 3,7-dimethyl-, (S)-; 脂肪族不飽和アルコール(C 9 ~ 24) | **Synonyms:** α-Citronellol; 7-Octen-1-ol, 3,7-dimethyl- (isomer unspecified); 脂肪族不飽和アルコール（C = 9 ~ 24） | **Synonyms:** (+)-β-Citronellol; (R)-3,7-Dimethyloct-6-en-1-ol; 3,7-Dimethyloct-6-en-1-ol; 6-Octen-1-ol, 3,7-dimethyl-, (R)- | **Synonyms:** N/A | **Synonyms:** 3,7-Dimethyl-(6-or 7-)octen-1-ol; 3,7-Dimethyl-7-octen-1-ol; 3,7-Dimethyloct-7-en-1-ol; 7-Octen-1-ol, 3,7-dimethyl-, (S)-; 脂肪族不飽和アルコール(C = 9 ~ 24) |
| **Molecular Formula:** $C_{10}H_{20}O$ | **Molecular Formula:** $C_{10}H_{20}O$ | **Molecular Formula:** $C_{10}H_{20}O$ | **Molecular Formula:** $C_{10}H_{20}O$ | **Molecular Formula:** $C_{10}H_{20}O$ | **Molecular Formula:** $C_{10}H_{20}O$ |
| **Molecular Weight:** 156.26 g/mol | **Molecular Weight:** 156.26 g/mol | **Molecular Weight:** 156.26 g/mol | **Molecular Weight:** 156.26 g/mol | **Molecular Weight:** 156.26 g/mol | **Molecular Weight:** 156.26 g/mol |
| **RIFM Number:** 118 | **RIFM Number:** 1303 | **RIFM Number:** 5167 | **RIFM Number:** 5227 | **RIFM Number:** 7318 | **RIFM Number:** 200 |
| **Stereochemistry:** Isomer not specified. One stereocenter and 2 stereoisomers are possible. | **Stereochemistry:** S-isomer not specified—one stereocenter and 2 stereoisomers possible. | **Stereochemistry:** Isomer not specified—one stereocenter and 2 stereoisomers possible. | **Stereochemistry:** R-isomer specified. One stereocenter and 2 stereoisomers are possible. | **Stereochemistry:** Isomer not specified. One stereocenter and 2 stereoisomers are possible. | **Stereochemistry:** Tautomer of the main material. S-Isomer specified. One stereocenter and 2 stereoisomers are possible. |

## 2. Physical data*

1. **Boiling Point:** 225 °C at 1013 mb (RIFM, 1989), 225 °C (Fragrance Materials Association [FMA] Database), (calculated) 228.21 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA Database)
3. **Log $K_{ow}$:** Log Pow = 2.7 and 3.1 (RIFM, 2004), 3.1 (RIFM, 1991), 3.1 at 35 °C (RIFM, 2006), 3.56 (EPI Suite)
4. **Melting Point**: −12.16 °C (EPI Suite)
5. **Water Solubility:** very slightly soluble (RIFM, 1989), 0.03% wV (BBA, 1990), (calculated) 105.5 mg/L (EPI Suite)
6. **Specific Gravity:** 0.854 (FMA Database), 0.86 g/mL (RIFM, 1994)
7. **Vapor Pressure:** 0.0714 torr (Vuilleumier et al., 1995), (calculated) 0.0102 mm Hg at 20 °C (EPI Suite v4.0), (calculated) 0.009 mm Hg at 20 °C (FMA Database), (calculated) 0.0169 mm Hg at 25 °C (EPI Suite)

*All physical data is identical for all materials in this assessment.

## 3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA, 2019)

## 4. EXPOSURE to fragrance ingredient*** (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.37% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0057 mg/kg/day or 0.45 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0094 mg/kg/day (RIFM, 2018)

*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 fine fragrance, inhalation exposure, and total exposure.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

## 5. Derivation of systemic absorption

1. **Dermal:** 36.7% (human); 60.2% (rat)

Geraniol (CAS # 106-24-1) is used as read-across for *dl*-citronellol for the repeated dose toxicity endpoint.

**RIFM SABS testing on geraniol (RIFM, 2021a):** *In vitro* human skin and rat skin absorption studies for geraniol (CAS # 106-24-1) were conducted following OECD TG 428 guidelines with the application of 1% w/v (50 μg/cm$^2$ dose in 5 μL) in 70/30 (v/v) ethanol/water under both unoccluded and occluded conditions for 24 h. For both unoccluded and occluded conditions, 12 active-dosed diffusion cells were prepared in addition to 4 control cells (unoccluded conditions). At the end of 24 h, 12.0% ± 1.1% (=6.00 ± 0.56 μg/cm$^2$), and 36.7% ± 1.2% (=18.3 ± 0.6 μg/cm$^2$) of the applied dose permeated through the human skin under unoccluded and occluded conditions, respectively. These values represent the worst-case scenario as a total of geraniol found in the epidermis, filter paper membrane support, and receptor fluid, and SC tape strips were 2–10. Overall recovery from the human skin assay was 15.1% ± 1.4% and 70.0% ± 1.3% under unoccluded and occluded conditions, respectively. At the end of 24 h, 40.2% ± 1.3% (=19.7 ± 0.7 μg/cm$^2$), and 60.2% ± 1.6% (=29.5 ± 0.8 μg/cm$^2$) of the applied dose permeated through the rat skin under unoccluded and occluded conditions, respectively. Overall recovery from the rat skin assay was 42.5% ± 1.6% and 74.7% ± 1.3% under unoccluded and occluded conditions, respectively.

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

## 6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

| Expert Judgment | Toxtree v3.1.0 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| I | I | I |

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Geraniol (CAS # 106-24-1); nerol (CAS # 106-25-2)
   c. **Reproductive Toxicity:** Geraniol (CAS # 106-24-1); nerol (CAS # 106-25-2)
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

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

## 8. Natural occurrence

*dl*-Citronellol is reported to occur in the following foods by the VCF*

| | |
|---|---|
| Apple brandy (Calvados) | Nutmeg (*Myristica fragrans* Houttuyn) |
| Loquat (*Eriobotrya japonica* Lindl.) | *Ocimum* species |
| Malt | Okra (*Hibiscus esculentus* L.) |
| Mustard (*Brassica* species) | Vanilla |
| Myrtle (*Myrtus communis* L.) | Wine |

*l*-Citronellol is not reported to occur in foods by the VCF.

3,7-Dimethyloct-7-en-1-ol is reported in the following foods by the VCF:

Lemon grass oil.

(+)-(R)-Citronellol is not reported to occur in foods by the VCF.

6-Octen-1-ol, 3,7-dimethyl-,(+/−)- is not reported to occur in foods by the VCF.

Rhodinol is reported to occur in the following foods by the VCF:

Citrus fruits.

*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. This is a partial list.

## 9. REACH dossier

dl-Citronellol has a dossier available; accessed 10/27/21 (ECHA, 2010). *l*-Citronellol and (+)-(R)-citronellol have dossiers available; accessed 10/27/21. 3,7-Dimethyloct-7-en-1-ol, 6-octen-1-ol, 3,7-dimethyl-,(+/−)-, and rhodinol are all pre-registered for 2010; no dossiers available as of 08/17/22.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for *dl*-citronellol are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.34 |
| 2 | Products applied to the axillae | 0.66 |
| 3 | Products applied to the face/body using fingertips | 0.41 |
| 4 | Products related to fine fragrances | 8.0 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 2.6 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.39 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.55 |
| 5D | Baby cream, oil, talc | 0.13 |
| 6 | Products with oral and lip exposure | 0.023 |
| 7 | Products applied to the hair with some hand contact | 0.46 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.13 |

(*continued on next page*)

(*continued*)

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 1.3 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.89 |
| 10B | Aerosol air freshener | 3.5 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.13 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | 90. |

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 dl-citronellol, the basis was the subchronic reference dose of 0.602 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 29 000 μg/cm$^2$.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data and use levels, *dl*-citronellol does not present a concern for genetic toxicity.

*11.1.1.1. Risk assessment.* A mammalian cell gene mutation assay was conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary cells were treated with citronellol in dimethyl sulfoxide (DMSO) at concentrations of 0, 6.3, 12.5, 25.0, 50.0, 100.0, 150.0, 175.0, and 200.0 μg/mL (as determined in a preliminary toxicity assay), for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2010). Under the conditions of the study, citronellol was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of citronellol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in 2:3 DMSO:corn oil via oral gavage to groups of male and female NMRI mice. Doses of 375, 750, or 1500 mg/kg were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes (PCEs). The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PCEs) in the bone marrow (ECHA, 2010). Under the conditions of the study, citronellol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, citronellol does not present a concern for genotoxic potential.

**Additional References:** Rockwell, 1979; Oda et al., 1978; Kono et al., 1995.

**Literature Search and Risk Assessment Completed On:** 10/15/21.

#### 11.1.2. Repeated dose toxicity

The MOE for *dl*-citronellol is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are insufficient repeated dose toxicity data on *dl*-citronellol. A dietary 90-day subchronic toxicity study was conducted in rats with a mixture of equal parts *dl*-citronellol and linalool. The dosage was 100 mg/kg body weight, resulting in a dosage of 50 mg/kg/day *dl*-citronellol. The NOAEL was determined to be 50 mg/kg/day, the only dosage tested (RIFM, 1958).

Read-across materials geraniol (CAS # 106-24-1; see Section VI) and nerol (CAS # 106-25-2) have sufficient data to support the repeated dose toxicity endpoint.

In a GLP- and OECD 422-compliant study, groups of 10 Han Wistar rats/sex/dose were administered nerol via diet at concentrations of 0, 3000, 6000, and 12 000 ppm (equivalent to 191.2, 374, and 720 mg/kg/day, respectively); however, only 5 male Han Wistar rats/dose received the control and high dose treatment. Females were treated from day 1 of pre-mating throughout mating and gestation until day 6 postpartum, while males were treated for 42 days. Additional groups of 5 Han Wistar rats/sex/dose at 0 and 12 000 ppm were maintained for a subsequent 14-day recovery period without treatment. No treatment-related mortality was observed throughout the study period. There were no treatment-related adverse effects on clinical signs, water consumption, hematology, behavior, or organ weights. Food consumption was reduced during the treatment period, which was attributed to a reluctance to eat the diet admixture due to its low palatability, particularly at the high dose. Bodyweight gain was resultantly reduced in both sexes at the high dose throughout the treatment period but became higher in both sexes of the high dose group (compared to the control group) during the recovery period. Levels of total bilirubin, sodium, globulin, and triglycerides were reduced in males at the high dose, while levels of creatinine, ALP, and albumin were increased in males at the high dose. Enlarged liver correlated with slight centrilobular hepatocellular hypertrophy was observed in high-dose males. Tubular basophilia and hyaline droplets were observed in the kidneys of males at the high dose; however, these were attributed to α-2μ-globulin nephropathy, and thus were not considered to be adverse. Based on clinical chemistry changes and liver enlargement observed at the high dose, the NOAEL for this study was considered to be 374 mg/kg/day (ECHA, 2013).

In another OECD 421 gavage study, 10 Wistar rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day were administered geraniol 60 (a mixture of geraniol and nerol, approximately 60:40) in corn oil. No treatment-related mortality or clinical signs of toxicity were reported in any of the groups. Food consumption was suppressed, especially in females, while body weight and bodyweight gain were significantly lower in both sexes at the highest dose. No treatment-related histopathological or organ weight changes were reported at any dose. However, increased fetal mortality and developmental effects were observed at both high- and mid-doses (see the developmental and reproductive toxicity section). Based on the alterations of food consumption and bodyweight alterations, the NOAEL for general toxicity was considered to be 300 mg/kg/day (RIFM, 2010).

In an OECD 421- and GLP-compliant study, groups of 10 Wistar rats/sex/dose were administered geraniol extra (geraniol) dermally under semi-occluded conditions for 6 h/day at dermal doses of 0 (corn oil vehicle control), 50, 150, and 450 mg/kg/day for 16 weeks. Due to observed local effects, the highest dose was lowered to 300 mg/kg on day 10 (until the end of study duration). Generally, males were euthanized on day 32, and females were euthanized on day 49. Local toxicity related to the irritating potential of geraniol extra (geraniol) was reported at all dose levels and not considered in determining the NOAEL for the study. Since no treatment-related adverse effects were observed in the F0 (paternal) generation at the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 300 mg/kg (RIFM, 2010a).

Furthermore, to account for bioavailability following the dermal application, data from a skin absorption test performed on rat skin (RIFM, 2021a; see section V) were used to revise the NOAEL of 300 mg/kg/day to represent the systemic dose. Hence, at a dermal penetration of 60.2% (over 24 h) of the applied dose, the revised geraniol toxicity NOAEL from the dermal study is 180.6 mg/kg/day.

Since the dermal OECD 421 study offers the most conservative NOAEL, the NOAEL for the repeated dose toxicity endpoint was considered to be 180.6 mg/kg/day. In addition, a default safety factor of 3 was used when deriving a NOAEL from the OECD 421 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 180.6/3, or 60.2 mg/kg/day.

Therefore, the *dl*-citronellol MOE for the repeated dose toxicity endpoint can be calculated by dividing the geraniol NOAEL in mg/kg/day by the total systemic exposure for *dl*-citronellol, 60.2/0.0094, or 6404.

In addition, the total systemic exposure for *dl*-citronellol (9.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10X) and intraspecies (10X) differences. These factors can be refined based on the availability of data. Due to insufficient intraspecies susceptibility data for *dl*-citronellol, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further subdivided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences, respectively (Renwick, 1993).

Section X 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, 2020) and a subchronic reference dose (RfD) of 0.602 mg/kg/day.

*11.1.2.1.1. Derivation of subchronic RfD.* The subchronic RfD for *dl*-citronellol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 60.2 mg/kg/day by the uncertainty factor, 100 = 0.602 mg/kg/day.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/15/21.

### *11.1.3. Reproductive toxicity*

The MOE for *dl*-citronellol is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* There are sufficient developmental toxicity data on *dl*-citronellol. In OECD 414-compliant study, groups of 25 time-mated female Wistar rats/dose were administered *dl*-citronellol via gavage at doses of 0 (corn oil), 75, 250, and 750 mg/kg body weight/day on gestation days (GD) 6 through 19. At terminal euthanasia on GD 20 and 24–25 females per group had implantation sites. There were no alterations in terms of food consumption or bodyweight gains, conception rate, mean number of corpora lutea, mean number of implantations, as well as pre- and post-implantation loss among the treated animals. A significant increase in liver weight among the mid- and high-dose animals was reported; however, histopathological examination or clinical chemistry parameters revealed no alterations in the tissue samples. Thus, this was considered to be an adaptive change. Treated animals showed transient salivation, which persisted in the animals for some minutes immediately after gavage; this was not considered to be treatment-related but mainly due to the bad taste of the test material. There was no alteration in terms of sex distribution among the fetus of the treated animals. Mean fetal weights of the high-dose offspring were slightly (6%) but statistically significantly below the mean fetal control weights in this study. However, they were close to the mean of the historical control and well within the historical control range (3.1–4.0 in the 95% spread). In addition, there were no other findings recorded in this study at all, which may hint at any potential influence of the test material on prenatal development. Thus, this isolated observation is not considered to be of toxicological concern. Overall, there was no evidence for toxicologically relevant adverse effects of the test material on fetal morphology at any dose. Thus, oral administration of citronellol to pregnant Wistar rats caused no maternal or fetal toxicity up to the highest dose tested; hence the NOAEL for developmental toxicity was considered to be 750 mg/kg/day, the highest dose tested (ECHA, 2010).

Therefore, the *dl*-citronellol MOE for the developmental toxicity endpoint can be calculated by dividing the *dl*-citronellol NOAEL in mg/kg/day by the total systemic exposure for *dl*-citronellol, 750/0.0094 or 79 787.

There are no fertility data on *dl*-citronellol. Read-across materials geraniol (CAS # 106-24-1; see Section VI) and nerol (CAS # 106-25-2; see section V) have sufficient data to support the fertility endpoint.

An OECD 421 dermal reproduction/developmental toxicity screening test was conducted in Wistar rats. Geraniol extra (geraniol) was administered dermally to 10 rats/sex/dose under semi-occlusion for 6 h/day at doses of 0, 50, 150, and 450 mg/kg/day in corn oil. The highest dose was decreased to 300 mg/kg/day from day 10 onwards due to local effects. Applications were made 7 days/week for 2 weeks prior to mating, during mating (2 weeks maximum), and for a post-mating period of 1 week (males only). Females continued to receive treatment until gestation day (GD) 19. Females were allowed to rear pups for 4 days. The males were euthanized on day 32, and females were euthanized on day 49. Local signs of toxicity related to the irritating potential of geraniol extra (geraniol) were reported at all dose levels. Local effects at the site of the application included slight to moderate erythema, focal red spots, and focal scaling. Histopathological examination of the skin sections revealed lymphocytic infiltration graded minimal to slight in treated skin sections in mid- and high-dose animals. There were no effects of treatment on the male and female mating index along with the male and female fertility index. The gestation index, implantation sites, live birth indices, pup viability index, pup sex ratio, and pup body weights among treated animals remained comparable to the control group. The NOAEL for reproductive performance, fertility, and developmental toxicity was considered to be 300 mg/kg/day, the highest dose tested (RIFM, 2010a). Furthermore, to account for bioavailability

**Table 1**
Data summary for *dl*-citronellol.

| LLNA Weighted Mean EC3 Value μg/Cm$^2$ [No. Studies] | Potency Classification Based on Animal Data[a] | Human Data | | | |
|---|---|---|---|---|---|
| | | NOEL-CNIH (induction) μg/cm$^2$ | NOEL-HMT (induction) μg/cm$^2$ | LOEL[b] (induction) μg/cm$^2$ | WoE NESIL[c] μg/cm$^2$ |
| 10 875 [1] | Extremely Weak | 29 528 | 4138 | NA | 29 000 |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans 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 CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

following the dermal application, data from a skin absorption test performed on rat skin (RIFM, 2021a; see section V) were used to revise the NOAEL of 300 mg/kg/day to represent the fertility and developmental toxicity point of departure. Hence, at a dermal penetration of 60.2% (over 24 h) of the applied dose, the revised geraniol toxicity NOAEL from the dermal study is 180.6 mg/kg/day.

In another OECD 421 study, geraniol 60 (a mixture of geraniol and nerol (a stereoisomer, CAS # 106-25-2; see Section VI), approximately 60:40) was administered to groups of 10 Wistar rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. Rats were gavaged daily for 2 weeks plus a mating period (2 weeks maximum), a post-mating period of 1 week (males only), and through gestation, and 4 days postpartum for females. Males were euthanized after a minimum of 28 days, and females were euthanized after a minimum of 4 days postpartum. There were no alterations in the mating and fertility indices among treated animals as compared to the controls. The duration of gestation and gestation index was comparable to the female controls. There were no treatment-related alterations in the male and female reproductive organs up to the highest dose tested. The NOAEL for male and female fertility was considered to be 1000 mg/kg/day (RIFM, 2010).

In a GLP- and OECD 422-compliant study, groups of 10 Han Wistar rats/sex/dose were administered nerol via diet at concentrations of 0, 3000, 6000, and 12 000 ppm (equivalent to 191.2, 374, and 720 mg/kg/day, respectively); however, only 5 male Han Wistar rats/dose received the control and high dose treatment. Females were treated from day 1 of pre-mating throughout mating and gestation until day 6 postpartum, while males were treated for 42 days. Additional groups of 5 Han Wistar rats/sex/dose at 0 and 12 000 ppm were maintained for a subsequent 14-day recovery period without treatment. No treatment-related mortality was observed throughout the study period. There were no treatment-related adverse effects on mating, fertility, gestation length, offspring viability, or offspring growth and development. Post-implantation loss was significantly increased at the mid and high doses. Based on increased post-implantation loss at the high dose, the developmental toxicity NOAEL for this study was considered to be 191.2 mg/kg/day. Based on no adverse effects seen up to the highest dose, the fertility NOAEL for this study was considered to be 720 mg/kg/day (ECHA, 2013).

The fertility NOAEL was considered to be 1000 mg/kg/day, the highest dose tested from the oral gavage study conducted on geraniol/nerol mixture since no alterations in the reproductive performance were observed among treated animals up to the highest-dose group from both OECD 421 studies.

Therefore, the *dl*-citronellol MOE for the fertility endpoint can be calculated by dividing the geraniol NOAEL in mg/kg/day by the total systemic exposure for *dl*-citronellol, 1000/0.0094, or 106 382.

In addition, the total systemic exposure for *dl*-citronellol (9.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/15/21.

### 11.1.4. Skin sensitization

Based on the available data, *dl*-citronellol is considered a skin sensitizer with a defined NESIL of 29 000 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the existing data, *dl*-citronellol 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, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). However, similar to other terpenes, *dl*-citronellol may be expected to undergo autoxidation processes leading to potentially sensitizing degradation products (Rudback, 2014). *dl*-Citronellol was found to have low reactivity in the *in vitro* direct peptide reactivity assay (DPRA), was negative in the KeratinoSens assay, and positive in the human cell line activation test (h-CLAT) (RIFM, 2014; RIFM, 2015; Piroird et al., 2015; Urbisch, 2015). In a murine local lymph node assay (LLNA), *dl*-citronellol was found to be sensitizing with an EC3 value of 43.5% (10 875 μg/cm$^2$) (RIFM, 2005b). In another LLNA, *dl*-citronellol was found to be non-sensitizing when tested up to 80% (Rudback, 2014). In a human maximization test with *dl*-citronellol, no skin sensitization reactions were observed (Greif, 1967). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 29 528 μg/cm$^2$ of *dl*-citronellol in ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2005a).

The available data demonstrate that *dl*-citronellol is an extremely weak sensitizer with a Weight of Evidence (WoE) NESIL of 29 000 μg/cm$^2$ (Table 1). Section X 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, 2020) and a subchronic RfD of 0.602 mg/kg/day.

**Additional References:** RIFM, 1992; Ishihara et al., 1986; Klecak (1979); Klecak (1985); RIFM, 1971; RIFM, 1993; RIFM, 1973; RIFM, 1962; RIFM, 1965.

**Literature Search and Risk Assessment Completed On:** 10/15/21.

### 11.1.5. Photoirritation/photoallergenicity

Based on UV/Vis absorbance spectra along with available data, *dl*-citronellol would not be expected to present a concern for photoirritation. Based on UV/Vis absorbance spectra, *dl*-citronellol would not be expected to present a concern for photoallergenicity.

*11.1.5.1. Risk assessment.* The available UV absorption spectrum for *dl*-citronellol demonstrates that this material does not absorb UV light in the region of 290–700 nm; the molar absorption coefficient for the same region is below the benchmark of concern for photoirritating effects (Henry et al., 2009). In a guinea pig photoirritation study, topical application of 3% and 10% solutions of *dl*-citronellol followed by UV exposure did not result in photoirritating reactions (RIFM, 1983). Based on the *in vivo* experimental data and lack of absorbance, *dl*-citronellol does not present a concern for photoirritation. Based on the lack of absorbance, *dl*-citronellol would not be expected to present a concern for photoallergenicity.

*11.1.5.2. UV spectra analysis.* The available UV/Vis absorption spectra (OECD TG 101) for *dl*-citronellol demonstrate that this material does not absorb UV light in the region of 290–700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity, 1000 L mol$^{-1}$ • cm$^{-1}$ (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/28/21.

### 11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *dl*-citronellol is below the Cramer Class I TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are limited inhalation data available on *dl*-citronellol. Based on the Creme RIFM Model, the inhalation exposure is 0.45 mg/day. This exposure is 3.1 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:** Troy (1977); Buchbauer et al., 1993; Corsi (2007); RIFM, 1983.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 23.24 | | | 1000000 | 0.02324 | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 5.148 | 3.375 | 4.552 | 10000 | 0.3375 | Neutral Organics |
| **Tier 3: Measured Data** | | | | | | |
| | LC50 | EC50 | NOEC | AF | PNEC | Comments |
| Fish | 14.6 | | | | | |
| *Daphnia* | | 17.48 | | | | |
| Algae | | 5.6 | | 1000 | 5.6 | |

**Literature Search and Risk Assessment Completed On:** 10/15/21.

### 11.2. Environmental endpoint summary

#### 11.2.1. Screening-level assessment

A screening-level risk assessment of *dl*-citronellol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *dl*-citronellol was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *dl*-citronellol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api 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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*11.2.1.1. Risk assessment.* Based on the current VoU (2019), *dl*-citronellol presents a risk to the aquatic compartment in the screening-level assessment.

*11.2.1.2. Key studies*

*11.2.1.2.1. Biodegradation.* **RIFM, 1992b**: A 28-day respirometric biodegradation study was conducted according to the OECD 301D method using activated sludge. Biodegradation of 80% was observed.

**RIFM, 2005c**: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the conditions of the study, 100 mg/L of the test material underwent 85% biodegradation in 28 days.

**RIFM, 2012**: The ready biodegradability of the test material was determined by the manometric respirometry test following the OECD 301F method. Under the conditions of the study, 30 mg/L of the test material underwent 81% biodegradation in 28 days.

**RIFM, 1986**: Biodegradation of the test material was determined in a respirometric test following the OECD 301F method. Mean biodegradation of the test material after 28 days was 80%–90% biochemical

oxygen demand/theoretical oxygen demand.

**RIFM, 1989a**: A biodegradation study was conducted according to the OECD 301C method using activated sludge. 30 mg/L of sludge and 108 mg/L of *dl*-citronellol were incubated at 20 °C for 28 days. Biodegradation, as determined by BOD, was 63.5%

**RIFM, 1990a**: A biodegradation study was conducted according to Method F in The Assessment of Biodegradability (1981) using activated sludge. *dl*-Citronellol at 41.6 mg DOC/L was incubated with 30 mg of activated sludge for 28 days. The test material underwent 91.6% biodegradation in 10 days and 100% biodegradation in 15 days.

**RIFM, 1994**: A study was conducted to determine the ultimate biodegradability of the test material using the sealed vessel test and following OECD 301F method. Biodegradation of test material after 28 days (95% confidence limits) was 99.1%.

*11.2.1.2.2. Ecotoxicity.* **RIFM, 2021b**: An algae growth inhibition test was conducted according to the OECD 201 method in a closed system to minimize losses from volatilization. The 72-h EC50 was reported to be 7.2, 16, and 7.5 mg/L for the area under the curve, growth rate, and yield, respectively. The 96-h EC50 was reported to be 6.7, 15, and 5.6 mg/L for the area under the curve, growth rate, and yield, respectively. The 72- and 96-h NOEC of 0.69 mg/L was also reported.

**RIFM, 1989c**: A 48-h static acute immobilization test according to the C2 Annex V to EU Directive 79/831/EEC method was conducted with *Daphnia magna*. The EC50 of the test material was reported to be 17.48 mg/L.

**RIFM, 1989b**: A 96-h acute toxicity study was conducted with 10 Golden Orfe fish according to the German standard DIN 38 412, part L15 method. The LC50 value was calculated as the geometrical mean of LC0 (10 mg/L) and LC100 (21.5 mg/L) nominal values and was reported to be 14.6 mg/L.

**RIFM, 1990b**: A 72-h static algae inhibition study was conducted using *S. subspicatus*. Algae were exposed to *dl*-citronellol at 7 concentrations ranging from 0.195 to 12.5 mg/L. The EC50 was reported to be 2.38 mg/L.

*11.2.1.2.3. Other available data.* *dl*-Citronellol has been registered under REACH with no additional data at this time.

*11.2.1.3. Risk assessment refinement.* Since the 72-h static algae inhibition study (RIFM, 1990b) was a non-GLP/OECD guideline study with very little analytical documentation, it was concluded that the algae study by Arnie et al. (RIFM, 2021) should be used to refine the risk assessment.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 3.1 | 3.1 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | >1000* | 100–1000* |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

*Combined volumes for all CAS #

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

The RIFM PNEC is 5.6 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 08/10/22.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **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 08/17/22.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114150.

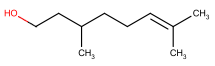
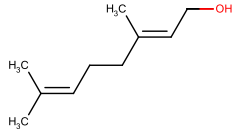
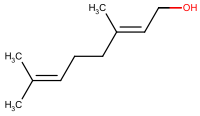
## Appendix

*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

| Principal Name | Target Material | Read-across Material | Read-across Material |
|---|---|---|---|
| | *dl*-Citronellol | Geraniol | Nerol |
| **CAS No.** | 106-22-9 | 106-24-1 | 106-25-2 |
| **Structure** | [  ] | [  ] | [  ] |
| **Similarity (Tanimoto Score)** | | 0.46 | 0.46 |
| **Read-across Endpoint** | | • Repeated dose toxicity<br>• Fertility | • Repeated dose toxicity<br>• Fertility |
| **Molecular Formula** | $C_{10}H_{20}O$ | $C_{10}H_{18}O$ | $C_{10}H_{18}O$ |
| **Molecular Weight (g/mol)** | 156.26 | 154.25 | 154.25 |
| **Melting Point (°C, EPI Suite)** | −12.16 | −10.78 | −10.78 |
| **Boiling Point (°C, EPI Suite)** | 224.00 | 225.00 | 225.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 5.87 | 4.00 | 4.00 |
| **Log $K_{OW}$ (KOWWIN v1.68 in EPI Suite)** | 3.91 | 3.47 | 3.47 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 105.50 | 531.00 | 531.00 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 88.278 | 64.258 | 64.258 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 5.76E+00 | 1.16E+00 | 1.16E+00 |
| ***Repeated Dose Toxicity*** | | | |
| **Repeated Dose (HESS)** | • Not categorized | • Not categorized | • Not categorized |
| ***Reproductive Toxicity*** | | | |
| **ER Binding (OECD QSAR Toolbox v4.2)** | • Non-binder, non-cyclic structure | • Non-binder, non-cyclic structure | • Non-binder, non-cyclic structure |
| **Developmental Toxicity (CAESAR v2.1.6)** | • Non-toxicant (low reliability) | • Non-toxicant (low reliability) | • Non-toxicant (low reliability) |
| ***Metabolism*** | | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 |

*Summary*

There are insufficient toxicity data on *dl*-citronellol (CAS # 106-22-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, geraniol (CAS # 106-24-1), and nerol (CAS # 106-25-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

*Conclusions*

- Geraniol (CAS # 106-24-1) was used as a read-across analog for the target material, *dl*-citronellol (CAS # 106-22-9), for the repeated dose toxicity and fertility endpoints.

- The target material and the read-across analog belong to a class of unsaturated primary alcohols.
- The target material and the read-across analog have the same number of carbons and share isobutylene and a primary alcohol group.
- The key difference between the target material and the read-across analog is that the read-across analog is an α, β-unsaturated primary alcohol. This structural difference is toxicologically insignificant.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog do not have toxicity alerts. Data are consistent with *in silico* alerts.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Nerol (CAS # 106-25-2) was used as a read-across analog for the target material, *dl*-citronellol (CAS # 106-22-9), for the repeated dose toxicity and fertility endpoints.
  - The target material and the read-across analog belong to a class of unsaturated primary alcohols.
  - The target material and the read-across analog have the same number of carbons and share isobutylene and a primary alcohol group.
  - The key difference between the target material and the read-across analog is that the read-across analog is an α, β-unsaturated primary alcohol. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog do not have toxicity alerts. Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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