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

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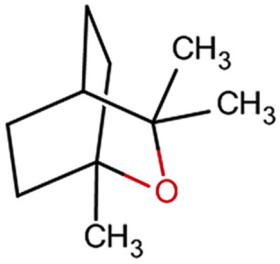
Name: Eucalyptol

CAS Registry Number: 470-82-6



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

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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., 2020)
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

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LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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.

Eucalyptol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/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. Data show that eucalyptol is a sensitizer with a No Expected Sensitization Induction Level (NESIL) of 590 μg/cm^2. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; eucalyptol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II 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 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)

ECHA REACH Dossier: Cineol; ECHA (2013)

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Reproductive Toxicity: Developmental toxicity NOAEL = 300. Fertility NOAEL = 600 mg/kg/day.
Skin Sensitization: NESIL = 590 μg/cm^2. RIFM (2016a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/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; 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 et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 7.669 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.7669 μg/L
- Revised PEC/PNECs (2015 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-エポキシ-p-メンタン; Eucalyptol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 333
7. **Stereochemistry:** Isomer not specified. Two stereocenters are present and 4 total stereoisomers are possible.

2. Physical data

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

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.069% (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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

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

6.1. *Cramer classification*

Class II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II*	III	III

*See the Appendix below for further details.

6.2. *Analogs selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Developmental and Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

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

Citrus fruits
Fennel (*Foeniculum vulg.,* ssp. capillaceum; var.)
Guava and feyoa
Laurel (*Laurus nobilis* L.)
Mentha oils
Ocimum species
Pimento (allspice) (*Pimenta dioica* L. Merr.)
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 09/15/21.

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)	0.045
2	Products applied to the axillae	0.014
3	Products applied to the face/body using fingertips	0.27
4	Products related to fine fragrances	0.25
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.064
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.064
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.064
5D	Baby cream, oil, talc	0.021
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	0.52
8	Products with significant ano-genital exposure (tampon)	0.021
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.49
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.8
10B	Aerosol air freshener	1.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.021
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 reference dose of 2 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 590 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, eucalyptol does not present a concern for genetic toxicity.

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 et al., 1989; Carneiro et al., 1997; Yoo, 1986; Brewer and Colditz, 1999; Oda et al., 1978; Pavlidou et al., 2004; Vukovic-Gacic et al., 2006; Horvathova et al., 2007; Mitic-Culafic et al., 2009.

Literature Search and Risk Assessment Completed On: 06/09/21.

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. An OECD 407/GLP 28-day oral gavage study was conducted with Wistar Han rats. Groups of 5 rats/sex/dose were administered via oral gavage test material eucalyptol at doses of 0, 30, 300, or 600 mg/kg/day in Arachis oil BP 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 and Caudill, 1992; Lehman-McKeeman et al., 1990). The NOAEL for repeated dose toxicity was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2013a; data also available at 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.

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.

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 22988.

Derivation of 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. (RIFM, 2020) and a reference dose 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 reference dose 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: National Toxicology Program National Center for Toxicological Research, 1987a; National Toxicology Program National Center for Toxicological Research, 1987b; Stoner et al., 1973; Zanker et al., 1980; Taylor and Austin, 1917; RIFM, 2013e; Keinan et al., 2005.

Literature Search and Risk Assessment Completed On: 06/03/21.

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. An OECD 421 developmental and reproductive toxicity study was conducted on Wistar Han rats. Groups of 10 rats/sex/dose were administered via oral gavage test material eucalyptol at dose levels of 0, 30, 300, or 600 mg/kg/day in Arachis oil BP. The animals were dosed 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. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on decreased body weight in high-dose group pups. The NOAEL for fertility was considered to be 600 mg/kg/day, the highest dose tested (ECHA, 2013).

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 34482.

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 68965.

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: 06/24/21.

11.1.4. Skin sensitization

Based on the existing data, eucalyptol is considered a skin sensitizer with a defined NESIL of 590 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, eucalyptol is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1; OECD Toolbox v4.2). Eucalyptol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and positive in both KeratinoSens and a human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2016c; RIFM, 2016d). 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). However, in an open epicutaneous test (OET), eucalyptol did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed at 16% (11040 μg/cm^2) (RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.5% or (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).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, eucalyptol is a sensitizer with a WoE NESIL of 590 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 2 mg/kg/day.

Additional References: Subiza et al., 1992; RIFM, 2017; Hausen et al., 1999.

Literature Search and Risk Assessment Completed On: 06/17/21.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 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 phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, eucalyptol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

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 no 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: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

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 et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1,

Table 1
Data summary for eucalyptol.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
16475 [1]	Weak	590	11040	NA	590

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 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 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, 2012). 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 Volume of Use (2015), eucalyptol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies.

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.

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 mean measured concentration was reported to be greater than 74 mg/L.

Other available data

Eucalyptol has been registered under REACH, but no additional data is available.

11.2.3. 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 et al., 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 Volume of Use 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: 06/21/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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

	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 Acute Endpoints **(Tier 2)** v1.11	12.16	7.669	8.805	10000	0.7669	Neutral Organics

- **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 09/15/21.

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 between 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.

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, 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? Ni
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 II (class intermediate)

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