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# RIFM fragrance ingredient safety assessment, 3-methyl-2-(n-pentanyl)-2--cyclopenten-1-one, CAS Registry Number 1128-08-1

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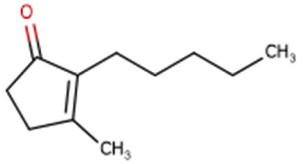


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Name: 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one CAS Registry Number: 1128-08-1

**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

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**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts
**DRF** - Dose Range Finding
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observed 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
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use
**vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

**The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.**

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

**Summary: The existing information supports the use of this material as described in this safety assessment.**

3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from the read-across analog 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4) show that 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data from read-across analog 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4) provided 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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**Human Health Safety Assessment**

**Genotoxicity:** Not expected to be genotoxic. (RIFM, 2015; RIFM, 2017)
**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC.
**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.
**Skin Sensitization:** NESIL = 1100 μg/cm$^2$. RIFM (2011)
**Phototoxicity/Photoallergenicity:** Not phototoxic/not expected to be photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1980)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessment**

**Hazard Assessment:**
**Persistence:**
Critical Measured Value: 70% (OECD 301B) RIFM (1995)
**Bioaccumulation:**
Critical Measured Value: 142 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:**
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.361 mg/L (ECOSAR; US ECHA, 2012b)
**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**
**Screening-level:** PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)
**Critical Ecotoxicity Endpoint:** 48-h *Daphnia magna* LC50: 2.361 mg/L (ECOSAR; US ECHA, 2012b)
**RIFM PNEC is:** 0.2361 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1

## 1. Identification

1. **Chemical Name:** 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one
2. **CAS Registry Number:** 1128-08-1
3. **Synonyms:** 2-Cyclopenten-1-one, 3-methyl-2-pentyl-; Dihydrojasmone; 2-Pentyl-3-methyl-2-cyclopenten-1-one; 1-(2′-メチル-5′-オクソ-1′-シクロペンテニル)ペンタン(又はヘキサン); 3-Methyl-2-pentylcyclopent-2-en-1-one; 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one
4. **Molecular Formula:** $C_{11}H_{18}O$
5. **Molecular Weight:** 166.26 g/mol
6. **RIFM Number:** 296
7. **Stereochemistry:** There is no stereocenter possible.

## 2. Physical data

1. **Boiling Point:** 219 °C (Fragrance Materials Association [FMA]), 250.68 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA), >93 °C (Globally Harmonized System)
3. **Log $K_{OW}$:** 3.77 (EPI Suite)
4. **Melting Point**: 41.22 °C (EPI Suite)
5. **Water Solubility:** 38.82 mg/L (EPI Suite)
6. **Specific Gravity:** 0.917 (FMA)

7. **Vapor Pressure:** 0.014 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA), 0.0298 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless, slightly oily liquid with a floral-like odor (Arctander, 1969)

## 3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.028% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000088 mg/kg/day or 0.0067 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00070 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; and Comiskey et al., 2017).

## 5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

## 6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| II | II | II |

2. Analogs Selected:
   a. **Genotoxicity:** 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization** 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

No relevant data available for inclusion in this safety assessment.

### 7.1. Additional References

None.

## 8. Natural occurrence

3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one is reported to occur in the following foods by the VCF*:

Capers (*Capparis spinoza*)

*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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

## 9. REACH dossier

Pre-registered for 2010; no dossier available as of 12/10/21.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%) |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.085 |
| 2 | Products applied to the axillae | 0.025 |
| 3 | Products applied to the face/body using fingertips | 0.51 |
| 4 | Products related to fine fragrances | 0.47 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5D | Baby cream, oil, talc | 0.12 |
| 6 | Products with oral and lip exposure | 0.28 |
| 7 | Products applied to the hair with some hand contact | 0.96 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.050 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.92 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 3.3 |
| 10B | Aerosol air freshener | 3.3 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 1.8 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | No Restriction |

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one, the basis was the skin sensitization NESIL of 1100 μg/$cm^2$.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

## 11. Summary

### 11.1. Human Health Endpoint Summaries

#### 11.1.1. Genotoxicity

Based on the current existing data, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive criteria: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013c). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential clastogenic effects of the target material.

The mutagenic activity of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one 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 TA1535, TA1537, TA98, TA100, and *Escherichia coli* strains WP2uvrA were treated with 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one 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, 2015). Under the conditions of the study, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one; however, read-across can be made to 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4; see Section VI).

The clastogenic activity of 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG487. Human peripheral blood lymphocytes were treated with 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one in DMSO at concentrations up to 1820 μg/mL in the presence and absence of S9 for 3 and 24 h 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one.

Based on the data available, 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one does not present a concern for genotoxic potential, and this can be extended to 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one.

**Additional References:** RIFM, 2013b; RIFM, 2013c; Sasaki et al., 1989; RIFM, 2003; RIFM, 2013a.

**Literature Search and Risk Assessment Completed On:** 04/23/21.

#### 11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one or any read-across materials. The total systemic exposure to 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.70 μg/kg/day) is below the TTC for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one (9 μg/kg/day; Kroes et al., 2007).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/21/21.

#### 11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one or any read-across materials. The total systemic exposure to 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.70 μg/kg/day) is below the TTC for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/21/21.

#### 11.1.4. Skin sensitization

Based on the existing data and read-across analog 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4), 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is a weak skin sensitizer with a NESIL of 1100 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Limited skin sensitization studies are available for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one. Based on the existing data and read-across 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4; see Section VI), 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is a skin sensitizer with a NESIL of 1100 μg/cm$^2$. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig open epicutaneous test, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one (RIFM, 1972a). In a Confirmation of No Induction in Humans test (CNIH) with 826 μg/cm$^2$ of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2012). In another CNIH with 775 μg/cm$^2$ of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one in ethanol, no reactions indicative of sensitization was observed in any of the 38 volunteers (RIFM, 1972b). In a CNIH with the read-across material, 1/50 subject exhibited 1 reaction at the original site only, and no reactions were observed at naive challenge sites in any of the 50 subjects when 10% 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one in petrolatum was used for (RIFM, 1981). In another CNIH with the read-across material, no reactions indicative of sensitization were observed in any of the 107 volunteers when 1181 μg/cm$^2$ in 3:1 diethyl phthalate:ethanol for induction and challenge (RIFM, 2011).

The available data on the read-across demonstrate that 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is a skin sensitizer with a Weight of Evidence (WoE) NESIL of 1100 μg/cm$^2$. (See Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b).

**Table 1**
Data summary for 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one as read-across for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one.

| LLNA weighted mean EC3 value μg/cm$^2$ [No. Studies] | Potency Classification Based on Animal Data[1] | Human Data | | | |
|---|---|---|---|---|---|
| | | NOEL-CNIH (induction) μg/cm$^2$ | NOEL-HMT (induction) μg/cm$^2$ | LOEL[2] (induction) μg/cm$^2$ | WoE NESIL[3] μg/cm$^2$ |
| N/A | N/A | 1181 | N/A | N/A | 1100 |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; N/A = Not Available.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/15/21.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the UV/Vis absorption spectra and the available *in vivo* study data, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one would not be expected to present a concern for phototoxicity. Based on the UV/Vis absorption spectra, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one would not be expected to present a concern for photoallergenicity.

*11.1.5.1. Risk assessment.* UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Phototoxicity of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one was also evaluated *in vivo* in guinea pigs. A 10% solution of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one in alcohol was applied topically to guinea pigs, followed by UVA or UVB irradiation. There were no phototoxic effects in either group (RIFM, 1980). Based on the *in vivo* study data and the lack of absorbance, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one does not present a concern for phototoxicity. Based on the lack of absorbance, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one would not be expected to present a concern for photoallergenicity.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/14/21.

*11.1.6. Local respiratory toxicity*

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one is below the Cramer Class III* TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0067 mg/day. This exposure is 70.1 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 for the local respiratory toxicity endpoint.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 04/16/21.

*11.2. Environmental Endpoint Summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one 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 v4.11 (US EPA, 2012a) did not identify 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*11.2.2. Risk assessment*

Based on the current Volume of Use (2015), 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one presents a risk to the aquatic compartment in the screening-level assessment.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 6.47 | | | 1000000 | 0.00647 | |
| ECOSAR Acute Endpoints **(Tier 2)** v1.11 | 7.586 | 2.911 | 2.440 | | | Vinyl/Allyl Ketones |
| ECOSAR Acute Endpoints **(Tier 2)** v1.11 | 6.533 | 2.361 | 3.454 | 10000 | 0.2361 | Neutral Organic SAR (Baseline Toxicity) |

*11.2.1.1. Key studies*

*11.2.1.1.1. Biodegradation.* **RIFM, 1995:** A sealed test based on the OECD 301B guideline was conducted to determine the biodegradability of 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one. The biodegradation rate after 28 days was 70.1%.

*11.2.1.1.2. Ecotoxicity.* No data available.

*11.2.1.1.3. Other available data.* 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one has been pre-registered for REACH with no additional data at this time.

*11.2.1.2. 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.

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 3.77 | 3.77 |
| Biodegradation Factor Used | 1 | 1 |
| 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 further assessment is necessary.

The RIFM PNEC is 0.2361 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 04/23/21.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241%26ShowComments=Yes%26sqlstr=null%26recordcount=0%26User_title=DetailQuery%20Results%26EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/10/21.

## Declaration of competing interest

The authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112926.

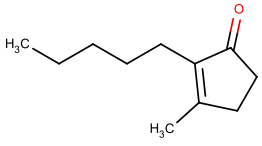
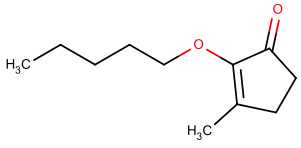
## Appendix

*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | 3-Methyl-2-(n-pentanyl)-2-cyclopenten-1-one | 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one |
| **CAS No.** | 1128-08-1 | 68922-13-4 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 0.50 |
| **Endpoint** | | • Genotoxicity<br>• Skin Sensitization |
| **Molecular Formula** | $C_{11}H_{18}O$ | $C_{11}H_{18}O_2$ |
| **Molecular Weight (g/mol)** | 166.26 | 182.26 |
| **Melting Point (°C, EPI Suite)** | 41.22 | 57.49 |
| **Boiling Point (°C, EPI Suite)** | 250.68 | 268.33 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 3.97 | 1.17 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 38.82 | 144.10 |
| **Log $K_{OW}$** | 3.77 | 3.01 |
| **Jmax (μg/cm$^2$/h, SAM)** | 4.96 | 6.59 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 13.98 | 5.86 |
| **Genotoxicity** | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)** | No alert found | No alert found |
| **DNA Binding (OECD QSAR Toolbox v4.2)** | No alert found | No alert found |
| **Carcinogenicity (ISS)** | α,β-unsaturated carbonyls (Genotox)\|Structural alert for genotoxic carcinogenicity | α,β-unsaturated carbonyls (Genotox)\|Structural alert for genotoxic carcinogenicity |
| **DNA Binding (Ames, MN, CA, OASIS v1.1)** | No alert found | No alert found |
| ***In Vitro* Mutagenicity (Ames, ISS)** | α,β-unsaturated carbonyls | α,β-unsaturated carbonyls |
| ***In Vivo* Mutagenicity (Micronucleus, ISS)** | α,β-unsaturated carbonyls | α,β-unsaturated carbonyls\|H-acceptor-path3-H-acceptor |

(*continued on next page*)

(*continued*)

| | Target Material | Read-across Material |
|---|---|---|
| **Oncologic Classification** | Not classified | Not classified |
| **Skin Sensitization** | | |
| **Protein Binding (OASIS v1.1)** | No alert found | No alert found |
| **Protein Binding (OECD)** | No alert found | No alert found |
| **Protein Binding Potency** | Moderately reactive (GSH)\|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN) | Not possible to classify according to these rules (GSH) |
| **Protein Binding Alerts for Skin Sensitization (OASIS v1.1)** | No alert found | No alert found |
| **Skin Sensitization Reactivity Domains (Toxtree v2.6.13)** | Alert for Schiff base formation identified. | Alert for Schiff base formation identified. |
| **Metabolism** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one (CAS # 1128-08-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 3-methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4) was identified as a read-across material with sufficient data for toxicological evaluation.

*Conclusions*

- 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one (CAS # 68922-13-4) was used as a read-across analog for the target material 3-methyl-2-(n-pentanyl)-2-cyclopenten-1-one (CAS # 1128-08-1) for the genotoxicity and skin sensitization endpoints.
  - The target material and the read-across analog belong to the class of cyclic ketones.
  - The target material and the read-across analog share a 2-cyclopenten-1-one, 3-methyl- fragment.
  - The key difference between the target material and the read-across analog is that the target material has a C5 saturated chain attached to the cyclopentene ring, and the read-across analog has a C5-based pentyloxy fragment attached to the cyclopentene ring. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the 2-cyclopenten-1-one, 3-methyl- fragment.
  - Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There is a structural alert for genotoxic carcinogenicity for both the target material and the read-across analog. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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