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RIFM fragrance ingredient safety assessment, terpinolene, CAS Registry Number 586-62-9

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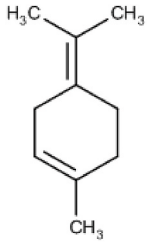


Name: Terpinolene
CAS Registry Number: 586-62-9

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
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

(*continued on next column*)

(*continued*)

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.

Terpinolene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that terpinolene is not genotoxic. Data on terpinolene provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analogs *d*-limonene (CAS # 5989-27-5), *l*-limonene (CAS # 5989-54-8), and *dl*-limonene (racemic) (CAS # 138-86-3) show that there are no safety concerns for terpinolene for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; terpinolene is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog *d*-limonene (CAS # 5989-27-5). The environmental endpoints were evaluated; terpinolene 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]) and read-across to *d*-limonene (CAS # 5989-27-5), are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: *p*-Mentha-1,4(8)-diene; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 52 mg/kg/day.	(ECHA REACH Dossier: *p*-Mentha-1,4(8)-diene; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity NOAEL = 155 mg/kg/day. Fertility NOAEL = 295 mg/kg/day.	(ECHA REACH Dossier: *p*-Mentha-1,4(8)-diene; ECHA, 2013)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1975; RIFM, 2006a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 54.3 mg/m^3.	RIFM (2013a)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 80% (OECD 302C)	RIFM (1998)
Bioaccumulation: Screening-level: 413.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: *Daphnia magna* chronic 21-day study: NOEC: 0.08 mg/L for *d*-limonene (CAS # 5989-27-5)	RIFM (2016)
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: *Daphnia magna* chronic 21-day study: NOEC: 0.08 mg/L for *d*-limonene (CAS # 5989-27-5)	RIFM (2016)
RIFM PNEC is: 1.6 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe: <1	

1. Identification

1. **Chemical Name:** Terpinolene
2. **CAS Registry Number:** 586-62-9
3. **Synonyms:** Cyclohexene, 1-methyl-4-(1-methylethylidene)-; p-Mentha-1,4(8)-diene; 1-Methyl-4-isopropylidene-1-cyclohexene; 1,4(8)-Terpadiene; Terpinene; 1,4-テレピネン; 4-Isopropylidene-1-methyl-cyclohexene; Terpinolene
4. **Molecular Formula:** $C_{10}H_{16}$
5. **Molecular Weight:** 136.23 g/mol

6. **RIFM Number:** 650
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 185 °C (Fragrance Materials Association [FMA]), 178.17 °C (EPI Suite)
2. **Flash Point:** 61 °C (Globally Harmonized System), 125 °F; CC (FMA)
3. **Log K_{OW}:** 3.3, 3.5, 5.3, 5.3 at 30 °C (RIFM, 1996a), 4.88 (EPI Suite)
4. **Melting Point**: −29.51 °C (EPI Suite)
5. **Water Solubility:** 3.838 mg/L (EPI Suite)
6. **Specific Gravity:** 0.8786 (Essential Oil Association, 1975 Sample 75–132)
7. **Vapor Pressure:** 0.702 mm Hg at 20 °C (EPI Suite v4.0), 0.5 mm Hg at 20 °C (FMA), 1 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:** Colorless or very pale straw-colored, oily liquid. Sweet piney oily and a relatively pleasant odor of moderate to poor tenacity. Not nearly as harsh as Pinene, often slightly anisic in its sweetness, and generally free from Turpentine-like notes (Arctander, 1969).

3. Volume of use (worldwide band)

1. >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:** 0.015% (RIFM, 2018a)
2. **Inhalation Exposure*:** 0.00006 mg/kg/day or 0.0044 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.00067 mg/kg/day (RIFM, 2018a)

*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

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** *d*-limonene, (CAS # 5989-27-5); *l*-limonene, (CAS # 5989-54-8) and *dl*-limonene (racemic), (CAS # 138-86-3); *p*-mentha-1,4-diene (CAS # 99-85-4) added for weight of evidence (WoE)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** *d*-limonene (CAS # 5989-27-5)
   g. **Environmental Toxicity:** *d*-limonene (CAS # 5989-27-5)
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)

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

Pimento (Allspice) (*Pimenta dioica* L. Merr.)	Curry (*Bergera koenigii* L.)
Salvia species	Mastic (*Pistacia lentiscus*)
Thyme (*Thymus* species)	Mentha Oils
Turpentine Oil (*Pistacia terebinthus*)	*Mangifera* species
Fennel (*Foeniculum vulg.*, ssp. capillaceum; var.)	Citrus fruits

*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 12/13/21 (ECHA, 2013)

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, terpinolene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of terpinolene (CAS # 586-62-9) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA97A, TA98, TA100, and TA102 were treated with terpinolene in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, terpinolene was not mutagenic in the Ames test.

The clastogenicity of terpinolene was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with terpinolene in either ethanol or DMSO at concentrations up to 100 μg/mL in the presence and absence of

exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test material, either with or without S9 at the 3-h exposure period or the 20-h exposure period in the presence of S9. However, a significant increase in chromosomal aberrations was observed at the 20-h exposure period in the absence of S9 when compared with ethanol as a solvent control, but the results did not show any significant change when compared with DMSO as a solvent control. Therefore, the study authors concluded that the biological relevance of the increases induced while using ethanol as the vehicle are unclear, as the effects may have been dependent on the vehicle used to solubilize the test material (ECHA, 2013). Under the conditions of the study, terpinolene was considered to be non-clastogenic to human cells at all time points of the study, except at the 20-h exposure period (without S9) using ethanol as a solvent.

The clastogenic activity of terpinolene 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 terpinolene in solvent DMSO at concentrations up to 100 μg/L in the absence of S9 at the 24-h timepoint. Terpinolene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in non-activated test systems (ECHA, 2013). Under the conditions of the study, terpinolene was considered to be non-clastogenic in the *in vitro* micronucleus test.

In a recent *in vitro* micronucleus test and sister chromatid exchange (SCE) assay conducted using terpinolene up to 200 mg/L, no significant increases in micronuclei or SCE were induced at any dose level (Turkez et al., 2015). Under the conditions of the study, terpinolene is considered to be non-clastogenic.

Furthermore, DEREK software (v3.0.1) was used to predict the mutagenicity and chromosomal damage potential of terpinolene as a mono-constituent *in vitro*. No structural alert was identified for terpinolene mono-constituent for the mutagenicity endpoint as well as for the chromosomal damage potential *in vivo* (ECHA, 2013). Moreover, no protein binding alerts were found for chromosomal aberrations using terpinolene (OECD Toolbox v4.2).

Based on the current existing data and use levels along with structural alert predictions using *in silico* tools, terpinolene does not present a concern for genetic toxicity.

Additional References: RIFM, 2001; RIFM, 1983.

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on terpinolene. In an OECD 422-compliant study, 10 Sprague Dawley rats were administered terpinolene via diet at doses of 0, 800, 2500, or 5000 ppm (equivalent to 0, 50, 155, and 310 mg/kg/day; ECHA, 2013). The dosing schedule was as follows: in the main phase, males were dosed daily during premating and mating periods and up to 42 days; females were dosed up to 56 consecutive days (including a 3-week maturation phase, pairing, gestation, and early lactation). In the toxicity phase, females were dosed daily up to 42 consecutive days; in the recovery phase, animals were treated with the high dose or basal laboratory diet alone for 42 consecutive days and then maintained without treatment for a further 14 days. There was no mortality observed, and no clinical signs were considered to be related to the toxicity of the test material. Reduced bodyweight gain was evident in animals of either sex treated with 5000 ppm (−24% in males, −50% in females) and in females treated with 2500 ppm (−41%). Males treated with 2500 ppm and females treated with 800 ppm also showed a reduction in bodyweight gain during the first week of treatment (−22% and −28%, respectively). No such effects were detected in males treated with 800 ppm. Reduced dietary intake was evident during the first week of treatment in animals of either sex treated with 5000 ppm (−14% in males, −24% in females). No adverse effects of treatment were detected in the hematological and blood chemistry parameters examined. Based on decreased body weight and food consumption at the high dose, the NOAEL was 155 mg/kg/day (2500 ppm) (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 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 155/3, or 52 mg/kg/day.

Therefore, the terpinolene MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpinolene NOAEL in mg/kg/day by the total systemic exposure for terpinolene, 52/0.00067, or 77611.

In addition, the total systemic exposure for terpinolene (0.67 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) at the current level of use for the repeated dose toxicity endpoint.

*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: RIFM, 1984; Imaizumi et al., 1985; Lehman-McKeeman et al., 1990; Lehman-McKeeman and Caudill, 1992

Literature Search and Risk Assessment Completed On: 10/12/21.

11.1.3. Reproductive toxicity

The MOE for terpinolene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. The developmental toxicity data on terpinolene are sufficient for the developmental toxicity endpoint. In an OECD 422 diet study, male and female Sprague Dawley rats received doses of 800, 2500, or 5000 ppm. Males were dosed daily during premating and mating periods and up to 42 days, and females were dosed up to 63 consecutive days (including a 3-week maturation phase, pairing, gestation, and early lactation). Reduced litter weights were observed for females treated with 5000 ppm on day 7 postpartum when compared to controls. Mean offspring weights were also reduced from these litters on day 7 postpartum, resulting in a reduction in bodyweight gain between days 4 and 7 postpartum. The NOAEL for developmental toxicity was 155 mg/kg/day (2500 ppm) based on reduced litter weights in the high-dose group. Maternal toxicity was also observed at 5000 ppm (ECHA, 2013). **Therefore, the terpinolene MOE for the developmental toxicity endpoint can be calculated by dividing the terpinolene NOAEL in mg/kg/day by the total systemic exposure for terpinolene, 155/0.00067, or 231343.**

The fertility data on terpinolene are sufficient for the fertility endpoint. In an OECD 422 diet study, male and female Sprague Dawley rats received doses of 800, 2500, or 5000 ppm. Males were dosed daily during premating and mating periods and up to 42 days, and females were dosed up to 63 consecutive days (including a 3-week maturation phase, pairing, gestation, and early lactation). No treatment-related effects were detected in mating performance, fertility, and gestation lengths. All animals mated within the first 5 days of pairing; furthermore, there were no differences in conception rates for treated animals, and the distribution of gestation lengths for treated females was comparable to controls. The NOAEL for fertility was 295 mg/kg/day (5000 ppm), the highest dose tested (ECHA, 2013). **Therefore, the terpinolene MOE for the fertility endpoint can be calculated by dividing the terpinolene NOAEL in mg/kg/day by the total systemic exposure for terpinolene, 295/0.00067, or 440299.**

In addition, the total systemic exposure for terpinolene (0.67 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use for the reproductive toxicity

endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/20.

11.1.4. Skin sensitization

Based on the existing data, read-across materials (*d*-limonene, CAS # 5989-27-5; *l*-limonene, CAS # 5989-54-8; and *dl*-limonene [racemic], CAS # 138-86-3), and WoE from p-mentha-1,4-diene (CAS # 99-85-4), terpinolene does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for terpinolene. Based on the available data for the read-across materials (*d*-limonene, CAS # 5989-27-5; *l*-limonene, CAS # 5989-54-8; and *dl*-limonene [racemic], CAS # 138-86-3; see Section VI) and WoE from *p*-mentha-1,4-diene (CAS # 99-85-4; see Section VI), terpinolene does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2)*. Read-across material *d*-limonene was found to be positive and negative in 2 *in chemico* Direct Peptide Reactivity Assays (DPRAs), negative in 2 *in vitro* KeratinoSens, and positive in the human cell line activation test (h-CLAT) and U937-CD86 test (RIFM, 2015c; RIFM, 2015b; Urbisch et al., 2015; Piroird et al., 2015). In a murine local lymph node assay (LLNA), terpinolene was found to be sensitizing with an EC3 of 8% or 2000 μg/cm^2 (ECHA, 2013). While positive responses to read-across material *d*-limonene have also been reported in guinea pig test methods (Klecak et al., 1977) and LLNAs (Christensson et al., 2008; RIFM, 2005b; RIFM, 2004d; RIFM, 2004e; RIFM, 2004c; Warbrick et al., 2001), these results have been attributed to autoxidation products and the irritant potential of *d*-limonene (Karlberg et al., 1991; RIFM, 2006b). Human maximization tests were conducted on terpinolene and read-across material *dl*-limonene (racemic), and the materials did not result in skin sensitization at 20.0% (13860 μg/cm^2) (RIFM, 1975; RIFM, 1972). Moreover, read-across materials *l*-limonene and *d*-limonene did not result in skin sensitization reactions in human maximization tests at concentrations of 4.0% (2760 μg/cm^2) and 8% (5520 μg/cm^2), respectively (RIFM, 1975; Greif, 1967). Additionally, in a confirmatory Confirmation of No Induction in Humans test (CNIH) with read-across material *d*-limonene at 8.5% (10038 μg/cm^2) in 1:3 ethanol:diethyl phthalate, no skin sensitization was observed (RIFM, 2006a).

Based on WoE from animal and human studies, as well as taking into account the irritation and auto-oxidation potential of the read-across materials pure *dl*-limonene (racemic) or individual *d* and *l* isomers, terpinolene does not present a concern for skin sensitization.

*Note: Whereas *d*- and *l*-limonene and terpinolene are considered to be non-sensitizing, autoxidation products of these materials would be expected to be contact allergens (OASIS TIMES v2.27.18.3). *d*-/*l*-Limonene and natural products rich in *dl*-limonene are subject to an IFRA standard that defines a good manufacturing practice specification limiting peroxide levels to 20 mmol/L with a recommendation to add an antioxidant at the time of production (IFRA, 2004).

Additional References: Karlberg et al., 1994; OECD, 2015; ECHA, 2018; RIFM, 1996c; RIFM, 2005a; Bruze et al., 2012; Loveless et al., 1996; Basketter and Kimber, 2010; RIFM, 2018b; Basketter and Allenby, 1991; Ishihara et al., 1986; Klecak (1979); Klecak (1985); RIFM, 1973.

Literature Search and Risk Assessment Completed On: 05/28/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, terpinolene 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 terpinolene 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, terpinolene 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: 08/07/20.

11.1.6. Local respiratory toxicity

There are no inhalation data available on terpinolene; however, in an acute, 2-week inhalation study for the analog *d*-limonene (CAS # 5989-27-5; see Section VI), a NOAEC of 54.3 mg/m^3 was reported (RIFM, 2013a).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week, acute inhalation study conducted in rats, a NOAEC of 54.3 mg/m^3 was reported for *d*-limonene (RIFM, 2013a). Treatment-related effects were found in the respiratory tract at the 543 and 5430 mg/m^3 concentrations; these were minor and consisted of minimally increased mucus in the respiratory epithelium of nasal levels II and III, minimal to mild olfactory cell degeneration in nasal levels III and IV, minimal transitional cell degeneration in the larynx, and minimal acute inflammation and alveolar macrophage aggregates in the lung.

This NOAEC expressed in mg/kg lung weight/day is:

- (54.3 mg/m^3) × (1 m^3/1000 L) = 0.0543 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0543 mg/L) × (61.2 L/day) = 3.32 mg/day
- (3.32 mg/day)/(0.0016 kg lung weight of rat*) = 2075 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0044 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0068 mg/kg lung weight/day resulting in a MOE of 305147 (i.e., [2075 mg/kg lung weight/-day]/[0.0068 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0044 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

Additional References: Ito and Ito, 2011; Kovar et al., 1987; Hink and Fee, 1986; Troy, 1977; Sheppard and Boyd, 1970; Duchamp (1982); Revial et al., 1982; Falk-Filipsson et al., 1993; Wolkoff et al., 2008; Silver (1992); Ellis and Baxendale, 1997; Karr and Coats, 1992; Perrucci et al., 1995; Coats et al., 1991; Helmig et al., 1999a; Helmig et al.,

1999b; Larsen et al., 2000; Heuberger et al., 2001; Rohr et al., 2002; RIFM, 2003b; RIFM, 2002; RIFM, 2003c; Isola et al., 2004; Clausen et al., 2001; RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; Larsen et al., 1997; Wilkins et al., 2003; RIFM, 2004b; Keinan et al., 2005; RIFM, 2004f; Isola et al., 2004a; Kimoto (1997); Rogers et al., 2005; Sunil et al., 2007; Corsi et al., 2007; Forester and Wells, 2009; Frederick et al., 2009; Wolkoff et al., 2012; Hirota et al., 2012; Satou et al., 2013; RIFM, 2012.

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of terpinolene 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, terpinolene 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 is > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify terpinolene as possibly persistent and 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 $\geq$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), terpinolene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1997:** The ready biodegradability of the test material was evaluated using the manometric respirometry test according to OECD 301F guidelines. Biodegradation of 51% was observed after 28 days.

RIFM, 1998: The inherent biodegradability of the test material was evaluated using the manometric respirometry test according to OECD 302C guidelines. Biodegradation of 80% was observed after 28 days.

RIFM, 1996b: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test according to OECD 301B guidelines. Biodegradation of 62% was observed after 28 days.

RIFM, 2013b: The purpose of this study was to assess the ready biodegradability of the test material with a manometric respirometry test according to OECD 301F guidelines. Under the conditions of the study, biodegradation of 78% was achieved after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Terpinolene has been registered under REACH, with the following data available (ECHA, 2013):

A fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 201 method under semi-static conditions. The 96-h LC50 value based on the mean measured concentration was reported to be 0.805 mg/L (95% CI: 0.670–0.928 mg/L).

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 0.634 mg/L (95% CI: 0.332–0.823 mg/L).

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on mean measured concentration were 0.302 mg/L (95% CI: 0.180–0.494 mg/L) and 0.692 mg/L (95% CI: 0.604–0.811 mg/L) for yield and growth rate, respectively.

There are additional data available for the read-across material *d*-limonene (CAS # 5989–27–5) in the RIFM Database:

RIFM, 2016: A *Daphnia magna* reproduction test was conducted according to the OECD 211 method. As the test material was volatile, a closed system with a minor headspace was used. The 21-day NOEC value was reported to be 0.08 mg/L based on the time-weighted mean measured concentration.

RIFM, 2013c: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value (actual measured concentration) of the test material was reported to be 0.51 mg/L (95% CI: 0.46–0.59 mg/L).

RIFM, 2015a: A 48-h algae growth inhibition test was conducted according to the OECD 201 method. As the test material is volatile, a closed system with a minor headspace was used. The 48-h ErC50 (growth rate) was reported to be 0.25 mg/L(95% CI: 0.24–0.27 mg/L) and EyC50 (yield) was 0.18 mg/L (95% CI: 0.17–0.19 mg/L). The 48-h NOEC value (growth) was reported to be 0.09 mg/L (geometric mean concentration).

RIFM, 2011: A study was conducted to determine the lethal and, to a limited extent, the sublethal effects of the test material on embryos and sac-fry stages of the freshwater fish fathead minnow (*Pimephales promelas*) according to the OECD 212 method. The EC/LC50 (survival) was 0.41 mg/L and the EC/LC50 growth (length) was >0.37–<0.57 mg/L. Based on the significant effect seen on the growth of the hatched larvae at the termination of the test (measured as length), the overall No Observed Effect Concentration (NOEC) was 0.059 mg/L (measured concentration) and Lowest Observed Effect Concentration was 0.19 mg/L (measured concentration).

Passino and Smith, 1987: A 48-h static *Daphnia magna* acute study (non-GLP) was conducted with the test material. Under the conditions of the study, the 48-h EC50 value was 69.6 mg/L.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.2473			1000000	0.0002473	
ECOSAR Acute Endpoints **(Tier 2)** v2.0	0.291	0.215	0.482	10000	0.0215	Neutral Organic
Tier 3: Measured Data (including REACH data and read-across data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.805					
Daphnia		0.51	0.08	50	1.6	
Algae		0.18	0.09			

Environmental Framework: Salvito et al., 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.3	5.3
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 further assessment is necessary.

The RIFM PNEC is 1.6 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 08/21/20.

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
- **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 12/13/21.

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113195.

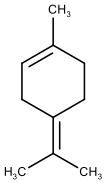
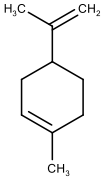
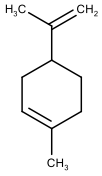
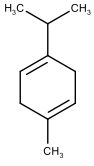
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	WoE Material
Principal Name	Terpinolene	dl-Limonene (racemic)	d-Limonene, *l*-limonene	*p*-Mentha-1,4-diene
CAS No.	586-62-9	138-86-3	5989-27-5, 5989-54-8	99-85-4
Structure				
Similarity (Tanimoto Score)		0.57	0.57	0.59
SMILES	CC1CCC(CC = 1) = C(C)C	CC(=C)C1CCC(C)=CC1	CC(=C)C1CCC(C)=CC1	CC(C)C1CC=C(C)CC = 1
Endpoint		Skin sensitization	• Skin sensitization • Local respiratory toxicity • Environmental	Skin sensitization
Molecular Formula	$C_{10}H_{16}$	$C_{10}H_{16}$	$C_{10}H_{16}$	$C_{10}H_{16}$
Molecular Weight (g/mol)	136.238	136.238	136.238	136.238
Melting Point (°C, EPI Suite)	−29.51	−40.76	−40.76	−10.00
Boiling Point (°C, EPI Suite)	186.00	178.00	178.00	183.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.33E+02	1.92E+02	1.92E+02	1.45E+02
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	9.50E+00	1.38E+01	1.38E+01	8.68E+00
Log KOW	4.47	4.38	4.38	4.5
J_{max} (μg/cm^2/h, SAM)	1.95	2.80	2.80	1.79
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.65E+03	3.23E+03	3.23E+03	2.61E+03
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.
Environmental				
BIOWIN 3	2.90	2.90	2.90	
ECOSAR (96-h Fish LC50) for hydrocarbons in mg/L	0.291	0.323	0.323	0.380
ECOSAR (48-h *Daphnia* LC50) for hydrocarbons mono in mg/L	0.215	0.238	0.238	0.278
	0.482	0.522	0.522	0.502

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	WoE Material
ECOSAR (96-h Algae LC50) for hydrocarbons in mg/L				
Metabolism				
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 terpinolene (CAS # 586-62-9). Hence *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, *dl*-limonene (racemic) (CAS # 138-86-3), *l*-limonene (CAS # 5989-54-8), and *d*-limonene (CAS # 5989-27-5) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- *dl*-Limonene (racemic) (CAS # 138-86-3), *l*-limonene (CAS # 5989-54-8), and *d*-limonene (CAS # 5989-27-5) are used as read-across analogs, while *p*-mentha-1,4-diene (CAS # 99-85-4) is used as a WoE material for terpinolene (CAS # 586-62-9) for the skin sensitization endpoint.
  - o The target material and read-across analog are structurally similar and belong to a class of cyclic terpenes.
  - o The key difference between the target material and the read-across is the position of the double bond. The target material has an endocyclic and exocyclic vinylene bond while the read-across analog has an endocyclic vinylene and exocyclic vinylene bond. The target material also has a bis-allylic carbon in the cycle. The read-across analog lacks this feature, while the WoE material has bis-allylic carbon in the cycle. The read-across analog together with WoE material fulfills structural reactive features of the target material.
  - o The target material and read-across analog have a Tanimoto score of 0.44 which is mainly driven by terpene fragment. The differences in the structure that are responsible for the low Tanimoto score are not relevant from a toxicology endpoint perspective.
  - o The physical–chemical properties of the target material and the read-across analog are very similar.
  - o The structural alerts for the toxicological endpoints are consistent between the target material as well as the read-across material.
  - o The structural alerts for the predicted metabolic products show that the read-across material is similarly reactive for the skin sensitization toxicological endpoint as compared to the target material.
  - o The structural alerts show that the read-across material is similarly reactive for the skin sensitization endpoint as compared to the target material.
  - o The structural alerts show that the predicted metabolites of the read-across material are more reactive as compared to the target material or its predicted metabolites.
  - o The target material and read-across analog are expected to be metabolized similarly as shown by the metabolism simulator. OECD QSAR Toolbox v4.2 showed that the read-across analog has observed metabolites with no structural alerts for skin sensitization toxicological endpoint. The target material did not have any observed metabolites.
  - o The structural differences between the target material and the read-across analog appear to be toxicologically insignificant.
- *d*-Limonene (CAS # 5989-27-5) is used as a structurally similar read-across analog for terpinolene (CAS # 586-62-9) for the skin sensitization, local respiratory toxicity, and environmental endpoints.
  - o The target material and read-across analog are structurally similar and belong to a class of cyclic terpenes.
  - o The key difference between the target material and the read-across analog is the position of the double bond and degree of unsaturation. The target has 3 degrees of unsaturation while the read-across analog has 2.5 degrees of unsaturation.
  - o The target material and read-across analog have a Tanimoto score of 0.44 which is mainly driven by terpene fragment. The differences in the structure that are responsible for the low Tanimoto score are not relevant from a toxicology endpoint perspective.
  - o The physical–chemical properties of the target and the read-across analog are similar.
  - o Structural alerts for the toxicological endpoints are consistent between the target as well as the read-across material.
  - o The structural alerts show that the read-across material is similarly reactive for the respiratory endpoints as compared to the target material.
  - o The structural alerts show that the predicted metabolites of read-across material are more reactive as compared to the target material or its predicted metabolites.
  - o The target material and read-across analog are expected to be metabolized similarly as shown by the metabolism simulator. OECD QSAR Toolbox v4.2 showed that the read-across have observed metabolites with no structural alerts for respiratory toxicological endpoints. The target material did not have any observed metabolites.
  - o The structural differences between the target material and the read-across analog appear to be toxicologically insignificant.

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