Food and Chemical Toxicology 192 (2024) 114769

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, nerol oxide, CAS Registry Number 1786-08-9

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

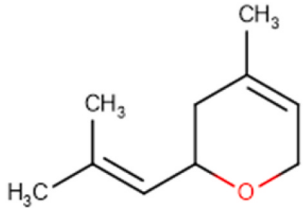
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677 USA*
[b] *Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Expert Panel for Fragrance Safety, Pharmaceutical Sciences, Wayne State University, 42 W. Warren Ave., Detroit, MI, 48202, USA*
[e] *Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[f] *Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

Version: 052124. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Nerol oxide
CAS Registry Number: 1786-08-9



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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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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

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

https://doi.org/10.1016/j.fct.2024.114769
Received 21 May 2024; Accepted 27 May 2024
Available online 31 May 2024

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estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals

IFRA - The International Fragrance Association

IRB - Institutional Review Board

ISS - Istituto Superiore di Sanità (Italian National Institute of Health)

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

OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)

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

Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach

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 who 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 oxide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1) show that nerol oxide is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to nerol oxide is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data from read-across analog tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1) show that there are no safety concerns for nerol oxide for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; nerol oxide is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; nerol oxide 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 expected to be genotoxic. (RIFM, 2002; RIFM, 2012)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not a concern for skin sensitization. (RIFM, 1993d; RIFM, 1993a; RIFM, 1993c; RIFM, 1993b)

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:

Screening-level: 2.85 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Critical Measured Value: BCF 6–72 (OECD 305C) RIFM (1988)

Ecotoxicity:

Screening-level: Fish LC50: 10.57 mg/L (Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (Salvito et al., 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 10.57 mg/L (Salvito et al., 2002)

RIFM PNEC is: 0.01057 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not Applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Nerol oxide
2. **CAS Registry Number:** 1786-08-9
3. **Synonyms:** 3,6-Dihydro-4-methyl-2-(2-methylpropen-1-yl)-2H-pyran; 2H-Pyran, 3,6-dihydro-4-methyl-2-(2-methyl-1-propenyl)-; 4-メチル-2-(2-メチル-1-プロペニル)-3,6-ジヒドロ-2H-ピラン; 4-Methyl-2-(2-methylprop-1-en-1-yl)-3,6-dihydro-2H-pyran; 2H-Pyran, 3,6-dihydro-4-methyl-2-(2-methyl-1-propenyl)-; 2H-Pyran, 3,6-dihydro-4-methyl-2-(2-methylpropenyl)-; (±)-Nerol oxide; 3,6-Dihydro-4-methyl-2-(2-methyl-1-propenyl)-2H-pyran; Isoneroloxide; Nerol oxide
4. **Molecular Formula:** $C_{10}H_{16}O$
5. **Molecular Weight:** 152.23 g/mol
6. **RIFM Number:** 1139
7. **Stereochemistry:** No isomer specified. One stereocenter is present, and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 201.67 °C (EPI Suite v4.11)

2. **Flash Point:** 70 °C (Globally Harmonized System), 158 °F (closed cup) (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 3.49 (EPI Suite v4.11)
4. **Melting Point**: 19.21 °C (EPI Suite v4.11)
5. **Water Solubility:** 77.23 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** 0.900–0.908 (RIFM), 0.901 (FMA)
7. **Vapor Pressure:** 0.1 mm Hg at 20 °C (FMA), 0.478 mm Hg (EPI Suite v4.11)
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:** A colorless liquid

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00023% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000003 mg/kg/day or 0.000019 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.000018 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II*, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5 (OECD, 2021)
II	III	III

*See the Appendix below for details.

2. Analogs Selected:

a. **Genotoxicity:** Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1); Weight of Evidence (WoE) - terpinolene (CAS # 586-62-9)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Tetrahydro-4-methyl-2-(2-methylpropen-1-yl) pyran (CAS # 16409-43-1)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

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 oxide is reported to occur in the following foods by the VCF*:

Babaco fruit (*Carica pentagona* Heilborn)	Elderberry (*Sambucus nigra* L.)
Citrus fruits	Grape (*Vitis* species)
Grape brandy	Passion fruit (*Passiflora* species)
Litchi (*Litchi chinensis* Sonn.)	*Salvia* species
Litchi wine	Wine

*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

Nerol oxide has been pre-registered for 2010; no dossier available as of 10/11/23.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Nerol oxide was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of nerol oxide; however, read-across can be made to tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1; see Section VI).

The mutagenic activity of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran 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, 2002). Under the conditions of the study, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was not mutagenic in the Ames test, and this can be extended to nerol oxide.

As additional WoE, the mutagenic activity of terpinolene (CAS # 586-62-9) has been evaluated in a bacterial reverse mutation assay

conducted in compliance with GLP regulations and in accordance with OECD TG 471. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, terpinolene was not mutagenic in the Ames test, and this can be extended to nerol oxide.

The clastogenic activity of tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran 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 corn oil via oral gavage to groups of male and female NMRI mice. Doses of 250, 500, or 1000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did result in a weak, dose-related increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2012). However, no statistical significance was calculated for the dose groups. Therefore, due to the lack of statistical significance and a large inter-animal variability, the increase was deemed biologically irrelevant. To confirm this, a repeat experiment was performed. Again, the test material did result in a weak, dose-related increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow, but no statistical significance was calculated for any of the doses. Therefore, due to the lack of statistical significance and a large inter-animal variability, the increase was deemed biologically irrelevant. Under the conditions of the study, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran was considered not to be clastogenic in the *in vivo* micronucleus test, and this can be extended to nerol oxide.

As additional WoE, the clastogenic activity of terpinolene (CAS # 586-62-9) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Terpinolene did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2013b). Under the conditions of the study, terpinolene was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to nerol oxide.

Based on the data available, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran and terpinolene do not present a concern for genotoxic potential, and this can be extended to nerol oxide.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/06/23.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on nerol oxide or any read-across materials. The total systemic exposure to nerol oxide is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on nerol oxide or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to nerol oxide (0.018 μg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material (9 μg/kg/day; Kroes et al., 2007) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/06/23.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on nerol oxide or any read-across materials. The total systemic exposure to nerol oxide is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on nerol oxide or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to nerol oxide (0.018 μg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/06/23.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran, nerol oxide presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for nerol oxide. Therefore, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1; see Section VI) was used for the risk assessment of nerol oxide. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, nerol oxide is not considered a skin sensitizer. Nerol oxide and read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl) pyran are predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a guinea pig maximization test, read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran did not lead to skin sensitization reactions (RIFM, 1993d). In 3 separate guinea pig Buehler tests with read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl) pyran and isomers *d*-rose oxide and *l*-rose oxide, no reactions indicative of sensitization were observed (RIFM, 1993a; RIFM, 1993c; RIFM, 1993b). In a human maximization test, no skin sensitization reactions were observed when nerol oxide was tested at 6900 μg/cm^2 (RIFM, 1980). In a human maximization test, skin sensitization reactions were observed when nerol oxide was tested at 13800 μg/cm^2 (RIFM, 1979). In 2 separate human maximization tests, no skin sensitization reactions were observed when read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran and read-across material isomer rose oxide levo were tested at 1380 μg/cm^2 (RIFM, 1978; RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 969 μg/cm^2 of read-across material tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 40 volunteers (RIFM, 1964).

Based on the WoE from structural analysis, animal studies, and human studies on the read-across material as well as the target material, nerol oxide does not present a concern for skin sensitization.

Additional References: Klecak (1985); RIFM, 1963; RIFM, 1965.

Literature Search and Risk Assessment Completed On: 09/28/23.

11.1.5. Photoirritation/photoallergenicity

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

11.1.5.1. Risk assessment. 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). An *in vivo* photoallergenicity study was conducted in guinea pigs with 1.5% nerol oxide, but without proper controls, it is not possible to make any conclusion on photoallergenic potential. Based on the lack of absorbance in the critical range, nerol oxide does not present a concern for photoirritation or photoallergenicity.

Table 1
Summary of existing data on tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran as a read-across for nerol oxide.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[2]	Buehler[2]
No evidence of sensitization[3]	969	1380	N/A	N/A	N/A	Negative	Negative
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	Radical reactions	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
1WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
2Studies conducted according to the OECD TG 406 are included in the table.
3Determined based on Criteria for the RIFM safety evaluation process for fragrance ingredients (Api et al., 2015).

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 and photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/03/23.

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for nerol oxide is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on nerol oxide. Based on the Creme RIFM Model, the inhalation exposure is 0.000019 mg/day. This exposure is 24737 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II defaults to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of nerol oxide 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 of 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 oxide was identified as a fragrance material with no 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 oxide 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, 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), nerol oxide does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1988: Bioaccumulation of the test material was evaluated in carp (*Cyprinus carpio*) according to the OECD 305C method. The test concentrations were 0.6 and 0.06 mg/L for Level I and Level II, respectively. The BCF after 8 weeks of exposure was between 6 and 72.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Nerol oxide has been pre-registered for REACH with no additional data at this time.

11.2.1.3. 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.49	3.49
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.01057 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: 09/26/23.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/21/24.

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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.57 mg/L			1000000	0.01057 μg/L	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2024.114769.

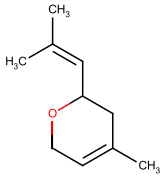
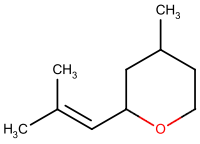
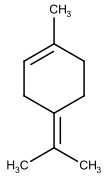
Appendix

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 Chemicals 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 v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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 v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	WoE Material
Principal Name	Nerol oxide	Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran	Terpinolene
CAS No.	1786-08-9	16409-43-1	586-62-9
Structure			
Similarity (Tanimoto Score)		0.51	0.34
SMILES	CC(C)=CC1CC(C)=CCO1	CC1CCOC(C1)C=C(C)C	CC1CCC(CC = 1) = C(C)C
Endpoint		Genotoxicity Skin sensitization	Genotoxicity
Molecular Formula	$C_{10}H_{16}O$	$C_{10}H_{18}O$	$C_{10}H_{16}$
Molecular Weight	152.237	154.253	136.238
Melting Point (°C, EPI Suite)	−19.21	−29.92	−29.51
Boiling Point (°C, EPI Suite)	201.67	194.97	186.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.37E+01	8.76E+01	1.33E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.72E+01	6.40E+01	9.50E+00
Log K_{OW}	3.49	3.58	4.47
J_{max} (μg/cm^2/h, SAM)	9.73	8.36	1.95
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.00E+02	4.85E+01	2.65E+03
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	
Protein Binding (OECD)	No alert found	No alert found	

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	WoE Material
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)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on nerol oxide (CAS # 1786-08-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1) was identified as a read-across analog and terpinolene (CAS # 586-62-9) was identified as a WoE material with sufficient data for toxicological evaluation.

Conclusions

- Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran (CAS # 16409-43-1) was used as a read-across analog for the target material, nerol oxide (CAS # 1786-08-9), for the genotoxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the group of alkyl-substituted pyrans with an alkene functionality.
  - o The key difference between the target material and the read-across analog is that the target material contains an additional internal vinylene not present in the read-across analog. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog do not display *in silico* alerts for the skin sensitization endpoint. Data for the read-across analog indicates that it is not a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - o Both the target material and read-across analog do not display *in silico* alerts for the genotoxicity endpoint. Data for the read-across analog indicates that it is not a concern for genotoxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Terpinolene (CAS # 586-62-9) was used as a WoE material for the target material, nerol oxide (CAS # 1786-08-9), for the genotoxicity endpoint.
  - o The target material and the WoE material are structurally similar and belong to the group of unsaturated monocyclics.
  - o The key difference between the target material and the WoE material is that the target material contains an in-ring ether while the WoE material does not. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the WoE material 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 WoE material are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE material.
  - o Neither the target material nor the WoE material has alerts for genotoxicity. The data from the genotoxicity section confirms that the WoE material is not genotoxic. Therefore, based on the structural similarity between the target material and read-across analog and the data on the read-across analog, the *in silico* alerts are consistent with the data.
  - o The target material and the WoE material 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 WoE material and the target material.

Explanation of Cramer Class

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

Q1.Normal constituent of the body? No.
Q2.Contains functional groups associated with enhanced toxicity? No.
Q3.Contains elements other than C, H, O, N, divalent S? No

Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6.Benzene derivative with certain substituents? No.
Q7.Heterocyclic? Yes.
Q8.Lactone or cyclic diester? No.
Q10.3-membered heterocycle? No.
Q11.Has a heterocyclic ring with complex substituents? No.
Q12.Heteroaromatic? No.
Q22.A common component of food? Yes, Class Intermediate (Class II)

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