RIFM fragrance ingredient safety assessment, 5-methyl-2-hepten-4-one, CAS Registry Number 81925-81-7


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Handling editor: Dr. Jose Luis Domingo

Version: 072221. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available.

Name: 5-Methyl-2-hepten-4-one
CAS Registry Number: 81925-81-7
Additional CAS Number*: 102322-83-8
Name: 2-Hepten-4-one, 5-methyl-, (2E)- (no reported use)

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)

* Included because the materials are isomers

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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, 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

MOB - 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 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 data as compared to controls with a p < 0.05 using appropriate statistical tests

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 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.

5-Methyl-2-hepten-4-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on 5-methyl-2-hepten-4-one and read-across analog (E)-7-methyl-3-octen-2-one (CAS # 33046-81-0) provided 5-methyl-2-hepten-4-one is not expected to be 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 5-methyl-2-hepten-4-one is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/kg/day, respectively). Data on read-across analog 5,6,7-trimethylcyclo-2,5-dien-4-one (CAS # 358331-95-0) provided 5-methyl-2-hepten-4-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 5-methyl-2-hepten-4-one 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 expected to be genotoxic. (RIFM, 2016a; RIFM, 2009; RIFM, 2012)

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

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: NESIL = 250 μg/cm². RIFM (2006)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 76% (OECD 310; Headspace test) for CAS # 81925-81-7

Bioaccumulation:

Screening-level: 13.56 L/kg

Ecotoxicity:

Screening-level: Fish LC50: 97.15 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1

Critical Ecotoxicity Endpoint: Fish LC50: 97.15 mg/L

RIFM PNEC: 0.0971 g/L

• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at the screening-level

1. Identification

Chemical Name: 5-Methyl-2-hepten-4-one

CAS Registry Number: 81925-81-7

Synonyms: Filbertone; Hazelone; 2-Hepten-4-one; 5-methyl-Filbertone

Molecular Formula: C₈H₁₀O

Molecular Weight: 126.19 g/mol

Molecular Formula: C₈H₁₀O

Molecular Weight: 126.19 g/mol

Stereochemistry: Isomer not specified. Two stereocenters present and 4 total stereoisomers (2 enantiomers and 2 diastereomers) possible.

2. Physical data

CAS # 81925-81-7

Boiling Point: 157.22 °C (EPI Suite), 167–169 °C at 1013 hPa (RIFM, 2016)

Flash Point: 61 °C (Globally Harmonized System)

Log Kow: 2.22 (EPI Suite), 2.28 (RIFM, 2016)

Melting Point: –42.63 °C (EPI Suite), no melting point down to –100 °C at 1013 hPa (RIFM, 2016)

CAS # 102322-83-8

Boiling Point: 157.22 °C (EPI Suite), 167–169 °C at 1013 hPa (RIFM, 2016)

Flash Point: Not Available

Log Kow: 2.22 (EPI Suite), 2.28 (RIFM, 2016)

Melting Point: –42.63 °C (EPI Suite), no melting point down to –100 °C at 1013 hPa (RIFM, 2016)
3. Exposure to fragrance ingredient*

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)
2. 95th Percentile Concentration in Hydroalcohols: 0.0026% (IFRA, 2017a)
3. **Inhalation Exposure**: 0.0000085 mg/kg/day or 0.00061 mg/day (IFRA, 2017a)
4. **Total Systemic Exposure**: 0.000055 mg/kg/day (IFRA, 2017a)

*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 hydroalcohols, inhalation exposure, and total exposure.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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, 2017; Safford, 2015, 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I*, Low (Expert Judgment)

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v3.1</th>
<th>OECD QSAR Toolbox v4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>II</td>
</tr>
</tbody>
</table>

*See the Appendix below for further details.

2. Analogos Selected:
   a. **Genotoxicity:** (E)-7-Methyl-3-octen-2-one (CAS # 33046-81-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 5,6,7-Trimethylocta-2,5-dien-4-one (CAS # 358331-95-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment. Additional References: None.

7. Natural occurrence

5-Methyl-2-hepten-4-one (CAS # 81925-81-7) is not reported to occur in foods by the VCF*.

Additional material 2-hepten-4-one, 5-methyl-, (2E)- (CAS # 102322-83-8) is reported to occur in the following foods by the VCF: Cocoa category. Filbert, hazelnut (Corylus avellano).


8. REACH dossier

5-Methyl-2-hepten-4-one (CAS # 81925-81-7) has been pre-registered for 2018; no dossier available as of 07/22/21; dossier available for additional material 2-hepten-4-one, 5-methyl-, (2E)- (CAS # 102322-83-8); accessed on 07/22/21.

9. Conclusion

The maximum acceptable concentrations in finished products for 5-methyl-2-hepten-4-one are detailed below.

<table>
<thead>
<tr>
<th>IFRA Category</th>
<th>Description of Product Type</th>
<th>Maximum Acceptable Concentrations in Finished Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Products applied to the lips (lipstick)</td>
<td>0.019</td>
</tr>
<tr>
<td>2</td>
<td>Products applied to the axillae</td>
<td>0.0057</td>
</tr>
<tr>
<td>3</td>
<td>Products applied to the face/body using fingertips</td>
<td>0.12</td>
</tr>
<tr>
<td>4</td>
<td>Products related to fine fragrances</td>
<td>0.11</td>
</tr>
<tr>
<td>5A</td>
<td>Body lotion products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.027</td>
</tr>
<tr>
<td>5B</td>
<td>Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.027</td>
</tr>
<tr>
<td>5C</td>
<td>Hand cream products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.027</td>
</tr>
<tr>
<td>5D</td>
<td>Baby cream, oil, talc</td>
<td>0.027</td>
</tr>
<tr>
<td>6</td>
<td>Products with oral and lip exposure</td>
<td>0.063</td>
</tr>
<tr>
<td>7</td>
<td>Products applied to the hair with some hand contact</td>
<td>0.22</td>
</tr>
<tr>
<td>8</td>
<td>Products with significant anogenital exposure (tampon)</td>
<td>0.011</td>
</tr>
<tr>
<td>9</td>
<td>Products with body and hand exposure, primarily rinse-off (bar soap)</td>
<td>0.21</td>
</tr>
<tr>
<td>10A</td>
<td>Household care products with mostly hand contact (hand dishwashing detergent)</td>
<td>0.75</td>
</tr>
<tr>
<td>10B</td>
<td>Aerosol air freshener</td>
<td>0.75</td>
</tr>
<tr>
<td>11</td>
<td>Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Note: 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
5-methyl-2-hepten-4-one, the basis was a skin sensitization NESIL of 250 μg/cm².


Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, 5-methyl-2-hepten-4-one does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 5-methyl-2-hepten-4-one 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 methods. Salmonella typhimurium strains TA98, TA100, TA1537, and Escherichia coli strain WP2uvrA were treated with 5-methyl-2-hepten-4-one in dimethyl sulfoxide (DMSO) at concentrations up to 1000 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, 5-methyl-2-hepten-4-one was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of 5-methyl-2-hepten-4-one; however, read-across can be made to (E)-7-methyl-3-octen-2-one (CAS # 33046-81-0; see Section V). The clastogenic activity of (E)-7-methyl-3-octen-2-one 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 (E)-7-methyl-3-octen-2-one in DMSO at concentrations up to 100 μg/mL for a dose range finding (DRF) study. Micronucleus analysis was conducted up to 60 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. (E)-7-Methyl-3-octen-2-one induced binucleated cells with micronuclei in the absence of an S9 activation system only in the 24-h treatment group (RIFM, 2009). Under the conditions of the study, (E)-7-methyl-3-octen-2-one was considered to be clastogenic in the in vitro micronucleus test.

In the follow-up study, the clastogenic activity of (E)-7-methyl-3-octen-2-one was evaluated in an in vivo micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in aqueous methylcellulose via the oral route to groups of male Han Wistar rats. Doses of 500, 1000, and 2000 mg/kg were administered. Rats from each dose level were euthanized at 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes (PCEs). The test material did not induce a statistically significant increase in the incidence of micronucleated PCEs in the bone marrow (RIFM, 2012). Under the conditions of the study, (E)-7-methyl-3-octen-2-one was considered to be not clastogenic in the in vivo micronucleus test, and this can be extended to 5-methyl-2-hepten-4-one.

Based on the data available, 5-methyl-2-hepten-4-one and read-across material (E)-7-methyl-3-octen-2-one does not present a concern for genotoxic potential.


10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 5-methyl-2-hepten-4-one or any read-across materials. The total systemic exposure to 5-methyl-2-hepten-4-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 5-methyl-2-hepten-4-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 5-methyl-2-hepten-4-one (0.055 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.


10.1.3. Reproductive toxicity

There are no reproductive toxicity data on 5-methyl-2-hepten-4-one or on any read-across materials. The total systemic exposure to 5-methyl-2-hepten-4-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 5-methyl-2-hepten-4-one or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 5-methyl-2-hepten-4-one (0.055 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Lauferweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.


10.1.4. Skin sensitization

Based on the existing data and read-across material 5,6,7-trimethylocta-2,5-dien-4-one (CAS # 358331-95-0), 5-methyl-2-hepten-4-one is considered a skin sensitizer with a defined NESIL of 250 μg/cm².

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 5-methyl-2-hepten-4-one. Based on the existing data and read-across material 5,6,7-trimethylocta-2,5-dien-4-one (CAS # 358331-95-0; see Section V), 5-methyl-2-hepten-4-one is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 5-Methyl-2-hepten-4-one was found to be positive in the in vitro direct peptide reactivity assay (DPRA) and the KeratinoSens assay (RIFM, 2015b; RIFM, 2015a). Read-across material 5,6,7-trimethylocta-2,5-dien-4-one was found to be inconclusive in a DPRA (RIFM, 2016h). However, in the KeratinoSens and human cell line activation test (h-CLAT), read-across material 5,6,7-trimethylocta-2,5-dien-4-one was found to be positive (RIFM, 2016i; RIFM, 2017c). In a murine local lymph node assay (LLNA), 5-methyl-2-hepten-4-one was found to sensitizing with an EC3 value of 2.16% (540 μg/cm²) (RIFM, 1995). However, in another LLNA, 5-methyl-2-hepten-4-one was found to be non-sensitizing up to 30% (RIFM, 1996). An LLNA with read-across material 5,6,7-trimethylocta-2,5-dien-4-one exhibited an EC3 value of 1.6% (400 μg/cm²) (RIFM, 2004). In 2 guinea pig maximization tests, 5-methyl-2-hepten-4-one presented reactions indicative of sensitization to support the repeated dose toxicity endpoint. The total systemic exposure to 5-methyl-2-hepten-4-one (0.055 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Lauferweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

is considered to be a moderate skin sensitizer with a defined NESIL of 250 g/cm². Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

Table 1

<table>
<thead>
<tr>
<th>Animal Data</th>
<th>Value (No. Studies)</th>
<th>Mean EC3</th>
<th>NOEL</th>
<th>Confirmation of No Induction in Humans</th>
<th>HMT</th>
<th>NOEL</th>
<th>LOEL</th>
<th>WoE HMT</th>
<th>NESIL</th>
</tr>
</thead>
</table>

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.

Based on the available UV/Vis spectra, 5-methyl-2-hepten-4-one does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 5-methyl-2-hepten-4-one 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 phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of significant absorbance in the critical range, 5-methyl-2-hepten-4-one does not present a concern for phototoxicity or photoallergenicity.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 5-methyl-2-hepten-4-one 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 Kow, 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, 2012c), 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, 5-methyl-2-hepten-4-one 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 5-methyl-2-hepten-4-one 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 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1. Risk assessment. Based on the current Volume of Use (2015), 5-methyl-2-hepten-4-one presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2. Key studies

10.2.2.1. Biodegradation. For CAS # 81925-81-7.

RIFM, 2013: A ready biodegradability study was conducted using the headspace test according to the OECD 310 method, and biodegradation of 76% was observed after 28 days.

10.2.2.2. Ecotoxicity. RIFM, 2016c: A Daphnia magna immobilization study was conducted according to the OECD 202 method under static conditions, and the 48-h EC50 value based on the geometric mean of (ECo/ECl0) of nominal concentration was reported to be 3.2 mg/L.

RIFM, 2016d: An algae growth inhibition study was conducted according to the OECD 201 method under static conditions in a closed system. The 72-h ErC50 (growth rate) and EyC50 (yield) were reported...
to be 3.1 mg/L and 1.5 mg/L, respectively. The results were based on nominal concentrations.

10.2.2.3. Other available data. 5-Methyl-2-hepten-4-one has been pre-registered for REACH with no additional data available at this time.

10.2.2.4. Risk assessment refinement. Since 5-methyl-2-hepten-4-one has passed the screening criteria, measured data was 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, 2002).

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Kow</td>
<td>2.28</td>
<td>2.28</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band*</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Risk Characterization: PEC/PNEC</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Combined regional Volume of Use from both the CAS numbers.

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

The RIFM PNEC is 0.0971 μg/L. The revised PEC/PNECs for the EU and North America 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 volumes of use.


11. 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/
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- National Library of Medicine’s Toxicology Information Services: https://toxnet.nlm.nih.gov/
- EPA ACToR: https://actor.epa.gov/actor/home.xhtml
- US EPA HPVIS: https://ofmpub.epa.gov/opthpv/public.search.publicdetails?submission_id=24959241&ShowComments=Yes&qstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- Japan Existing Chemical Data Base (JECDB): http://dra4.nihs.go.jp/nihlw_data.jsp/SearchPageENG.jsp
- Google: https://www.google.com

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 07/22/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112879.

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
First, 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).

The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree. Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010). ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).

DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).

<table>
<thead>
<tr>
<th>Similarity (Tanimoto Score)</th>
<th>Target Material</th>
<th>Read-across Material</th>
<th>Read-across Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read-across Endpoint</td>
<td>0.47</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C₇H₁₂O</td>
<td>C₁₁H₁₈O</td>
<td>C₉H₁₄O</td>
</tr>
<tr>
<td>Melting Point (°C, EPI Suite)</td>
<td>–42.63</td>
<td>–25.67</td>
<td>–30.77</td>
</tr>
<tr>
<td>Boiling Point (°C, EPI Suite)</td>
<td>157.22</td>
<td>213.90</td>
<td>178.53</td>
</tr>
<tr>
<td>Vapor Pressure (Pa)</td>
<td>497.00</td>
<td>35.40</td>
<td>189.00</td>
</tr>
<tr>
<td>Log KOW (KOWWIN v1.68 in EPI Suite)</td>
<td>2.22</td>
<td>3.59</td>
<td>2.71</td>
</tr>
<tr>
<td>Water Solubility (mg/L) @ 25°C, WSKOW v1.42 in EPI Suite)</td>
<td>1208.00</td>
<td>54.88</td>
<td>403.80</td>
</tr>
<tr>
<td>Henry’s Law (Pa m²/mol, Bond Method, EPI Suite)</td>
<td>171.04</td>
<td>50.30</td>
<td>29.80</td>
</tr>
<tr>
<td>DNA Binding (OASIS v1.4, QSR Toolbox v4.2)</td>
<td>No alert found</td>
<td>Michael addition</td>
<td>Michael addition ⇒ Polarized Alkenes-Michael addition</td>
</tr>
<tr>
<td>DNA Binding (OECD QSAR Toolbox v4.2)</td>
<td>Michael addition</td>
<td>Michael addition ⇒ Polarized Alkenes-Michael addition</td>
<td>Michael addition ⇒ Polarized Alkenes-Michael addition</td>
</tr>
<tr>
<td>Carcinogenicity (ISS)</td>
<td>Carcinogen (moderate reliability)</td>
<td>No alert found</td>
<td>Michael addition</td>
</tr>
<tr>
<td>DNA Binding (Ames, MN, CA, OASIS v1.1)</td>
<td>α,β-unsaturated carbonyls</td>
<td>No alert found</td>
<td>Michael addition</td>
</tr>
<tr>
<td>In Vitro Mutagenicity (Ames, ISS)</td>
<td>α,β-unsaturated carbonyls</td>
<td>α,β-unsaturated carbonyls</td>
<td>Michael addition</td>
</tr>
<tr>
<td>Oncologic Classification</td>
<td>Reactive Ketone Reactive Functional Groups</td>
<td>Reactive Ketone Reactive Functional Groups</td>
<td>Michael addition</td>
</tr>
</tbody>
</table>

(continued on next page)
Conclusions

• 5,6,7-Trimethylocta-2,5-dien-4-one (CAS # 358331-95-0) was used as a read-across analog for the target material 5-methyl-2-hepten-4-one (CAS # 81925-81-7) for the skin sensitization endpoint.
  o The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated ketones.
  o The target material and the read-across analog share branched aliphatic ketone structures with α,β-unsaturation.
  o The key difference between the target material and the read-across analog is that the read-across analog has α,β-unsaturation on both sides of the ketone substituents, whereas the target has a single unsaturation, which is similarly substituted and reactive in both molecules. The additional unsaturation in the read-across analog is dimethyl-substituted and has little reactivity. The substituted α,β unsaturation will increase the solubility of the read-across analog. These structural differences are toxicologically insignificant.
  o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable 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 Based on the data on the read-across analog and limited data on the target material, the target material is considered to be a skin sensitizer. The in silico alerts are consistent with the data.
  o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Summary

There are insufficient toxicity data on 5-methyl-2-hepten-4-one (CAS # 81925-81-7). 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, 5,6,7-trimethylocta-2,5-dien-4-one (CAS # 358331-95-0) and (E)-7-methyl-3-octen-2-one (CAS # 33046-81-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

• 5,6,7-Trimethylocta-2,5-dien-4-one (CAS # 358331-95-0) was used as a read-across analog for the target material 5-methyl-2-hepten-4-one (CAS # 81925-81-7) for the skin sensitization endpoint.
  o The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated ketones.
  o The target material and the read-across analog share branched aliphatic ketone structures with α,β-unsaturation.
  o The key difference between the target material and the read-across analog is that the read-across analog has α,β-unsaturation on both sides of the ketone substituents, whereas the target has a single unsaturation, which is similarly substituted and reactive in both molecules. The additional unsaturation in the read-across analog is dimethyl-substituted and has little reactivity. The substituted α,β unsaturation will increase the solubility of the read-across analog. These structural differences are toxicologically insignificant.
  o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable 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 Based on the data on the read-across analog and limited data on the target material, the target material is considered to be a skin sensitizer. The in silico alerts are consistent with the data.
  o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

<table>
<thead>
<tr>
<th>Protein Binding Potency</th>
<th>Protein Binding Alerts for Skin Sensitization (OASIS v1.1)</th>
<th>Skin Sensitization Reactivity Domains (Toxtree v2.6.13)</th>
<th>Metabolism Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Highly reactive (GSH)</td>
<td>Highly reactive (GSH)⇒3-Alken-2-ones (MA)</td>
<td>Alert for Michael acceptor identified</td>
</tr>
</tbody>
</table>
Explanation of Cramer Classification

Due to potential discrepancies between the current in silico tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, and N, and divergent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list (see Cramer et al., 1978 for a detailed explanation on the list of categories)? No. Class I (Class Low)

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