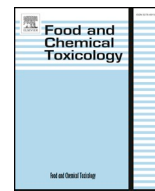




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Short Review

RIFM fragrance ingredient safety assessment, methyl cyclopentylideneacetate, CAS Registry Number 40203-73-4

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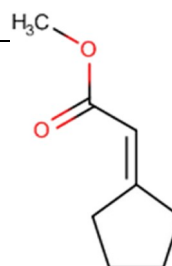
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Version: 020519. This version replaces any previous versions.

Name: Methyl cyclopentylideneacetate CAS Registry Number: 40203-73-4



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

Creame RIFM Model - The Creame 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., 2015, 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

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

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<https://doi.org/10.1016/j.fct.2020.111132>

Received 1 August 2019; Received in revised form 19 November 2019; Accepted 14 January 2020

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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
 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, 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.

Methyl cyclopentylideneacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl cyclopentylideneacetate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to methyl cyclopentylideneacetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for methyl cyclopentylideneacetate for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; methyl cyclopentylideneacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl cyclopentylideneacetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016b; RIFM, 2016a)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not a sensitization concern under the current, declared levels of use. (RIFM (2014a)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:Critical Measured Value: 73% (OECD 301 D) (RIFM (2014b)

Bioaccumulation: Screening-level: 22.61 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 61.59 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 61.59 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.06159 $\mu\text{g/L}$

● Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Methyl cyclopentylideneacetate

2. **CAS Registry Number:** 40203-73-4

3. **Synonyms:** Acetic acid, cyclopentylidene-, methyl ester; シクロピデン (シクロペンチリデン酢酸メチル); シクロピデン (シクロペンチ

リデン酢酸メチル); Cyclopidene; Methyl cyclopentylideneacetate

4. **Molecular Formula:** $\text{C}_8\text{H}_{12}\text{O}_2$

5. **Molecular Weight:** 140.18

6. **RIFM Number:** 5696

7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 186.28 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{ow}:** 2.56 (EPI Suite)
4. **Melting Point:** -15.15 °C (EPI Suite)
5. **Water Solubility:** 547.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.49 mm Hg @ 20 °C (EPI Suite v4.0), 0.711 mm Hg @ 25 °C (EPI Suite)
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:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcohols:** 0.07% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00028 mg/kg/day or 0.021 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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, 2015, 2017; Safford, 2015, 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 I, Low

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

2. Analogs Selected:

- a. **Genotoxicity:** None
- b. **Repeated Dose Toxicity:** None
- c. **Reproductive Toxicity:** None
- d. **Skin Sensitization:** None
- e. **Phototoxicity/Photoallergenicity:** None
- f. **Local Respiratory Toxicity:** None
- g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

6. Metabolism

No relevant data are available for inclusion in this safety assessment.

Additional References:None.

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

Methyl cyclopentylideneacetate is not reported to occur in foods 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 12/18/18 (ECHA, 2015).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, methyl cyclopentylideneacetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of cyclopentylideneacetate 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, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with cyclopentylideneacetate 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 concentration in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, cyclopentylideneacetate was not mutagenic in the Ames test.

The clastogenic activity of cyclopentylideneacetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with cyclopentylideneacetate in DMSO at concentrations up to 1400 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 700 µg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Cyclopentylideneacetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, cyclopentylideneacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, cyclopentylideneacetate does not present a concern for genotoxic potential.

Additional References:None.

Literature Search and Risk Assessment Completed On:01/27/19.

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on methyl cyclopentylideneacetate or on any read-across materials. The total systemic exposure to methyl cyclopentylideneacetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on

methyl cyclopentylideneacetate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl cyclopentylideneacetate (1.2 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References:None.

Literature Search and Risk Assessment Completed On:02/05/19.

10.1.3. Reproductive toxicity

There are no reproductive toxicity data on methyl cyclopentylideneacetate or on any read-across materials. The total systemic exposure to methyl cyclopentylideneacetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl cyclopentylideneacetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl cyclopentylideneacetate (1.2 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References:None.

Literature Search and Risk Assessment Completed On:01/07/19.

10.1.4. Skin sensitization

Based on the existing data, methyl cyclopentylideneacetate does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, methyl cyclopentylideneacetate is not considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0). However, in a murine local lymph node assay, methyl cyclopentylideneacetate was found to be non-sensitizing up to 100% (RIFM, 2014a). In a confirmatory human repeat insult patch test with 10% or 5000 µg/cm² of methyl cyclopentylideneacetate in petrolatum, no reactions indicative of sensitization were observed in any of the 51 volunteers (RIFM, 1977).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, methyl cyclopentylideneacetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References:None.

Literature Search and Risk Assessment Completed On:02/01/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl cyclopentylideneacetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl cyclopentylideneacetate in experimental models. 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 (Henry, 2009). Based on the lack of absorbance, methyl cyclopentylideneacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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, 2009).

Additional References:None.

Literature Search and Risk Assessment Completed On:01/15/19.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for methyl cyclopentylideneacetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on methyl cyclopentylideneacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.021 mg/day. This exposure is 66.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References:None.

Literature Search and Risk Assessment Completed On:01/29/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl cyclopentylideneacetate was performed following the RIFM Environmental Framework (Salvito, 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, methyl cyclopentylideneacetate 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 EPI Suite v4.11 (US EPA, 2012a) did not identify methyl cyclopentylideneacetate as 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, 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl cyclopentylideneacetate presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2014b: The ready biodegradability of the test material was determined in the Closed bottle test according to the OECD 301 D method. Biodegradation of 73% was observed at the end of 28 days.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Methyl cyclopentylideneacetate has been registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>)	EC50 (Algae)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>61.59</u>			1,000,000	0.06159	

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

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	2.56	2.56
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 further assessment is necessary.

The RIFM PNEC is 0.06159 µg/L. The revised PEC/PNECs for EU and North America are: not applicable. The material was cleared at the 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: 01/23/19.

11. 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**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>

[derExplore.jsf](https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf)

- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <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/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=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 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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