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Short review

RIFM fragrance ingredient safety assessment, 3-methyl-2-pentylcyclopentan-1-one, CAS Registry Number 13074-63-0

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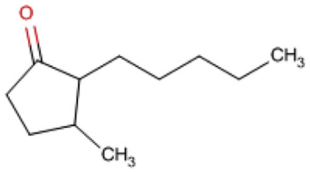


Abbreviation/Definition List:
2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions 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).
*fragrancesafetypanel.org/ 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 (3-methyl-2-pentylcyclopentan-1-one) 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 3-methyl-2-pentylcyclopentan-1-one is not genotoxic. Data from the read across analog 2-heptylcyclopentanone (CAS # 137-03-1) show that 3-methyl-2-pentylcyclopentan-1-one is not a concern for skin sensitization. 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 UV spectra. The environmental endpoints were evaluated, 3-methyl-2-pentylcyclopentan-1-one 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, 2012)
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: Screening Level: 3.1 (Biowin 3) (US EPA, 2012a)
Bioaccumulation: Screening Level: 85.7 l/kg (US EPA, 2012a)

(*continued*)

Ecotoxicity: Screening Level: Fish LC50: 12.93 mg/l	(RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 12.93 mg/l	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.01293 μg/l	
• **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not Applicable; cleared at screening level	

1. Identification

1 **Chemical Name:** 3-Methyl-2-pentylcyclopentan-1-one
2 **CAS Registry Number:** 13074-63-0
3 **Synonyms:** 3-Methyl-2-pentylcyclopentan-1-one; Tetrahydro jasmone; Tetrahydro jasmone [3-methyl-2-pentylcyclopentanone); Tetrahydrojasmone
4 **Molecular Formula:** $C_{11}H_{20}O$
5 **Molecular Weight:** 168.28
6 **RIFM Number:** 6928

2. Physical data

1 **Boiling Point:** 241.13 °C [US EPA, 2012a]
2 **Flash Point:** 200.00 °F TCC (93.33 °C)*
3 **Log K_{OW}:** 3.43 [US EPA, 2012a]
4 **Melting Point:** 21.29 °C [US EPA, 2012a]
5 **Water Solubility:** 73.11 mg/l [US EPA, 2012a]
6 **Specific Gravity:** 0.88000 to 0.89000 @ 25.00 °C*
7 **Vapor Pressure:** 0.0452 mm Hg @ 20 °C [US EPA, 2012a], 0.0691 mm Hg @ 25 °C [US EPA, 2012a]
8 **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 l mol^{-1} cm^{-1})
9 **Appearance/Organoleptic:** Arctander Volume II 1969: Colorless or almost colorless oily liquid. Practically insoluble in water, soluble in alcohol and oils. Fruity-sweet in dilution somewhat floral odor of moderate to poor tenacity. The fruity notes are much more pronounced in the ketone then in dihydrojasmone and the floral notes not nearly as warm-herbaceous.

*http://www.thegoodscentscompany.com/data/rw1050791.html, retrieved 5/21/2015.

3. Exposure

1 **Volume of Use (Worldwide Band):** <0.1 metric tons per year (IFRA, 2011)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.0057% (RIFM, 2014f)
3 **Inhalation Exposure*:** 0.000021 mg/kg/day or 0.0017 mg/day (RIFM, 2014f)
4 **Total Systemic Exposure**:** 0.00019 mg/kg/day (RIFM, 2014f)

*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 **Analogues 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

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)

3-Methyl-2-pentylcyclopentan-1-one 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

Pre-registered for 05/31/2013; no dossier available as of 6/13/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, 3-methyl-2-pentylcyclopentan-1-one does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The material, 3-methyl-2-pentylcyclopentan-1-one, was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014e). There are no studies assessing the mutagenic activity of 3-methyl-2-pentylcyclopentan-1-one; 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 3-methyl-2-pentylcyclopentan-1-one.

There are no studies assessing the clastogenic activity of 3-methyl-2-pentylcyclopentan-1-one; 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 cells with 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 3-methyl-2-pentylcyclopentan-1-one.

Based on the available data, 3-methyl-2-pentylcyclopentan-1-one 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 3-methyl-2-pentylcyclopentan-1-one or any read across materials. The total systemic exposure to 3-methyl-2-pentylcyclopentan-1-one 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 3-methyl-2-pentylcyclopentan-1-one or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-methyl-2-pentylcyclopentan-1-one (0.19 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.

Additional References: 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 3-methyl-2-pentylcyclopentan-1-one or any read across materials. The total systemic exposure to 3-methyl-2-pentylcyclopentan-1-one 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 3-methyl-2-pentylcyclopentan-1-one or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 3-methyl-2-pentylcyclopentan-1-one (0.19 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 3-methyl-2-pentylcyclopentan-1-one or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-methyl-2-pentylcyclopentan-1-one (0.19 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.

Additional References: Belsito et al., 2012.

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

10.1.4. Skin sensitization

Based on the existing data on read across material 2-heptylcyclopentanone (CAS # 137-03-1), 3-methyl-2-pentylcyclopentan-1-one does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization data are available for 3-methyl-2-pentylcyclopentan-1-one. Based on the animal and human studies conducted on read across material 2-heptylcyclopentanone (CAS # 137-03-1; see Section 5), 3-methyl-2-pentylcyclopentan-1-one does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In guinea pig test methods, 2-heptylcyclopentanone was reported to be a non-sensitizer (Belsito et al., 2012; Klecak, 1979, 1985; RIFM, 1981). In human studies, no sensitization reactions were observed to 2-heptylcyclopentanone (RIFM, 1964; RIFM, 2012; RIFM, 1973). Based on structural analysis and read across to 2-heptylcyclopentanone; 3-methyl-2-pentylcyclopentan-1-one 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 available UV/Vis spectra, 3-methyl-2-pentylcyclopentan-1-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. The available UV/Vis spectra for 3-methyl-2-pentylcyclopentan-1-one indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on the lack of absorbance in the critical range, 3-methyl-2-pentylcyclopentan-1-one does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/22/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3-methyl-2-pentylcyclopentan-1-one, 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 3-methyl-2-pentylcyclopentan-1-one. Based on the Creme RIFM model, the inhalation exposure is 0.0017 mg/day. This exposure is 276 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: 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 3-methyl-2-pentylcyclopentan-1-one 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, 3-methyl-2-pentylcyclopentan-1-one was identified as a fragrance material with no 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 (US EPA, 2012a) did not identify 3-methyl-2-pentylcyclopentan-1-one 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 EPISUITE ver 4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3-methyl-2-pentylcyclopentan-1-one does not present a risk to the aquatic compartment in the screening level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data:

3-Methyl-2-pentylcyclopentan-1-one has been pre-registered at 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	12.93 mg/l			1,000,000	0.01293 µg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.43	3.43
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
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 0.01293 µg/l. The revised PEC/PNECs for EU and NA: not applicable; cleared at screening level 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: 6/19/15.

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.2017.08.035.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.08.035.

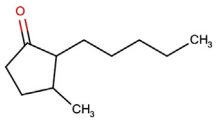
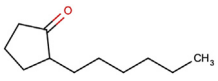
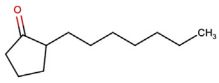
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015) 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 physicochemical 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	3-Methyl-2-pentylcyclopentan-1-one	2-Hexylcyclopentanone	2-Heptylcyclopentanone
CAS No.	13074-63-0	13074-65-2	137-03-1
Structure			
Similarity (Tanimoto score)		0.89	0.86
Read across endpoint		• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{11}H_{20}O$	$C_{11}H_{220}O$	$C_{12}H_{22}O_1$
Molecular Weight	168.28	168.28	182.31
Melting Point (°C, EPISUITE)	21.29	24.92	35.59
Boiling Point (°C, EPISUITE)	241.13	271[1]	263.53
Vapor Pressure (Pa @ 25 °C, EPISUITE)	9.22	7.1	2.38
Log Kow (KOWWIN v1.68 in EPISUITE)	3.43	3.9[2]	4.4[4]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	252.41	59.5[3]	91.27
J_{max} (mg/cm^2/h, SAM)	24.122	8.044	13.696
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.14E+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	

(*continued*)

	Target material	Read across material	
Carcinogenicity (genotox and non-genotox) 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)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3
Rat liver S9 metabolism simulator and structural alerts for metabolites			

1. RIFM, 2014b.
2. RIFM, 2014c.
3. RIFM, 2014a.
4. RIFM, 2014d.

Summary

There are insufficient toxicity data on the target material 3-methyl-2-pentylcyclopentan-1-one (CAS # 13074-63-0). 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, 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 3-methyl-2-pentylcyclopentan-1-one (CAS # 13074-63-0), 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.
  - The target substance and the read across analogs are structurally similar and belong to the structural class of cyclopentanone.
  - The target substance and the read across analogs share an alkyl-substituted cyclopentanone substructure.
  - The key difference between the target substance and the read across analogs is that the read across analogs have a longer aliphatic chain substituted on the cyclopentanone ring than the target substance. This structural difference between the target substance and the read across analogs does not affect consideration of the toxicity endpoints.
  - Similarity between the target substance and the read across analogs are indicated by the Tanimoto scores in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - The physical-chemical properties of the target substance and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target substance and the read across analogs.
  - 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 a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the availability of data.
  - The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

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