Food and Chemical Toxicology 161 (2022) 112912

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, (−)-(R)-α-phellandrene, CAS Registry Number 4221-98-1

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ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Conflicts of interest

The authors declare that they have no conflicts of interest.

Version: 092321. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

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Name: (−)-(R)-α-Phellandrene
CAS Registry Number: 4221-98-1
Additional CAS Numbers*: 99-83-2 α-Phellandrene
1329-99-3 (No Reported Use) Phellandrene
*Included because the materials are isomers

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https://doi.org/10.1016/j.fct.2022.112912
Received 23 September 2021; Received in revised form 30 November 2021; Accepted 5 March 2022
Available online 9 March 2022

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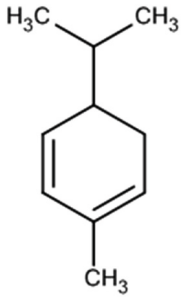

Abbreviation/Definition List:

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., 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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this

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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.

(−)-(R)-α-Phellandrene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that (−)-(R)-α-phellandrene is not genotoxic. Data on (−)-(R)-α-phellandrene provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog *p*-mentha-1,3-diene (CAS # 99-86-5) provided (−)-(R)-α-phellandrene 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; (−)-(R)-α-phellandrene 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; (−)-(R)-α-phellandrene was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2000; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 8.33 mg/kg/day.	RIFM (2018c)
Reproductive Toxicity: Developmental toxicity NOAEL = 75 mg/kg/day; Fertility NOAEL = 200 mg/kg/day.	RIFM (2018c)
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: 25% (day 60, OECD 301D) for CAS # 4221-98-1	RIFM (2018b)
Bioaccumulation:	
Screening-level: 518 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 0.36 mg/L	(ECOSAR; US ECHA, 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: 0.36 mg/L	(ECOSAR; US ECHA, 2012b)

RIFM PNEC is: 0.036 μg/L

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

1. Identification

Chemical Name: (−)-(R)-α-Phellandrene	**Chemical Name**: α-Phellandrene	**Chemical Name**: Phellandrene
CAS Registry Number: 4221-98-1	**CAS Registry Number:** 99-83-2	**CAS Registry Number:** 1329-99-3
Synonyms: 1,3-Cyclohexadiene, 2-methyl-5-(1-methylethyl)-, (R)-; (R)-5-Isopropyl-2-methylcyclohexa-1,3-diene; 5-Isopropyl-2-	**Synonyms:** 1,5-Cyclohexadiene, 1-isopropyl-4-methyl-; Dihydro-*p*-cymene; 1-Isopropyl-4-methyl-2,4-cyclohexadiene; 4-Isopropyl-1-methyl-1,5-cyclohexadiene; 5-	**Synonyms:** Cyclohexane, 1-methyl-4-(1-methylethyl)-, tetradehydro deriv.; 1-Isopropyl-4-methylcyclohexane; Isopropylmethylcyclohexane, tetradehydro derivative; *p*-Menthadiene; フェランドレン

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methylcyclohexa-1,3-diene	Isopropyl-2-methyl-cyclohexa-1,3-diene; *p*-Mentha-1,5-diene; 1-Methyl-4-isopropyl-1,5-cyclohexadiene	
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
RIFM Number: 5310	**RIFM Number:** 270	**RIFM Number:** 5110
Stereochemistry: (−)-R isomer specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

CAS # 4221–98–1	**CAS # 99–83–2**	**CAS # 1329–99–3**
Boiling Point: 165.01 °C (EPI Suite)	**Boiling Point:** 175 °C (Fragrance Materials Association [FMA] Database), 165.01 °C (EPI Suite)	**Boiling Point:** 154.91 °C (EPI Suite)
Flash Point: 43 °C (Globally Harmonized System [GHS])	**Flash Point:** 115 °F; CC (FMA Database)	**Flash Point:** 53 °C (GHS)
Log K_{OW}: 4.62 (EPI Suite)	**Log K_{OW}:** 4.62 (EPI Suite)	**Log K_{OW}:** 4.92 (EPI Suite)
Melting Point: 40.8 °C (EPI Suite)	**Melting Point:** 40.8 °C (EPI Suite)	**Melting Point:** 52.89 °C (EPI Suite)
Water Solubility: 2.862 mg/L (EPI Suite)	**Water Solubility:** 2.862 mg/L (EPI Suite)	**Water Solubility:** 0.4331 mg/L (EPI Suite)
Specific Gravity: Not available	**Specific Gravity:** 0.850 (FMA Database)	**Specific Gravity:** N/A
Vapor Pressure: 1.91 mm Hg at 25 °C (EPI Suite), 1.36 mm Hg at 20 °C (EPI Suite v4.0)	**Vapor Pressure:** 1.36 mm Hg at 20 °C (EPI Suite v4.0), 1.1 mm Hg at 20 °C (FMA Database), 1.91 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 1.91 mm Hg at 25 °C (EPI Suite), 1.36 mm Hg at 20 °C (EPI Suite v4.0), 1.0 mm Hg at 20 °C (FMA Database)
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Sample not available for testing.
Appearance/ Organoleptic: A colorless to pale yellow clear liquid with a medium, terpenic, spicy, medicinal odor	**Appearance/ Organoleptic:** Colorless, mobile liquid with a fresh, citrusy, peppery, woody odor	**Appearance/ Organoleptic:** A colorless to pale yellow clear liquid with a minty odor

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate exposure model v1.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.030% (RIFM, 2018a)
2. **Inhalation Exposure**:** 0.000022 mg/kg/day or 0.014 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure***:** 0.00040 mg/kg/day (RIFM, 2018a)

*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, inhalation exposure, and total exposure.

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

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

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** *p*-Mentha-1,3-diene (CAS # 99-86-5)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** *d*-Limonene (CAS # 5989-27-5)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix

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

(−)-(R)-α-Phellandrene is reported to occur in the following foods by the VCF*:

Citrus fruits.
Mastic (*Pistacia lentiscus*)

α-Phellandrene is reported to occur in the following foods by the VCF:

Citrus fruits.
Curry (*Bergera koenigii* L.)
Fennel (*Foeniculum vulg.*, ssp. *capillaceum*; var.)
Laurel (*Laurus nobilis* L.)
Lovage (*Levisticum officinale* Koch)
Mangifera species.
Mastic (*Pistacia lentiscus*)
Pepper (*Piper nigrum* L.)
Pimento (allspice) (*Pimenta dioica* L. Merr.)
Thyme (*Thymus* species)
Turpentine oil (*Pistacia terebinthus*)

Phellandrene is reported to occur in the following foods by the VCF:

Citrus fruits.

Dill (*Anethum* species)
Mastic (*Pistacia lentiscus*)
Myrtle (*Myrtus communis* L.)
Thyme (*Thymus* species)
Wild marjoram (*Origanum vulgare* L.)

*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

Dossier available for (−)-(R)-α-phellandrene; accessed 09/23/21; α-phellandrene and phellandrene are pre-registered for 2010; no dossiers available as of 09/23/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for (−)-(R)-α-phellandrene 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)	0.0027
2	Products applied to the axillae	0.050
3	Products applied to the face/body using fingertips	0.0080
4	Products related to fine fragrances	0.94
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.069
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0053
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.013
5D	Baby cream, oil, talc	0.0018
6	Products with oral and lip exposure	0.19
7	Products applied to the hair with some hand contact	0.0053
8	Products with significant ano-genital exposure (tampon)	0.0018
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.069
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.013
10B	Aerosol air freshener	0.088
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0018
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	2.6

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 (−)-(R)-α-phellandrene, 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, (−)-(R)-α-phellandrene does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. (−)-(R)-α-Phellandrene 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). 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 (−)-(R)-α-phellandrene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with (−)-(R)-α-phellandrene 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 (RIFM, 2000). Under the conditions of the study, (−)-(R)-α-phellandrene was not mutagenic in the Ames test.

The clastogenic activity of (−)-(R)-α-phellandrene 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 (−)-(R)-α-phellandrene in acetone at concentrations up to 1364 μg/mL in the DRF study. Micronuclei analysis in the main study was conducted up to 255 μg/mL in the presence and absence of S9 for 4 h and the absence of S9 for 20 h (−)-(R)-α-phellandrene did not induce binucleated cells with micronuclei when tested up to cytotoxic or the maximum recommended concentrations in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, (−)-(R)-α-phellandrene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, (−)-(R)-α-phellandrene 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 (−)-(R)-α-phellandrene is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. 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 quantification 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. 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, 2018c).

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 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 (−)-(R)-α-phellandrene was calculated by dividing the NOAEL of 8.33 mg/kg/day by the uncertainty factor, 100 = 0.0833 mg/kg/day.

11.1.2.2. Derivation of reference dose (RfD). 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.

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 reference dose for (−)-(R)-α-phellandrene 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.

In addition, the total systemic exposure to (−)-(R)-α-phellandrene (0.40 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.

*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, 2017a.

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

11.1.3. Reproductive toxicity

The MOE for (−)-(R)-α-phellandrene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient data on (−)-(R)-α-phellandrene 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. At postnatal day (PND) 4, an increase (not statistically significant) in post-implantation loss and decreases in the live birth and viability indices of pups were observed in 2 dams whose pups were all found dead at 200 mg/kg/day. Additionally, in 1 low-dose group dam, all pups were deceased. The litter losses could not be attributed to a dose-response relationship. Furthermore, it could not be concluded with certainty whether the deaths in the 2 high-dose dams with litter losses were treatment-related or incidental in nature. Among the 3 dams whose pups were all dead, only 1 dam exhibited dilatation with gas in the stomach, enlarged adrenal glands, and small thymus and spleen at necropsy. The others showed no gross findings. A statistically significant decrease in pup body weights was observed at 200 mg/kg/day (PND 13: 26% and 25% for male and female pups, respectively, as compared to controls); these effects were jointly observed with overt signs of systemic toxicity in dams that presented a statistically significant reduction in body weight and food consumption (GD 7 to PPD 13) as well as liver effects. 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 fertility for both males and females was considered to be 200 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 75 mg/kg/day, based on a decrease in body weight among high-dose group pups (RIFM, 2018c).

The (−)-(R)-α-phellandrene MOE for the developmental toxicity endpoint can be calculated by dividing the (−)-(R)-α-phellandrene NOAEL in mg/kg/day by the total systemic exposure to (−)-(R)-α-phellandrene, 75/0.00040, or 187500.

The (−)-(R)-α-phellandrene MOE for the fertility endpoint can be calculated by dividing the (−)-(R)-α-phellandrene NOAEL in mg/kg/day by the total systemic exposure to (−)-(R)-α-phellandrene, 200/0.00040, or 500000.

In addition, the total systemic exposure to (−)-(R)-α-phellandrene (0.40 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, 2017a.

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

11.1.4. Skin sensitization

Based on the existing data and read-across material *p*-mentha-1,3-diene (CAS # 99-86-5), (−)-(R)-α-phellandrene is considered a weak sensitizer.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for (−)-(R)-α-phellandrene. Based on the existing data and read-across material *p*-mentha-1,3-diene (CAS # 99-86-5; see Section VI), (−)-(R)-α-phellandrene is considered a moderate sensitizer. The chemical structures of these materials indicate that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree v3.1; OECD Toolbox v4.2). In a BrdU local lymph node assay (LLNA), (−)-(R)-α-Phellandrene was found to be a moderate sensitizer with an EC1.6 value of 15% (3750 μg/cm^2). In a murine LLNA on read-across material *p*-mentha-1,3-diene, the material 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). However, in a human maximization test, no skin sensitization reactions were observed with read-across material *p*-mentha-1,3-diene (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2244 μg/cm^2 of read-across material *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 available data on read-across material *p*-mentha-1,3-diene summarized in Table 1, (−)-(R)-α-phellandrene is considered to be

Table 1
Data Summary for *p*-mentha-1,3-diene as a read-across material for (−)-(R)-α-phellandrene.

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.

a moderate skin sensitizer with a defined NESIL of 2200 μg/cm^2. 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); α-phellandrene (CAS # 99-83-2); (−)-(R)-α-phellandrene (CAS # 4221-98-1) and *p*-mentha-1,4-diene (CAS # 99-85-4) are expected to undergo autoxidation resulting in products that 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.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, (−)-(R)-α-phellandrene would not be expected to present a concern for phototoxicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for (−)-(R)-α-phellandrene 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, (−)-(R)-α-phellandrene does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV Spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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.

11.1.6. Local respiratory toxicity

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

11.1.6.1. 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 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:

- (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 0.014 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 0.022 mg/kg lung weight/day resulting in an MOE of 94318 (i.e., [2075 mg/kg lung weight/day]/[0.022 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 0.014 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: None.

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 (−)-(R)-α-phellandrene 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, (−)-(R)-α-phellandrene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified (−)-(R)-α-phellandrene as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document

(Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). 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 VoU (2015), (−)-(R)-α-phellandrene 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 CAS # 4221-98-1.

RIFM, 1999: The ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D guidelines. Under the conditions of this study, biodegradation of 19% was observed after 28 days.

RIFM, 2018b: The ready biodegradability of the test material was evaluated in an enhanced closed bottle method according to the OECD 301D guidelines. Under the conditions of this study, biodegradation of 25% was observed after 60 days.

11.2.2.1.2. Ecotoxicity. For CAS # 4221-98-1.

RIFM, 1999: A *Daphnia magna* immobilization test was conducted according to the Council Directive 92/69/EEC C.2 method under static conditions in closed bottles. The 48-h EC0 was reported to be greater than 4.0 mg/L (based on nominal concentration).

RIFM, 2017c: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of the study, the 48-h EC50 was reported to be 0.513 mg/L based on geometric mean concentration.

RIFM, 2017b: An algae growth inhibition test was conducted according to the OECD 201 method. Under the conditions of the study, the 72-h EC50 was reported to be 0.465 mg/L and 0.147 mg/L based on growth rate and yield, respectively.

RIFM, 2017d: A fish (*Danio rerio*) acute toxicity study was conducted according to the OECD 203 method (threshold approach) under semi-static conditions. The 96-h LC50 of (−)-(R)-α-phellandrene was greater than 0.590 mg/L (the geometric mean measured concentration of a saturated solution).

11.2.2.1.3. Other available data. (−)-(R)-α-Phellandrene has been registered with REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since (−)-(R)-α-phellandrene 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	4.9	4.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for all CAS #

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

The RIFM PNEC is 0.036 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: 06/15/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.6			1000000	0.0006	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.497	0.360	0.720	10000	0.0360	Neutral Organics

- **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 09/23/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112912.

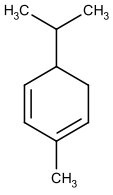
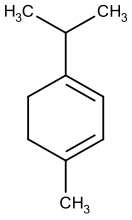
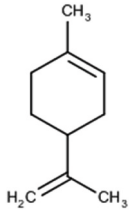
Appendix

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	(−)-(R)-α-Phellandrene	*p*-Mentha-1,3-diene	*d*-Limonene
CAS No.	4221-98-1	99-86-5	5989-27-5
Structure			
Similarity (Tanimoto Score)		1.0	1.0
Read-across Endpoint		• Skin sensitization	• Local respiratory toxicity
Molecular Formula	$C_{10}H_{16}$	$C_{10}H_{16}$	$C_{10}H_{16}$
Molecular Weight	136.38	136.24	136.24
Melting Point (°C, EPI Suite)	−40.80	−31.15	−40.76
Boiling Point (°C, EPI Suite)	165.01	169.36	167.66
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.87E+002	2.22E+002	1.93E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.62	4.25	4.38
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.86	5.915	13.8
J_{max} (μg/cm^2/h, SAM)	67.12	131.94	2.802
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.13E+004	3.70E+004	3.85E+004

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found		• No alert found
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 (−)-(R)-α-phellandrene (CAS # 4221-98-1). 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, *p*-mentha-1,3-diene (CAS # 99-86-5) and *d*-limonene (CAS # 5989-27-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions.

- *p*-Mentha-1,3-diene (CAS # 99-86-5) was used as a read-across analog for the target material (−)-(R)-α-phellandrene (CAS # 4221-98-1) for the skin sensitization endpoint.
  - 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 The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the read-across material. The data for the read-across material confirms that it is a weak sensitizer. Therefore, data supersedes the alerts.
  - 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 (−)-(R)-α-phellandrene (CAS # 4221-98-1) 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 the read-across analog more reactive and therefore toxicologically significant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o 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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