Short Review

RIFM fragrance ingredient safety assessment, Valencene, CAS Registry Number 4630-07-3

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Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary \textit{in silico} tool used to calculate fragrance air exposure concentration

Version: 031618. This version replaces any previous versions.
Name: Valencene
CAS Registry Number: 4630-07-3

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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,b; 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
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
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.
Valencene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photocytotoxicity/phototoallergenicity, skin sensitization, and environmental safety. Data show that valencene is not genotoxic. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm²). The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The photocytotoxicity/phototoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; valencene 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. (RIFM, 2016a; RIFM, 2017)
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/photoallergenic (UV Spectra, RIFM DB)

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

### Environmental Safety Assessment

#### Hazard Assessment:
- **Persistence:** Critical Measured Value: 66% (OECD 301F; day 67) (RIFM, 2011b)
- **Bioaccumulation:** Screening-level: 6682 L/kg (EPI Suite v4.1; US EPA, 2012a)
- **Ecotoxicity:** Screening-level: 48-h *Daphnia magna* LC50: 0.019 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-h *Daphnia magna* LC50: 0.019 mg/L (ECOSAR; US EPA, 2012b)

**RIFM PNEC is:** 0.0019 μg/L

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

### Identification

1. **Chemical Name:** Valencene
2. **CAS Registry Number:** 4630-07-3
3. **Synonyms:** Naphthalene, 1,2,3,5,6,7,8,8α-LαPHA-octahydro-1,8α-LαPHA-dimethyl-7-(1-methyleneylethyl); (1R-(1α,7β,αLPHA))-1,2,3,5,6,7,8,8αLPHA-Octahydro-1,8αLPHA-dimethyl-7-(1-methyleneylethyl)napthalene; (+)-Valencene; 4α,10α-Dimethyl-6β-isopropyl-delta1,9-octalin; 4βH,5α-Eremophila-1(10),11-diene; Valencen; オレンジ抽出物; 3-Isopropenyl-4α,5-dimethyl-1,2,3,4,4α,5,6,7-octahydronaphthalene; Valencene
4. **Molecular Formula:** C₁₅H₂₄
5. **Molecular Weight:** 204.36
6. **RIFM Number:** 1154
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

### Physical data

1. **Boiling Point:** 253.52 °C (US EPA, 2012a)
2. **Flash Point:** > 93 °C (GHS), 122 °F (Firmenich [FFIDS, 2000])
3. **Log KOW:** 6.3 (US EPA, 2012a), > 6.5 (RIFM, 2011a)
4. **Melting Point:** 29.52 °C (US EPA, 2012a)
5. **Water Solubility:** 0.05011 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.92 g/cc (Firmenich [FFIDS, 2000])
7. **Vapor Pressure:** 0.0194 mm Hg @ 20 °C (US EPA, 2012a), 0.0331 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorption between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹)
9. **Appearance/Organoleptic:** A clear colorless or pale yellow oily liquid with an orange, citrusy, warm and woody odor.*


### Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0036% (RIFM, 2016)
3. **Inhalation Exposure**: 0.000030 mg/kg/day or 0.0022 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**: 0.000090 mg/kg/day (RIFM, 2016)

### Computational toxicology evaluation

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

### Metabolism

No relevant data available for inclusion in this safety assessment.
7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Valencene is reported to occur in the following foods* and is found in some natural complex substances (NCS):


8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 03/12/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, valencene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Valencene was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). The mutagenic activity of valencene 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 *Escherichia coli* strain WP2uvrA were treated with valencene 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 (RIFM, 2016a). Under the conditions of the study, valencene was not mutagenic in the Ames test.

The clastogenic activity of valencene 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 valencene in dimethyl formamide (DMF) at concentrations up to 2000 µg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Valencene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, valencene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, valencene does not present a concern for genotoxic potential.

Additional References: None.

10.1.2.Repeated dose toxicity

There are insufficient repeated dose toxicity data on valencene or any read-across materials. The total systemic exposure to valencene 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 valencene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to valencene (0.09 µg/kg bw/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.

Additional References: None.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on valencene or any read-across materials. The total systemic exposure to valencene is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on valencene or any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to valencene (0.09 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Lawfersweiler 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 existing data and application of DST, valencene 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 valencene or read-across materials. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1980). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (Safford et al., 2015a). 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 valencene which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

10.1.5. Photoxicity/photoallergenicity

Based on available UV/Vis spectra, valencene would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for valencene in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, valencene does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for valencene were obtained. The spectra indicate no significant
absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol\(^{-1}\) cm\(^{-1}\), of concern for phototoxic effects (Henry et al., 2009).

**Additional References**: None.

**Literature Search and Risk Assessment Completed On**: 08/17/17.

### 10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for valencene 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 valencene. Based on the Creme RIFM Model, the inhalation exposure is 0.0022 mg/day. This exposure is 636 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 valencene 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, valencene 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 identified valencene 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 Safety Assessment section prior to Section 1.

#### 10.2.2. Risk assessment

Based on current Volume of Use (2015), valencene presents a risk to the aquatic compartment in the screening level assessment.

##### 10.2.2.1. Biodegradation. **RIFM, 2011b**: Ready biodegradability of the test material was evaluated according to the OECD 301F method. Under the conditions of the study, biodegradation of 66% was observed after 67 days.

##### 10.2.2.2. Ecotoxicity. No data available.

##### 10.2.2.3. Other available data. Valencene has been pre-registered under REACH with no additional data at this time.

##### 10.2.3. Risk assessment refinement

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

### Table 1

<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>Products applied to the lips</td>
<td>0.069%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products applied to the axillae</td>
<td>0.021%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products applied to the face using fingertips</td>
<td>0.41%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Fine fragrance products</td>
<td>0.39%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.10%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products with oral and lip exposure</td>
<td>0.227%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products applied to the hair with some hand contact</td>
<td>0.79%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Products with significant ano-genital exposure</td>
<td>0.04%</td>
<td>No Data</td>
<td></td>
</tr>
<tr>
<td>Products with body and hand exposure, primarily rinse-off</td>
<td>0.75%</td>
<td>0.00%</td>
<td></td>
</tr>
<tr>
<td>Household care products with mostly hand contact</td>
<td>2.70%</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Products not intended for direct skin contact, minimal or insignificant transfer to skin</td>
<td>Not Restricted</td>
<td>0.089%</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**

* For a description of the categories, refer to the IFRA/RIFM Information Booklet.

b Negligible exposure (< 0.01%).

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A.M. Api et al.  
Food and Chemical Toxicology 118 (2018) S141–S146
Endpoints used to calculate PNEC are underlined.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Kow</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
<td>0.1</td>
<td>0.1</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>
</tbody>
</table>

Risk Characterization: PEC/PNEC

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

The RIFM PNEC is 0.0019 µg/L. The revised PEC/PNECs for EU and NA are < 1, therefore, 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: http://echa.europa.eu/
- NTP: https://ntp.niehs.nih.gov/
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- 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%20submission
- Japan Existing Chemical Data Base (JECDB): http://dra4.nihs.go.jp/mhvd/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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References


RIFM (Research Institute for Fragrance Materials, Inc), 2016a. Valencene: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 70467. RIFM, Woodcliff Lake, NJ, USA.


