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Short review

RIFM fragrance ingredient safety assessment, 2,2,5-trimethyl-5-pentylcyclopentanone, CAS Registry Number 65443-14-3

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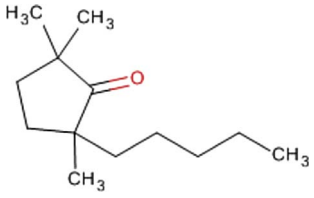
Version: 071317. This version replaces any previous versions.
Name: 2,2,5-Trimethyl-5-pentylcyclopentanone
CAS Registry Number: 65443-14-3



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

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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 (2,2,5-trimethyl-5-pentylcyclopentanone) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog 2-hexylcyclopentanone (CAS # 13074-65-2) show that 2,2,5-trimethyl-5-pentylcyclopentanone is not genotoxic. Target data on 2,2,5-trimethyl-5-pentylcyclopentanone as well as data from the read across analog 2-heptylcyclopentanone (CAS # 137-03-1) show that 2,2,5-trimethyl-5-pentylcyclopentanone does not 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, 0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was evaluated based on UV spectra along with data on the target material 2,2,5-trimethyl-5-pentylcyclopentanone. The environmental endpoints were evaluated, 2,2,5-trimethyl-5-pentylcyclopentanone was found not to be a 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, 2016a; RIFM, 2016b)

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 a concern for skin sensitization. (RIFM, 1981; RIFM, 2012b)

Phototoxicity/Photoallergenicity: Not Phototoxic/Photoallergenic. (UV Spectra, RIFM DB; RIFM, 1984a; RIFM, 1984b)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening Level: 55% (OECD 301D) Day 84 (ECHA REACH Dossier; accessed 3/17)

Bioaccumulation: Critical Measured Value: BCF: 402 (OECD 305C) (RIFM, 1986)

Ecotoxicity: Screening Level: 48-h *Daphnia magna* LC50: 0.897 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)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.897 mg/l (US EPA, 2012a)

RIFM PNEC is: 0.0897 μg/l

- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe < 1

1. Identification

1. **Chemical Name:** 2,2,5-Trimethyl-5-pentylcyclopentanone
2. **CAS Registry Number**: 65443-14-3
3. **Synonyms:** Cyclopentanone, 2,2,5-trimethyl-5-pentyl-; 2,2,5-Trimethyl-5-pentylcyclopentanone; Veloutone; 2-Pentyl-2,5,5-trimethylcyclopentanone; 2,2,5-Trimethyl-5-pentylcyclopentan-1-one; 2,5,5-トリメチル-2-ペンチルシクロペンタノン; 2,5,5-トリメチル-2-ペンチルシクロペンタノン
4. **Molecular Formula**: $C_{13}H_{24}O$
5. **Molecular Weight**: 196.33
6. **RIFM Number**: 1296

2. Physical data

1. **Boiling Point:** 257.68 °C (US EPA, 2012a)
2. **Flash Point:** 194 °F [Firmenich (FFIDS 2000)], 90 °C [GHS]
3. **Log K_{OW}**: 4.34 (US EPA, 2012a)
4. **Melting Point**: 53.13 °C (US EPA, 2012a)
5. **Water Solubility:** 8.956 mg/l (US EPA, 2012a)
6. **Specific Gravity:** 0.87 g/cc [Firmenich (FFIDS 2000)]
7. **Vapor Pressure:** 0.00938 mm Hg @ 20 °C (US EPA, 2012a), 0.4 mm Hg @20C [FMA Database], 0.0163 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} cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with as odor described as fruity, peach, apricot, jasmin, lactonic, herbal and lavender.*

*http://www.thegoodscentscompany.com/data/rw1000241.html, retrieved 03/15/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.013% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.000032 mg/kg/day or 0.0023 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00053 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 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; Safford et al., 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:** 2-hexylcyclopentanone (CAS # 13074-65-2)
   b. **Repeated Dose Toxicity**: None
   c. **Developmental and Reproductive Toxicity**: None
   d. **Skin Sensitization:** 2-heptylcyclopentanone (CAS # 137-03-1)
   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)

2,2,5-Trimethyl-5-pentylcyclopentanone is not 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 on 03/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, 2,2,5-trimethyl-5-pentylcyclopentanone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2,2,5-Trimethyl-5-pentylcyclopentanone was tested using the BlueScreen assay and found not to be genotoxic with or without S9 metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 2,2,5-trimethyl-5-pentylcyclopentanone; however, read across can be made to 2-hexylcyclopentanone (CAS # 13074-65-2; see Section 5). The mutagenic activity of 2-hexylcyclopentanone 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 2-hexylcyclopentanone 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, 2-hexylcyclopentanone was not mutagenic in the Ames test and this can be extended to 2,2,5-Trimethyl-5-pentylcyclopentanone.

There are no studies assessing the clastogenic activity of 2,2,5-trimethyl-5-pentylcyclopentanone; however, read across can be made to 2-hexylcyclopentanone (CAS # 13074-65-2; see Section 5). The clastogenic activity of 2-hexylcyclopentanone 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-hexylcyclopentanone in DMSO at concentrations up to 225 μg/ml in the presence and absence of metabolic activation (S9) for 4 and 24 h. 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, 2016b). Under the conditions of the study, 2-hexylcyclopentanone was considered not clastogenic in human cells and this can be extended to 2,2,5-trimethyl-5-pentylcyclopentanone.

Based on the available data, 2,2,5-trimethyl-5-pentylcyclopentanone 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 2,2,5-trimethyl-5-pentylcyclopentanone or any read across materials. The total systemic exposure to 2,2,5-trimethyl-5-pentylcyclopentanone 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 2,2,5-trimethyl-5-pentylcyclopentanone or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2,2,5-trimethyl-5-pentylcyclopentanone (0.53 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Key Studies: None.

Additional References: RIFM, 2012a; Belsito et al., 2012.

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 2,2,5-trimethyl-5-pentylcyclopentanone or any read across materials. The total systemic exposure to 2,2,5-trimethyl-5-pentylcyclopentanone 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 2,2,5-trimethyl-5-pentylcyclopentanone or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 2,2,5-trimethyl-5-pentylcyclopentanone (0.53 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no reproductive toxicity data on 2,2,5-trimethyl-5-pentylcyclopentanone or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2,2,5-trimethyl-5-pentylcyclopentanone (0.53 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Key Studies: None.

Additional References: RIFM, 2012a; Belsito et al., 2012.

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

10.1.4. Skin sensitization

Based on the existing data and read across to 2-heptylcyclopentanone (CAS # 137-03-1), 2,2,5-trimethyl-5-pentylcyclopentanone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the material specific data and read across to 2-heptylcyclopentanone (CAS # 137-03-1; see Section 5), 2,2,5-trimethyl-5-pentylcyclopentanone does not present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). There are no predictive tests available in animal models for 2,2,5-trimethyl-5-pentylcyclopentanone. However, in guinea pig test methods, read across material 2-heptylcyclopentanone was reported to be a non-sensitizer (Belsito et al., 2012; Klecak, 1979, 1985; RIFM, 1981). Furthermore, in human studies no sensitization reactions were observed to both 2,2,5-trimethyl-5-pentylcyclopentanone and 2-heptylcyclopentanone (RIFM, 1978; RIFM, 1964; RIFM, 2012b; RIFM, 1973). Based on structural analysis, available data and read across to 2-heptylcyclopentanone; 2,2,5-trimethyl-5-pentylcyclopentanone does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/09/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available, *in vivo* experimental data, 2,2,5-trimethyl-5-pentylcyclopentanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra 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} cm^{-1} (Henry et al., 2009). Phototoxicity and photoallergenicity of 3% and 10% 2,2,5-trimethyl-5-pentylcyclopentanone, respectively, were evaluated in guinea pigs; there were no reactions indicative of either phototoxicity or photoallergenicity (RIFM, 1984b; RIFM, 1984a). Based on the lack of absorbance in the critical range, and *in vivo* study data, 2,2,5-trimethyl-5-pentylcyclopentanone would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/03/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2,2,5-trimethyl-5-pentylcyclopentanone, 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 2,2,5-trimethyl-5-pentylcyclopentanone. Based on the Creme RIFM model, the inhalation exposure is 0.0023 mg/day. This exposure is 204 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.

Key Studies: None.

Additional References: None.

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 2,2,5-trimethyl-5-pentylcyclopentanone 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, which is considered proprietary information, 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, 2,2,5-trimethyl-5-pentylcyclopentanone 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) identified 2,2,5-trimethyl-5-pentylcyclopentanone as possibly persistent but not 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.43 mg/l			1,000,000	0.00243 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.273 mg/l	0.897 mg/l	1.634 mg/l	10,000	0.0897 µg/l	Neutral Organic

10.2.2. Risk assessment

Based on current Volume of Use (2011), 2,2,5-trimethyl-5-pentylcyclopentanone presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Bioaccumulation. RIFM, 1986: A bioaccumulation study was conducted in Carp (*Cyprinus carpio*) according to the OECD 305C method under flow-through conditions. The bioconcentration factor (BCF) was 180–402 and 71–341 for 0.01 mg/l and 0.1 mg/l of 2,2,5-trimethyl-5-pentylcyclopentanone, respectively.

10.2.3.2. Ecotoxicity. RIFM, 1986: An acute fish toxicity test was conducted with Orange-red killifish (*Oryzias latipes*) under semi static conditions. The 48-h LC50 was 5.45 mg/l.

10.2.4. Other available data

2,2,5-Trimethyl-5-pentylcyclopentanone has been registered under REACH with the following additional data:

A Ready biodegradability study was conducted according to the OECD 301D method. Biodegradation of 21% was observed after 28 days, and 55% after 84 days.

A bioaccumulation study was conducted in Carp (*Cyprinus carpio*) according to the OECD 305C method under flow-through conditions. The bioconcentration factor (BCF) was between 43 and 883 for 0.01 mg/l and 0.1 mg/l.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static cons. The 48-h EC50 was reported to be 2.9 mg/l.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on the growth rate was reported to be rater than 3.4 mg/l.

10.2.5. Risk assessment refinement

Since 2,2,5-trimethyl-5-pentylcyclopentanone has passed the screening criteria, measured data is included in this document for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.34	4.34
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0897 µg/l. The revised PEC/PNECs for EU and NA are < 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 3/11/17.

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.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.10.009.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.009.

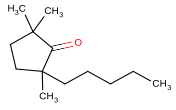
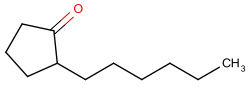
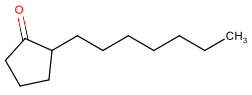
Appendix

Read across justification

Methods

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

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, appropriate read across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated 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).

	Target material	Read across material	
Principal Name	2,2,5-trimethyl-5-pentylcyclopentanone	2-Hexylcuclopentanone	2-Heptylcyclopentanone
CAS No.	65443-14-3	13074-65-2	137-03-1
Structure			
Similarity (Tanimoto score)		0.89	0.86
Read across endpoint		• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{13}H_{24}O$	$C_{11}H_{220}O$	$C_{12}H_{22}O_1$
Molecular Weight	196.34	168.28	182.31
Melting Point (°C, EPISUITE)	53.13	24.92	35.59
Boiling Point (°C, EPISUITE)	257.68	271[a]	263.53
Vapor Pressure (Pa @ 25°C, EPISUITE)	2.17	7.1	2.38
Log Kow (KOWWIN v1.68 in EPISUITE)	4.34	3.9[b]	4.4[d]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	8.956	59.5[c]	91.27
J_{max} (mg/cm^2/h, SAM)	1.151	8.044	13.696
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.76E+001	2.14E+001	2.84E+001
Genotoxicity			

DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Skin Sensitization			
Protein binding by OASIS v1.1	• No alert found		• No alert found
Protein binding by OECD	• No alert found		• No alert found
Protein binding potency	• Not possible to classify (GSH)		• Not possible to classify (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found		• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)		• Sensitizer (good reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	See supplemental data 3

[a] RIFM, 2014b.
[b] RIFM, 2014a.
[c] RIFM, 2014d.
[d] RIFM, 2014c.

Summary

There are insufficient toxicity data on the target material 2,2,5-trimethyl-5-pentylcyclopentanone (CAS # 65443-14-3). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, analogs 2-hexylcyclopentanone (CAS # 13074-65-2) and 2-heptylcyclopentanone (CAS # 137-03-1) were identified as read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale

- For the target material, 2,2,5-trimethyl-5-pentylcyclopentanone (CAS # 65443-14-3), 2-hexylcyclopentanone (CAS # 13074-65-2) was used as a read across analog for the genotoxicity endpoint and 2-heptylcyclopentanone (CAS # 137-03-1) was used as a read across analog for the skin senzitization endpoint.
  - o The target substance and the read across analogs are structurally similar and belong to the structural class of cyclopentanones.
  - o The target substance and the read across analogs share an alkyl-substituted cyclopentanone substructure.
  - o The key difference between the target substance and the read across analog is that the target has a 2,2,5-trimethyl substitution on the cyclopentanone ring, whereas the read across analogs lack it. This structural difference between the target substance and the read across analogs does not affect consideration of the toxicity endpoints.
  - o Similarity between the target substance and the read across analogs are indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical-chemical properties of the target substance and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoints are consistent between the target substance and the read across analogs.
  - o The CAESAR model for skin sensitization predicts the target substance and the read across analog 2-heptylcyclopentanone (CAS # 137-03-1) to be sensitizers. There are no other protein binding alerts for the skin sensitization endpoint. Data described in the skin sensitization section above show that the read across analog does not pose as concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the available data.
  - o The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renkers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Dagli, M.L., Dekant, W., Fryer, A.D., Greim, H., Miyachi, Y., Saurat, J.H., Sipes, I.G., 2012. A toxicologic and dermatologic assessment of cyclopentanones and cyclopentenones when used as fragrance ingredients. Food Chem. Toxicol. 50 (Suppl. 3), S517–S556.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Central J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H.,

Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
ECHA REACH Dossier: 2,2,5-Trimethyl-5-pentylcyclopentanone, https://echa.europa.eu/, accessed 03/2017.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2011. Volume of Use Survey. February 2011. .
Klecak, G., 1979. The Open Epicutaneous Test (OET), a Predictive Test Procedure in the Guinea Pig for Estimation of Allergenic Properties of Simple Chemical Compounds, Their Mixtures and of Finished Cosmetic Preparations. 9/18/79. International Federation Societies Cosmetic Chemists.
Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Problems Dermatol. Curr. Problems Dermatol. 14, 152–171.
OECD, 2012. The OECD QSAR Toolbox. v. 3.4. Retrieved from. http://www.qsartoolbox.org/.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964. Repeated Insult Patch Test with 2-heptylcyclopentanone. Unpublished report from International Flavors and Fragrances. RIFM report number 51019. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1802. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Human Repeated Insult Patch Test with 2,2,5-trimethyl-5-pentylcyclopentanone. Unpublished report from Firmenich Incorporated. RIFM report number 17955. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Guinea pig Skin Sensitisation Test with 2-heptylcyclopentanone. Unpublished report from Quest International. RIFM report number 46130. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984a. Determination of Photoallergenicity of 2,2,5-trimethyl-5-pentylcyclopentanone in Guinea Pigs. Unpublished report from Firmenich Incorporated. RIFM report number 17956. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984b. Determination of Phototoxicity of 2,2,5-trimethyl-5-pentylcyclopentanone in Guinea Pigs. Unpublished report from Firmenich Incorporated. RIFM report number 17957. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1986. Test on Bioaccumulation of 2,5,9-trimethyl-4,9-decadienal in Carp. Unpublished report from Firmenich Incorporated. RIFM report number 40687. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012a. Fragrance Material Review on 2,2,5-trimethyl-5-pentylcyclopentanone. RIFM report number 64499. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012b. Repeated Insult Patch Test with 2-heptylcyclopentanone (Fleuroamone). Unpublished report from International Flavors and Fragrances. RIFM report number 64141. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of 2,2,5-trimethyl-5-pentylcyclopentanone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65409. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Partition Coefficient N-octanol/water of 2-hexylcyclopentanone (Jasmatone). Unpublished report from Givaudan. RIFM report number 67196. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Boiling Point of 2-hexylcyclopentanone (Jasmatone). Unpublished report from Givaudan. RIFM report number 67199. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014c. Partition Coefficient N-octanol/water of 2-heptylcyclopentanone (Heptone). Unpublished report from Givaudan. RIFM report number 67201. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014d. 2-Hexylcyclopentanone (Jasmatone): Water Solubility. [Amendment attached] Unpublished report from Givaudan. RIFM report number 68747. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Use Level Survey. February 2015. .
RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. 2-Hexylcyclopentanone: Bacterial Reverse Mutation Assay. RIFM report number 70059. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. 2-Hexylcyclopentanone: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 70093. RIFM, Woodcliff Lake, NJ, USA.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
US EPA, 2012a. Estimation Programs Interface Suite™ for Microsoft® Windows. v4.0-v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft® Windows. v1.11. United States Environmental Protection Agency, Washington, DC, USA.