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Short Review

RIFM fragrance ingredient safety assessment, nerol, CAS Registry Number 106-25-2

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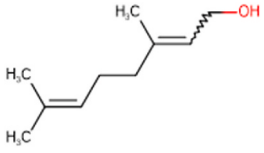
Name: Nerol CAS Registry Number: 106-25-2



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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 that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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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 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.

Nerol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that nerol is not genotoxic. Data on nerol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog geraniol (CAS # 106-24-1) provided nerol a No Expected Sensitization Induction Level (NESIL) of 11000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; nerol 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, and the exposure to nerol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; nerol 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic	(RIFM, 2000c; ECHA REACH Dossier: Nerol; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	RIFM (2010)
eproductive Toxicity: Developmental toxicity NOAEL = 191.2 mg/kg/day. Fertility NOAEL = 1000 mg/kg/day.	**R** (ECHA REACH Dossier: Nerol; RIFM, 2010; ECHA, 2013)
Skin Sensitization: NESIL = 11000 μg/cm^2	RIFM (2004)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 91% (OECD 301F) (RIFM, 1999a)

Bioaccumulation:

Screening-level: 90.47 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Critical Ecotoxicity Endpoint: 72-h Algae EyC50: 2.16 mg/L (ECHA REACH Dossier: Nerol; ECHA, 2013)

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 EyC50: 2.16 mg/L	(ECHA REACH Dossier: Nerol; ECHA, 2013)

RIFM PNEC is: 2.16 μg/L

- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Nerol
2. **CAS Registry Number:** 106-25-2
3. **Synonyms:** Allerol; *cis*-3,7-Dimethyl-2,6-octadien-1-ol; *cis*-2,6-Dimethyl-2,6-octadien-8-ol; Neraniol; Nergenol; 2,6-Octadien-8-ol, 2,6-dimethyl-, (z); 脂肪族不飽和アルコール(C = 9 ~ 14); 3,7-Dimethyl-octa-2,6-dien-1-ol; Nerol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 181
7. **Stereochemistry:** *Trans*-isomer specified. One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 225 °C (Fragrance Materials Association [FMA]), 239.89 °C (EPI Suite)
2. **Flash Point:** 97 °C (Globally Harmonized System), >200 °F; closed cup (FMA)
3. **Log K_{OW}:** 2.7 (RIFM, 1999b), 3.47 (EPI Suite)
4. **Melting Point**: -10.78 °C (EPI Suite)
5. **Water Solubility:** 255.8 mg/L (EPI Suite)
6. **Specific Gravity:** 0.88 g/mL (RIFM, 1994), 0.877 (FMA)
7. **Vapor Pressure:** 0.00954 mm Hg at 20 °C (EPI Suite v4.0), 0.06 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 sweet rose odor sweet rosy refreshing and wet, seashore odor (Arctander, 1969)

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.080% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00046 mg/kg/day or 0.033 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0025 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low.

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

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Geraniol (CAS # 106-24-1)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

Nerol is reported to occur in the following foods by the VCF*:
Chamomile.
Citrus fruits.
Curry (*Bergera koenigii* L.)
Ginger (*Zingiber* species)
Lemon balm (*Melissa officinalis* L.)
Lemon grass oil (Cymbopogon)
Mentha oils.
Salvia species.
Thyme (*Thymus* species)
Wormwood oil (*Artemisia absinthium* L.)
*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; accessed on 02/07/22 (ECHA, 2013).

10. Conclusion

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

IFRA Category[b]	Descript[a]on of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.85
2	Products applied to the axillae	0.25
3	Products applied to the face/body using fingertips	0.97
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	0.48
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.97
5D	Baby cream, oil, talc	0.16
6	Products with oral and lip exposure	0.97
7	Products applied to the hair with some hand contact	0.97
8	Products with significant ano-genital exposure (tampon)	0.16
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.5
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)	0.16
12	Other air care products not intended for direct skin contact, minimal or insign[a]ficant transfer to skin	No Restriction

Note.
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.
[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)[b] For nerol, the basis was a subchronic reference dose of 1 mg/kg/day, a predicted skin absorption value of 80%, 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; December 2019).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Nerol was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) 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.

The mutagenic activity of nerol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with nerol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000c). Under the conditions of the study, nerol was not mutagenic in the Ames test.

The clastogenicity of nerol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with nerol in DMSO at concentrations up to 1534 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2013). Under the conditions of the study, nerol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, nerol 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 nerol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient data on nerol 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 12000 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 12000 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-2μglobulin nephropathy, and thus were not considered to be relevant to human health. 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 the mid and high 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, 2010).

Bodyweight alterations were observed in both studies. Hence, the most conservative NOAEL of 300 mg/kg/day from the OECD 421 study was determined for the repeated dose toxicity endpoint.

A default safety factor of 3 was used when deriving a NOAEL from an OECD 421 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. Thus, the derived NOAEL for the repeated dose toxicity endpoint is 300/3 or 100 mg/kg/day.

Therefore, the MOE for repeated dose toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.0025, or 40000.

In addition, the exposure (2.5 μg/kg/day) for nerol 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 1 mg/kg/day.

11.1.2.1.1. 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 nerol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 100 mg/kg/day by the uncertainty factor, 100 = 1 mg/kg/day.

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

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for nerol 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 nerol. An OECD 414/GLP prenatal developmental toxicity study was conducted on female Wistar rats. Groups of 25 time-mated rats/dose were administered Geraniol 60 (a mixture of geraniol [a stereoisomer, CAS # 106-24-1; see Section VI] and nerol, approximately 60:40) via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil on

gestation days (GDs) 6–19. A treatment-related decrease in food consumption was reported among animals in 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 also was significantly decreased (13% below the control), indicating systemic toxicity due to treatment 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 treatment 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. Based on a decrease in fetal weights at 1000 mg/kg/day and incidences of the dilated renal pelvis and incomplete skeletal ossifications secondary to maternal toxicity at 1000 mg/kg/day, the NOAEL for prenatal developmental toxicity was considered to be 300 mg/kg/day (RIFM, 2015).

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 12000 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 treatments. 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 12000 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).

In an OECD 421 study, Geraniol 60 (mixture of geraniol [stereoisomer, CAS # 106-24-1; see Section VI] and nerol, 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), 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 the gestation index was comparable to the female controls. Based on 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. In the same study, 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 an empty stomach 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. Based on a decrease in viability index and an increase in stillborn pups at 300 mg/kg/day, the NOAEL for developmental toxicity was considered to be 100 mg/kg/day (RIFM, 2010).

Although the developmental toxicity NOAEL of 100 mg/kg/day from the OECD 421 study was the most conservative, this study was conducted using Geraniol 60 (60% geraniol, 40% nerol) rather than using pure nerol. Thus, the developmental toxicity NOAEL of 191.2 mg/kg/day from the OECD 422 study, which was considered to be the most relevant study, was selected for the developmental toxicity endpoint.

Therefore, the nerol MOE for developmental toxicity can be calculated by dividing the nerol NOAEL in mg/kg/day by the total systemic exposure to nerol, 191.2/0.0025, or 76480.

Because the fertility NOAEL was considered to be the highest tested dose for both OECD 422 and OECD 421 studies, the NOAEL of 1000 mg/kg/day was selected from the OECD 421 study conducted on the geraniol/nerol mixture.

Therefore, the nerol MOE for the reproductive toxicity endpoint can be calculated by dividing the nerol NOAEL in mg/kg/day by the total systemic exposure to nerol, 1000/0.0025, or 400000.

In addition, the total systemic exposure to nerol (2.5 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 materials 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 and read-across to geraniol (CAS # 106-24-1), nerol is considered a skin sensitizer with a defined NESIL of 11000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for nerol. Based on the existing data and read-across material geraniol (CAS # 106-21-1; see Section VI), nerol is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). Read-across material geraniol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), while it was found to be positive in the KeratinoSens, human cell line activation test (h-CLAT), and U-SENS tests (Urbisch, 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), nerol was found to be sensitizing with an EC3 value of 23% (5750 μg/cm^2) (ECHA, 2013). In additional LLNAs, read-across material geraniol was found to be sensitizing with a weighted mean EC3 value of 3752 μg/cm^2 (Isola and Lalko, 2001; RIFM, 2003b). A guinea pig Buehler test did not present reactions indicative of sensitization (RIFM, 1992). In a Confirmation of No Induction in Humans test (CNIH) with 11811 μg/cm^2 of geraniol in 1:3 ethanol: diethyl phthalate (EtOH:DEP), no reactions indicative of skin sensitization reactions were observed (RIFM, 2004).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and the read-across material geraniol, nerol is considered 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. described by Api et al. (2020) and a subchronic RfD of 1 mg/kg/day.

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, 2000a; RIFM, 2001a; RIFM, 2001b; RIFM, 2001c; RIFM, 2001d; RIFM, 2003a; RIFM, 2003b; RIFM, 2002; Lalko et al., 2004a; Lalko and Api, 2004b;

Table 1
Data Summary for geraniol as read-across for nerol.

LLNA Weighted Mean EC3 Value [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3]
3752 [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

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003

[2] Data derived from CNIH or HMT

[3] WoE NESIL limited to 2 significant figures

Lalko and Api, 2006; RIFM, 1964b.

Literature Search and Risk Assessment Completed On: 10/06/21.

11.1.5. Photoirritation/photoallergenicity

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

11.1.5.1. Risk assessment. There are no photoirritation studies available for nerol 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 photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, nerol does not present a concern for photoirritation 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 photoirritating 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 nerol 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 nerol. Based on the Creme RIFM Model, the inhalation exposure is 0.033 mg/day. This exposure is 42.42 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); Buchbauer et al., 1993; Perrucci et al., 1995.

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 nerol 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, nerol 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 nerol 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.

11.2.2. Risk assessment. Based on the current VoU (2019), nerol 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, 1994**: The biodegradability of nerol was determined using a CO_2 production test based on OECD guideline 301B. The incubation period was 28 days. The biodegradation rate was 85.9%.

RIFM, 1999a: The biodegradability of nerol was determined by the manometric respirometry test based on OECD guideline 301F. A mineral medium was inoculated with fresh activated sludge, and 100 mg/L of nerol was stirred in a closed flask for 32 days. The biodegradation rate was 92% after 32 days (91% after 28 days).

11.2.2.1.2. Ecotoxicity. **RIFM, 2000b:** A 48-h *Daphnia magna* acute toxicity test was conducted according to the Council Directive 92/69/EEC C.2 guidelines under static conditions. The EC0 after 48 h was 24.7 mg/L. EC100 after 48 h was 48.8 mg/L, and the geometric mean (EC0/EC100) was 34.7 mg/L.

11.2.2.1.3. Other available data. Nerol is registered under REACH with the following additional data (ECHA, 2013):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 90% was observed at the end of 28 days.

A 96-h semi-static fish (*Danio rerio*) study was conducted according to the OECD 203 method. The LC50 value based on nominal test concentration was reported to be 20.3 mg/L (95% CI: 18.9–21.8 mg/L).

A *Daphnia magna* 48-h static acute test according to the OECD 202 method was conducted, and an EC50 value based on nominal test concentration was reported to be 32.4 mg/L (95% CI: 21.4–46.3 mg/L).

An algae acute study was conducted according to the OECD 201 method under static conditions. The 72-h ErC50 and EyC50 values based on nominal test concentration were reported to be 9.54 mg/L (95% CI: 7.68–11.85 mg/L) and 2.16 mg/L (95% CI: 1.55–2.91 mg/L), respectively.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.7	2.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 2.16 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: 08/09/22.

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 08/10/22.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	51.2			1000000	0.0512	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	6.06	3.94	5.15			Neutral organics
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.80	0.283	3.19	10000	0.0283	Vinyl/Allyl alcohols
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	20.3					
Daphnia		32.4				
Algae		2.16		1000	2.16	

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.2023.113859.

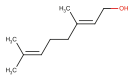
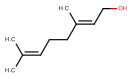
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 (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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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 alert system.

	Target Material	Read-across Material
Principal Name	Nerol	Geraniol
CAS No.	106-25-2	106-24-1
Structure		
Similarity (Tanimoto Score)		1.00
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight (g/mol)	154.25	154.25
Melting Point (°C, EPI Suite)	−10.78	−10.78
Boiling Point (°C, EPI Suite)	225.00	225.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.00	4.00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.47	3.47
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	531.00	531.00
J_{max} (μg/cm^2/h, SAM)	64.258	64.258
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.16E+00	1.16E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Schiff base formation	• Alert for Schiff base formation
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on nerol (CAS # 106-25-2). 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) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Geraniol (CAS # 106-24-1) was used as a read-across analog for the target material nerol (CAS # 106-25-2) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a group of α,β-unsaturated branched primary alcohols.
  - o The target material and the read-across analog are stereoisomers.
  - o The key difference between the target material and the read-across analog is that the read-across analog is the E-stereoisomer, whereas the target material is the *Z*-stereoisomer. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both materials present an alert for Schiff base formation for the Skin Sensitization Reactivity Domains categorization scheme because both chemicals are α,β-unsaturated alcohols with a β-methyl substitution. As reported in the skin sensitization section, both materials are skin sensitizers. Data are consistent with the *in silico* alerts.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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