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Short Review

RIFM fragrance ingredient safety assessment, dihydroisocaryophyllene epoxide, CAS Registry Number 1209-61-6

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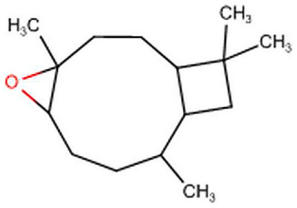
CAS Registry Number: 1209-61-6



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
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.

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).

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*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.

Dihydroisocaryophyllene epoxide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog caryophyllene oxide (CAS # 1139-30-6) show that dihydroisocaryophyllene epoxide is not expected to be genotoxic. Data on read-across analogs caryophyllene oxide (CAS # 1139-30-6) and trimethyl-13-oxabicyclo [10.1.0]trideca-4,8-diene (CAS # 71735-79-0) provide calculated MOEs >100 for the repeated dose toxicity and the reproductive toxicity endpoints, respectively. Data from the target material and read-across analog octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol (CAS # 68845-01-2) show that there are no safety concerns for dihydroisocaryophyllene epoxide for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; dihydroisocaryophyllene epoxide is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class III material, and the exposure to dihydroisocaryophyllene epoxide is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; dihydroisocaryophyllene epoxide was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 1979; RIFM, 2018)

Repeated Dose Toxicity: NOAEL = 109 mg/kg/day. RIFM (2013)

Reproductive Toxicity: Developmental toxicity: 223 mg/kg/day. Fertility: 223 mg/kg/day. RIFM (2017)

Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.

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: 2.28 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 811.1 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 0.882 mg/L (RIFM Framework; Salvito, 2002)

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: Fish LC50: 0.882 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.000882 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Dihydroisocaryophyllene epoxide
2. **CAS Registry Number:** 1209-61-6
3. **Synonyms:** 5-Oxatricyclo[8.2.0.04,6]dodecane, 4,9,12,12-tetramethyl-; 4,9,12,12-Tetramethyl-5-oxatricyclo[8.2.0.04,6]dodecane; Tabacarol; 4,9,12,12-Tetramethyl-5-oxatricyclo[8.2.0.0–4,6~]dodecane; Dihydroisocaryophyllene epoxide
4. **Molecular Formula:** $C_{15}H_{26}O$
5. **Molecular Weight:** 222.37
6. **RIFM Number:** 5232

7. **Stereochemistry:** Isomer not specified. Five chiral centers present and 25 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 262.79 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.91 (EPI Suite)
4. **Melting Point**: 56.71 °C (EPI Suite)
5. **Water Solubility:** 2.128 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00668 mm Hg at 20 °C (EPI Suite v4.0), 0.0117 mm Hg at 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} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015).

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.54% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.00055 mg/kg/day or 0.040 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0034 mg/kg/day (RIFM, 2016)

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v3.2
III	III	III

2. Analogs Selected:
   a. **Genotoxicity:** Caryophyllene oxide (CAS # 1139-30-6)
   b. **Repeated Dose Toxicity:** Caryophyllene oxide (CAS # 1139-30-6)
   c. **Reproductive Toxicity:** Trimethyl-13-oxabicyclo[10.1.0] trideca-4,8-diene (CAS # 71735-79-0)
   d. **Skin Sensitization:** Octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol (CAS # 68845-01-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

Dihydroisocaryophyllene epoxide is not reported to occur in foods by the VCF*.

*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

Dihydroisocaryophyllene epoxide has been pre-registered for 2010; no dossier available as of 10/07/20.

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, dihydroisocaryophyllene epoxide does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of dihydroisocaryophyllene epoxide; however, read-across can be made to caryophyllene oxide (CAS # 1139-30-6; see Section VI).

The mutagenic activity of caryophyllene oxide 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 TA1538 were treated with caryophyllene oxide in dimethyl sulfoxide (DMSO) at concentrations up to 10000 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, 1979). Under the conditions of the study, caryophyllene oxide was not mutagenic in the Ames test, and this can be extended to dihydroisocaryophyllene epoxide.

The clastogenic activity of caryophyllene oxide 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 caryophyllene oxide in ethanol at concentrations up to 2000 μg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted at concentrations up to 200 μg/mL in the presence and absence of metabolic activation. Caryophyllene oxide did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2018). Under the conditions of the study, caryophyllene oxide was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to dihydroisocaryophyllene

epoxide.

Based on the data available, caryophyllene oxide does not present a concern for genotoxic potential, and this can be extended to dihydroisocaryophyllene epoxide.

Additional References: RIFM, 1999.

Literature Search and Risk Assessment Completed On: 04/15/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for dihydroisocaryophyllene epoxide is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on dihydroisocaryophyllene epoxide. Read-across material caryophyllene oxide (CAS # 1139-30-6) has sufficient data for the repeated dose toxicity endpoint. In an OECD 408 and GLP-compliant subchronic toxicity study, 10 Crl:Sprague Dawley rats/sex/dose were administered a diet containing caryophyllene oxide at doses of 0 (control), 1750, 10500, and 21000 ppm (equivalent to 109, 672, and 1398 mg/kg/day for males and 137, 800, and 1660 mg/kg/day for females) for 90 days. No treatment-related effects were reported for mortality, clinical signs, ophthalmoscopic examinations, body weight, bodyweight gain, food consumption and food efficiency, hematology, coagulation, clinical chemistry, or urinalysis. A statistically significant increase in absolute and relative kidney weights in males and liver weights in both sexes of the mid- and high-dose groups was reported. In females, spleen weights (absolute and relative in the high-dose group) and relative kidney weights (mid- and high-dose groups) were significantly decreased. However, treatment-related macroscopic alterations were not reported at any dose level. At all doses, male kidneys demonstrated α-2u-globulin nephropathy along with a dose-dependent presence of cytoplasmic droplets in proximal tubule epithelial cells. Since α-2u-globulin nephropathy is species- and gender-specific, this effect is not considered a human health hazard (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). In both sexes at the mid and high doses, treatment-related microscopic findings were reported in the liver and mesenteric lymph nodes. The incidence and severity of these microscopic changes were dose dependent. Liver changes were characterized by hepatocellular hypertrophy in centrilobular to midzonal regions, which correlated with the increased liver weights (<2-fold). Due to the evidence for adaptive alterations in the liver and the fact that serum activities of liver enzymes were not elevated, these liver effects were not considered treatment-related adverse events (Hall, 2012). There was a dose-dependent presence of erythrocytes in the sinusoids of mesenteric lymph nodes reported in both sexes at the 10500 and 21000 ppm doses. No histopathological changes in the stomach or intestine were reported. Considering that α-2u-globulin nephropathy is not considered a human health hazard and that alterations in the liver were considered to be adaptive changes, the NOAEL for repeated dose toxicity was determined based on the observed effects in the mid- and high-dose groups. The NOAEL for repeated dose toxicity was considered to be 1750 ppm (equivalent to 109 mg/kg/day for males and 137 mg/kg/day for females). The more conservative NOAEL of 109 mg/kg/day was chosen for this risk assessment (RIFM, 2013).

Therefore, the dihydroisocaryophyllene epoxide MOE for the repeated dose toxicity endpoint can be calculated by dividing the caryophyllene oxide NOAEL in mg/kg/day by the total systemic exposure to dihydroisocaryophyllene epoxide, 109/0.0034 or 32059.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/20.

11.1.3. Reproductive toxicity

The MOE for dihydroisocaryophyllene epoxide 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 2-prenylcyclopentanone. Read-across material trimethyl-13-oxabicyclo [10.1.0]trideca-4,8-diene (CAS # 71735-79-0; Section VI) has sufficient data to support the reproductive toxicity endpoint. In an OECD/GLP 422 study groups of Crl:CD(SD) rats were administered test material, trimethyl-13-oxabicyclo[10.1.0]trideca-4,8-diene via the diet at doses of 0, 417, 1250, or 3750 ppm. The study design included the main phase of 10 animals/sex/dose, a toxicity phase of 5 control and high-dose females, and a recovery phase of 5 control males and females. Main-study males were treated daily for 2 weeks before pairing and for a minimum total of 6 weeks prior to necropsy. Main-study females were treated daily for 2 weeks before pairing, throughout pairing, gestation, and until day 14 of lactation. Females were allowed to give birth and to rear their offspring to weaning and were euthanized on day 14 of lactation. The F1 generation was euthanized on day 4 or day 13 of age but received no direct administration of the test material; any exposure occurred *in utero* or via the milk. Toxicity-phase females were treated daily for a minimum of 6 consecutive weeks. Recovery-phase animals were treated daily up to necropsy after a minimum of 6 consecutive weeks, followed by a recovery period of a minimum of 2 weeks. The mean daily intake values for males from weeks 1–6 were 0, 25, 75, and 223 mg/kg/day. The mean daily intake values for females from weeks 1–6 were 0, 26.9, 75.6, and 232 mg/kg/day. There were no treatment-related mortalities. There were no adverse effects on fertility or development of the pups among treated animals. The only finding among the offspring included lower bodyweight gains from days 7–13, resulting in statistically significant lower absolute mean body weights on day 13 for high-dose male offspring and mid- and high-dose female offspring. This effect was attributed to slightly larger litter size in these treatment groups. Thus, the NOAEL for fertility and developmental toxicity was considered to be 223 mg/kg/day, the highest dose tested among males and females (RIFM, 2017).

Therefore, the 2-prenylcyclopentanone MOE for the reproductive toxicity endpoint can be calculated by dividing the trimethyl-13-oxabicyclo[10.1.0]trideca-4,8-diene NOAEL in mg/kg/day by the total systemic exposure to 2-prenylcyclopentanone, 223/0.0034, or 65588.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/14/20.

11.1.4. Skin sensitization

Based on the existing data and read-across material octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol (CAS # 68845-01-2), dihydroisocaryophyllene epoxide does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for dihydroisocaryophyllene epoxide. Based on the existing data and read-across material octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b] oxiren-7-ol (CAS # 68845-01-2; see Section VI), dihydroisocaryophyllene epoxide is not considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, read-across material octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol did not present reactions indicative of sensitization (RIFM, 1998). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 1938 μg/cm^2 of dihydroisocaryophyllene epoxide in SDA 39C, no reactions indicative of sensitization was observed in any of the 38 volunteers (RIFM, 1972).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dihydroisocaryophyllene epoxide 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 dihydroisocaryophyllene epoxide 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, 2009). Based on the lack of absorbance, dihydroisocaryophyllene epoxide 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 $mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for dihydroisocaryophyllene epoxide 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 dihydroisocaryophyllene epoxide. Based on the Creme RIFM Model, the inhalation exposure is 0.040 mg/day. This exposure is 11.75 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dihydroisocaryophyllene epoxide 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 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, dihydroisocaryophyllene epoxide was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified dihydroisocaryophyllene epoxide as possibly persistent but 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), dihydroisocaryophyllene epoxide presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Dihydroisocaryophyllene epoxide has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.91	4.91
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.000882 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.882			1000000	0.000882	

- **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 09/30/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.111988.

Appendix

Read-across Justification

Methods

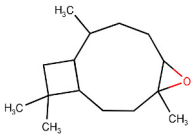
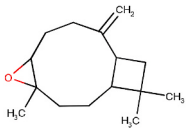
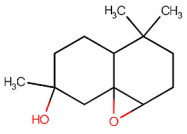
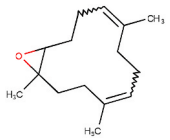
The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) 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).

Principal Name	Target Material	Read-across	Read-across	Read-across
	Dihydroisocaryophyllene epoxide	Caryophyllene oxide	Octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol	Trimethyl-13-oxabicyclo[10.1.0] trideca-4,8-diene
CAS No.	1209-61-6	1139-30-6	68845-01-2	71735-79-0
Structure				

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across	Read-across	Read-across
	Dihydroisocaryophyllene epoxide	Caryophyllene oxide	Octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol	Trimethyl-13-oxabicyclo[10.1.0]trideca-4,8-diene
				
Similarity (Tanimoto Score)		0.70	0.61	0.41
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity	• Skin Sensitization	• Reproductive toxicity
Molecular Formula	$C_{15}H_{26}O$	$C_{15}H_{24}O$	$C_{13}H_{22}O_2$	$C_{15}H_{24}O$
Molecular Weight	222.37	220.35	210.31	220.35
Melting Point (°C, EPI Suite)	56.71000	62.00000	74.49000	64.75000
Boiling Point (°C, EPI Suite)	262.79000	263.48000	273.13000	289.85000
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.55987	1.33322	0.03373	0.33864
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.91000	4.91000	2.50000	5.72000
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.12800	2.21000	913.10000	0.44300
Jmax (mcg/cm^2/h, SAM)	0.28	0.30	9.85	0.07
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	94.13093	82.88385	0.00196	230.00775
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	SN2|SN2 ≫ Alkylation, direct acting epoxides and related|SN2 ≫ Alkylation, direct acting epoxides and related ≫ Epoxides and Aziridines	SN2|SN2 ≫ Alkylation, direct acting epoxides and related|SN2 ≫ Alkylation, direct acting epoxides and related ≫ Epoxides and Aziridines		
DNA Binding (OECD QSAR Toolbox v4.2)	SN2|SN2 ≫ Direct Acting Epoxides and related|SN2 ≫ Direct Acting Epoxides and related ≫ Epoxides	SN2|SN2 ≫ Direct Acting Epoxides and related|SN2 ≫ Direct Acting Epoxides and related ≫ Epoxides		
Carcinogenicity (ISS)	Epoxides and aziridines (Genotox)| Structural alert for genotoxic carcinogenicity	Epoxides and aziridines (Genotox)| Structural alert for genotoxic carcinogenicity		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	Epoxides and aziridines	Epoxides and aziridines		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Epoxides and aziridines	Epoxides and aziridines		
Oncologic Classification	Epoxide Reactive Functional Groups	Epoxide Reactive Functional Groups		
Repeated Dose Toxicity				
Repeated dose (HESS)	Not categorized	Not categorized		
Reproductive and Developmental 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)	Toxicant (good reliability)			Toxicant (good reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ Ring-opening SN2 reaction|SN2 ≫ Ring-opening SN2 reaction ≫ Epoxides, Aziridines, and Sulfuranes		SN2|SN2 ≫ Ring-opening SN2 reaction|SN2 ≫ Ring-opening SN2 reaction ≫ Epoxides, Aziridines, and Sulfuranes	
Protein binding (OECD)	SN2|SN2 ≫ Epoxides and Related Chemicals|SN2 ≫ Epoxides and Related Chemicals ≫ Epoxides		SN2|SN2 ≫ Epoxides and Related Chemicals|SN2 ≫ Epoxides and Related Chemicals ≫ Epoxides	
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		SN2|SN2 ≫ Ring-opening SN2 reaction|SN2 ≫ Ring-opening SN2 reaction ≫ Epoxides, Aziridines, and Sulfuranes	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for SN2 identified		Alert for SN2 identified	
Metabolism				

(*continued on next page*)

(*continued*)

Principal Name	Target Material	Read-across	Read-across	Read-across
	Dihydroisocaryophyllene epoxide	Caryophyllene oxide	Octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol	Trimethyl-13-oxabicyclo[10.1.0] trideca-4,8-diene
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4

Summary

There are insufficient toxicity data on dihydroisocaryophyllene epoxide (CAS # 1209-61-6). 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, caryophyllene oxide (CAS # 1139-30-6), cctahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol (CAS # 68845-01-2), and trimethyl-13-oxabicyclo[1010]trideca-4,8-diene (CAS # 71735-79-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Caryophyllene oxide (CAS # 1139-30-6) was used as a read-across analog for the target material dihydroisocaryophyllene epoxide (CAS # 1209-61-6) for the genotoxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of epoxides of bicyclic sesquiterpene.
  - o The target material and the read-across analog share a macrocycle and epoxide functionality.
  - o The key difference between the target material and the read-across analog is that the target material is a saturated dihydro version of the read-across analog. This structural difference is predicted to increase the reactivity of the read-across analog compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have alerts for epoxide ring-opening and SN2 reaction. With the high molecular weight and high water-octanol partition coefficient and low water solubility, bioavailability is expected to be severely affected. Based on existing data on the target material and the read-across analog, the target material does not present a concern for skin sensitization under the current, declared levels 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.
- Octahydro-4,4,7-trimethyl-3H-naphth[1,8a-b]oxiren-7-ol (CAS # 68845-01-2) was used as a read-across analog for the target material dihydroisocaryophyllene epoxide (CAS # 1209-61-6) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of epoxides of bicyclic sesquiterpene.
  - o The target material and the read-across analog share an epoxide functionality on the bicyclic hydrocarbon skeleton.
  - o The key difference between the target material and the read-across analog is that the target material has one macrocycle while the read-across analog has both cycles of 6 carbons. Also, the read-across analog has one of its branched carbons oxidized to tertiary hydroxy. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert of epoxide ring-opening and SN2 reaction. Current existing data on the target material and the read-across analog confirms that it does not present a concern for skin sensitization under the current, declared levels of use. Therefore, 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.
- Trimethyl-13-oxabicyclo[1010]trideca-4,8-diene (CAS # 71735-79-0) was used as a read-across analog for the target material dihydroisocaryophyllene epoxide (CAS # 1209-61-6) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of epoxides of macrocyclic sesquiterpene.
  - o The target material and the read-across analog share a macrocycle and epoxide functionality.
  - o The key difference between the target material and the read-across analog is that the target material is a saturated bicyclic sesquiterpene while the read-across analog is an unsaturated monocyclic microcyclic sesquiterpene. This structural difference is predicted to increase the reactivity of the read-across analog compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog have alerts for being toxicants by the CAESAR model. The MOE of the read-across analog is adequate at the current level of use. Therefore, the predictions are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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