Food and Chemical Toxicology 110 (2017) S496–S501

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short review

RIFM fragrance ingredient safety assessment 2-heptylcyclopentanone, CAS Registry Number 137-03-1

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ARTICLE INFO

Article history:
Received 20 August 2017
Accepted 14 September 2017
Available online 20 September 2017

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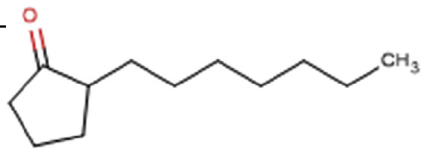
https://doi.org/10.1016/j.fct.2017.09.034

Version: 072417. This version replaces any previous versions.

Name: 2-Heptylcyclopentanone
CAS Registry Number: 137-03-1



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; Safford et al., 2015; Safford et al., 2017; Comiskey 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
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

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 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 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
The material (2-heptylcyclopentanone) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that 2-heptylcyclopentanone is not genotoxic nor does it have skin sensitization potential. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day, 0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was evaluated based on data on 2-heptylcyclopentanone and UV spectra. The environmental endpoints were evaluated, 2-heptylcyclopentanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2000c; RIFM, 2015)
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: Not sensitizing.	(RIFM, 1981; RIFM, 2012f)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB; RIFM, 1982)
Local Respiratory Toxicity: No NOAEC available.	Exposure is below the TTC.

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 32% (OECD 301D)	(RIFM, 2000b)
Bioaccumulation: Screening Level: 202.1 l/kg	(US EPA, 2012a)
Ecotoxicity: Screening Level: 48-h *Daphnia magna* LC50: 1.639 mg/l	(US EPA, 2012a)
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)

(*continued on next page*)

(*continued*)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 1.639 mg/l (US EPA, 2012a)
RIFM PNEC is: 0.1639 μg/l
- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe <1

1. Identification

1. **Chemical Name:** 2-heptylcyclopentanone
2. **CAS Registry Number:** 137-03-1
3. **Synonyms:** Alismone; Cyclopentanone, 2-heptyl-; Fleuramone; 2-Heptylcyclopentanone; Projasmon; アルキル(C = 4 ~ 7)シクロペンタノン; Heptone
4. **Molecular Formula:** $C_{12}H_{22}O$
5. **Molecular Weight:** 182.31
6. **RIFM Number:** 402

2. Physical data

1. **Boiling Point:** 263.53 °C [US EPA, 2012a]
2. **Flash Point:** > 200 °F, CC [FMA Database]
3. **Log K_{OW}:** 4 [US EPA, 2012a]
4. **Melting Point:** 35.59 °C [US EPA, 2012a]
5. **Water Solubility:** 20.63 mg/l [US EPA, 2012a]
6. **Specific Gravity:** 0.884 °F, CC [FMA Database]
7. **Vapor Pressure:** 0.0103 mm Hg @ 20 °C [US EPA, 2012a], 0.006 mm Hg 20 °C [FMA Database], 0.0178 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 l $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a medium fruity, fresh, peach, isojasmone, oily, tropical odor.*

* http://www.thegoodscentscompany.com/data/rw1004971.html, retrieved 03/10/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.034% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.012 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0012 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 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 II, Intermediate

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** None
   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:** None

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

2-Heptylcyclopentanone has not been reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 07/24/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the available data, 2-heptylcyclopentanone does not present a concern for genotoxicity.

9.1.1.1. Risk assessment. The mutagenicity of 2-heptylcyclopentanone was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 were treated with the test material in DMSO (dimethyl sulfoxide) at concentrations up to 1500 μg/plate in the presence and absence of metabolic activation. No significant increase in the number of revertant colonies was observed compared to negative control (RIFM, 2000c). Under the conditions of the study, 2-heptylcyclopentanone was not mutagenic in the Ames test.

The clastogenic activity of 2-heptylcyclopentanone was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-heptylcyclopentanone in DMSO at concentrations of 10–200 μg/ml for the non-activated and S9-activated 4-h exposure groups and from 5 to 70 μg/ml for the non-activated 24-h exposure groups. The percentage of micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level (RIFM, 2015). Under the conditions of the study, 2-heptylcyclopentanone was considered not clastogenic in human cells.

Based on the available data, 2-heptylcyclopentanone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/08/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-heptylcyclopentanone or any read across materials. The total systemic exposure to 2-heptylcyclopentanone is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-heptylcyclopentanone or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-heptylcyclopentanone (1.2 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: RIFM, 2012b; Belsitoet al., 2012; RIFM, 2012d; RIFM, 2012c; RIFM, 2012e; RIFM, 2012a.

Literature Search and Risk Assessment Completed on: 02/28/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 2-heptylcyclopentanone or any read across materials. The total systemic exposure to 2-heptylcyclopentanone is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 2-heptylcyclopentanone or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 2-heptylcyclopentanone (1.2 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no reproductive toxicity data on 2-heptylcyclopentanone or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-heptylcyclopentanone (1.2 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: RIFM, 2012b; Belsito et al., 2012; RIFM, 2012d; RIFM, 2012c; RIFM, 2012e; RIFM, 2012a.

Literature Search and Risk Assessment Completed on: 02/28/2017.

10.1.4. Skin sensitization

Based on the available data, 2-heptylcyclopentanone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data; 2-heptylcyclopentanone does not present a concern for skin sensitization. The chemical structure indicates that this material would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In guinea pig test methods, this material was reported to be a non-sensitizer (Belsito et al., 2012; Klecak, 1979, 1985; RIFM, 1981). In human studies, no sensitization reactions were observed from 2-heptylcyclopentanone (RIFM, 1964; RIFM, 2012f; RIFM, 1973).

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/09/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, 2-heptylcyclopentanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra were obtained and indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). The material, 2-heptylcyclopentanone, was not phototoxic in an *in vivo* phototoxicity study (RIFM, 1982). Based on lack of absorbance in the critical range and *in vivo* study data, 2-heptylcyclopentanone does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/20/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-heptylcyclopentanone, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-heptylcyclopentanone. Based on the Creme RIFM model, the inhalation exposure is 0.012 mg/day. This exposure is 39.2 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: RIFM, 1997.

Literature Search and Risk Assessment Completed on: 3/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2-heptylcyclopentanone was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} 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 (US EPA, 2012b) (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). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-heptylcyclopentanone was identified as a fragrance material with the 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 (US EPA, 2012a) did not identify 2-heptylcyclopentanone as either being possibly persistent nor 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 BCFBAF found in EPI Suite v4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current Volume of Use (2011), 2-heptylcyclopentanone presents a risk to the aquatic compartment in the screening level assessment.

Key Studies:

Biodegradation: RIFM, 2000b: Biodegradability of the test material was evaluated by the closed bottle test according to the 92/69/EEC, Method C.4-E. 2.3 mg/l of 2-heptylcyclopentanone suspended in a mineral medium, was inoculated with activated sludge from a sewage treatment plant for 28 days. A biodegradation rate of 32% was achieved after 28 days and 2-heptylcyclopentanone was classified as “not readily biodegradable”.

Ecotoxicity: RIFM, 2000a: A 48-h acute toxicity study was conducted with *Daphnia magna*. The geometric mean of EC0/EC100 was reported to be 2.5 mg/l.

Other available data:

2 -Heptylcyclopentanone has been pre-registered for REACH with no additional data at this time.

10.2.1.2. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>2.006 mg/L</u>			1,000,000	0.002006 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.399 mg/L	<u>1.639 mg/L</u>	2.618 mg/L	10,000	0.1639 μg/L	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.4	4.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1639 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.

Literature Search and Risk Assessment Completed on: 07/01/2014.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2017.09.034.

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