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Short review

# RIFM fragrance ingredient safety assessment, *p*-mentha-1,8-dien-7-al, CAS Registry Number 2111-75-3

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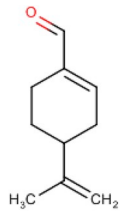


**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**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
**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
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected 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-1,8-dien-7-al was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to *p*-mentha-1,8-dien-7-al is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data on the target material provided a NESIL of 700 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *p*-mentha-1,8-dien-7-al is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-mentha-1,8-dien-7-al was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are $< 1$.

**Human Health Safety Assessment**

**Genotoxicity**: Not genotoxic. (RIFM, 2012; RIFM, 2014)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** NESIL = 700 μg/cm$^2$. RIFM (2007)
**Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:** Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
**Bioaccumulation:** Screening-level: 53.97 L/kg (ECOSAR; US EPA, 2012a)
**Ecotoxicity:** Screening-level: Fish LC50: 13.83 mg/L

(RIFM Framework; Salvito et al., 2002)

**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**

**Screening-level:** PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

**Critical Ecotoxicity Endpoint:** Fish LC50: 13.83 mg/L (RIFM Framework; Salvito et al., 2002)

**RIFM PNEC is:** 0.01383 μg/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-al
2. **CAS Registry Number:** 2111-75-3
3. **Synonyms:** 1-Cyclohexene-1-carboxaldehyde, 4-(1-methylethenyl)-; Dihydrocuminic aldehyde; 4-Isopropenyl-1-cyclohexene-1-carboxaldehyde; Perilla aldehyde; Perillaldehyde; ヘßリリルアルデヒド; ヘßリリルアルデヒド; 4-Isopropenylcyclohex-1-ene-1-carbaldehyde; Peryllic aldehyde; Aldehyde Peryllique; *p*-Mentha-1,8-dien-7-al
4. **Molecular Formula:** $C_{10}H_{14}O$
5. **Molecular Weight:** 150.22
6. **RIFM Number:** 1041

## 2. Physical data

1. **Boiling Point:** 237 °C (FMA Database), 218.82 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log $K_{OW}$:** 3.34 (EPI Suite)
4. **Melting Point**: 4.83 °C (EPI Suite)
5. **Water Solubility:** 160.7 mg/L (EPI Suite)
6. **Specific Gravity:** 0.960 (FMA Database)
7. **Vapor Pressure:** 0.0297 mm Hg @ 20 °C (EPI Suite v4.0), 0.03 mm Hg 20C (FMA Database), 0.0463 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Pale, yellowish oily liquid with a powerful, fatty-spicy, oily-herbaceous odor

## 3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00051% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.0000061 mg/kg/day or 0.00044 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.00013 mg/kg/day (RIFM, 2016)

*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 v 2.6 | OECD QSAR Toolbox v 3.2 |
|---|---|---|
| I | I | I |

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: None

## 7. Metabolism

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 (discrete chemical) or COMPOSITION (NCS)

*p*-Mentha-1,8-dien-7-al is reported to occur in the following foods* and in some natural complex substances (NCS):

Calamus (sweet flag) (*Acorus calamus* L.)
Caraway (*Carum carvi* L.)
Citrus fruits.
Ginger (*Zingiber* species)
Guava and feyoa
Macadamia nut (*Macadamia integrifolia*)
*Mangifera* species.
Mastic (*Pistacia lentiscus*)
Mentha oils.
Pistachio oil (*Pistacia vera*)
Raspberry, blackberry, and boysenberry.
Tea.
Wormwood oil (*Artemisia absinthium* 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.

## 9. REACH dossier

Pre-registered for 2010; no dossier available as of 02/18/19.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-mentha-1,8-dien-7-al are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%) |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.054 |
| 2 | Products applied to the axillae | 0.016 |
| 3 | Products applied to the face/body using fingertips | 0.32 |
| 4 | Products related to fine fragrances | 0.30 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.076 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.076 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.076 |
| 5D | Baby cream, oil, talc | 0.076 |
| 6 | Products with oral and lip exposure | 0.18 |
| 7 | Products applied to the hair with some hand contact | 0.61 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.032 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.59 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 2.1 |
| 10B | Aerosol air freshener | 2.1 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 1.2 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | Not Restricted |

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-1,8-dien-7-al, the basis was the skin sensitization NESIL of 700 μg/cm$^2$.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (http://www.rifm.org/doc).

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

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

*11.1.1.1. Risk assessment.* The mutagenic activity of *p*-mentha-1,8-dien-7-al has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with *p*-mentha-1,8-dien-7-al in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 in TA100, TA1535, TA1537, and TA102 or in TA98 in the presence of S9. However, statistically significant and dose-dependent increases were observed in the strain TA98 strain in the absence of S9 (RIFM, 2011). Under the conditions of the study, *p*-mentha-1,8-dien-7-al was not mutagenic in the Ames test. In order to verify the mutagenic potential further, a mammalian cell gene mutation assay was conducted. A mammalian cell gene mutation assay mouse lymphoma assay was conducted according to OECD TG 476/GLP guidelines. L5178Y mouse lymphoma cells were treated with *p*-mentha-1,8-dien-7-al in DMSO at concentrations up to 200 and 40 μg/mL, for 3 and 24 h, respectively. Effects were evaluated both with and without metabolic activation. No toxicologically significant increases in the frequency of mutant colonies were observed with any dose of the test item, either with or without metabolic activation (RIFM, 2012). Under the conditions of the study, *p*-mentha-1,8-dien-7-al was not mutagenic to mammalian cells *in vitro*. Additionally, an *in vivo* comet was conducted in compliance with GLP regulations. The test material was administered in corn oil via oral gavage to groups of male Han Wistar rats (6/dose). Doses of 175, 350, or 700 mg/kg bw were administered. Rats from each dose level were euthanized at the end of the study, and liver tissue was analyzed for % DNA in the tail (tail intensity) in the comet assay. A small but statistically significant increase in DNA damage observed in the liver was detected by the comet assay following treatment with *p*-mentha-1,8-dien-7-al at the highest assessed dose of 700 mg/kg bw/day. However, as this increase was concomitant with the changes in liver enzymes and evidence of the perturbation of hepatocyte function, the DNA damage could be attributed to a mechanism other than genotoxicity. Additionally, the induction of gene expression related to metabolism, cellular damage, and DNA repair have been correlated with liver damage and healing due to hepatotoxicants (Gerrish and Malarkey, 2007). Therefore, the DNA damage observed in this assay may be due to a mechanism other than genotoxicity. Additionally, no DNA migration was observed at 175 or 350 mg/kg bw/day, where there was also no evidence of liver toxicity detected (RIFM, 2014). Under the conditions of the study, *p*-mentha-1,8-dien-7-al was considered to be non-mutagenic in the comet assay *in vivo*.

The clastogenic activity of *p*-mentha-1,8-dien-7-al (CAS # 2111-75-3) was evaluated in a combined *in vivo* micronucleus test conducted in compliance with GLP regulations. The test material was administered in corn oil via oral gavage to groups of male Han Wistar rats (6/dose). Doses of 175, 350, or 700 mg/kg bw were administered. Doses were administered at 3 different time intervals: 0, 24, and 45 h. Rats from each dose level were euthanized at the end of the study, and the bone marrow was extracted and examined for polychromatic erythrocytes for *in vivo* micronucleus study. The test material did not induce an increase in micronucleated polychromatic erythrocytes of the bone marrow of male rats following oral gavage administration of doses up to 700 mg/kg/day (RIFM, 2014). Under the conditions of the study, *p*-mentha-1,8-dien-7-al was considered to be not clastogenic in the combined *in vivo* micronucleus/comet OMET test.

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

**Additional References:** Ishidate et al., 1984; Yoo (1986); Hayashi et al., 1988; Kuroda et al., 1984; Sasaki et al., 1990; Tayama et al., 1990; Suzuki et al., 1990; Eder et al., 1993; Suzuki and Suzuki, 1994.

**Literature Search and Risk Assessment Completed On:** 03/21/17.

#### 11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on *p*-mentha-1,8-dien-7-al or on any read-across materials. The total systemic exposure to *p*-mentha-1,8-dien-7-al 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 insufficient repeated dose toxicity data on *p*-mentha-1,8-dien-7-al or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to *p*-mentha-1,8-dien-7-al (0.13 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Table 1**
Data Summary for *p*-mentha-1,8-dien-7-al.

| LLNA Weighted Mean EC3 Value μg/cm[b] (No. Studies) | Potency Classification Based on Animal Data[a] | Human Data | | | |
|---|---|---|---|---|---|
| | | NOEL-HRIPT (induction) μg/cm[b] | NOEL-HMT (induction) μg/cm[b] | LOEL[b] (induction) μg/cm[b] | WoE NESIL[c] μg/cm[b] |
| 2175 (2) | Moderate | 709 | 690 | 2760 | 700 |

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.
[c] WoE NESIL limited to 3 significant figures.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 03/10/17.

*11.1.3. Reproductive toxicity*

There are insufficient reproductive toxicity data on *p*-mentha-1,8-dien-7-al or on any read-across materials. The total systemic exposure to *p*-mentha-1,8-dien-7-al 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 insufficient reproductive toxicity data on *p*-mentha-1,8-dien-7-al or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to *p*-mentha-1,8-dien-7-al (0.13 μg/kg/day) is below the TTC (30 μg/kg bw/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:** None.

**Literature Search and Risk Assessment Completed On:** 03/10/17.

*11.1.4. Skin sensitization*

Based on the existing data, *p*-mentha-1,8-dien-7-al is considered a moderate skin sensitizer with a NESIL of 700 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Based on the existing data, *p*-mentha-1,8-dien-7-al is considered a moderate skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). *p*-Mentha-1,8-dien-7-al was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U937-CD86 test (Natsch et al., 2013). In a murine local lymph node assay (LLNA), *p*-mentha-1,8-dien-7-al was found to be sensitizing with a weighted mean EC3 value of 8.7% (2175 μg/cm$^2$) (RIFM, 2008a; Gerberick et al., 2005; Roberts et al., 2007). In a human maximization test, 4% or 2760 μg/cm$^2$ *p*-mentha-1,8-dien-7-al in petrolatum resulted in sensitization reactions (RIFM, 1978). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 0.6% or 709 μg/cm$^2$ *p*-mentha-1,8-dien-7-al in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 116 volunteers (RIFM, 2007).

Based on the weight of evidence from structural analysis and animal and human studies, *p*-mentha-1,8-dien-7-al is a moderate sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 700 μg/cm$^2$ (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, 2008b; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf).

**Additional References:** Okazaki et al., 1982.

**Literature Search and Risk Assessment Completed On:** 03/19/17.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, *p*-mentha-1,8-dien-7-al 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-al in experimental models. UV/Vis absorption spectra indicate minor absorbance 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 significant absorbance in the critical range, *p*-mentha-1,8-dien-7-al does not present a concern for phototoxicity or photoallergenicity.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) for *p*-mentha-1,8-dien-7-al were obtained. The spectra indicate minor 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:** 03/02/17.

*11.1.6. Local Respiratory Toxicity*

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for *p*-mentha-1,8-dien-7-al 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 *p*-mentha-1,8-dien-7-al. Based on the Creme RIFM Model, the inhalation exposure is 0.00044 mg/day. This exposure is 3181.82 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:** Rice and Coats, 1994.

**Literature Search and Risk Assessment Completed On:** 03/21/17.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of *p*-mentha-1,8-dien-7-al 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-1,8-dien-7-al 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 v4.1 did not identify *p*-mentha-1,8-dien-7-al 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 v4.1).

*11.2.1.1. Risk assessment.* Based on the current Volume of Use (2015), *p*-mentha-1,8-dien-7-al does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.1.2. Key studies.* ***Biodegradation:*** No data available.

***Ecotoxicity:*** No data available.

*11.2.1.3. Other available data. p*-Mentha-1,8-dien-7-al has been pre-registered for REACH with no additional data at this time.

*11.2.1.4. Risk assessment refinement***Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in µg/L)**

**Endpoints used to calculate PNEC are underlined.**

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ used | 3.34 | 3.34 |
| 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 class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.01383 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 02/20/18.

## 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (µg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>13.83</u> | | | 1000000 | 0.01383 | |

- **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 03/22/19.

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