ELSEVIER

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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





RIFM fragrance ingredient safety assessment, *p*-mentha-1,8-dien-7-yl acetate, CAS Registry Number 15111-96-3

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

- ^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA
- b Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA C Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance
- d Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109. USA
- ^e Member Expert Panel for Fragrance Safety, 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
- f Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany
- g Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA
- h Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA
- i Member of Expert Panel for Fragrance Safety, 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
- ^j Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA
- k Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA
- ¹ Member Expert Panel for Fragrance Safety, 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

ARTICLE INFO

47. Malmo, SE-20502, Sweden

Handling Editor: Dr. Jose Luis Domingo

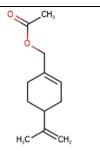
E-mail address: gsullivan@rifm.org (G. Sullivan).

^{*} Corresponding author.

Version: 021722. 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: fragrancematerialsafetyresour

Name: p-Mentha-1,8-dien-7-yl acetate CAS Registry Number: 15111-96-3



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration

AF - Assessment Factor

BCF - Bioconcentration Factor

CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an in silico tool used to identify structural alerts

DRF - Dose Range Finding

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observed Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An in silico model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.

ORA - 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

RO - 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, 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

(continued on next column)

(continued)

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

*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-1,8-dien-7-yl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that p-mentha-1,8-dien-7-yl acetate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to p-mentha-1,8-dien-7-yl acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for p-mentha-1.8-dien-7yl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/ visible (UV/Vis) spectra; p-mentha-1,8-dien-7-yl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; pmentha-1.8-dien-7-vl acetate 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, 2016a: RIFM,

Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC. Reproductive Toxicity: No NOAEL available. Exposure is below TTC.

(RIFM, 2021a: RIFM, Skin Sensitization: No concern for skin sensitization

under the current, declared levels of use. 2021b) Phototoxicity/Photoallergenicity: Not expected to be (UV/Vis Spectra; RIFM phototoxic/photoallergenic. Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.91 (BIOWIN 3) (EPI Suite v4.11; US EPA,

2012a)

(EPI Suite v4.11; US EPA, Bioaccumulation: Screening-level: 354.1 L/kg 2012a)

Ecotoxicity: Screening-level: Fish LC50: 2.27 mg/L (RIFM Framework; Salvito, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and (RIFM Framework: Salvito, 2002) Europe) < 1Critical Ecotoxicity Endpoint: Fish LC50: 2.27 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: $0.00227 \square g/L$

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

1. Identification

- 1. Chemical Name: p-Mentha-1,8-dien-7-yl acetate
- 2. CAS Registry Number: 15111-96-3
- 3. Synonyms: 1-Cyclohexen-1-methanol, 4-(1-methylethenyl)-, acetate; Dihydrocuminyl acetate; 4-Isopropenyl-1-cyclohexene carbinol acetate; Menthadien-7-carbinyl acetate; 1,8-para-Menthadien-7-yl acetate; 4-(1-Methylvinyl)cyclohex-1-ene-1-methylacetate; Perillyl acetate; アルカン酸(C = 1 ~ 5)ヘβリリル; (4-Isopropenylcyclohex-1-en-1-yl) methyl acetate; p-Mentha-1,8-dien-7-yl acetate
- 4. Molecular Formula: C₁₂H₁₈O₂
- 5. Molecular Weight: 194.27 g/mol
- 6. RIFM Number: 5102
- 7. Stereochemistry: Stereoisomer not mentioned. One chiral center is present, and a total of 2 enantiomers are possible.

2. Physical data

1. Boiling Point: 250.24 °C (EPI Suite)

2. Flash Point: >200 °F; CC (Fragrance Materials Association [FMA])

3. Log Kow: 4.37 (EPI Suite)

4. Melting Point: 15.78 °C (EPI Suite) 5. Water Solubility: 8.704 mg/L (EPI Suite)

6. Specific Gravity: 0.970 (FMA)

7. Vapor Pressure: 0.017 mm Hg at 20 °C (EPI Suite v4.0), 0.0269 mm Hg at 25 °C (EPI Suite)

8. UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $\mathrm{mol}^{-1} \bullet \mathrm{cm}^{-1}$)

9. Appearance/Organoleptic: An almost colorless or pale yellowish oily liquid which has a warm-herbaceous, spicy odor, suggestive of dill or spearmint, but rather diffusive and refreshing.

3. Volume of use (Worldwide band)

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

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

- 1. 95th Percentile Concentration in Fine Fragrance: 0.0085% (RIFM, 2017)
- 2. Inhalation Exposure*: 0.0000028 mg/kg/day or 0.00021 mg/day (RIFM, 2017)
- 3. Total Systemic Exposure**: 0.00044 mg/kg/day (RIFM, 2017)

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

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

6.1. Cramer Classification

Class I, Low

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

6.2. Analogs Selected

a. Genotoxicity: None

b. Repeated Dose Toxicity: None

- c. Reproductive Toxicity: None
- d. Skin Sensitization: None
- e. Phototoxicity/Photoallergenicity: None
- f. Local Respiratory Toxicity: None
- g. Environmental Toxicity: None

6.3. Read-across Justification

None

7. Metabolism

No relevant data are available for inclusion in this safety assessment. Additional References:

None.

8. Natural occurrence

p-Mentha-1,8-dien-7-yl acetate is reported to occur in the following foods by the VCF*:

Citrus fruits.

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

9. REACH dossier

Pre-registered for 2013; no dossier available as of 02/17/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, p-mentha-1,8-dien-7-yl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. p-Mentha-1,8-dien-7-yl acetate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of p-mentha-1,8-dien-7-yl acetate 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 p-mentha-1,8-dien-7-yl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean

number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, p-mentha-1,8-dien-7-yl acetate was not mutagenic in the Ames test.

The clastogenic activity of p-mentha-1,8-dien-7-yl acetate 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-1,8-dien-7-yl acetate in DMSO at concentrations up to 1943 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 500.0 µg/mL in the presence and absence of metabolic activation. p-mentha-1,8-dien-7-yl acetate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, p-mentha-1,8-dien-7-yl acetate was considered to be non-clastogenic in the $in\ vitro$ micronucleus test.

Based on the data available, p-mentha-1,8-dien-7-yl acetate does not present a concern for genotoxic potential.

Additional References: RIFM, 2010a; RIFM, 2010b.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on p-mentha-1,8-dien-7-yl acetate or any read-across materials. The total systemic exposure to p-mentha-1,8-dien-7-yl acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on p-mentha-1,8-dien-7-yl acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.44 μ g/kg/day) is below the TTC for p-mentha-1,8-dien-7-yl acetate (30 μ g/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/25/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on p-mentha-1,8-dien-7-yl acetate or any read-across materials. The total systemic exposure to p-mentha-1,8-dien-7-yl acetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on p-mentha-1,8-dien-7-yl acetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.44 μ g/kg/day) is below the TTC for p-mentha-1,8-dien-7-yl acetate (30 μ g/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/25/21.

11.1.4. Skin sensitization

Based on the existing data, *p*-mentha-1,8-dien-7-yl acetate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, p-mentha-1,8-dien-7-yl acetate is not considered a skin sensitizer. The chemical

structure of this material indicates that it is not expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). *p*-Mentha-1,8-dien-7-yl acetate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) test and KeratinoSens (RIFM, 2021a; RIFM, 2021b).

Based on the weight of evidence (WoE) from structural analysis and *in vitro* studies, *p*-mentha-1,8-dien-7-yl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/22/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, *p*-mentha-1,8-dien-7-yl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for *p*-mentha-1,8-dien-7-yl acetate in experimental models. UV/Vis absorption spectra indicate no significant 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-1,8-dien-7-yl acetate 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, $1000 \text{ L mol}^{-1} \bullet \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for p-mentha-1,8-dien-7-yl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on pmentha-1,8-dien-7-yl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.00021 mg/day. This exposure is 6667 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/19/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of p-mentha-1,8-dien-7-yl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW} , and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR

with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, *p*-mentha-1,8-dien-7-yl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify p-mentha-1,8-dien-7-yl acetate 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), *p*-mentha-1,8-dien-7-yl acetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. p-Mentha-1,8-dien-7-yl acetate has been pre-registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

Since 2-ethylhexanal has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC

derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K _{ow} Used	4.37	4.37
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	< 1	< 1

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

The RIFM PNEC is $0.00227~\mu g/L$. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 07/15/21.

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-assess ment/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_sear ch/systemTop
- Japan Existing Chemical Data Base (JECDB): http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com

	LC50 (Fish)	EC50	EC50	AF	PNEC (μg/L)	Chemical Class
	(mg/L)	(Daphnia)	(Algae)			
		(mg/L)	(mg/L)			
RIFM Framework						
Screening-level (Tier	<u>2.27</u>			1000000	0.00227	
1)						
		/	/			

• 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 02/17/22.

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.

References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
- ECHA, 2012. $\bar{\text{G}}$ uidance On Information Requirements And Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule?

 J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015. Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
- Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352. 2021 Sep-Oct 01.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2010a. p-Mentha-1,8-dien-7-yl Acetate (1(7),8-P-Menthadien-2-Yl Acetate): Reverse Mutation in Five Histidine-Requiring Strains of Salmonella typhimurium. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Beevers, C. RIFM report number 72375.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2010b. p-Mentha-1,8-dien-7-yl Acetate (1(7),8-P-Menthadien-2-Yl Acetate): Induction of Micronuclei in Cultured Human Peripheral Blood Lymphocytes. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Whitwell, J. RIFM report number 72376.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Report on the Testing of P-Mentha-1,8-Dien-7-Yl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 67040.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. p-Mentha-1,8-dien-7-yl Acetate: Bacterial Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from LLoyd, M. RIFM report number 72370.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. p-Mentha-1,8-dien-7-yl Acetate: in Vitro Human Lymphocyte Micronucleus Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Lloyd, M. RIFM report number 72373.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey 15, March 2017.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2021a. p-Mentha-1,8-dien-7-yl Acetate: Direct Peptide Reactivity Assay (DPRA). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 77427.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2021b. p-Mentha-1,8-dien-7-yl Acetate: Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE-Reporter Cell Line KeratinoSens^{NM}, RIFM, Woodcliff Lake, NJ, USA, RIFM report number 78161.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11.
 United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.