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Short Review

Update to RIFM fragrance ingredient safety assessment, eucalyptol, CAS Registry Number 470-82-6

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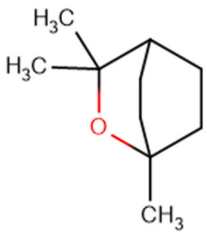
Name: Eucalyptol CAS Registry Number: 470-82-6



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 estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; B. Safford et al., 2015; 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
ISS - Instituto Superiore di Sanita (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 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.

(*continued on next page*)

(*continued*)

Eucalyptol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that eucalyptol is not genotoxic. Data on eucalyptol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints and a No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; eucalyptol 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 III material, and the exposure to eucalyptol is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; eucalyptol 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.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(Haworth et al., 1983; Gomes-Carneiro et al., 1998; NTP, 1982)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2013a)
Reproductive Toxicity: Developmental toxicity NOAEL = 300 mg/kg/day. Fertility NOAEL = 600 mg/kg/day.	ECHA (2013)
Skin Sensitization: NESIL = 7000 μg/cm^2.	RIFM (2022a)
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: 90.2% (OECD 301B)	(RIFM, 1995)
Bioaccumulation:	
Screening-level: 29.84 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 7.669 mg/L	(ECOSAR v2.0; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 7.669 mg/L	(ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.7669 μg/L	
• Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: <1	

1. Identification

1. **Chemical Name:** Eucalyptol
2. **CAS Registry Number:** 470-82-6
3. **Synonyms:** Cajeputol; Cineole; 1,8-Cineole; 1,8-Epoxy-p-menthane; 2-Oxabicyclo[2.2.2]octane, 1,3,3-trimethyl-; 1,8-Oxido-p-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane; 1,8-ｴﾎﾟｷｼﾊﾟﾗﾒﾝﾀﾝ; Eucalyptol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 333
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 176 °C (Fragrance Materials Association [FMA]), 174.13 °C (EPI Suite v4.11)
2. **Flash Point:** 52 °C (Globally Harmonized System), 115 °F; closed cup (FMA)
3. **Log K_{OW}:** 2.82 ± 0.27 (Cal, 2006), 3.4 at 35 °C (RIFM, 1998), 3.13 (EPI Suite v4.11)
4. **Melting Point**: 8.14 °C (EPI Suite v4.11)
5. **Water Solubility:** 332.1 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.923–0.926 (FMA), 0.921–0.924 (FMA)
7. **Vapor Pressure:** 1.11 mm Hg at 20 °C (EPI Suite v4.0), 1.4 mm Hg at 20 °C (FMA), 1.56 mm Hg at 25 °C (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 clear, colorless to very pale yellow liquid having a characteristic aromatic camphoraceous odor

3. Volume of use (worldwide band)

1. >1000 metric tons per year	IFRA (2019)

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

1.95th **Percentile Concentration in Fine Fragrance:** 0.061%	RIFM (2018)
2.Inhalation Exposure*: 0.00061 mg/kg/day or 0.045 mg/day	RIFM (2018)
3. Total Systemic Exposure:** 0.0087 mg/kg/day	RIFM (2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class II, Intermediate (Expert Judgment).

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

*See the Appendix below for further details.

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/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

Eucalyptol is reported to occur in the following foods by the VCF*.

Alpinia species	Date (*Phoenix dactylifera* L.)
Anise brandy	Gin
Buckwheat	Mangifera species
Chamomile	Peach (*Prunus persica* L.)
Cocoa category	Tea

*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 (ECHA, 2013); accessed on 11/10/23.

10. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.54
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	2.0
4	Products related to fine fragrances	3.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.76
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.76
5D	Baby cream, oil, talc	0.25
6	Products with oral and lip exposure	1.8
7	Products applied to the hair with some hand contact	1.0
8	Products with significant ano-genital exposure (tampon)	0.25
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	7.1
10B	Aerosol air freshener	14
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.25
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 eucalyptol, the basis was the subchronic reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 7000 μg/cm^2.
bFor 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).
cCalculations by Creme RIFM Aggregate Exposure Model v3.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of eucalyptol has been evaluated in 2 bacterial reverse mutation assays conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. The first assay used *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 preincubated with eucalyptol in solvent dimethyl sulfoxide (DMSO) at concentrations up to 3333 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in any of the strains at the concentrations tested (Haworth et al., 1983). Additionally, eucalyptol was assessed in an Ames assay using *Salmonella typhimurium* strains TA102, TA100, TA98, and TA97a treated in the presence or absence of S9 at concentrations up to 2500 μg/plate. No increases in the number of revertant colonies were observed (Gomes-Carneiro et al., 1998). Under the conditions of the study, eucalyptol was not mutagenic in the Ames test.

The clastogenicity of eucalyptol was assessed in an *in vitro* chromosome aberration study. Chinese hamster ovary cells were treated with eucalyptol in ethanol at concentrations up to 810 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 with or without S9 metabolic activation (NTP, 1982). Under the conditions of the study, eucalyptol was considered to be non-clastogenic to mammalian cells.

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

Additional References: Yoo (1986); Sasaki (1989); Carneiro (1997); Yoo (1985); Brewer (1999); Oda (1978); Pavlidou (2004); Vukovic-Gacic (2006); Horvathova (2007); Mitic-Culafic (2009).

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

11.1.2. Repeated dose toxicity

The MOE for eucalyptol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There is sufficient repeated dose toxicity data on eucalyptol. In an OECD 407- and GLP-compliant study, groups of 5 Wistar Han rats/sex/dose were administered eucalyptol via gavage (vehicle: Arachis oil BP) at doses of 0, 30, 300, or 600 mg/kg/day for 28 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups. Statistically significant increases in both the relative and absolute kidney weights for males in the mid- and high-dose groups were reported. There was also a statistically significant increase in liver weight among females at 30 mg/kg/day and in both sexes at 300 and 600 mg/kg/day. This increase was also evident among animals in the recovery group, and the difference attained statistical significance. Since there was no histopathological or clinical chemistry evidence of liver degeneration or necrosis, the liver weight increases were considered to be adaptive (Hall et al., 2012). Centrilobular hypertrophy of hepatocytes was observed in both sexes at 300 and 600 mg/kg bw/day doses but was not observed after the 2-week recovery period. Males in the mid- and high-dose groups showed an increase in the severity of hyaline droplets in the proximal tubules, accompanied by sporadic tubular cell degeneration at the high dose. Increased mean severity of multifocal tubular basophilia and/or interstitial mononuclear cell foci were observed in association with renal tubules where hyaline droplets were excessively deposited and were also observed at these dose levels. For males at 600 mg/kg/day, following the treatment-free recovery period, these findings decreased in severity. However, the report did not confirm the presence of α-2u-globulin in kidney tubules. These kidney changes in males were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This alteration is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman et al., 1990). Since no treatment-related adverse effects were observed up to the highest dose tested, the repeated dose NOAEL for this study was considered to be 600 mg/kg/day (RIFM, 2013a; data also available in ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 600/3 or 200 mg/kg/day.

Therefore, the eucalyptol MOE for the repeated dose toxicity endpoint can be calculated by dividing the eucalyptol NOAEL in mg/kg/day by the total systemic exposure to eucalyptol, 200/0.0087, or 22989.

In addition, the total systemic exposure to eucalyptol (8.7 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). 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 2 mg/kg/day.

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 eucalyptol was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 200 mg/kg/day by the uncertainty factor, 100 = 2 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: NTP, 1987a; NTP, 1987b.

Literature Search and Risk Assessment Completed On: 01/25/23.

11.1.3. Reproductive toxicity

The MOE for eucalyptol 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 eucalyptol. In an OECD 421-compliant study, groups of 10 Wistar Han rats/sex/dose were administered eucalyptol via gavage (vehicle: Arachis oil BP) at doses of 0, 30, 300, or 600 mg/kg/day for up to 11 weeks (including a 2-week pre-pairing phase, pairing, gestation, and early lactation for females). An additional pairing for high-dose females that failed to achieve pregnancy was performed to fully assess mating performance and fertility. Adult males were terminated on day 52 of the study following the completion of the second pairing at 600 mg/kg/day. Females and offspring were terminated on day 5 post-partum. At 600 mg/kg/day, only 7 females delivered a litter following the initial pairing, but subsequent re-mating and additional assessment of male organ weight and detailed testicular histopathology did not indicate any treatment-related effect on fertility for either sex. At 600 mg/kg/day, the initial body weights of the offspring were similar to the control, but weight gain to day 4 was statistically significantly lower than the control. No effect on the mean body weight of the offspring or litter weight on day 1 or day 4 was observed at 30 and 300 mg/kg/day. There were no treatment-related adverse effects in gestation, number of corpora lutea and implantations counts, pre- and post-implantation loss, number of offspring born, or subsequent offspring survival to day 4 of age, litter size, or sex ratio. Based on no adverse mating effects observed up to the highest dose, the fertility NOAEL for this study was considered to be 600 mg/kg/day (ECHA, 2013). Based on decreased body weight in high-dose group pups (600 mg/kg/day), the developmental toxicity NOAEL for this study was considered to be 300 mg/kg/day.

The eucalyptol MOE for the developmental toxicity endpoint can be calculated by dividing the eucalyptol NOAEL in mg/kg/day by the total systemic exposure to eucalyptol, 300/0.0087, or 34483.

The eucalyptol MOE for the fertility endpoint can be calculated by dividing the eucalyptol NOAEL in mg/kg/day by the total systemic exposure to eucalyptol, 600/0.0087, or 68966.

In addition, the total systemic exposure to eucalyptol (8.7 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/25/23.

11.1.4. Skin sensitization

Based on the existing data, eucalyptol is considered a skin sensitizer with a defined NESIL of 7000 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.1.4.1. Risk assessment. Based on the existing data, eucalyptol is considered a skin sensitizer. This material is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Eucalyptol was found to be negative in a direct peptide reactivity assay (DPRA) but positive in both the KeratinoSens

Table 1
Summary of existing data on eucalyptol.

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[2] µg/cm²	LLNA[3] Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
Weak	7003	11040	N/A	7000	16475	N/A	N/A
	In vitro Data[4]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Positive	Positive		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; 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).
2WoE NESIL limited to 2 significant figures.
3Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
4Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

and a human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2016c; RIFM, 2016d). Based on the 2 out of 3 Defined Approach, following OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), eucalyptol is predicted *in vitro* to be a sensitizer. In a murine local lymph node assay (LLNA), eucalyptol was found to be sensitizing with an EC3 value of 65.9% (16475 µg/cm^2) (RIFM, 2013d). In a human maximization test, no skin sensitization reactions were observed when tested at 11040 µg/cm^2 (RIFM, 1972). In a Confirmation of No Induction in Humans test (CNIH) with 590 µg/cm^2 of eucalyptol in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2016a). Additionally, in another CNIH with 7003 µg/cm^2 of eucalyptol in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 98 volunteers (RIFM, 2022a).

Based on weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies, eucalyptol is a sensitizer with a WoE NESIL of 7000 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 2 mg/kg/day.

Additional References: RIFM, 2017; Hausen et al., 1999; RIFM, 2020; Klecak (1985); Klecak (1979).

Literature Search and Risk Assessment Completed On: 03/02/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, eucalyptol 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 eucalyptol 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, eucalyptol 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 or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/23.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for eucalyptol is below the Cramer Class III* TTC

value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on eucalyptol. Based on the Creme RIFM Model, the inhalation exposure is 0.045 mg/day. This exposure is 10.4 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: Kovar (1987); Madyastha (1986); Melis (1989); Zanker (1980); Duchamp (1982); Revial (1982); Nasel (1994); Laude (1994); Stimpfl (1995); Jager (1996); Cometto-Muniz (1998); Ilmberger (2001); Bensafi (2002); Keinan (2005); Kimoto (1997); Sato (2007); Hummel (2003); Willis (2011); Satou (2013).

Literature Search and Risk Assessment Completed On: 03/06/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of eucalyptol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio 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, eucalyptol 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 eucalyptol 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

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

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1995**:** A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to the OECD 301B method. Under the conditions of the study, biodegradation of 90.2% was observed after 28 days.

RIFM, 1997**:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F guidelines. Biodegradation of 82% was observed after 28 days.

RIFM, 2000: The biodegradation of the test material was evaluated using a closed bottle test according to the OECD 301D method. Under the conditions of this study, the test material underwent a 72% degradation within 28 days.

11.2.1.2.2. Ecotoxicity. **RIFM, 2013b:** A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 value based on nominal test concentration was greater than 100 mg/L.

RIFM, 2012: The acute toxicity of the test material to the freshwater fish rainbow trout (*Oncorhynchus mykiss*) was evaluated according to the OECD 203 method under semi-static conditions. The 96-h LC50 value based on nominal test concentration was reported to be 57 mg/L.

RIFM, 2013c: An algae growth inhibition study was conducted according to the OECD 201 method under static conditions. The 72-h EC50 (growth and biomass) based on the mean measured concentration was reported to be greater than 74 mg/L.

RIFM, 2014: An algae growth inhibition test was conducted according to the OECD 201 method. Based on nominal exposure concentrations, the 72-h EC50 was reported to be 204 mg/L and 128.5 mg/L for growth rate and yield, respectively.

RIFM, 2013e: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Based on the geometric means of the measured concentration, the 48-h

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	12.59			1000000	0.01259	
ECOSAR v2.0 Acute Endpoints **(Tier 2)**	12.16	7.669	8.805	10000	0.7669	Neutral Organics

EC50 was reported to be 307 mg/L.

RIFM, 2013f: A zebrafish (*Danio rerio*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. Based on the nominal exposure concentrations, the 96-h LC50 was reported to be 121.4 mg/L.

11.2.1.2.3. Other available data. Eucalyptol has been registered under REACH, but no additional data are available at this time.

11.2.1.3. Risk assessment refinement. Since eucalyptol passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.4	3.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	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 0.7669 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search **and Risk Assessment Completed On:** 03/02/23.

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 01/03/24.

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.

Appendix

Explanation of Cramer Classification

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. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and 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 heterocycles? 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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