Food and Chemical Toxicology 138 (2020) 111272

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone, CAS Registry Number 68133-79-9

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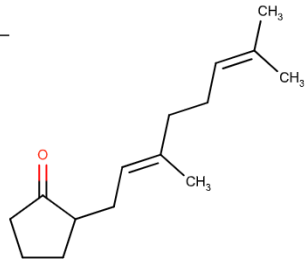
Version: 042919. This version replaces any previous versions.

Name: 2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone
CAS Registry Number: 68133-79-9



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, 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

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https://doi.org/10.1016/j.fct.2020.111272
Received 7 November 2019; Accepted 13 March 2020
Available online 19 March 2020
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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
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.
2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) show that 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone 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 2-(p-menth-1-ene-10-yl)cyclopentanone (CAS # 95962-14-4) show that there are no safety concerns for the target material, 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone, for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone 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 expected to be genotoxic.	(ECHA REACH Dossier: 6,10-Dimethylundeca-5,9-dien-2-one; ECHA, 2012a; 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: Not a concern for skin sensitization under the current, declared levels of use.	(RIFM, 1992; RIFM, 1989)
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:	
Screening-level: 2.7 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 1170 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 0.540 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: 0.540 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00054 μg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

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1. Identification

1. **Chemical Name:** 2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone
2. **CAS Registry Number:** 68133-79-9
3. **Synonyms:** Apritone; Cyclopentanone, 2-(3,7-dimethyl-2,6-octadienyl)-; (E)-2-(3,7-Dimethyl-2,6-octadienyl) cyclopentanone; Decenyl cyclopentanone; 2-(3,7-Dimethylocta-2,6-dien-1-yl)cyclopentanone; 2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone
4. **Molecular Formula:** $C_{15}H_{24}O$
5. **Molecular Weight:** 220.35
6. **RIFM Number:** 1312
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 geometric centers making a total of 8 isomers possible.

2. Physical data

1. **Boiling Point:** 130 °C @ 3 mm (Bedoukian Research), 310.79 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.15 (EPI Suite)
4. **Melting Point**: 36.97 °C (EPI Suite)
5. **Water Solubility:** 1.358 mg/L (EPI Suite)
6. **Specific Gravity:** 0.91 ± 0.01 @ 20 °C (Bedoukian Research)
7. **Vapor Pressure:** 0.000887 mm Hg @ 20 °C (EPI Suite v4.0), 0.00162 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A fresh, apricot fruity note with a hint of kernal character, reminiscent of the ripe fruit

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.015% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00017 mg/kg/day or 0.011 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00077 mg/kg/day (RIFM, 2016)

*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 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and 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)

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** 6,10-Dimethylundeca-5,9-dien-2-one (CAS # 689-67-8)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-(*p*-Menth-1-ene-10-yl)cyclopentanone (CAS # 95962-14-4)
   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)

2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone 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. REACH dossier

2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone has been pre-registered for 2010; no dossier available as of 04/29/19.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone was assessed in the BlueScreen assay and found positive for both cytotoxicity with and without metabolic activation (positive: < 80% relative cell density) and for genotoxicity with metabolic activation (RIFM, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone. However, read-across can be made to 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8; see Section V).

The mutagenic activity of 6,10-dimethylundeca-5,9-dien-2-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 TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6,10-dimethylundeca-5,9-dien-2-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 concentration in the presence or absence of S9 (ECHA, 2012a). Under the conditions of the study, 6,10-dimethylundeca-5,9-dien-2-one was not mutagenic in the Ames test, and this can be extended to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone.

The clastogenic activity of 6,10-dimethylundeca-5,9-dien-2-one 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 6,10-dimethylundeca-5,9-dien-2-one in DMSO at concentrations up to 1943 μg/mL in a DRF study. Micronuclei analysis was conducted at 150 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h 6,10-Dimethylundeca-5,9-dien-2-one 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, 2017). Under the conditions of the study, 6,10-dimethylundeca-5,9-dien-2-one was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/19/19

10.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone or on any read-across materials. The total systemic exposure to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone 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-(3,7-dimethyl-2,6-octadienyl)cyclopentanone or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone (0.77 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 04/04/19

10.1.3. Reproductive Toxicity

There are no reproductive toxicity data on 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone or on any read-across materials. The total systemic exposure to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone (0.77 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 03/28/19

10.1.4. Skin Sensitization

Based on the existing data, 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for the target material 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone. Based on the existing data and the read-across material 2-(*p*-menth-1-ene-10-yl)cyclopentanone (2-(2-(4-methyl-3-cyclohexen-1-yl)propyl)cyclopentanone) (CAS # 95962-14-4; see Section V), is not considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a modified Buehler delayed contact hypersensitivity study, no reactions indicative of skin sensitization were observed. In guinea pigs, a maximization test with the read-across material 2-(*p*-menth-1-ene-10-yl)cyclopentanone did not present reactions indicative of sensitization (ECHA, 2011; RIFM, 1989). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2500 μg/cm^2 of the read-across material 2-(*p*-menth-1-ene-10-yl)cyclopentanone in dimethyl phthalate, no reactions indicative of sensitization were observed in any of the 53 volunteers (RIFM, 1996).

Based on weight of evidence from structural analysis, animal data, and the read-across material 2-(*p*-menth-1-ene-10-yl)cyclopentanone, the target material 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone does not present a safety concern for skin sensitization under the current declared levels of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 04/17/19

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone 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 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone were obtained. The spectra indicate minor 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: 04/16/19

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 42.7 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: Belsito et al., 2012.

Literature Search and Risk Assessment Completed On: 04/08/19

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone 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, 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone 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 2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone 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, 2012b). 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.

10.2.1.1. Risk assessment. Based on current VoU (2015), 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2. Key studies

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.3. Other available data

2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone has been pre-registered for REACH with no additional information at this time.

10.2.4. 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 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>0.540</u>			1000000	0.00054	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.15	5.15
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

The RIFM PNEC is 0.00054 μg/L. The revised PEC/PNECs for EU and NA 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: 03/12/19

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
- **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/oppthpv/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 09/30/19.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111272.

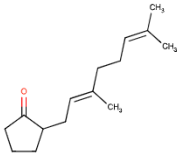
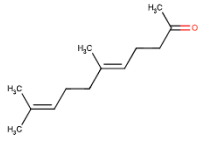
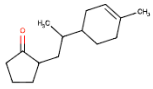
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material	Read-across Material
Principal Name	2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone	6,10-Dimethylundeca-5,9-dien-2-one	2-(p-Menth-1-ene-10-yl)cyclopentanone
CAS No.	68133-79-9	689-67-8	95962-14-4
Structure			
Similarity (Tanimoto Score)		0.69	0.69
Read-across Endpoint		• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{15}H_{24}O$	$C_{13}H_{22}O$	$C_{15}H_{24}O$
Molecular Weight	220.35	194.31	220.35
Melting Point (°C, EPI Suite)	36.97	6.85	68.37
Boiling Point (°C, EPI Suite)	310.79	260.99	308.22
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.215	3.35	0.123
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.15	4.36	5.05
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.358	8.867	1.655
J_{max} (μg/cm^2/h, SAM)	4.802 7.15E+001	7.816 9.20E+001	11.830 3.04E+001

Henry's Law ($Pa \cdot m^3/mol$, Bond Method, EPI Suite)			
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)	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
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	• Not possible to classify according to these rules (GSH)		• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones		• Nucleophilic addition|Nucleophilic addition ≫ Addition to carbon-hetero double bonds|Nucleophilic addition ≫ Addition to carbon-hetero double bonds ≫ Ketones
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone (CAS # 68133-79-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 6,10-dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) and 2-(*p*-menth-1-ene-10-yl)cyclopentanone (CAS # 95962-14-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 6,10-Dimethylundeca-5,9-dien-2-one (CAS # 689-67-8) was used as a read-across analog for the target material 2-(3,7-dimethyl-2,6-octadienyl) cyclopentanone (CAS # 68133-79-9) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of unsaturated ketones.
  - The target material and the read-across analog share a ketone functionality and an extended unsaturated alkyl chain of the same length and 2 vinylene functionalities in the same positions.
  - The key difference between the target material and the read-across analog is that the target material is a cyclic ketone with a multiene chain, whereas the read-across is a multiene ketone. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. 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 a 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.
  - 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.
- 2-(*p*-Menth-1-ene-10-yl)cyclopentanone (CAS # 95962-14-4) was used as a read-across analog for the target material 2-(3,7-dimethyl-2,6-octadienyl)cyclopentanone (CAS # 68133-79-9) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of cyclic ketones.
  - The target material and the read-across analog share a cyclopentanone moiety.
  - The key difference between the target material and the read-across analog is that the target material has a multiene branch in the 2-position, whereas the read-across analog has an alkylcyclic unsaturated branch in the 2-position. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. 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 a 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.
  - The target material and the read-across analog are predicted to have protein binding alerts for skin sensitization by OASIS because of the ketone functionalities. This shows that the alerts for the target material and read-across analog are comparable. However, the 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 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.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

1N, 2N, 3N, 5N, 6N, 7N, 16N, 17N, 19N, 23N, 24N, 25N, 26Y
Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Intermediate (Class II).

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