Short Review

RIFM fragrance ingredient safety assessment, 2,6-Dimethyl-5-heptenal, CAS Registry Number 106-72-9

A.M. Api a, D. Belsito b, S. Bhatia a, M. Bruze c, P. Calow d, M.L. Dagli e, W. Dekant f, A.D. Fryer g, L. Kromidas a,k, S. La Cava a, J.F. Lalko h, A. Lapczynski a, D.C. Liebler h, Y. Miyachi i, V.T. Politano a, G. Ritacco a, D. Salvito a, J. Shen a, T.W. Schultz j, I.G. Sipes k, B. Wall a, D.K. Wilcox a

a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, United States
b Member RIFM Expert Panel, Department of Dermatology, Columbia University Medical Center, 161 Fort Washington Ave., New York, NY 10032, United States
c Member RIFM Expert Panel, Department of Occupational & Environmental Dermatology, Malmo University Hospital, Sodra Forstadsstgatan 101, Entrance 47, Malmo SE-20502, Sweden
d Member RIFM Expert Panel, 230 Whittier Research Center, University of Nebraska Lincoln, Lincoln, NE 68583-0857, United States
e Member RIFM Expert Panel, School of Veterinary Medicine and Animal Science, Department of Pathology, University of Sao Paulo, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo CEP 05508-900, Brazil
f Member RIFM Expert Panel, Department of Toxicology, University of Wuerzburg, Versbacher Str. 9, Würzburg 97078, Germany
g Member RIFM Expert Panel, Oregon Health Science University, 3381 SW Sam Jackson Park Rd., Portland, OR 97239, United States
h Member RIFM Expert Panel, Department of Biochemistry, Center in Molecular Toxicology, Vanderbilt University School of Medicine, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, United States
i Member RIFM Expert Panel, Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
j Member RIFM Expert Panel, College of Veterinary Medicine, Department of Comparative Medicine, The University of Tennessee, 2407 River Dr., Knoxville, TN 37996-4500, United States
k Member RIFM Expert Panel, Department of Pharmacology, College of Medicine, University of Arizona, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, United States

ARTICLE INFO

Article history:
Received 19 November 2014
Accepted 13 January 2015
Available online

Keywords:
Genotoxicity
Repeated dose toxicity/developmental and reproductive toxicity
Skin Sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety assessment

Version: 091514. This version replaces any previous versions.

Name: 2,6-Dimethyl-5-heptenal

CAS Registry Number: 106-72-9

* Corresponding author. Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, United States. Tel.: +1 201 689 8089 ext 110; fax: (201) 689-8090.
E-mail address: lkromidas@rifm.org (L. Kromidas).

http://dx.doi.org/10.1016/j.fct.2015.01.007
0278-6915/© 2015 Elsevier Ltd. All rights reserved.
Identification

1 Chemical Name: 2,6-Dimethyl-5-heptenal
2 CAS Registry Number: 106-72-9

Abbreviation/Definition list:

- 2-Box Model – a RIFM, Inc proprietary in silico tool used to calculate fragrance air exposure concentration
- 97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
- AF – Assessment Factor
- 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
- OECD – Organisation for Economic Co-operation and Development
- PBT – Persistent, Bioaccumulative, and Toxic
- PECPNEC – Predicted Environmental Concentration/Predicted No Effect Concentration
- QRA – quantitative risk assessment
- REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
- RIFM – Research Institute for Fragrance Materials
- RQ – Risk Quotient
- TTC – Threshold of Toxicological Concern
- UV/Vis Spectra – Ultra Violet/Visible spectra
- VCF – Volatile Compounds in Food
- VoU – Volume of Use
- vPvB – (very) Persistent, (very) Bioaccumulative
- WOE – Weight of Evidence

RIFM’s Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on RIFM’s Criteria Document (Api et al., 2014) and should be referred to for clarifications. Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

* RIFM’s Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 37 mg/kg/day, based on a dietary 90-day subchronic toxicity study conducted in rats, that resulted in an MOE of 4744 assuming 100% absorption from skin contact and inhalation. An MOE of >100 is deemed acceptable.

Environmental Safety Assessment

- Hazard Assessment:
  - Persistence: Critical Measured Value: 75% (OECD 301F) (RIFM, 2012)
  - Bioaccumulation: Screening Level: 470 L/Kg (EpiSuite ver 4.1)
  - Ecotoxicity: Screening Level: 48 hr Daphnia Magna EC50: 2.2 mg/l (ECOSAR ver 1.11)
  - Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

- Risk Assessment:
  - Screening-Level: PECPNEC (North America and Europe) >1 (Salvito et al., 2002)
  - Critical Ecotoxicity Endpoint: 48 hr Daphnia Magna EC50: 2.2 mg/l (ECOSAR ver 1.11)

RIFM PNEC is: 0.22 μg/L
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe <1
5. Computational toxicology evaluation

3. Exposure

1 Volume of Use (worldwide band): <1000 metric tons per year (IFRA, 2011)
2 Average Maximum Concentration in Hydroalcohols: 0.29% (IFRA, 2008)
3 97.5th Percentile: 0.29% (IFRA, 2008)
4 Dermal Exposure*: 0.0073 mg/kg/day (IFRA, 2008)
5 Oral Exposure: Not available
6 Inhalation Exposures**: 0.0045 mg/kg/day (IFRA, 2008)
7 Total Systemic Exposure (Dermal + Inhalation): 0.0078 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000). ** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM’s 2-Box/MPPD in silico models, based on the IFRA survey results for the 97.5th percentile use in hydroalcohols for a 60 kg individual.

4. Derivation of systemic absorption

1 Dermal: Assumed 100%
2 Oral: Data not available – not considered.
3 Inhalation: Assumed 100%
4 Total: Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.0078 mg/kg/day

5. Computational toxicology evaluation

1 Cramer Classification: Class I, Low

Expert Judgment

<table>
<thead>
<tr>
<th>Toxtree v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

2 Analogs Selected:

a. Genotoxicity: None
b. Repeated Dose Toxicity: None
c. Developmental and Reproductive Toxicity: Citral (CAS # 5392-40-5)
d. Skin Sensitization: 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal], CAS # 24048-13-3
e. Phototoxicity/Photoallergenicity: 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal], (CAS# 24048-13-3)

f. Local Respiratory Toxicity: Citral (CAS# 5392-40-5)
g. Environmental Toxicity: None

3 Read-across justifications: See Appendix 1 below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or composition (NCS)

2,6-Dimethyl-5-heptenal is reported to occur in food* and as a component in some natural complex substances (NCS):

- Citrus fruits
- Ginger (zingiber officinale rosc.)
- Lemon peel oil (citrus limon burm. f.)
- Lime oil (candpressed)
- Sudachi oil (Citrus sudachi Hort. ex Shirai)


8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 12/13/13.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 2,6-dimethyl-5-heptenal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic potential of the 2,6-dimethyl-5-heptenal was assessed in a bacterial reverse mutation assay performed in compliance with GLP regulations and in accordance with OECD TG (RIFM, 2006). Under the conditions of the study 2,6-dimethyl-5-heptenal was considered not mutagenic.

The clastogenic potential of 2,6-dimethyl-5-heptenal was assessed in an in vivo micronucleus test in which groups of male and female NMRI mice were dosed once at 3–4 dose levels up to a maximum of 1540 mg/kg b.w. in olive oil (Wild et al., 1983). Under the conditions of the study 2,6-dimethyl-5-heptenal was considered non-clastogenic.

Taken together, 2,6-dimethyl-5-heptenal does not present a concern for genotoxic potential.


10.1.2. Repeated dose toxicity

The margin of exposure for 2,6-dimethyl-5-heptenal is adequate for the repeated dose toxicity endpoint at the current level of use.
10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2,6-dimethyl-5-heptenal is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. The developmental toxicity data on 2,6-dimethyl-5-heptenal are sufficient for the developmental toxicity endpoint. A gavage developmental and reproductive toxicity screening study conducted in rats with 2,6-dimethyl-5-heptenal determined the developmental NOAEL to be 300 mg/kg/day, based on reduced pup weights and viability (RIFM, 1990a). These effects were observed at dosages that were maternally toxic. Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0078 or 38,462.

The reproductive toxicity data on 2,6-dimethyl-5-heptenal are insufficient for the reproductive toxicity endpoint. The gavage developmental and reproductive toxicity screening study conducted in rats determined the maternal NOAEL to be 300 mg/kg/day, based on clinical signs, body weight, and feed consumption (RIFM, 1990a). There are no male reproductive data on 2,6-dimethyl-5-heptenal. Read across material cetral (CAS # 5392-40-5; see Section 5) has an OECD 421 gavage reproduction toxicity screening test conducted in rats which determined the maternal NOAEL to be 300mg/kg/day, based on reduced pup weights and viability (RIFM, 1990a). These effects were observed at dosages that were maternally toxic. Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0078 or 38,462.

Additional References: RIFM, 1990b; Abramovici, 1972; Forschmidt et al., 1979; Abramovici et al., 1983; Howes et al., 2002; Ishida et al., 1989; Songkro et al., 2003; Meyer, 1965; Meyer et al., 1950; Jorgensen et al., 1993; Res et al., 2003; National Toxicology Program, 2003; Gaworski et al., 1992; York et al., 1989; Nogueira et al., 1995; Hoberman et al., 1989; Jackson et al., 1987; Dieter et al., 1993; Hagan et al., 1967; Bär et al., 1967; Abramovici et al., 1983; Sandbank et al., 1988; Abramovici et al., 1985; RIFM, 1958; Leach et al., 1956; Shillinger, 1950; Abramovici et al., 1980; Toaff et al., 1979; Geldof et al., 1992; Servadio et al., 1985; Servadio et al., 1986; Servadio et al., 1987; Abramovici et al., 1986; Scolini et al., 1994a; Scolini et al., 1994b; Engelslein et al., 1996; Kessler et al., 1998; Golomb et al., 2001; Diliberto et al., 1988a; Diliberto et al., 1990; Diliberto et al., 1989; Diliberto et al., 1988b; Boyer et al., 1990; Philips et al., 1976; Barbier & Benezra, 1982; http://rifmdatabase.rifm.org/RifmDatabase/Studies/5002.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.5. Phototoxicity/photoallergenicity

Based on the UV spectra for the read across analog 2,6,10-trimethylundeca-5,9-dienal [dihydropriapofarnesal] (CAS# 24048-13-3), 2,6-dimethyl-5-heptenal does not present a concern for phototoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.6. Local respiratory toxicity

The margin of exposure is adequate for the respiratory end-point at the current level of use.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. There are no inhalation data available on 2,6-dimethyl-5-heptenal. Read across material cetral (CAS # 5392-40-5; see Section 5) has an inhalation developmental toxicity study conducted in rats which only stated that maternal toxicity was observed at 68 ppm, but did not evaluate local respiratory tract effects following exposure (Gaworski et al., 1992). In an inhalation 21-day repeated dose toxicity study conducted in rats breathing effects and nasal discharge were noted at 68 ppm, thus a NOAEC of 34 ppm or 211 mg/m³ for cetral by vapor inhalation was determined (Gaworski et al., 1993).

This latter NOAEC expressed in mg/kg lung weight/day is:

- (211 mg/m³) (1m³/1000 L) = 0.211 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat × duration of exposure of 360 minutes per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.211 mg/L) (61.2 L/d) = 12.91 mg/d

Please cite this article in press as: A.M. Api et al., RIFM fragrance ingredient safety assessment, 2,6-Dimethyl-5-heptenal, CAS Registry Number 106-72-9, Food and Chemical Toxicology (2015), doi: 10.1016/j.fct.2015.01.007
10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2,6-dimethyl-5-heptenal was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material’s volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOsAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework 2,6-dimethyl-5-heptenal 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 EPISUITE ver 4.1 did not identify 2,6-dimethyl-5-heptenal as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material’s physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA’s BIOWIN and BCFOAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate 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 VoU (2011), 2,6-dimethyl-5-heptenal presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. The ready biodegradability of 2,6-dimethyl-5-heptenal was evaluated using the Manometric Respirometry Test according to the OECD 301F method. After 28 days a biodegradation of 75% was observed (RIFM, 2012).

In a modified Manometric Respirometry Test 2,6-dimethyl-5-heptenal underwent 72% biodegradation after 39 days and 68% biodegradation after 28 days under the test conditions (RIFM, 2000b).

Ecotoxicity: No data available.

Other available data: 2,6-Dimethyl-5-heptenal has been pre-registered for 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).

Endpoints used to calculate PNEC are underlined.

Endpoints used to calculate PNEC are underlined.

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>LC50 (mg/L)</th>
<th>EC50 (mg/L)</th>
<th>AF</th>
<th>PNEC (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldehydes (Minn)</td>
<td>11.45 mg/L</td>
<td>2.2 mg/L</td>
<td>10,000</td>
<td>0.01145 μg/L</td>
</tr>
<tr>
<td>Neutral Organic SAR</td>
<td>2.288 mg/L</td>
<td>4.247 mg/L</td>
<td>1.00000</td>
<td>0.01145 μg/L</td>
</tr>
<tr>
<td>(Baseline toxicity)</td>
<td>2.2 mg/L</td>
<td>13.42 mg/L</td>
<td>1.00000</td>
<td>0.01145 μg/L</td>
</tr>
</tbody>
</table>

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

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

The RIFM PNEC is 0.022 μg/L. The revised PEC/PNECs for EU and NA <1 and, 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/
- OECD Toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
Appendix 1

<table>
<thead>
<tr>
<th>Target Material</th>
<th>Read across Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-Dimethyl-5-heptenal</td>
<td>Citral</td>
</tr>
<tr>
<td>2,6,10-Trimethylundeca-5,9-dienal (dihydroapafarnesal)</td>
<td></td>
</tr>
</tbody>
</table>

**Developmental and Reproductive Toxicity**

- **ER binding (OECD)**: Non binder, non-cyclic structure
- **Developmental toxicity model (CAESAR v2.1.6)**: Non-Toxicant (low reliability)

**Skin Sensitization**

- **Protein binding (OASIS v1.1)**:
  - Schiff base formation
  - Schiff base formation \(\Rightarrow\) Schiff base formation with carbonyl compounds
  - Schiff base formation \(\Rightarrow\) Schiff base formation with carbonyl compounds \(\Rightarrow\) Aldehydes

**Protein binding (OECD)**

- Schiff Base Formers
- Schiff Base Formers \(\Rightarrow\) Direct Acting
- Schiff Base Formers \(\Rightarrow\) Direct Acting

**Protein binding potency (OECD)**

- Not possible to classify according to these rules (GSH)

**Protein binding alerts for skin sensitization (OASIS v1.1)**

- Schiff base formation
- Schiff base formation \(\Rightarrow\) Schiff base formation with carbonyl compounds
- Schiff base formation \(\Rightarrow\) Schiff base formation with carbonyl compounds \(\Rightarrow\) Aldehydes

**Skin sensitization model (CAESAR v2.1.6)**

- Sensitizer (good reliability)

**Metabolism**

- Rat liver S9 metabolism simulator (OECD)

---

* Values calculated using OpenBabel with FP2 fingerprint (O’Boyle et al., 2011).
**Conclusion/rationale**

There are insufficient toxicity data on 2,6-Dimethyl-5-heptenal (CAS # 106-72-9). Hence, in silico evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across analogs for their respective toxicity endpoints.

**Methods**

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v.4.11 developed by US EPA (USEPA, 2012).
- The Jacc were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- ER binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012).

**Appendix 2: Supplementary material**

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.007.

**References**


A.M. Api et al./Food and Chemical Toxicology 83 (2015) 101–107

Please cite this article in press as: A.M. Api, et al., RIFM fragrance ingredient safety assessment, 2,6-Dimethyl-5-heptenal, CAS Registry Number 106-72-9, Food and Chemical Toxicology (2015), doi: 10.1016/j.fct.2015.01.007


