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RIFM fragrance ingredient safety assessment, 1,4-cineole, CAS Registry Number 470-67-7

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Skin sensitization
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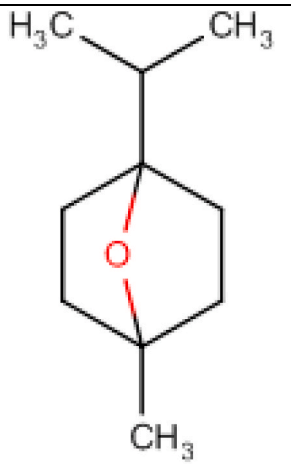

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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.

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(*continued*)

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.

1,4-Cineole was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,4-cineole is not genotoxic. Data on read-across analog eucalyptol (CAS # 470-82-6) provide a calculated margin on exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 1,4-cineole is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to 1,4-cineole is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 1,4-cineole was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2019a; RIFM, 2019b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2013b)
Reproductive Toxicity: NOAEL = 300 and 600 mg/kg/day, respectively.	(ECHA REACH Dossier: Cineol; ECHA, 2013)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.43 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 42.33 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:** 1,4-Cineole
2. **CAS Registry Number:** 470-67-7
3. **Synonyms:** 1,4-Epoxy-p-menthane; Isocineole; 7-Oxabicyclo[2.2.1]heptane, 1-methyl-4-(1-methylethyl)-; 1-ｲｿﾌﾟﾛﾋﾟﾙ-4-ﾒﾁﾙ-7-ｵｷｻﾋﾞｼｸﾛ[2.2.1]ﾍﾌﾟﾀﾝ; 1-Isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane; 1,4-Cineole
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 1156

7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 176 °C (Fragrance Materials Association [FMA]), 165.54 °C (EPI Suite)
2. **Flash Point:** 45 °C (Globally Harmonized System), 113 °F; CC (FMA)
3. **Log K_{OW}:** 3.13 (EPI Suite)
4. **Melting Point**: 2.01 °C (EPI Suite)
5. **Water Solubility:** 211.3 mg/L (EPI Suite)
6. **Specific Gravity:** 0.921 (FMA)
7. **Vapor Pressure:** 1.27 mm Hg @ 20 °C (EPI Suite v4.0), 1.0 mm Hg 20 °C (FMA), 1.78 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless mobile liquid which has a diffusive camphoraceous-fresh odor and a cool, somewhat spicy-herbaceous taste

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.013% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000070 mg/kg/day or 0.0054 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0012 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., 2015a; 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., 2015a; 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

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

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
II	III	III

*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). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Eucalyptol (CAS # 470-82-6)
   c. **Reproductive Toxicity:** Eucalyptol (CAS # 470-82-6)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

7. Metabolism

The metabolism of 1,4-cineole and eucalyptol has been extensively reviewed by the World Health Organization (WHO, 2004). Fig. 1 shows the schematic representation of eucalyptol metabolism in rats and humans producing similar metabolites in both species (WHO, 2004).

Additional References: None.

8. Natural occurrence (discrete chemical) or composition (NCS)

1,4-Cineole is reported to occur in the following foods by the VCF*:
Apricot (*Prunus armeniaca* L.)
Black currants (*Ribes nigrum* L.)
Buchu oil.
Bullock's heart (*Annona reticulata* L.)
Cardamom (*Ellettaria cardamomum* Maton.)
Citrus fruits.
Cocoa category.
Grape (*Vitis* species)
Grape brandy.
Honey.
Laurel (*Laurus nobilis* L.)
Mace (*Myristica fragrans* Houttuyn)
Mangifera species.
Mastic (*Pistacia lentiscus*)
Nutmeg (*Myristica fragrans* Houttuyn)
Plum (*Prunus* species)
Pomegranate juice (*Punica granatum* L.)
Rosemary (*Rosmarinus officinalis* L.)
Tequila (*Agave tequilana*)
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.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 06/14/19.

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 and use levels, 1,4-cineole does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. 1,4-Cineole was assessed in the BlueScreen

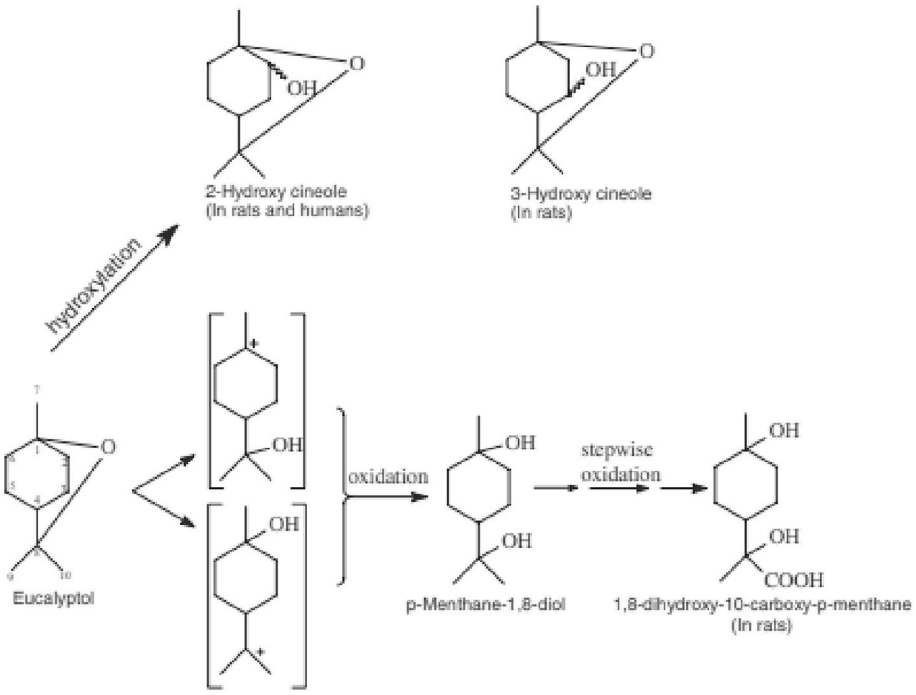


Fig. 1. Metabolism of eucalyptol in rats and humans.

assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). The mutagenic activity of 1,4-cineole has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1,4-cineole in water 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, 2019a). Under the conditions of the study, 1,4-cineole was not mutagenic in the Ames test.

The clastogenic activity of 1,4-cineole was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 1,4-cineole in water at concentrations up to 1540 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 800 μg/mL in the presence and absence of metabolic activation. 1,4-Cineole did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2019b). Under the conditions of the study, 1,4-cineole was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 1,4-cineole does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/11/19.

11.1.2. Repeated dose toxicity

The MOE for 1,4-cineole is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There is insufficient repeated dose toxicity data on 1,4-cineole. Read-across material eucalyptol (CAS 470-82-6; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. An OECD 407/GLP 28-day oral gavage study was conducted on Wistar Han rats. Groups of 5 rats/sex/dose were administered the test material eucalyptol at doses of 0, 30, 300, or 600 mg/kg/day in Arachis oil BP via oral gavage 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). Absolute and relative brain weight in males and absolute and relative thymus weight in females also attained significance after the recovery period, but all individual values remained within historical ranges. Centrilobular hypertrophy of hepatocytes was observed in both sexes at 300 and 600 mg/kg/day doses but was not observed after the 2-week recovery period. Males in the mid- and high-dose groups showed an increase in 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 infiltrations were observed in association with renal tubules where hyaline droplets were excessively deposited. For males at 600 mg/kg/day, following the treatment-free recovery period, these findings decreased in severity. 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, 2013b; 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*.

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

Therefore, the 1,4-cineole 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 1,4-cineole, 200/0.0012 or 166667.

In addition, the total systemic exposure to eucalyptol (1.2 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.

*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; Stoner et al., 1973; Zanker et al., 1980; Taylor and Austin, 1917; RIFM, 2013c; Keinan et al., 2005

Literature Search and Risk Assessment Completed On: 08/13/19.

11.1.3. Reproductive toxicity

The MOE for 1,4-cineole is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 1,4-cineole. Read-across material eucalyptol (CAS # 470-82-6; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

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

The 1,4-cineole MOE for the fertility endpoint can be calculated by dividing the eucalyptol NOAEL in mg/kg/day by the total systemic exposure to 1,4-cineole, 600/0.0012 or 500000.

The 1,4-cineole MOE for the developmental toxicity endpoint can be calculated by dividing the eucalyptol NOAEL in mg/kg/day by the total systemic exposure to 1,4-cineole, 300/0.0012 or 250000.

In addition, the total systemic exposure to 1,4-cineole (1.2 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: 08/06/19.

11.1.4. Skin sensitization

Based on existing data and the application of DST, 1,4-cineole does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for 1,4-cineole. In a modified Draize procedure, no skin sensitization reactions were observed (Sharp, 1978). In a human maximization test, no skin sensitization reactions were observed up to 16% (11040 μg/cm^2) (RIFM, 1981). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 1,4-cineole that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST

Table 1
Maximum acceptable concentrations for 1,4-cineole that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	1.4×10^{-5}%
2	Products applied to the axillae	0.021%	0.0048%
3	Products applied to the face using fingertips	0.41%	0.0013%
4	Fine fragrance products	0.39%	0.012%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0065%
6	Products with oral and lip exposure	0.23%	0.053%
7	Products applied to the hair with some hand contact	0.79%	4.6×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.34%
10	Household care products with mostly hand contact	2.7%	0.0090%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.56%

Note.
[b]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1,4-cineole 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 1,4-cineole in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 1,4-cineole 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 significant 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: 07/22/19.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 1,4-cineole 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 1,4-cineole. Based on the Creme RIFM Model, the inhalation exposure is 0.0054 mg/day. This exposure is 87 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: Heuberger and Ilberger, 2010.

Literature Search and Risk Assessment Completed On: 08/05/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 1,4-cineole was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 1,4-Cineole 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) identified 1,4-cineole as possibly persistent and not 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 1,4-cineole presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. Not available.

11.2.1.2.2. Ecotoxicity. Not available.

11.2.1.3. Other available data. 1,4-Cineole has been pre-registered for REACH with no additional data available at this time.

11.2.2. Risk assessment refinement

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

Endpoints used to calculate PNEC are highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.13	3.13
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is > 1. 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: 07/23/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	21.63			1000000	0.02163	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	12.165	7.669	8.805	10000	0.7669	Neutral Organics

- **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
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/31/20.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111659.

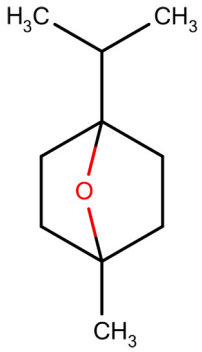
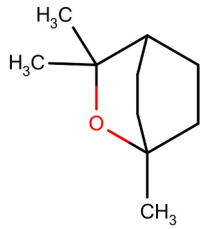
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2017).

- 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	1,4-Cineole	Eucalyptol
CAS No.	470-67-7	470-82-6
Structure		
Similarity (Tanimoto Score)		0.75
Read-across Endpoint		• Reproductive Toxicity • Repeated Dose Toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{10}H_{18}O$
Molecular Weight	154.25	154.25
Melting Point (°C, EPI Suite)	1.0	1.5
Boiling Point (°C, EPI Suite)	173.5	176.4
Vapor Pressure (Pa @ 25 °C, EPI Suite)	257.31146	253.3118
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.97	2.74
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	211.3	3500.0
J_{max} (μg/cm^2/h, SAM)	253.283	202.725
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.07E+001	1.11E+001
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (good reliability)
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 1,4-cineole (CAS # 470-67-7). 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, eucalyptol (CAS # 470-82-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Eucalyptol (CAS # 470-82-6) was used as a read-across analog for the target material 1,4-cineole (CAS # 470-67-7) for the reproductive toxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of bridged bicyclic ethers.
  - o The target material and the read-across analog are structural isomers.
  - o The key difference between the target material and the read-across analog is that the target material is a saturated tetrahydrofuran whereas the read-across analog is a saturated tetrahydropyran. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has a toxicant alert for developmental toxicity (CAESAR v2.1.6), which is not found for the target material. The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by 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.

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? No
Q10. 3-membered heterocycles? No
Q11. Has a heterocyclic ring with complex substituents? No
Q12. Heteroaromatic? No
Q22. Common component of food? Yes, Class II (Intermediate)

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