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RIFM fragrance ingredient safety assessment, *p*-mentha-1,3-diene, CAS Registry Number 99-86-5

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc, 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St, Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr, Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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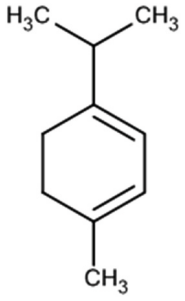
Name: *p*-Mentha-1,3-diene
CAS Registry Number: 99-86-5



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al.,

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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
DST - Dermal Sensitization Threshold
DRF - Dose Range Finding
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

p-Mentha-1,3-diene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that *p*-mentha-1,3-diene is not genotoxic. Data on read-across material (−)-(R)-α-phellandrene (CAS # 4221-98-1) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and fertility endpoints. Data provide a calculated MOE >100 for the developmental toxicity endpoint. Data provided *p*-mentha-1,3-diene a No Expected Sensitization Induction Level (NESIL) of 2200 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; *p*-mentha-1,3-diene 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; *p*-mentha-1,3-diene 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

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Genotoxicity: Not genotoxic.	(Gomes-Carneiro et al., 2005; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 8.33 mg/kg/day.	RIFM (2018a)
Reproductive Toxicity: Developmental toxicity NOAEL = 30 mg/kg/day. Fertility toxicity NOAEL = 200 mg/kg/day, respectively.	(Araujo et al., 1996; RIFM, 2018a)
Skin Sensitization: NESIL = 2200 μg/cm^2.	(Kern et al., 2010; RIFM, 2014)
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 66% (70 days; OECD 301F)	(ECHA REACH Dossier: p-Mentha-1,3-diene; ECHA, 2018)
Bioaccumulation: Screening-level: 295.9 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.278 mg/L	(ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.278 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0278 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

1. Identification

1. **Chemical Name**: *p*-Mentha-1,3-diene
2. **CAS Registry Number**: 99-86-5
3. **Synonyms**: Citronella Terpenes; 1,3-Cyclohexadiene, 1-methyl-4-(1-methylethyl)-; 1-Isopropyl-4-methylcyclohexa-1,3-diene; 1-Methyl-4-isopropyl-1,3-cyclohexadiene; Terpilene; α-Terpinene; ｐ - メンタ - １ ，３ （ - ３ ，７又は - １ ，４ ） - ジエン
4. **Molecular Formula**: $C_{10}H_{16}$
5. **Molecular Weight**: 136.23 g/mol
6. **RIFM Number**: 426
7. **Stereochemistry**: Isomer not specified. No stereocenter and no stereoisomer possible.

2. Physical data

1. **CAS Number**: 99-86-5
2. **Boiling Point**: 169.36 °C (EPI Suite)
3. **Flash Point**: 116 °F; CC
4. **Log K_{OW}**: 4.75 (EPI Suite)
5. **Melting Point**: (calculated) −31.15 °C (EPI Suite)
6. **Water Solubility**: 5.915 mg/L (EPI Suite)
7. **Specific Gravity**: 0.840 (Fragrance Materials Association [FMA] Database)
8. **Vapor Pressure**: 1.18 mm Hg at 20 °C (EPI Suite v4.0), 0.5 mm Hg at 20 °C (FMA Database), 1.66 mm Hg at 25 °C (EPI Suite)
9. **UV Spectra**: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
10. **Appearance/Organoleptic**: Colorless, oily liquid with a refreshing, lemon-citrusy odor of poor tenacity; the taste is mostly lemony in concentrations below 40 ppm but becomes rather bitter at higher levels (Arctander, 1969)

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0073% (RIFM, 2018b)
2. **Inhalation Exposure*:** 0.000023 mg/kg/day or 0.0017 mg/day (RIFM, 2018b)
3. **Total Systemic Exposure**:** 0.00024 mg/kg/day (RIFM, 2018b)

*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
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2. **Analogs Selected**:
   1. **Genotoxicity**: None
   2. **Repeated Dose Toxicity**: (−)-(R)-α-Phellandrene (CAS # 4221-98-1)
   3. **Reproductive Toxicity**: (−)-(R)-α-Phellandrene (CAS # 4221-98-1)
   4. **Skin Sensitization**: None
   5. **Phototoxicity/Photoallergenicity**: None
   6. **Local Respiratory Toxicity**: *d*-Limonene (CAS # 5989-27-5)
   7. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

7. Metabolism

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

8. Natural occurrence

p-Mentha-1,3-diene is reported to occur in the following foods by the VCF*:	
Citrus fruits	Pimento (allspice) (*Pimenta dioica* L. Merr.)
Dill (*Anethum* species)	Pistachio oil (*Pistacia* vera)
Mangifera species	*Salvia* species
Mastic (*Pistacia lentiscus*)	*Satureja* species
Mentha oils	Thyme (*Thymus* species)

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH Dossier

Available; accessed 09/21/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for p-mentha-1,3-diene are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.059
2	Products applied to the axillae	0.050
3	Products applied to the face/body using fingertips	0.024
4	Products related to fine fragrances	0.53
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.11
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.024
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.024
5D	Baby cream, oil, talc	0.0078
6	Products with oral and lip exposure	0.18
7	Products applied to the hair with some hand contact	0.012
8	Products with significant ano-genital exposure (tampon)	0.0078
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.094
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.49
10B	Aerosol air freshener	0.13
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0078
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	5.3

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For p-mentha-1,3-diene, the basis was the reference dose of 0.083 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2200 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, *p*-mentha-1,3-diene does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. *p*-Mentha-1,3-diene was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013b).

The mutagenic activity of *p*-mentha-1,3-diene has been evaluated in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella*

typhimurium strains TA97, TA98, TA100, and TA1535 were treated with *p*-mentha-1,3-diene in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Gomes-Carneiro et al., 2005). Under the conditions of the study, *p*-mentha-1,3-diene was not mutagenic in the Ames test.

The clastogenic activity of *p*-mentha-1,3-diene 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 *p*-mentha-1,3-diene in dimethyl sulfoxide (DMSO) at concentrations up to 1360 μg/mL for the dose range finding (DRF) study. Micronuclei analysis in the main study was conducted up to 100 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. *p*-Mentha-1,3-diene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, *p*-mentha-1,3-diene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, *p*-mentha-1,3-diene does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for *p*-mentha-1,3-diene is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no available repeated dose toxicity data on *p*-mentha-1,3-diene. Read-across material (−)-(R)-α-phellandrene (CAS # 4221-98-1; see Section VI) has sufficient repeated dose toxicity data. In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 12 Sprague Dawley rats/sex/dose were administered (−)-(R)-α-phellandrene via oral gavage at doses of 0, 25, 75, or 200 mg/kg/day in corn oil. Males were treated for 49 days (2 weeks prior to mating, during 2 weeks of mating, and for 21 days post-mating), while females were treated for 51–52 days (2 weeks prior to mating, throughout gestation, and for 13 days post-delivery). Additional groups of 6 rats/sex/dose were administered 0 or 200 mg/kg/day (−)-(R)-α-phellandrene for 49 days and were assigned to serve as the recovery groups. No treatment-related adverse effects were observed for sensory function, motor activity, urinalysis, hematology, clinical chemistry, or thyroid hormone analysis for either sex at all tested doses. Females in the 200 mg/kg/day high-dose group had statistically significant decreases in body weight and food consumption. Similarly, body weights from females in the recovery group were decreased (not statistically significant) at the end of the recovery time. In males, absolute and relative liver weights were statistically significantly increased in animals receiving 75 and 200 mg/kg/day doses. In females, absolute liver weights were statistically significantly increased at 200 mg/kg/day, while relative liver weights were statistically significantly increased at 75 and 200 mg/kg/day compared to control animals. Recovery groups also demonstrated an increase (not statistically significant) in relative liver weights in both males and females. Moreover, centrilobular hepatocellular hypertrophy was observed at 75 mg/kg/day (males) and 200 mg/kg/day (both sexes). However, hypertrophy was not observed in any of the males and females from the recovery groups at the end of the recovery period. Therefore, the NOAEL for repeated dose toxicity was considered to be 25 mg/kg/day based on the adverse events observed in the liver (RIFM, 2018a).

A default safety factor of 3 was used when deriving a NOAEL from an 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 25/3 or 8.33 mg/kg/day.

The NOAEL 8.33 mg/kg/day is considered for the repeated dose toxicity endpoint. **Therefore, the *p*-mentha-1,3-diene MOE for the repeated dose toxicity endpoint can be calculated by dividing the (−)-(R)-α-phellandrene NOAEL in mg/kg/day by the total systemic exposure to *p*-mentha-1,3-diene, 8.33/0.00024 or 34708.**

In addition, the total systemic exposure to *p*-mentha-1,3-diene (0.24 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020), and a reference dose (RfD) of 0.083 mg/kg/day.

11.1.2.1.1. Derivation of RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for p-mentha-1,3-diene was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 8.33 mg/kg/day by the uncertainty factor, 100 = 0.083 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 2017.

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

11.1.3. Reproductive toxicity

The MOE for *p*-mentha-1,3-diene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on *p*-mentha-1,3-diene. A developmental toxicity study was conducted on pregnant female Wistar rats. *p*-Mentha-1,3-diene at doses of 0, 30, 60, 125, or 250 mg/kg/day in corn oil were administered via oral gavage to groups of female rats (28, 15, 20, 26, and 27 rats corresponding to the 0, 30, 60, 125, or 250 mg/kg/day dose groups, respectively) from gestational days (GDs) 6–15. Cesarean sections were performed on GD 21. Statistically significant reductions in the total bodyweight gain minus gravid uterus weight were observed during GDs 0–21 at the 2 highest dose groups of 125 and 250 mg/kg/day. At 250 mg/kg/day, there was a significant decrease in the ratio of pregnant/treated female rats (56% vs. 86% in controls) without any significant increase in the ratio of resorptions/implantations. The absence of a reduction in implantations per pregnant female shows that this finding was caused by whole litter loss in the presence of maternal toxicity as indicated by bodyweight loss. Significant decreases in fetal body weights accompanied by significant increases in the absolute fetal kidney weights were reported among high-dose group fetuses. The significant increases in the absolute fetal kidney weights extended to the 60 and 125 mg/kg/day dose groups. Signs of delayed ossification and greater incidences of skeletal anomalies in a statistically significant, dose-dependent manner were observed at concentrations ≥60 mg/kg/day (delayed ossification: 53.0%, 73.4%, and 88.6% vs. 11.1% in controls; skeletal anomalies: 33.1%, 61.3%, and 89.5% vs. 19.6% in controls, corresponding to the 60, 125, and 250 mg/kg/day dose groups). It was unclear if the significant reduction in pregnant females at 250 mg/kg/day was an effect on fertility or developmental toxicity. The authors of the study considered the NOAEL for developmental toxicity to be 30 mg/kg/day, based on increased fetal kidney weights, delayed ossification, and skeletal anomalies. The NOAEL for maternal toxicity was 60 mg/kg/day, based on decreased bodyweight gain among dams in the 2 highest dose groups (Araujo et al., 1996). The REACH CLH report has argued

that, given the absence of effects at 125 mg/kg/day on the fetal body weight, the changes in ossification were too minimal to be considered indicative of developmental toxicity, whereas the reduction in fetal body weight contributed to alterations in the rate of ossification for the 250 mg/kg/day dose group fetuses. Additionally, no historical control data was provided. At 60 mg/kg/day, only 1 area of the fetal skeleton (skull, irregularly shaped *os squamosum*) was less well ossified as compared with the controls. The CLH report stated that the effect on embryofetal development reported in the study was incorrectly classified as adverse and represented a change in the timing of ossification. Therefore, although dose-related, this single finding at 60 mg/kg/day should not represent developmental toxicity on the basis of the appearance of 1 ossification center only. The CLH report considered the developmental toxicity NOAEL to be 125 mg/kg/day (Araujo et al., 1996; data also available in the CLH Report for Alpha-Terpinene; ECHA, 2008). Since there were statistically significant increases in the occurrence of delayed ossification and skeletal anomalies, in a dose-related manner, in the development of fetuses at doses ≥60 mg/kg/day; thus, the most conservative NOAEL of 30 mg/kg/day was selected for the developmental toxicity endpoint, based on decreased fetal weight, increased fetal kidney weights, delayed ossification, and skeletal anomalies among higher dose group fetuses. **Therefore, the *p*-mentha-1,3-diene MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-mentha-1,3-diene NOAEL in mg/kg/day by the total systemic exposure to *p*-mentha-1,3-diene, 30/0.00024, or 125000.**

There are no fertility data on *p*-mentha-1,3-diene. Read-across material, (−)-(R)-α-phellandrene (CAS # 4221-98-1; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test, groups of 12 Sprague Dawley rats/sex/dose were administered (−)-(R)-α-phellandrene via oral gavage at doses 0, 25, 75, or 200 mg/kg/day in corn oil. Males were treated for 49 days (2 weeks prior to mating, during 2 weeks of mating, and 21 days post-mating), while females were treated for 51–52 days (2 weeks prior to mating, throughout gestation, and for 13 days post-delivery). Additional groups of 6 rats/sex/dose were administered 0 or 200 mg/kg/day (−)-(R)-α-phellandrene for 49 days and were assigned to serve as the 14-day treatment-free recovery groups. In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. No treatment-related adverse effects were observed in estrous cycling, spermatogenesis, mating, gestation period, or fertility. No gross abnormalities were reported in pups. The authors of the study report determine the NOAEL for reproductive toxicity to be 200 mg/kg/day for males, the highest dose tested, and 75 mg/kg/day for females, based on statistically significant decreases in body weight and food consumption during gestation and postpartum periods in the 200 mg/kg/day dose group. Since no substantial fertility effect was reported, the NOAEL for reproductive toxicity for both males and females was considered to be 200 mg/kg/day, the highest dose tested (RIFM, 2018a). **Therefore, the *p*-mentha-1,3-diene MOE for the reproductive toxicity endpoint can be calculated by dividing the (−)-(R)-α-phellandrene NOAEL in mg/kg/day by the total systemic exposure to *p*-mentha-1,3-diene, 200/0.00024, or 833333.**

In addition, the total systemic exposure to *p*-mentha-1,3-diene (0.24 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2017.

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

11.1.3.2. Skin sensitization. Based on existing data, *p*-mentha-1,3-diene is considered a skin sensitizer with a defined NESIL of 2200 μg/cm^2.

11.1.3.3. Risk assessment. Based on existing data, *p*-mentha-1,3-diene is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree v3.1; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), *p*-mentha-1,3-diene was found to be sensitizing with an EC3 value of 8.9% (2225 μg/cm^2) (Kern et al., 2010; Bergstrom et al., 2006; Rudback et al., 2012). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2244 μg/cm^2 of *p*-mentha-1,3-diene in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2014).

Based on the weight of evidence (WoE) from structural analysis as well as animal and human studies, *p*-mentha-1,3-diene is a moderate sensitizer with a WoE NESIL of 2200 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.083 mg/kg/day.

Note: *p*-mentha-1,3-diene (CAS # 99-86-5) is expected to undergo autoxidation resulting in products which could be sensitizing (Bergstrom et al., 2006; Rudback et al., 2012; Oasis TIMES v2.27.18).

Additional References: Hausen et al., 1999.

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

11.1.4. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, *p*-mentha-1,3-diene would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.4.1. Risk assessment. There are no phototoxicity studies available for *p*-mentha-1,3-diene in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, *p*-mentha-1,3-diene does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.4.3. Local respiratory toxicity. There are no inhalation data available on *p*-mentha-1,3-diene; however, in an acute, 2-week inhalation study on read-across analog *d*-limonene (CAS # 5989-27-5; see Section VI), a NOAEC of 54.3 mg/m^3 was reported (RIFM, 2013a).

11.1.4.4. 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 inhalation study conducted in rats, a NOAEC of 54.3 mg/m^3 was reported for *d*-limonene (RIFM, 2013a). Test material-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:

Table 1
Data summary for *p*-mentha-1,3-diene.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
2225 [1]	Moderate	2244	3450	NA	2200

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

- (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 0.0017 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 0.0026 mg/kg lung weight/day, resulting in an MOE of 798077 (i.e., [2075 mg/kg lung weight/day]/[0.0026 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0017 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; 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 and Rogers, 2002; Rogers et al., 2003a; 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, 2004c; Selim, 2005; RIFM, 1972; 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.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-mentha-1, 3-diene 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, *p*-mentha-1,3-diene 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 *p*-mentha-1, 3-diene as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current VoU (2015) *p*-mentha-1, 3-diene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. Not Available.

11.2.3.2. Ecotoxicity. Broderius et al., 1990: A 96-h flow-through acute study with Fathead minnows was conducted according to the ASTM, 1989 method. The calculated LC50 was reported to be 3.150 mg/L, and the EC50 1.480 mg/L based on the mean measured concentration.

Broderius et al., 1990: A 48-h flow-through acute study with *Daphnia magna* was conducted according to the ASTM, 1989 method. The calculated EC50 and LC50 were 1.850 mg/L.

Broderius et al., 1990: A 72- to 96-h static renewal test with algae was conducted according to the ASTM, 1988 method. No significant effects were observed at the maximum concentration of 6.3 mg/L.

11.2.4. Other available data

p-Mentha-1,3-diene has been pre-registered for REACH, and the following additional data is available (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Biodegradation of 40% was observed after 28 days and 66% at day 70 under the test conditions.

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under semi-static conditions for 48 h. An EC50 of 1.7 mg/L (based on geometric mean measured concentrations) has been reported for this study.

An algae growth inhibition study was conducted according to the OECD 201 method. The 72-h NOEC (geometric mean measured concentration) of 3.7 mg/L has been reported for this study.

11.2.5. Risk assessment refinement

Since *p*-Mentha-1, 3-diene has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} used	4.75	4.75
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0278 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/14/21.

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 09/21/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.744			1000000	0.000744	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.379	0.278	0.591	10000	0.0278	Neutral Organics

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112712.

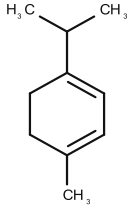
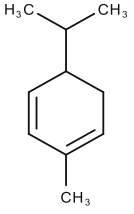
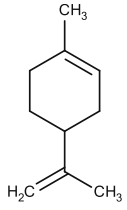
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, the materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	*p*-Mentha-1,3-diene	(−)-(R)-α-Phellandrene	*d*-Limonene
CAS No.	99-86-5	4221-98-1	5989-27-5
Structure			
Similarity (Tanimoto Score)		1.0	1.0
Read-across Endpoint		• Repeated dose toxicity • Fertility	• Local respiratory toxicity
Molecular Formula	$C_{10}H_{16}$	$C_{10}H_{16}$	$C_{10}H_{16}$
Molecular Weight	136.23	136.38	136.24
Melting Point (°C, EPI Suite)	−31.15	−40.80	−40.76
Boiling Point (°C, EPI Suite)	169.36	165.01	167.66
Vapor Pressure (Pa @ 25°C, EPI Suite)	222	255	193
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.25	4.62	4.38
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.915	2.862	13.8
J_{max} (μg/cm2/h, SAM)	131.94	67.116	2.802
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	3.70×10^4	3.13×10^4	3.85×10^4
Repeated Dose Toxicity			
Repeated dose (HESS)	• Not categorized	• Aliphatic/alicyclic hydrocarbons (α-2u-globulin nephropathy) Rank C	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)	
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

Summary

There are insufficient toxicity data on *p*-mentha-1,3-diene (CAS # 99-86-5). Hence, *in silico* evaluation was conducted to determine read-across

analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, (−)-(R)-α-phellandrene (CAS # 4221-98-1) and *d*-limonene (CAS # 5989-27-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- (−)-(R)-α-Phellandrene (CAS # 4221-98-1) was used as a read-across analog for the target material *p*-mentha-1,3-diene (CAS # 99-86-5) for the fertility and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of monocyclic monoterpenes hydrocarbons.
  - o The target material and the read-across analog are structural isomers. They differ only in the position of vinylene double bonds.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has an aliphatic/alicyclic hydrocarbons (α-2u-globulin nephropathy) Rank C aliphatic alert. The data described in the repeated dose toxicity and developmental and reproductive toxicity endpoint sections confirm that the MOE is adequate for the read-across analog under the current conditions. Therefore, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *d*-Limonene (CAS # 5989-27-5) was used as a read-across analog for the target material *p*-mentha-1,3-diene (CAS # 99-86-5) for the local respiratory toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of monocyclic monoterpenes hydrocarbons.
  - o The key difference between the target material and the read-across analog is that the target material has vinylene unsaturations while the read-across analog has vinyl unsaturation. This structural difference is predicted to make read-across analog more reactive and so toxicologically significant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80% and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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