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RIFM fragrance ingredient safety assessment, *dl*-limonene (racemic), CAS Registry Number 138-86-3☆

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☆ Based on the data available, stereoisomers *d*-limonene and *l*-limonene do not present a concern for genotoxic potential, and this can be extended to *dl*-limonene (racemic).

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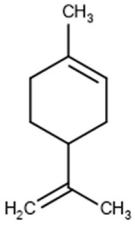

Name: *dl*-Limonene (racemic)
CAS Registry Number: 138-86-3
Additional CAS Numbers:
5989-27-5; *d*-Limonene
5989-54-8; *l*-Limonene
7705-14-8; *d,l*-Limonene (isomer unspecified)
*Included because the materials are isomers.

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, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
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.

(*continued on next column*)

(*continued*)

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.
dl-Limonene (racemic) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *dl*-limonene (racemic) is not genotoxic. Data on *dl*-limonene (racemic) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data show that there are no safety concerns for *dl*-limonene (racemic) for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *dl*-limonene (racemic) is not expected to be phototoxic/photoallergenic. Data on *dl*-limonene (racemic) provide a calculated MOE >100 for the local respiratory endpoint. The environmental endpoints were evaluated; *dl*-limonene (racemic) 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.	(ECHA REACH Dossier: (S)-p-Mentha-1,8-diene; ECHA, 2013; ECHA REACH Dossier: (R)-p-Mentha-1,8-diene; ECHA, 2011; Nesslany et al., 2007; Sekihashi et al., 2002)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	(National Toxicology Program, 1990)
Reproductive Toxicity: Developmental NOAEL = 250 mg/kg/day. Fertility: 2000 mg/kg/day.	(Environmental Protection Agency, 1992; National Toxicology Program, 1990)
Skin Sensitization: Not sensitizing (see note in the section below).	(RIFM, 1975a; Greif, 1967; RIFM, 1972; 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: 71% (OECD 301B; *d*-limonene CAS # 5989-27-5)	RIFM, (1993a)
Bioaccumulation: Screening-level: 360.5 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: Fish (Fathead minnow embryo); NOEC: 0.059 mg/L	RIFM, (2011a)

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: Fish (Fathead minnows embryo); NOEC: 0.059 mg/L	RIFM, (2011a)

RIFM PNEC is: 5.9 µg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: <1

Chemical Name: *dl*-Limonene (racemic)	Chemical Name: *d*-Limonene	Chemical Name: *l*-Limonene	Chemical Name: *d,l*-Limonene (isomer unspecified)
CAS Registry Number: 138-86-3	**CAS Registry Number:** 5989-27-5	**CAS Registry Number:** 5989-54-8	**CAS Registry Number:** 7705-14-8
Synonyms: Cyclohexene, 1-methyl-4-(1-methylethenyl)-; Dipentene; Eulimene; 1,8-(9)-*p*-Menthadiene; *p*-Mentha-1,8-diene; 1-Methyl-4-isopropenyl-1-cyclohexene; 1-Methyl-4-(1-methylethenyl)cyclohexene; 1-Methyl-4-isopropenylcyclohexene; リモネン; 4-Isopropenyl-1-methylcyclohexene; Limonene; *dl*-Limonene (racemic)	**Synonyms:** Cyclohexene, 1-methyl-4-(1-methylethenyl)-, (R)-; 4-Isopropenyl-1-methylcyclohexene; Limonene; Limonene Extra; (R)-(+)-*p*-Mentha-1,8-diene; (R)-*p*-Mentha-1,8-diene; *d*-*p*-Mentha-1,8-diene; *p*-1,8(9)-Menthadiene; d-1-Methyl-4-isopropenyl-1-cyclohexene; リモネン	**Synonyms:** Cyclohexen, 1-methyl-4-(1-methylethenyl)-, (S)-; 4-Isopropenyl-1-methylcyclohexene; (S)-*p*-Mentha-1,8-diene; リモネン	**Synonyms:** Cyclohexene, 1-methyl-4-(1-methylethenyl)-, (.+-.)-; 4-Isopropenyl-1-methylcyclohexene; d,l-1-Methyl-4-isopropenylcyclohexene; *d,l*-1-Methyl-4-(1-methylethenyl)cyclohexene; (.+-.)-1-Methyl-4-(1-methylvinyl)cyclohexene
Molecular Formula: $C_{10}H_{16}$	**Molecular Formula:** $C_{10}H_{16}$	**Molecular Formula:** $C_{10}H_{16}$	**Molecular Formula:** $C_{10}H_{16}$
Molecular Weight: 136.23	**Molecular Weight:** 136.23	**Molecular Weight:** 136.23	**Molecular Weight:** 136.23
RIFM Number: 389	**RIFM Number:** 137	**RIFM Number:** 724	**RIFM Number:** 5362

1. Identification

2. Physical data

1. **Boiling Point:** 178 °C (Fragrance Materials Association [FMA]), 167.66 °C (EPI Suite)
2. **Flash Point:** 46 °C (Globally Harmonized System), 115 °F; CC (FMA)
3. **Log K_{OW}:** 4.83 (EPI Suite)
4. **Melting Point**: −40.76 °C (EPI Suite)
5. **Water Solubility:** 4.581 mg/L (EPI Suite)
6. **Specific Gravity:** 0.844 (FMA)
7. **Vapor Pressure:** 1.03 mm Hg at 20 °C (EPI Suite v4.0), 0.8 mm Hg at 20 °C (FMA), 1.45 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (0, 99, and 129 L • mol^{-1} • cm^{-1}), under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L • mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless mobile liquid with a citrus-like odor (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 v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance**: 0.00064% (RIFM, 2018)
2. **Inhalation Exposure***: 0.0035 mg/kg/day or 0.26 mg/day (RIFM, 2018)
3. **Total Systemic Exposure****: 0.038 mg/kg/day (RIFM, 2018)

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

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

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 95th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

1. **Dermal:** 12%

RIFM SABS testing on *d*-Limonene (Api et al., 2013): An *in vivo* skin absorption study for *d*-Limonene (CAS # 5989-27-5) was conducted on humans and Long-Evans rats. In the rat study, radioactive *d*-Limonene in ethanol was applied to 12 adult male rats at 5 mg/kg (10–20 mCi/mg) over a 9-cm^2 shaved area of the back for 6 h. The treated area was covered with aluminum foil and held in place with waterproof adhesive dressing for occlusion. After removing the occlusion, the treated area was washed with ethanol, and the dressing, foil, and swabs were retained for radioactivity measurement. Urine, feces, and cage air samples were collected at several time points for up to 72 h after treatment; tissue samples were collected after euthanasia. The total mean recovery of applied radioactivity after 72 h was 78.4%; most of this was recovered from skin area washing (47.9%) and air traps (17.5%). The remaining 21% of the radioactivity was likely volatilized and/or evaporated during application. Thus, approximately 12% of the applied dose was absorbed through the skin.

In the human study, 12 mg radioactive *d*-Limonene in 1 mL ethanol (50 mCi/mL) was applied to 2 adult males to a 100-cm^2 area of intact unshaven skin on the back for 6 h. For the first hour, the material was allowed to dry, and thereafter the treated areas were occluded with light gauze dressing held in place with waterproof adhesive tape. After removing the occlusion, the treated area was washed with ethanol, and the dressing, foil, and swabs were retained for radioactivity measurement. A 2 x 5-cm^2 treated area was stripped with 5 successive applications of adhesive tape, and each tape strip was retained separately for radioactivity measurement. Urine, feces, air trappings, and blood samples were collected at several time points for up to 120 h after treatment. The total mean recovery of radioactivity after the 120-h study was only 0.6%. It was concluded that the remainder of the applied dose evaporated either during the drying time before occlusion or from the dressing after removal. Approximately 0.36% of the dose was recovered from gauze dressing and 0.06% from swabs. Skin strips yielded only 0.01%–0.03% of the applied dose. The mean recovery from urine during the 120-h study period was 0.16% of the dose. Thus, it was concluded that only approximately 0.16% of the applied dose was absorbed.

The most conservative value of 12% from the rat study was taken as the skin absorption value for *d*-Limonene.

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:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional references

None.

8. Natural occurrence

dl-Limonene (racemic) is reported to occur in the following foods by the VCF*:

Citrus fruits	Mentha oils
Dill (*Anethum* species)	*Ocimum* species
Fennel (*Foeniculum vulg.*, Ssp. *Capillaceum*; Var.)	*Salvia* species
Mangifera species	Tea
Mastic (*Pistacia lentiscus*)	Thyme (*Thymus* species)

d-Limonene is reported to occur in the following foods by the VCF:

Angelica (*Angelica archangelica* L.)	*Mangifera* species
Apple Fresh (*Malus* species)	Mastic (*Pistacia lentiscus*)
Calamus (Sweet Flag) (*Acorus calamus* L.)	Pepper (*Piper nigrum* L.)
Citrus Fruits	Tea
Fennel (*Foeniculum Vulg.*, Ssp. *Capillaceum*; Var.)	Tomato (*Lycopersicon esculentum* Mill.)

l-Limonene is reported to occur in the following foods by the VCF:

Angelica (*Angelica archangelica* L.)	Fennel (*Foeniculum vulg.*, Ssp. *Capillaceum*; Var.)
Calamus (Sweet Flag) (*Acorus calamus* L.)	*Mangifera* species
Caraway (*Carum carvi* L.)	Mastic (*Pistacia lentiscus*)
Citrus fruits	Pepper (*Piper nigrum* L.)
Coriander seed (*Coriandrum sativum* L.)	Tea

d,l-Limonene (isomer unspecified) is not reported to occur in food 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

Available for dl-limonene (racemic), d-limonene, and l-limonene; accessed 09/25/21; *d,l*-limonene (isomer unspecified) has been pre-registered for 2010.

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, *dl*-limonene (racemic) does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. *dl*-Limonene (racemic) was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of *dl*-limonene (racemic) (CAS # 138-86-3) has been evaluated in a bacterial reverse mutation assay conducted in the preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were treated with limonene in dimethyl sulfoxide (DMSO) at concentrations up to 30 μmol/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Florin et al., 1980). Under the conditions of the study, *dl*-limonene was not mutagenic in the Ames test. There are no other data available for *dl*-limonene; however, read-across can be made to its stereoisomers *d*-limonene and *l*-limonene (CAS # 5989-27-5 and CAS # 5989-54-8). *l*-Limonene (CAS # 5989-54-8) was assessed in an Ames study conducted equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA100, TA98, and TA102 were treated with *l*-limonene in DMSO at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation and found to be not mutagenic (ECHA, 2013). The mutagenic activity of *d*-limonene has been evaluated in several bacterial reverse mutation assays conducted in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, TA1537, and TA1538, both with and without metabolic activation, and found to be not mutagenic (Florin et al., 1980; Zeiger et al., 1990; Connor et al., 1985; Heck et al., 1989; Vukovic-Gacic et al., 2006; Watabe et al., 1981; Haworth et al., 1983; Muller et al., 1993; RIFM, 1983). In mammalian cells, no mutagenic effects with *d*-limonene were produced in the L5178Y mouse lymphoma cell mutagenesis assay with or without metabolic activation (Heck et al., 1989; RIFM, 1982; Myhr et al., 1990; National Toxicology Program, 1990; Zeiger et al., 1990). Additionally, a lack of mutagenic potential in the liver or kidney was demonstrated *in vivo* when *d*-limonene was administered in the diet of male lacI transgenic Big Blue rats, at a dose of 500 mg/kg/day for 10 days (Turner et al., 2001). Taken together, the stereoisomers *d*-limonene and *l*-limonene do not present concern regarding mutagenicity, and this can be

applied to *dl*-limonene (racemic).

With regards to clastogenicity, read-across material *d*-limonene did not produce any effects in the sister chromatid exchange assay or chromosomal aberration test using Chinese hamster ovary cells, either with or without S9 (National Toxicology Program, 1990; Sasaki et al., 1989; Zeiger et al., 1990; ECHA, 2011). Two *in vivo* comet assays also show no DNA damage in the kidneys, stomach, colon, liver, urinary bladder, lung, brain, or bone marrow when *d*-limonene was administered by oral gavage at 2000 mg/kg (Nesslany et al., 2007; Sekihashi et al., 2002). Whereas *d*-limonene has been shown to cause cancer in the male rat (National Toxicology Program, 1990; see the repeated dose section below for more details), these data indicate that *d*-limonene does not have a genotoxic potential and is, therefore, a non-genotoxic carcinogen (in the male rat only; National Toxicology Program, 1990).

Additional references: RIFM, 1983; RIFM, 1982.

Literature search and risk assessment completed on: 03/11/21.

11.1.2. Repeated dose toxicity

The MOE for *dl*-limonene (racemic) 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 *dl*-limonene (racemic). In a GLP-compliant study, groups of 10 B6C3F1 mice/sex/dose were administered with *d*-Limonene via gavage (vehicle: corn oil) at dose levels of 0, 125, 250, 500, 1000, or 2000 mg/kg/day for 13 weeks (5 days/week). There was a decrease in body weight at the 2 highest doses. Lung adenoma was observed in 1 female of the high-dose group. The NOAEL was determined to be 500 mg/kg/day based on decreased body weight (National Toxicology Program, 1990). In another study, a 13-week, GLP-compliant study was performed on groups of 10 F344/N rats/sex/dose mixed in corn oil at dose levels of 0, 150, 300, 600, 1200, and 2400 mg/kg/day for 13 weeks (5 days/week). The final mean body weights of male rats in 600, 1200, or 2400 mg/kg/day groups were lower than the control. The surviving females among the 2400 mg/kg/day group also had lower body weights as compared to the control. Hyaline droplets (protein reabsorption droplets) were observed in the epithelium of proximal convoluted tubules in all groups of male rats, including vehicle controls; immunohistochemical staining indicated that this was indicative of alpha-2u-globulin nephropathy, which is species- and sex-specific to male rats. Thus, the NOAEL for was considered to be 600 mg/kg/day based on decreased body weights (National Toxicology Program, 1990). *d*-Limonene, when administered to rats and mice for up to 2 years, did not show any signs of carcinogenicity that could be translated to humans (National Toxicology Program, 1990). The NTP studies did not investigate hematology or clinical chemistry. These endpoints were unaffected in the studies by Tsuji where male and female Sprague Dawley rats (5/sex/group) received an oral dose of 227, 554, or 1385 mg/kg/day of *d*-limonene in 1% Tween 80 for 6 months. No effects were observed in terms of hematology and clinical chemistry parameters up to the highest dose tested (Tsuji et al., 1975a). Hence, the most conservative NOAEL of 500 mg/kg/day was selected for the repeated dose toxicity endpoint. **Therefore, the *dl*-limonene MOE for the repeated dose toxicity endpoint can be calculated by dividing the *d*-limonene NOAEL in mg/kg/day by the total systemic exposure for *dl*-limonene 500/0.038, or 13157.**

Additional references: VanDuuren and Goldschmidt, 1976; Imaizumi et al., 1985; Smith et al., 1969; Cal et al., 2001; Schafer and Schafer, 1982; RIFM, 2013a; RIFM, 2012; Kodama et al., 1977a; Tsuji et al., 1975b; Kodama et al., 1977b; Api et al., 2013; Ford et al., 1989; RIFM, 1990a; RIFM, 1990b; Tsuji et al., 1975c; Stoner et al., 1973; Dietrich and Swenberg, 1990; Dietrich and Swenberg, 1991a; Reicks, 1993; Lehman-McKeeman and Caudill, 1994; Saito et al., 1991; Saito et al., 1992; Saito et al., 1996; Lehman-McKeeman and Caudill, 1993; Leroy (1984); Keinan et al., 2005; Homburger et al., 1971; Kimura et al., 1996; Warnasuriya et al., 2000; Webb et al., 1990; Kodama et al., 1977c; Qureshi et al., 1988; Webb et al., 1989; Lehman-McKeeman et al., 1991; Kanerva et al., 1987; RIFM, 1975b; Tsuji et al., 1975d; Webb et al., 1988; Carmichael et al., 2000; Hursting et al., 1995; Dietrich and Swenberg, 1991b; Elegbede et al., 1986; Frei and Stephens, 1968; Holck et al., 1991; Abramovici and Rachmuth-Roizman, 1983; Howes et al., 2002; Meyer and Meyer, 1959; Monti et al., 2002; Obata et al., 1990; Godwin and Michniak, 1999; Ota et al., 2003; Schmitt et al., 2009; Godwin and Michniak, 1997; Diez et al., 1998; Jain et al., 1996; Obata et al., 1993; Kikuchi et al., 1992; Calpena et al., 1994; Schmitt et al., 2010; Zhao and Singh, 1998; Meyer (1965); Barbier and Benezra, 1983; Kristiansen and Madsen, 1995; Shimada et al., 2002; Pinching and Doving, 1974; Poon et al., 1996.

Literature search and risk assessment completed on: 02/16/21.

11.1.3. Reproductive toxicity

The MOE for *dl*-limonene (racemic) is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. The developmental toxicity data on *dl*-limonene (racemic) are sufficient for the developmental toxicity endpoint. A gavage developmental toxicity study was conducted in rats gavaged once daily with test material from days 6–15 of gestation at 0, 250, 500, and 1000 mg/kg/day in a corn oil vehicle. The NOAEL was determined to be 250 mg/kg/day for developmental toxicity, based on skeletal variations at higher doses (Environmental Protection Agency, 1992). A dermal absorption study was conducted with stereoisomer *d*-limonene (CAS # 5989-27-5) *in vitro* using human skin (Hotchkiss, 1998). **Therefore, the *dl*-limonene MOE for the developmental toxicity endpoint can be calculated by dividing the *d*-limonene NOAEL in mg/kg/day by the total systemic exposure for *dl*-limonene, 250/0.038, or 22727.**

There are sufficient fertility data on *dl*-limonene (racemic). In the gavage 13-week and 2-year toxicity studies in rats and mice conducted with stereoisomer *d*-limonene (CAS # 5989-27-5), reproductive organ histopathology was unaffected at dosages up to 2000 mg/kg/day (National Toxicology Program, 1990). Together, these indicate no specific concern for reproductive toxicity. **Therefore, the *dl*-limonene MOE for the fertility endpoint can be calculated by dividing the *d*-limonene NOAEL in mg/kg/day by the total systemic exposure for *dl*-limonene, 2000/0.038, or 52632.**

Additional references: None.

Literature search and risk assessment completed on: 03/11/21.

11.1.4. Skin sensitization

Based on the weight of evidence (WoE), taking into account the limited data specific to *dl*-limonene (racemic) and read-across to the individual isomers *d* and *l*-limonene, unoxidized *dl*-limonene (racemic) does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on existing data on *dl*-limonene (racemic) and *d* and *l*-limonene (CAS # 5989-27-5 and CAS # 5989-54-8), *dl*-limonene (racemic) does not present a concern for skin sensitization under the conditions of use. The chemical structure of the individual isomers, both *l*- and *d*-limonene, indicate that they would not have the potential to act as skin sensitizers directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2)*. However, the autoxidation products of d-limonene are skin sensitizers based on *in vivo* skin sensitization data

(Christensson et al., 2008). *d*-Limonene was found to be positive in *in chemico* direct peptide reactivity assay (DPRA), negative in the *in vitro* KeratinoSens, and positive in a human cell-line activation test (h-CLAT) and U937-CD86 test (Urbisch et al., 2015; Piroird et al., 2015). While positive responses to *d*-limonene have been reported in guinea pig test methods (Klecak et al., 1977) and the local lymph node assay (LLNA) (Christensson et al., 2008; RIFM, 2005a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Warbrick et al., 2001). These results have been attributed to autoxidation products and the irritant potential of *d*-limonene, respectively (Karlberg et al., 1991; Christensson et al., 2008; RIFM, 2011b; RIFM, 2011c; RIFM, 2011d; RIFM, 2006b). A human maximization test was conducted on *dl*-limonene (racemic); the material did not result in skin sensitization at a maximum tested concentration of 20.0% (13860 μg/cm^2) (RIFM, 1972). In a human maximization test, *l*-limonene was not observed to result in skin sensitization at a maximum tested concentration of 4.0% (2760 μg/cm^2) (RIFM, 1975a). Additionally, in a Confirmation of No Induction in Humans (CNIH), *d*-Limonene was not observed to result in skin sensitization at a maximum tested concentration of 8.5% (10039 μg/cm^2) in 1:3 ethanol:diethyl phthalate (RIFM, 2006a). Moreover, in a Primary Dermal Irritation (PDI) test, the application of *d*-limonene in various vehicles and concentrations led to slight to severe irritant reactions (RIFM, 2005b). Based on the WoE from all the *in vitro*, animal, and human studies, as well as taking into account the irritation and auto-oxidation potential, pure, unoxidized *dl*-limonene (racemic) or individual *d* and *l* isomers do not present a concern for skin sensitization.

*Note: Whereas *d*- and *l*-limonene in the absence of oxidation are not considered to be sensitizing, autoxidation products of these materials would be expected to be contact allergens. *dl*-Limonene (racemic), and natural products rich in *dl*-limonene (racemic), 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, 2018; RIFM, 2015a; RIFM, 2004g; Basketter and Allenby, 1991; Klecak (1985); Klecak et al., 1977; Karlberg et al., 1991; Greif (1967).

Literature search and risk assessment completed on: 03/11/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, *dl*-limonene (racemic) 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 *dl*-limonene (racemic) in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *dl*-limonene (racemic) 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 minor absorbance in the range of 290–700 nm. The molar absorption coefficients (0, 99, 129 L • mol^{-1} • cm^{-1}, under neutral, acidic, and basic conditions, respectively) are 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: 03/02/21.

11.1.6. Local Respiratory Toxicity

There are no inhalation data available on *dl*-limonene (racemic); however, in an acute, 2-week inhalation study for the analog *d*-limonene (CAS # 5989-27-5), 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; they 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 inhalation exposure was reported to be 0.26 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and 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 0.4 mg/kg lung weight/day resulting in a MOE of 5187.5 (i.e., [2075 mg/kg lung weight/day]/[0.4 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 0.26 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: Kovar et al., 1987; Hink and Fee, 1986; Sheppard and Boyd, 1970; Duchamp (1982); Revial et al., 1982; Falk--Filipsson et al., 1993; Wolkoff et al., 2008; 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, 2003a; RIFM, 2002; RIFM, 2003b; Isola and Rogers, 2002; Clausen et al., 2001; RIFM, 2003c; RIFM, 2003d; RIFM, 2004d; Larsen et al., 1997; Wilkins et al., 2003; RIFM, 2004e; 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: 03/12/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *dl*-limonene (racemic) 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, *dl*-limonene (racemic) was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify *dl*-limonene (racemic) as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *dl*-limonene (racemic) presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For *d*-limonene (CAS # 5989-27-5)

RIFM, 1993a: A biodegradation test according to the OECD 301B method was conducted with *d*-limonene. After 28 days, the mean biodegradation of the test material was 71.4%.

RIFM, 1993b: A manometric respirometry biodegradation test according to the EEC Directive 79–831, Annex V, Part C method was conducted. Within the test period of 28 days, a degradation of 20% was determined for *d*-limonene.

11.2.2.1.2. Ecotoxicity. For *dl*-limonene (racemic) (CAS # 138-86-3)

There are 3 aquatic ecotoxicity tests reported for *dl*-limonene (racemic) in the RIFM Database. However, these studies were conducted on a 75% pure racemic mixture of limonene and 25% *p*-cymene (4-isopropyltoluene) and are reported here only for completeness.

Broderius et al., 1990: A 48-h flow-through *Daphnia magna* acute toxicity test was conducted according to the ASTMA, 1989 method. The calculated LC50 was 31 mg/L, and the EC50 was calculated to be 28.2 mg/L.

Broderius et al., 1990: A 96-h flow-through fish (fathead minnow) acute toxicity test was conducted according to the ASTMA, 1989 method. The calculated LC50 was 38.5 mg/L, and the EC50 was 20.2 mg/L.

Broderius et al., 1990: A 96-h static algae (*Selenastrum caprocornutum*) toxicity test was conducted according to the ASTMA, 1988 method. The IC50 was reported to be 13.8 mg/L.

For *d*-limonene (CAS # 5989-27-5)

RIFM, 2016: A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC was reported to be 0.08 mg/L based on time-weighted mean measured concentration.

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

RIFM, 2015b: A 48-h algae growth inhibition test was conducted according to the OECD 201 method in a closed test system with a minor headspace. The 48-h ErC50 (growth rate) was reported to be 0.25 mg/L and EyC50 (yield) was 0.18 mg/L. The 48-h NOEC (growth) was reported to be 0.09 mg/L (geometric mean concentration).

RIFM, 2011a: An 8-day 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, under semi-static conditions. 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) is 0.059 mg/L (measured concentration), and the Lowest Observed Effect Concentration was 0.19 mg/L (measured concentration).

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

11.2.2.1.3. Other available data. *d*-Limonene (CAS # 5989-27-5) and *l*-limonene (CAS # 5989-54-8) have been registered under REACH, and the following additional information is available (ECHA, 2011; ECHA, 2013):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 85% was observed after 28 days.

A 96-h acute fish (Fathead minnows) according to the OECD 203 method was conducted under flow-through conditions. The 96-h LC50 value based on mean measured concentration was reported to be 0.702 mg/L (95% CI: 0.618–0.839 mg/L).

A 48-h acute *Daphnia magna* test according to the OECD 202 method was conducted under semi-static conditions. The 48-h EC50 value based on the mean measured concentration of 0.307 mg/L was reported.

A 48-h static *Daphnia magna* test according to the OECD 202 method was reported for *d*-limonene with the EC50 value based on nominal concentration calculated to be 0.36 mg/L.

A 96-h acute fish (*Oryzias latipes*) according to the OECD 203 method was conducted. The LC50 of 1.1 mg/L was reported.

A 48-h acute *Daphnia magna* test according to the OECD 202 method was conducted. The EC50 of 0.7 mg/L was reported.

A chronic *Daphnia magna* (21 days) test according to the OECD 211 method was conducted, resulting in a NOEC value of 0.27 mg/L.

An algae acute study according to the OECD 201 method was conducted. A 72-h ErC50 of >1.6 mg/L and EbC50 > 21 mg/L was reported.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.247			1000000	0.000247	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.322	0.234	0.520	10000	0.0234	Neutral Organics
Tier 3: Measured Data (Including REACH Data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.702		0.059	10	5.9	
Daphnia		0.307	0.08			
Algae		0.18	0.09			

The 72-h NOEC value was reported to be 1.6 mg/L for growth rate.

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 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**

*Regional Volume of Use added for all CAS #

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

The RIFM PNEC is 5.9 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: 03/15/21.

12. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **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 09/26/21.

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.

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