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RIFM fragrance ingredient safety assessment, geraniol, CAS registry number 106-24-1

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ABSTRACT

The existing information supports **the use of this material as described in this safety assessment**. Geraniol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that geraniol is not genotoxic. Data on geraniol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided geraniol a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; geraniol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to geraniol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; geraniol 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.

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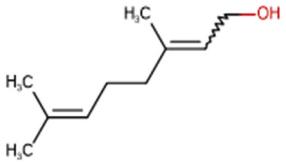

Name: Geraniol
CAS Registry Number: 106-24-1
Additional CAS Numbers*:624-15-7
Dimethyl-2,6-octadien-1-ol
*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api 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

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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.

Geraniol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that geraniol is not genotoxic. Data on geraniol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provided geraniol a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; geraniol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to geraniol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; geraniol 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. (RIFM, 2010a; RIFM, 2010b)
Repeated Dose Toxicity: NOAEL = 60.2 mg/kg/day. RIFM (2010c)
Reproductive Toxicity: Developmental toxicity NOAEL = 180.6 mg/kg/day; fertility NOAEL = 1000 mg/kg/day. (ECHA REACH Dossier: Geraniol; ECHA, 2011; RIFM, 2015; RIFM, 2010c; RIFM, 2010f)
Skin Sensitization: NESIL = 11000 μg/cm^2. RIFM (2004)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 101% (OECD 301B) RIFM (1994b)
Bioaccumulation:
Screening-level: 90.47 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EC50: 3.32 mg/L RIFM (2003c)
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: 72-h Algae EC50: 3.32 mg/L RIFM (2003c)
RIFM PNEC is: 3.32 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: Geraniol	Chemical Name: 3,7-Dimethyl-2,6-octadien-1-ol
CAS Registry Number: 106-24-1 **Synonyms:** *trans*-3,7-Dimethyl-2,7-octadien-1-ol; 2,6-Dimethyl-2,6-octadien-8-ol; *trans*-3,7-Dimethyl-2,6-octadien-1-ol; Meranol; 2,6-Octadien-1-ol, 3,7-dimethyl-, (e)-; Geraniol Coeur; 脂肪族不飽和アルコール(C = 9 ~ 14); 3,7-Dimethylocta-2,6-dien-1-ol; Geraniol extra; Rhodinol pure;	**CAS Registry Number:** 624-15-7 **Synonyms:** 2,6-Octadien-1-ol, 3,7-dimethyl-; 3,7-Dimethyl-2,6-octadien-1-ol; 3,7-Dimethylocta-2,6-dien-1-ol; Citrol

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Chemical Name: Geraniol	Chemical Name: 3,7-Dimethyl-2,6-octadien-1-ol
Geraniol 60; Geraniol SP; Geraniol Supra; Geraniol	
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25 g/mol	**Molecular Weight:** 154.25 g/mol
RIFM Number: 124	**RIFM Number:** 124
Stereochemistry: *Trans*-isomer specified. One stereocenter and 2 possible stereoisomers.	**Stereochemistry:** No isomer specified. One stereocenter and 2 possible stereoisomers.

2. Physical data*

1. **Boiling Point:** 230 °C (Fragrance Materials Association [FMA]), 239.89 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA), 108 °C (Globally Harmonized System [GHS]), 110 °C (230 °F) (RIFM, 1990)
3. **Log K_{OW}:** 2.6 at 25 °C (RIFM, 1995a), 2.6 at 25 °C (RIFM, 1995b), 3.47 (EPI Suite)
4. **Melting Point**: 15 °C (SAX), −10.78 °C (EPI Suite)
5. **Water Solubility:** 255.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.878 (FMA)
7. **Vapor Pressure:** 0.00954 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0159 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a mild and sweet floral rose-type odor

*All physical data is identical for both materials in the assessment.

3. Volume of use (worldwide band)

1. >1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)*

1. **1. 95**th **Percentile Concentration in Fine Fragrance:** 0.23% (RIFM, 2018)
2. **Inhalation Exposure**:** 0.00090 mg/kg/day or 0.067 mg/day (RIFM, 2018)
3. **Total Systemic Exposure***:** 0.0075 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 et al., 2015; Safford et al., 2015; 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 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

RIFM SABS testing on geraniol [RIFM, 2021]: *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.

Gilpin et al., 2010: The penetration abilities of geraniol in a typically used vehicle were evaluated using an *in vitro* skin penetration model under occluded conditions of human skin. The test compound ([14C]- geraniol) solutions were prepared by adding the correct amount of radiolabeled material to a prepared 3:1 solution of diethyl phthalate and ethanol. Human cadaver skin that was free of obvious signs of skin disease was obtained within 24 h of death. The cadaver skin was clamped onto a continuous flow diffusion cell (containing 6% polyethylene glycol and phosphate buffer saline) in a flow-through diffusion cell system. The receptor fluid was collected at 1 h, 2 h, 4 h, and every 4 h up to 24 h. Immediately after dose application (20 μL dose solution of approximately 0.5 μCi radioactivity with a syringe), the top of the cell was covered with a plastic chamber and a cotton pad and then sealed with Parafilm M Laboratory Wrapping Film to block and absorb the volatile fragrance. Adhesive tape was added as an additional occlusive layer and to keep the Parafilm and chamber in place. Three runs of 4 cadaver skin donors were completed for each fragrance concentration. At the end of the 24-h period, samples were collected and prepared for assay. For the sample collection and assay, the skin surface was washed twice with a small cotton ball wetted with 50% liquid dish soap. For each sample, the following was collected: receptor fluid, cover (the cotton pad and tape-sealed Parafilm), surface wash (which was collected with the liquid soap wash as residue dose), inner washing (i.e., samples wiped with a cotton swab from the inside walls of the epidermal chambers), the first and second tape strips as residue dose, stratum corneum (the next 3 to 10 tape strips removed from the skin as the dose penetrated the stratum corneum), separated epidermis, separated dermis, and edge skin (i.e., the non-dosed area around the dosed skin). Two concentrations of geraniol were tested, 2% and 5%. At 2% geraniol, the penetrated dose absorbed after 24 h was 3.5% ± 1.9%. The recovered dose after 24 h was 78.2% ± 5.2%. At 5% geraniol, the penetrated dose absorbed after 24 h was 7.3% ± 1.1%. The recovered dose after 24 h was 81.9% ± 1.1%. The most conservative skin absorption value of 7.3% was used for the safety assessment.

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
   3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

Geraniol is reported to occur in the following foods by the VCF*:
Allium species.
Cocoa.
Ginger (*Zingiber* species)
Grape (*Vitis* species)
Licorice (*Glycyrrhiza glabra* L.)
Plum (*Prunus* species)
Potato (*Solanum tuberosum* L.)
Strawberry (*Fragaria* species)
Tea.
Tomato (*Lycopersicon esculentum* Mill.)

Dimethyl-2,6-octadien-1-ol is not reported to occur in foods by the VCF.

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

9. REACH dossier

Available for geraniol; accessed on 10/18/21 (ECHA, 2011). Dimethyl-2,6-octadien-1-ol has been pre-registered for 2010; no dossier available as of 01/21/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for geraniol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.78
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	1.1
4	Products related to fine fragrances	4.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.2
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.78
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.94
5D	Baby cream, oil, talc	0.26
6	Products with oral and lip exposure	0.16
7	Products applied to the hair with some hand contact	0.78
8	Products with significant ano-genital exposure (tampon)	0.26
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.8
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.1
10B	Aerosol air freshener	5.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.26
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

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 geraniol, the basis was the subchronic reference dose of 0.602 mg/kg/day, a skin absorption value of 36.7%, and a skin sensitization NESIL of 11000 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, geraniol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Geraniol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary (CHO) cells were treated with geraniol in dimethyl sulfoxide (DMSO) at concentrations of 200 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 (RIFM, 2010a). Under the conditions of the study, geraniol was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of geraniol 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 DMSO/corn oil via the oral route to groups of male 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. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2010b). Under the conditions of the study, geraniol was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: Florin et al., 1980; Ishidate et al., 1984; Eder et al., 1980; Eder et al., 1982a; Eder et al., 1982b; Lutz et al., 1980; Sasaki et al., 1989; Rupa et al., 2003; 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 geraniol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data for geraniol. In an OECD 421/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, 2010c). Furthermore, to account for bioavailability following the dermal application, data from a skin absorption test performed on rat skin (RIFM, 2021; 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.

In another OECD 421/GLP-compliant study, 10 rats/sex/dose were administered geraniol 60 (a mixture of geraniol and nerol, approximately 60:40) via gavage (vehicle: corn oil) at doses of 0, 100, 300, or 1000 mg/kg/day. 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 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, 2010f).

In an OECD 443/GLP-compliant study, groups of 30 Wistar Han rats/sex/dose were administered geraniol via gavage (vehicle: corn oil) at doses of 0, 50, 200, and 800 mg/kg/day. F0 generation males were treated for 10 weeks prior to mating and continuing throughout and after mating, until termination; F0 females were treated for 10 weeks prior to mating and continuing throughout mating and gestation, until at least Lactation Day (LD) 21. F1 generation males were treated from PND 21, through mating and after mating, until termination, after the majority of females reached LD 21; F1 females were treated from PND 21, through mating, pregnancy, and littering until F2 pups reached PND 22–24. For the F1 generation, the highest dose level of 800 mg/kg/day was reduced to 600 and then 400 mg/kg/day due to mortality of 2 weanlings; it was later titrated back to 600 and then 800 mg/kg/day within the first 2 weeks of dosing (by PND 33). There were no treatment-related adverse effects on F0 generation adult survival, body weight, hematology, coagulation, urinalysis, or gross pathology. There were no effects on F1 generation coagulation, urinalysis, gross pathology, neuropathology, or spleen immunophenotyping. F0 animals showed low incidences of post-dose abnormal (uncoordinated) gait, decreased activity/subdued behavior, low carriage, erected fur, and chewing action at the high dose. F0 females showed increased food consumption during pre-mating (15%) and gestation (9–13%) at the high dose but decreased food consumption during lactation at the mid dose (10%) and the high dose (10–16%). F0 animals showed increased levels of bile acids (1.5- to 1.8-fold), ALP (1.4-fold), and GGT (1.5- to 1.7-fold) at the high dose. F0 animals showed increased TSH levels at all dose levels, but the effect was slight, and only a few individuals at the high dose showed levels outside of historical control ranges. F0 males showed increased thyroid and kidney weights, while F0 animals of both sexes showed increased liver weights at the high dose. F0 males showed degeneration in the olfactory epithelium and nasopharynx and increased hematopoiesis, while F0 females showed diffuse follicular cell hypertrophy. F1 animals showed low incidences of post-dose abnormal (uncoordinated) gait, decreased activity/subdued behavior, low carriage, erected fur, and chewing action, as well as partially closed eyes, irregular respiration/breathing, and pallor at the high dose. F1 animals showed slightly higher food consumption during mating and gestation at the mid and high doses. F1 females showed increased levels of basophils at the mid dose (1.6-fold) and the high dose (1.7- to 2.1-fold) and monocytes (1.6-fold) at the high dose. F1 animals showed increased levels of large unstained cells (1.6- to 1.7-fold) at the high dose. F1 females showed increased levels of bile acids (5.3-fold) at the mid dose, and this effect was seen in both sexes at the high dose (1.9-fold in males, 5.3-fold in females). F1 animals showed increased levels of ALT and ALP (1.4- to 1.5-fold) at the high dose. F1 females showed increased levels of triglycerides (1.5-fold) at the high dose and cholesterol (1.3- to 1.4-fold) at the mid and high doses. F1 males also showed increased TSH levels at all dose levels, but the effect was slight, and only a few individuals at the high dose showed levels outside of historical control ranges. F1 females showed increased thyroid weights (16%–19%), F1 males showed increased kidney weights (11%–15%) at the high dose, and F1 animals of both sexes showed increased liver weights (21%–36%). Based on olfactory epithelium degeneration in F0 animals at 800 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered 200 mg/kg/day (ECHA Dossier on Geraniol).

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 geraniol 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 geraniol, 60.2/0.0075, or 8026.

In addition, the total systemic exposure for geraniol (7.5 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.

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

Derivation of subchronic RfD:

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for

interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for geraniol 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.

*The Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for geraniol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on geraniol. 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 or 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. During pup necropsy, there were no treatment-related alterations reported among treatment groups as compared to the controls. In addition, there were no treatment-related histopathological alterations in the reproductive organs evaluated among treated animals up to the highest dose tested. The NOAEL for reproductive performance, fertility, and developmental toxicity was considered to be 300 mg/kg/day, the highest dose tested (RIFM, 2010c). Furthermore, to account for bioavailability following the dermal application, data from a skin absorption test performed on rat skin (RIFM, 2021; 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 were 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. At 1000 mg/kg/day, the number of live-born pups was statistically significantly decreased in high-dose females, resulting from a lower number of pups delivered and a higher number of stillborn pups. The viability index indicating pup mortality during early lactation (postnatal days 0–4) was distinctly reduced (−25%) in the high-dose group, resulting from significantly higher numbers of dead (7 vs. 0 in control) and cannibalized pups (11 vs. 0 in control). In the mid-dose group, the viability index was reduced (91% of controls), resulting from a higher number of dead pups (5 vs. 0 in control) and a significantly higher number of cannibalized pups (6 vs. 0 in control). The pups from 1000 mg/kg/day dams were not properly nursed, resulting in a decreased viability index and a statistically significant reduction in body weights. At 300 mg/kg/day, the number of stillborn pups was slightly increased (5.6% vs. 0.0%–4.5% in historical control data), and some pups were not properly nursed due to insufficient maternal care resulting in a reduced viability index. Increased incidences (5% and 10%) of empty stomachs were observed in the mid- and high-dose group pups, respectively. The increased total number of stillborn pups in the high-dose group was only influenced by one dam's litter. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, based on a decrease in viability index and an increase in stillborn pups among higher dose group animals (RIFM, 2010f).

An OECD/GLP 414 prenatal developmental toxicity study was conducted on female Wistar rats. Groups of 25 time-mated rats/dose were administered geraniol 60 (mixture of geraniol and nerol [a stereoisomer, CAS # 106-25-2; see Section VI], approximately 60:40) via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil on gestation day (GD) 6–19. A treatment-related decrease in food consumption was reported among animals of the high-dose group. There was a significant decrease in bodyweight gain (14% below the control) among dams of the high-dose group. The bodyweight gain among dams of the mid-dose group was also significantly decreased (13% below the control), indicating systemic toxicity due to test material administration. High-dose group fetal weights were statistically significantly reduced (8% below the control) as compared to the controls. This slight reduction was considered to be subsequent to the lower bodyweight gain among the dams of the high-dose group. Fetal examination revealed no effect of test material administration on the morphological structures up to the highest dose tested. Incidences of a dilated renal pelvis and incomplete ossification of various skeletal elements represented temporary delays in development, which have no permanent effect on the morphology and function of the affected organs or structures. The NOAEL for prenatal developmental toxicity was considered to be 300 mg/kg/day, based on a decrease in fetal weights among high-dose group fetuses and incidences of a dilated renal pelvis and incomplete skeletal ossifications secondary to maternal toxicity among high-dose group animals (RIFM, 2015).

In another OECD 414 study, groups of 25 time-mated female Wistar rats/dose were administered geraniol at doses of 0, 30, 100, or 300 mg/kg/day in corn oil on GD 6–19 and euthanized on GD 20. For all test groups, skeletal variations of different bone structures were observed, with or without effects on corresponding cartilages. The observed skeletal variations were related to several parts of the fetal skeleton and appeared without relation to dosing. The overall incidences of skeletal variations were comparable to the historical control data. Some isolated cartilage findings, which were designated as unclassified cartilage observations, occurred in all test groups but were without impact on the respective bone structures. The observed unclassified cartilage findings were related to the skull, sternum, and ribs and did not show any relation to dosing. The incidence of branched rib cartilage was significantly increased in the 100 mg/kg/day group. However, this finding showed no dose-dependency and was therefore assessed to be without biological relevance. The NOAEL for maternal and developmental toxicity was considered to be 300 mg/kg/day, the highest dose tested (ECHA, 2011).

In an OECD 443/GLP-compliant study, groups of 30 Wistar Han rats/sex/dose were administered geraniol via gavage (vehicle: corn oil) at doses of 0, 50, 200, and 800 mg/kg/day. F0 generation males were treated for 10 weeks prior to mating and continuing throughout and after mating, until termination; F0 females were treated for 10 weeks prior to mating and continuing throughout mating and gestation, until at least Lactation Day (LD) 21. F1 generation males were treated from PND

21, through mating and after mating, until termination, after the majority of females reached LD 21; F1 females were treated from PND 21, through mating, pregnancy, and littering until F2 pups reached PND 22–24. For the F1 generation, the highest dose level of 800 mg/kg/day was reduced to 600 and then 400 mg/kg/day due to mortality of 2 weanlings; it was later titrated back to 600 and then 800 mg/kg/day within the first 2 weeks of dosing (by PND 33). There were no treatment-related adverse effects on F0 generation estrous cycles and mating performance, duration of gestation, litter performance, or sperm evaluation. There were no treatment-related adverse effects on F1 generation estrous cycles and mating performance, duration of gestation, litter survival and performance, anogenital distance, nipple retention, vaginal opening, balanopreputial separation, or ovarian follicle counts. Pup survival between LD 0 and 4 was reduced at the high dose (Viability Index 85.9%, with several litters losing 2 or 3 pups), with pup mortality occurring in 11 litters compared to 1 litter in each of the other groups (including the control). Based on no effects on fertility parameters seen up to the highest dose, the fertility NOAEL for this study was 800 mg/kg/day. Based on reduced pup survival at 800 mg/kg/day, the developmental toxicity NOAEL for this study was 200 mg/kg/day (ECHA, 2011).

Taken together, the developmental toxicity NOAEL of 180.6 mg/kg/day derived from the dermal OECD 421 study, which was considered to be the most relevant study, was selected for the developmental toxicity endpoint.

The fertility NOAEL was considered to be 1000 mg/kg/day, the highest dose tested from the oral gavage study conducted on the 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 geraniol MOE for the fertility endpoint can be calculated by dividing the geraniol NOAEL in mg/kg/day by the total systemic exposure to geraniol, 1000/0.0075, or 133333.

When correcting for skin absorption (see Section V), the total systemic exposure to geraniol (7.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material 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, geraniol is considered to be a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, geraniol is considered a sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). It is also predicted to auto-oxidize and result in protein-reactive products (OECD Toolbox v4.2). Accordingly, geraniol was found to be minimally reactive in an *in vitro* direct peptide reactivity assay (DPRA). However, in KeratinoSens, h-CLAT, and U937-CD86 tests, geraniol was found to be positive (Urbisch et al., 2015; Piroird et al., 2015). Similarly, in multiple murine local lymph node assays (LLNAs), geraniol was found to be sensitizing with a weighted mean EC3 value of 3525 μg/cm^2 (Isola and Lalko, 2001; RIFM, 2003b). In a Confirmation of No Induction in Humans test (CNIH) with 11811 μg/cm^2 of geraniol in 1:3 ethanol:diethyl phthalate, no reactions indicative of skin sensitization reactions were observed (RIFM, 2004).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, geraniol is a sensitizer with a WoE NESIL of 11000 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. (2020) and a subchronic RfD of 0.602 mg/kg/day.

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

11.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis absorption spectra, geraniol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for geraniol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, geraniol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry 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 geraniol 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 geraniol. Based on the Creme RIFM Model, the inhalation exposure is

Table 1
Data Summary for geraniol.

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
3525 (5)	Weak	11811	NA	NA	11000

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.

Additional References: RIFM, 1979; Marzulli and Maibach, 1980; Greif (1967); Kimber and Weisenberger, 1989; RIFM, 1964a; Kimber and Weisenberger, 1991; Basketter and Kimber, 1997; RIFM, 2000; RIFM, 2001a; RIFM, 2001b; RIFM, 2001c; RIFM, 2001d; RIFM, 2003a; RIFM, 2003b; RIFM, 2002; Lalko et al., 2004a; Lalko and Api, 2004b; Lalko and Api, 2006; RIFM, 1964b.

0.067 mg/day. This exposure is 20.9 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: Fukayama et al., 1999; Troy (1977); Boyd and Sheppard, 1970; Price (1977); UGCM, 1997; Buchbauer et al., 1993; Rice and Coats, 1994a; Rice and Coats, 1994b; Perrucci et al., 1995; Cometto-Muniz et al., 1998; Dorries et al., 1995; Leclerc et al., 2002; Hagvall et al., 2007; Sato et al., 2007; Forester and Wells, 2009; Schnuch et al., 2010.

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 geraniol 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, geraniol 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 geraniol as possibly being 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, 2017). 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), geraniol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1994a:** The ready biodegradability of geraniol has been determined by the manometric respirometry test according to OECD 301F guidelines. Under the conditions of the test, geraniol underwent 94% biodegradation after 28 days.

RIFM, 1992: A biodegradation test was conducted with geraniol according to OECD 301D guidelines. After 28 days, biodegradation was 82% at 2 mg/L and 60% at 5 mg/L.

RIFM, 2012: The ready biodegradability of geraniol has been determined by the manometric respirometry test according to OECD 301F guidelines. Under the conditions of the test, geraniol underwent 81% biodegradation after 28 days.

RIFM, 1994b: A study was conducted to determine the ultimate biodegradability of geraniol at 10 mg/L using the sealed vessel test (OECD 301B). After 28 days, biodegradation was 101.4%.

RIFM, 1990: A biodegradation study was conducted according to Method F in "The Assessment of Biodegradability" (1981), in the "Blue Book" series, using activated sludge. Geraniol at 42 mg DOC/L was incubated with 30 mg of activated sludge for 28 days. The test material underwent 100% biodegradation.

RIFM, 1994c: The ready biodegradability of geraniol (100 mg/L) was tested by the manometric respirometry test according to OECD 301F guidelines. Geraniol underwent 94% biodegradation after 28 days and was considered readily biodegradable.

RIFM, 2001f: A study was conducted to determine the biodegradability of geraniol supra at 100 mg/L using the manometric respirometry test according to OECD 301F guidelines. After 28 days under aerobic conditions, biodegradation was 86%.

11.2.2.1.2. Ecotoxicity. **RIFM, 2003d:** The acute toxicity of the test material to *Daphnia magna* was performed under static-renewal conditions in sealed vials without headspace, according to the OECD 202 method. The 48-h EC50 value based on the mean measured concentration was reported to be 7.75 mg/L (95% CI: 6.70–8.97 mg/L).

RIFM, 2010d: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 10.8 mg/L (95% CI: 8.6–13.5 mg/L).

RIFM, 2001e: A 96-h acute semi-static toxicity study was conducted with Zebrafish according to the council directive 92/69/EEC C.1. The LC0 was 9.8 mg/L, and the LC100 was 19.9 mg/L. The LC0/LC100 was 14.0 mg/L (geometric mean), based on the arithmetic mean of analytical values.

RIFM, 2003c: A 72-h growth and reproduction toxicity test was conducted under static conditions with geraniol in freshwater algae, according to OECD 201 guidelines. The EC50 was 5.93 mg/L when calculated using the average specific growth rate, 3.65 mg/L when calculated using the number of cells/mL, and 3.32 mg/L when calculated using the area under the growth curve. All results were based on initial measured concentrations.

RIFM, 2010e: A 72-h growth inhibition study in algae was conducted according to OECD 201 guidelines. For algal yield, the EyC50 was 6.42 mg/L, and for algal growth rate, the ErC50 was 13.1 mg/L. The 72-h NOEC value for growth rate was reported to be 1 mg/L. All results were based on nominal test concentrations.

11.2.2.1.3. Other available data. Geraniol has been registered under REACH with the following additional data available (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the DOC die-away test according to OECD 301A guidelines. Biodegradation of 90%–100% (DOC removal) was observed after 3 days.

A 96-h static acute fish test was conducted with *Brachydanio rerio* according to OECD 203 guidelines. The LC50 value based on nominal test concentration was reported to be around 22 mg/L.

11.2.2.1.4. 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)**	62.54			1000000	0.06254	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.8	0.283	3.194	10000	0.0283	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	6.062	3.943	5.148			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	14					
Daphnia		6.42				
Algae		3.32		1000	3.32	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.6	2.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	>1000	100–1000
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 3.32 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 10/13/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA 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 01/21/22.

Research Institute for Fragrance Materials, Inc.

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

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