RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 2,6-Dimethylocta-2,4,6-triene, CAS Registry Number 673-84-7


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

Version: 031618. This version replaces any previous versions.

Name: 2,6-Dimethylocta-2,4,6-triene
CAS Registry Number: 673-84-7
Additional CAS Numbers*: 3016-19-1, 2,6-Dimethyl-2,4,6-octatriene
*This material was included in this assessment because it is a mixture of isomers.

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., 2015, 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
EU - Europe/European Union

https://doi.org/10.1016/j.fct.2018.06.048
Received 17 April 2018; Accepted 19 June 2018
Available online 22 June 2018
0278-6915/ © 2018 Elsevier Ltd. All rights reserved.
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An in silico model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a p < 0.05 using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits 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 use of this material under current conditions is supported by existing information.

2,6-Dimethylocta-2,4,6-triene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog myrcene (CAS# 123-35-3) show that 2,6-dimethylocta-2,4,6-triene is not expected to be genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 µg/cm²/day). The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 2,6-dimethylocta-2,4,6-triene 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 expected to be genotoxic. (NTP, 2010)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.89 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 604.1 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-hour *Daphnia magna* LC50: 0.295 mg/L (ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-hour *Daphnia magna* LC50: 0.295 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0295 μg/L
*Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

**Chemical Name:** 2,6-Dimethylocta-2,4,6-triene
**CAS Registry Number:** 673-84-7
**Synonyms:** Allo-Ocimene (isomer unspecified); 2,4,6-Octatriene, 2,6-dimethyl-; 2,6-Dimethylocta-2,4,6-triene

**Molecular Formula:** C₁₀H₁₆
**Molecular Weight:** 136.38
**RIFM Number:** 5208
**Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

<table>
<thead>
<tr>
<th>CAS# 673-84-7</th>
<th>CAS# 3016-19-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boiling Point:</strong> 172.65 °C (US EPA, 2012a)</td>
<td><strong>Boiling Point:</strong> 172.65 °C (US EPA, 2012a)</td>
</tr>
<tr>
<td><strong>Flash Point:</strong> 163.00 °F TCC (72.78 °C)*</td>
<td><strong>Flash Point:</strong> 174 °F; CC (FMA), 79 °C (GHS)</td>
</tr>
<tr>
<td><strong>Log Kow:</strong> 4.72 (EPI Suite)</td>
<td><strong>Log Kow:</strong> 4.72 (US EPA, 2012a)</td>
</tr>
<tr>
<td><strong>Melting Point:</strong> −63.36 °C (US EPA, 2012a)</td>
<td><strong>Melting Point:</strong> −63.36 °C (US EPA, 2012a)</td>
</tr>
<tr>
<td><strong>Water Solubility:</strong> 2.348 mg/L (US EPA, 2012a)</td>
<td><strong>Water Solubility:</strong> Not Available</td>
</tr>
<tr>
<td><strong>Specific Gravity:</strong> 0.80900 to 0.81500 @ 25.00 °C*</td>
<td><strong>Specific Gravity:</strong> 0.809 (FMA)</td>
</tr>
<tr>
<td><strong>Vapor Pressure:</strong> 0.638 mm Hg @ 20 °C (US EPA, 2012a), 0.911 mm Hg @ 25 °C (US EPA, 2012a)</td>
<td><strong>Vapor Pressure:</strong> 0.911 mm Hg @ 25 °C (US EPA, 2012a), 0.638 mm Hg @ 20 °C (US EPA, 2012a)</td>
</tr>
<tr>
<td><strong>UV Spectra:</strong> No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹)</td>
<td><strong>Appearance/Organoletic:</strong> A colorless to pale yellow, yellow clear, liquid with a dry, woody, chrysanthemum, phenolic, powdery, and orrisl odor.*</td>
</tr>
</tbody>
</table>

**Appearance/Organoletic:** A colorless to greenish yellow clear liquid with a sweet, fresh, and floral.**


3. Exposure***

1. **Volume of Use (worldwide band):** < 1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.014% (RIFM, 2016)
3. **Inhalation Exposure:** 0.000022 mg/kg/day or 0.0016 mg/day (RIFM, 2016)
4. **Total Systemic Exposure:** 0.00036 mg/kg/day (RIFM, 2016)

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Myrcene (CAS # 123-35-3)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   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.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

2,6-Dimethylocta-2,4,6-triene is reported to occur in the following foods* and in some natural complex substances (NCS):
2,6-Dimethyl-2,4,6-octatriene is reported to occur in the following foods* and in some natural complex substances (NCS):

<table>
<thead>
<tr>
<th>Food/Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guava and feya</td>
<td>Ocimum species</td>
</tr>
<tr>
<td>Litchi (Litchi chinensis sonn.)</td>
<td>Olive (Olea europaea)</td>
</tr>
<tr>
<td>Lovage (Levisticum officinale koch)</td>
<td>Salvia species</td>
</tr>
<tr>
<td>Mangifera species</td>
<td>Tarragon (Artemisia dracunculus L)</td>
</tr>
</tbody>
</table>


8. **IFRA standard**

   None.

9. **REACH dossier**

   Pre-registered for 2010; No dossier available as of 03/12/18.

10. **Summary**

   **10.1. Human health endpoint summaries**

   **10.1.1. Genotoxicity**

   Based on the current existing data, 2,6-dimethylclocta-2,4,6-triene does not present a concern for genetic toxicity.

   **10.1.1.1. Risk assessment.** 2,6-Dimethylclocta-2,4,6-triene was tested in the BlueScreen assay and was found negative for genotoxicity in the presence and absence of metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 2,6-dimethylclocta-2,4,6-triene; however, read-across can be made to myrcene (CAS # 123-35-3; see Section V). The mutagenic activity of myrcene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and OECD TG 471 using the preincubation method.
Table 1

Acceptable concentrations limits for 2,6-dimethylocta-2,4,6-triene based on non-reactive DST.

<table>
<thead>
<tr>
<th>IFRA Category</th>
<th>Description of Product Type</th>
<th>Acceptable Concentrations in Finished Products</th>
<th>Reported 95th Percentile Use Concentrations in Finished Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Products applied to the lips</td>
<td>0.069%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Products applied to the axillae</td>
<td>0.021%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Products applied to the face using fingertips</td>
<td>0.41%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Fine fragrance products</td>
<td>0.39%</td>
<td>0.01%</td>
</tr>
<tr>
<td>5</td>
<td>Products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.10%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Products with oral and lip exposure</td>
<td>0.23%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Products applied to the hair with some hand contact</td>
<td>0.79%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Products with significant ano-genital exposure</td>
<td>0.04%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Products with body and hand exposure, primarily rinse-off</td>
<td>0.75%</td>
<td>No Data</td>
</tr>
<tr>
<td>10</td>
<td>Household care products with mostly hand contact</td>
<td>2.70%</td>
<td>0.000&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate</td>
<td>1.50%</td>
<td>No Data</td>
</tr>
<tr>
<td>12</td>
<td>Products not intended for direct skin contact, minimal or insignificant transfer to skin</td>
<td>Not Restricted</td>
<td>0.14%</td>
</tr>
</tbody>
</table>

Note.

<sup>a</sup> For a description of the categories, refer to the IFRA/RIFM Information Booklet.

<sup>b</sup> Negligible exposure (< 0.01%).

(30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.


10.1.4. Skin sensitization

Based on the application of DST, 2,6-dimethylocta-2,4,6-triene does not present a safety concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for 2,6-dimethylocta-2,4,6-triene or read-across materials. However, in a human maximization test, no skin sensitization reactions were observed (RFIM, 1982). Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm<sup>2</sup>. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for 2,6-dimethylocta-2,4,6-triene, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.


10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 2,6-dimethylocta-2,4,6-triene does not present a concern for phototoxicity or photoallergic.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained for 2,6-dimethylocta-2,4,6-triene. The spectra demonstrate minor absorbance between 290 and 700 nm. Molar absorption coefficient for λ max within that range is below the benchmark of concern for phototoxic effect, 1000 L·mol<sup>-1</sup>·cm<sup>-1</sup> (Henry et al., 2009).

Additional References: None.


10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2,6-dimethylocta-2,4,6-triene is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2,6-dimethylocta-2,4,6-triene. Based on the Creme RIFM Model, the inhalation exposure is 0.0016 mg/day. This exposure is 875 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.


10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethylocta-2,4,6-triene 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<sub>OW</sub>, 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, 2,6-dimethylocta-2,4,6-triene was identified as a fragrance material with 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 2,6-dimethylocta-2,4,6-triene as possibly being either 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Framework: Salvito et al., 2002).

### 10.2.2. Risk assessment

Based on current Volume of Use (2015), 2,6-dimethylocta-2,4,6-triene presents a risk to the aquatic compartment in the screening-level assessment.

#### 10.2.2.1. Key studies. Biodegradation: No data available.  
Ecotoxicity: No data available.

#### 10.2.2.2. Other available data. 2,6-Dimethylocta-2,4,6-triene has been pre-registered for REACH with no additional data at this time.

#### 10.2.2.3. 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 Environmental Framework: Salvito et al., 2002) |
|---|---|---|
| **Exposure** | **Europe (EU)** | **North America (NA)** |
| Log K<sub>ow</sub> used | 4.72 | 4.72 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | < 1 | < 1 |

### Risk Characterization: PEC/PNEC

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

The RIFM PNEC is 0.0295 μg/L. The revised PEC/PNECs for EU and NA < 1, therefore does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 9/11/17.

#### 11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **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&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://dra4.nihs.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mlbw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

*Information keywords: CAS number and/or material names.

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.
Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.06.048.

Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{\text{max}}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

<table>
<thead>
<tr>
<th>Target Material</th>
<th>Read-across Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Name</td>
<td>2,6-Dimethylocta-2,4,6-triene</td>
</tr>
<tr>
<td>CAS No.</td>
<td>673–84–7 and 3016-19-1 (mixture)</td>
</tr>
<tr>
<td>Structure</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Similarity (Tanimoto Score)</td>
<td>0.78</td>
</tr>
<tr>
<td>Read-across Endpoint</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C_{10}H_{16}</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>136.24</td>
</tr>
<tr>
<td>Melting Point (°C, EPI Suite)</td>
<td>−63.36</td>
</tr>
<tr>
<td>Boiling Point (°C, EPI Suite)</td>
<td>172.65</td>
</tr>
<tr>
<td>Vapor Pressure (Pa @ 25 °C, EPI Suite)</td>
<td>122</td>
</tr>
<tr>
<td>Log Kow</td>
<td>4.72</td>
</tr>
<tr>
<td>(KOWWIN v1.68 in EPI Suite)</td>
<td>4.17</td>
</tr>
<tr>
<td>Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)</td>
<td>2.348</td>
</tr>
<tr>
<td>$J_{\text{max}}$ (mg/cm²/h, SAM)</td>
<td>20.672</td>
</tr>
<tr>
<td>Henry’s Law (Pa·m³/mol, Bond Method, EPI Suite)</td>
<td>6.01E+004</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>No alert found</td>
</tr>
<tr>
<td>DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)</td>
<td>No alert found</td>
</tr>
<tr>
<td>DNA Binding (OECD QSAR Toolbox v3.4)</td>
<td>No alert found</td>
</tr>
<tr>
<td>Carcinogenicity (ISS)</td>
<td>Non-carcinogen (low reliability)</td>
</tr>
<tr>
<td>DNA Binding (Ames, MN, CA, OASIS v1.1)</td>
<td>No alert found</td>
</tr>
<tr>
<td>In Vitro Mutagenicity (Ames, ISS)</td>
<td>No alert found</td>
</tr>
</tbody>
</table>
In Vivo Mutagenicity (Micronucleus, ISS)  
Oncologic Classification  
Metabolism  
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites  
(OECD QSAR Toolbox v3.4)  

See Supplemental Data 1  
See Supplemental Data 2

Summary  
There are insufficient toxicity data on 2,6-dimethyl-octa-2,4,6-triene (CAS # 673-84-7). Hence, in silico evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, myrcene (CAS # 123-35-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions  
- Myrcene (CAS # 123-35-3) was used as a read-across analog for the target material 2,6-dimethyl-octa-2,4,6-triene (CAS # 673-84-7) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic hydrocarbons.
  - The target substance and the read-across analog share a triene structure.
  - The key difference between the target substance and the read-across analog is that the target substance has 3 vinylene groups, while the read-across analog has 2 vinyl and 1 vinylene groups. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the triene structure. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - Differences are predicted for Jmax, which estimates skin absorption. Jmax ≤ 80% for the target substance and ≤ 40% for the read-across analog. While the percentage of skin absorption estimated from Jmax indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References  


