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# RIFM fragrance ingredient safety assessment, oxacyclopentadec-10-en-2-one, 13-methyl-, CAS Registry Number 329925-33-9

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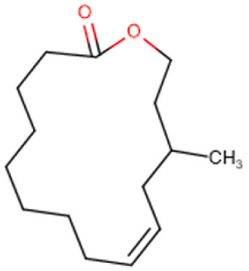



**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Safford et al., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
**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., 2020)
**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** - MOE
**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, 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,

(*continued on next column*)

(*continued*)

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.**

Oxacyclopentadec-10-en-2-one, 13-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that oxacyclopentadec-10-en-2-one, 13-methyl- is not genotoxic. Data on oxacyclopentadec-10-en-2-one, 13-methyl- provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog oxacyclohexadecen-2-one (CAS # 34902-57-3) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across analog oxacyclohexadecen-2-one (CAS # 34902-57-3) provided oxacyclopentadec-10-en-2-one, 13-methyl- a NESIL of 7500 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; oxacyclopentadec-10-en-2-one, 13-methyl- is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to oxacyclopentadec-10-en-2-one, 13-methyl- is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; oxacyclopentadec-10-en-2-one, 13-methyl- 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, 2000c; RIFM, 2003c; RIFM, 2003d) |
| **Repeated Dose Toxicity:** NOAEL = 333 mg/kg/day. | (RIFM, 2003e) |
| **Reproductive Toxicity:** NOAEL = 1000 mg/kg/day. | (RIFM, 2003b; RIFM, 2003a) |
| **Skin Sensitization:** NESIL = 7500 μg/cm$^2$. | RIFM (2016) |
| **Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. | (UV/Vis Spectra; RIFM Database) |
| **Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC. | |

**Environmental Safety Assessment**

| | |
|---|---|
| **Hazard Assessment:** | |
| **Persistence:** | |
| Critical Measured Value: 87% (OECD 301F) | RIFM (2000c) |
| **Bioaccumulation:** | |
| Screening-level: 3118 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Screening-level: 96-h Algae EC50: 0.307 mg/L | (ECOSAR; US EPA, 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, 2002) |
| **Critical Ecotoxicity Endpoint:** 96-h Algae EC50: 0.307 mg/L | (ECOSAR; US EPA, 2012b) |
| **RIFM PNEC is:** 0.0307 μg/L | |

- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

## 1. Identification

1. **Chemical Name:** Oxacyclopentadec-10-en-2-one, 13-methyl-
2. **CAS Registry Number:** 329925-33-9
3. **Synonyms:** Nirvanolide; Oxacyclopentadec-10-en-2-one, 13-methyl-
4. **Molecular Formula:** $C_{15}H_{26}O_2$
5. **Molecular Weight:** 238.37
6. **RIFM Number:** 6649
7. **Stereochemistry:** Isomer not specified. One chiral center and geometric center are present. Two enantiomers are possible.

## 2. Physical data

1. **Boiling Point:** 361.57 (EPI Suite)
2. **Flash Point:** Not Available
3. **Log $K_{OW}$:** 5.8/6.0 (RIFM, 2000b)
4. **Melting Point:** 25.81 °C (EPI Suite)
5. **Water Solubility:** 2.148 (mg/L, at 25 °C, WSKOW v1.42 in EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00919 (Pa 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:** Not Available

## 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 v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.68% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00018 mg/kg/day or 0.012 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0045 mg/kg/day (RIFM, 2019)

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

## 5. Derivation of systemic absorption

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

## 6. Computational toxicology evaluation

### 6.1. Cramer Classification

Class I, Low* (Expert Judgment).

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

*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 Appendix below for further detail.

### 6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
d. **Skin Sensitization:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

### 6.3. Read-across justification

See Appendix below.

## 7. Metabolism

No relevant data are available for inclusion in this safety assessment. **Additional References:** None.

## 8. Natural occurrence

Oxacyclopentadec-10-en-2-one, 13-methyl- 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.

## 9. REACH Dossier

Available (ECHA, 2012b).

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for oxacyclopentadec-10-en-2-one, 13-methyl- are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.58 |
| 2 | Products applied to the axillae | 0.17 |
| 3 | Products applied to the face/body using fingertips | 2.5 |
| 4 | Products related to fine fragrances | 3.2 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.82 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.82 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.82 |
| 5D | Baby cream, oil, talc | 0.27 |
| 6 | Products with oral and lip exposure | 0.83 |
| 7 | Products applied to the hair with some hand contact | 4.2 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.27 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 6.3 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.83 |
| 10B | Aerosol air freshener | 18 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.27 |
| 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 oxacyclopentadec-10-en-2-one, 13-methyl-, the basis was the reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 7500 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).

[c] Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data, oxacyclopentadec-10-en-2-one, 13-methyl- does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* The mutagenic activity of oxacyclopentadec-10-en-2-one, 13-methyl- 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 and the preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with oxacyclopentadec-10-en-2-one, 13-methyl- in ethanol 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, 2000c). Under the conditions of the study, oxacyclopentadec-10-en-2-one, 13-methyl- was not mutagenic in the Ames test.

The clastogenic potential of oxacyclopentadec-10-en-2-one, 13-methyl- was evaluated in an *in vitro* as well as *in vivo* study. Oxacyclopentadec-10-en-2-one, 13-methyl- was not clastogenic in cultured V-79 cells in the absence of S9 metabolic activation; however, a clastogenic effect was observed in the presence of S9 metabolic activation in an *in vitro* chromosomal aberration study (RIFM, 2003c). In an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474, oxacyclopentadec-10-en-2-one, 13-methyl- was administered via oral gavage in corn oil to groups of NMRI mice at doses up to 2000 mg/kg bodyweight. No evidence of a clastogenic effect was observed in the bone marrow of NMRI mice in any of the conditions tested (RIFM, 2003d). Under the conditions of the study, oxacyclopentadec-10-en-2-one, 13-methyl- was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, oxacyclopentadec-10-en-2-one, 13-methyl- does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/11/21.

#### 11.1.2. Repeated dose toxicity

The margin of exposure for oxacyclopentadec-10-en-2-one, 13-methyl- is adequate for the repeated dose toxicity at the current level of use.

*11.1.2.1. Risk assessment.* There are sufficient repeated dose toxicity data on oxacyclopentadec-10-en-2-one, 13-methyl- for the repeated dose toxicity endpoint. An OECD 407 gavage 28-day toxicity study was conducted in rats. Groups of 5 SPF-bred Wistar rats/sex/dose were administered via gavage the test material, oxacyclopentadec-10-en-2-one, 13-methyl-, at doses of 0, 50, 200, or 1000 mg/kg/day in a PEG 300 vehicle for 28 days. Two recovery groups of 5 rats/sex were added to the control and 1000 mg/kg/day groups and then maintained without treatment for 14 days. There was no difference in organ weights when compared to controls, and macroscopic and microscopic examinations showed no adverse effects. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003e).

A default safety factor of 3 (ECHA, 2012a) was used when deriving a NOAEL from a 28 day 407 study. The safety factor has been approved by The Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the oxacyclopentadec-10-en-2-one, 13-methyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the oxacyclopentadec-10-en-2-one, 13-methyl-NOAEL in mg/kg/day by the total systemic exposure to oxacyclopentadec-10-en-2-one, 13-methyl-, 333/0.0045, or 74000.

In addition, the total systemic exposure to oxacyclopentadec-10-en-2-one, 13-methyl- (4.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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) and a reference dose of 3.33 mg/kg/day.

*11.1.2.1.1. Derivation of reference dose (RfD).* The reference dose for oxacyclopentadec-10-en-2-one, 13-methyl- was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/05/21.

#### 11.1.3. Reproductive toxicity

The margin of exposure for oxacyclopentadec-10-en-2-one, 13-methyl- is adequate for the developmental toxicity and fertility endpoints at the current level of use.

*11.1.3.1. Risk assessment.* There are no developmental toxicity data for oxacyclopentadec-10-en-2-one, 13-methyl-. Read-across material, oxacyclohexadecen-2-one (CAS # 34902-57-3, see Section VI), has sufficient developmental toxicity data. An OECD 414/GLP gavage developmental toxicity study was conducted in rats. Groups of 24 mated Sprague Dawley CD strain female rats/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose from days 5–19 of gestation. There were no significant treatment-related effects on fetal viability, growth, and development up to the highest dose tested. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003b). **Therefore, the oxacyclopentadec-10-en-2-one, 13-methyl- MOE for the developmental toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to oxacyclopentadec-10-en-2-one, 13-methyl-, 1000/0.0045, or 222222.**

There are no fertility data on oxacyclopentadec-10-en-2-one, 13-methyl-. Read-across material, oxacyclohexadecen-2-one (CAS # 34902-57-3, see Section VI), has sufficient fertility data. An OECD 415/GLP gavage 1-generation reproductive toxicity study was conducted in rats. Groups of 28 Sprague Dawley Crl:CD(SD) IGS BR strain rats/sex/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose daily, throughout pre-mating, mating, gestation, and lactation. The males were dosed for 72 days, and females were dosed for 16 days prior to mating. There were no effects on the reproductive organs, fertility, and

mating performance up to the highest dose tested. Thus, the NOAEL for fertility was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003a). **Therefore, the oxacyclopentadec-10-en-2-one, 13-methyl- MOE for the fertility endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to oxacyclopentadec-10-en-2-one, 13-methyl-, 1000/0.0045, or 222222.**

In addition, the total systemic exposure to oxacyclopentadec-10-en-2-one, 13-methyl- (4.5 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** RIFM, 2011a; RIFM, 2011b; RIFM, 1995.

**Literature Search and Risk Assessment Completed On:** 01/16/21.

*11.1.4. Skin sensitization*

Based on the existing data and read-across to oxacyclohexadecen-2-one (CAS # 34902-57-3), oxacyclopentadec-10-en-2-one, 13-methyl- was assigned a NESIL of 7500 μg/cm$^2$, and the maximum acceptable concentrations in finished products are provided in Section 10.

*11.1.4.1. Risk assessment.* Limited data are available on the skin sensitization potential of Oxacyclopentadec-10-en-2-one, 13-methyl-. Therefore, a structurally related material, oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section 6) was used for the risk assessment of xacyclopentadec-10-en-2-one, 13-methyl-. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across oxacyclohexadecen-2-one was found to be sensitizing with an EC3 value of 35% (8750 μg/cm$^2$) (RIFM, 2010). However, in guinea pig studies, oxacyclopentadec-10-en-2-one, 13-methyl- and oxacyclohexadecen-2-one did not result in reactions classifiable as sensitization (RIFM, 2001d; RIFM, 1992; RIFM, 1997b; RIFM, 2004). In a Confirmation of No Induction in Humans test (CNIH), no sensitization reactions were observed to oxacyclopentadec-10-en-2-one, 13-methyl- (RIFM, 2002). In a CNIH, no sensitization reactions were observed when 6.4% or 7559 μg/cm$^2$ oxacyclohexadecen-2-one in 1:3 ethanol:diethyl phthalate (EtOH:DEP) was used for induction and challenge (RIFM, 2016). Additionally, no reactions were observed in another CNIH when 15% or 7500 μg/cm$^2$ oxacyclohexadecen-2-one in diethyl phthalate was used for induction and challenge (RIFM, 1997a).

Based on the available data on oxacyclohexadecen-2-one, summarized in Table 1, oxacyclopentadec-10-en-2-one, 13-methyl- was assigned a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 7500 μg/cm$^2$. 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) and a reference dose of 3.33 mg/kg/day.

**Table 1**
Data Summary for oxacyclohexadecen-2-one as read-across to oxacyclopentadec-10-en-2-one, 13-methyl-.

| 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$^2$ |
| 875 [1] | Weak | 7559 | NA | NA | 7500 |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = 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:** 02/14/21.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, oxacyclopentadec-10-en-2-one, 13-methyl- would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no phototoxicity studies available for oxacyclopentadec-10-en-2-one, 13-methyl- in experimental models. 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, 2009). Based on the lack of significant absorbance, oxacyclopentadec-10-en-2-one, 13-methyl- does not present a concern for phototoxicity or 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, 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/09/21.

*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 oxacyclopentadec-10-en-2-one, 13-methyl- is below the Cramer Class I TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on oxacyclopentadec-10-en-2-one, 13-methyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 116.7 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:** 02/12/21.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of oxacyclopentadec-10-en-2-one, 13-methyl- 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, oxacyclopentadec-10-en-2-one, 13-methyl- 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) identified oxacyclopentadec-10-en-2-one, 13-methyl- as not possibly persistent but 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, 2012a). 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 v4.1). 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), oxacyclopentadec-10-en-2-one, 13-methyl- presents a risk to the aquatic compartment in the screening-level assessment.

#### 11.2.2.1. Key studies

*11.2.2.1.1. Biodegradation.* **RIFM, 2000a:** The Ready Biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of this study, biodegradation of 87% was observed after 28 days.

*11.2.2.1.2. Ecotoxicity.* **RIFM, 2001a:** A 72-h algae growth inhibition test was conducted according to the OECD 201 guidelines. Under the conditions of this study, test material affected the growth of this freshwater alga species significantly at WAFs prepared at loadings higher than 10 mg/L.

**RIFM, 2001b:** A 96-h fish toxicity test was conducted with Carp (*Cyprinus carpio*) following the OECD 203 guidelines under flow-through conditions. Under the conditions of this study, the 96-h LC50 for carp exposed to test material exceeded the average exposure concentration of 0.884 ± 0.224 mg/L and thus also the maximum solubility of 0.6 mg/L.

**RIFM, 2001c:** A 48-h acute toxicity study was conducted with *Daphnia magna* neonates (less than 3 days old) following the OECD 203 method. Under the conditions of this study, the test material did not induce acute immobilization of *Daphnia magna* at or below an average exposure concentration of 0.686±0.062 mg/L (target concentration of 1.0 mg/L). The 48-h EC50 for *Daphnia magna* exposed to test material was above its solubility limit (0.6 mg/L) in an ISO-test medium.

*11.2.2.1.3. Other available data.* Oxacyclopentadec-10-en-2-one, 13-methyl- has been registered for REACH with the following additional information available at this time (ECHA, 2012b):

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 value based on measured concentration for growth rate was reported to be > 0.859 mg/L.

### 11.2.3. Risk assessment refinement

Since oxacyclopentadec-10-en-2-one, 13-methyl- passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 0.159 | | | 1,000,000 | 0.000159 | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 0.731 | 1.124 | 0.307 | 10,000 | 0.0307 | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 0.589 | 0.434 | 0.943 | | | Neutral Organics |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{OW}$ used | 5.9 | 5.9 |
| 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 class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.0307 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:** 02/05/21.

## 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&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 11/12/21.

## 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.2022.113248.

## Appendix

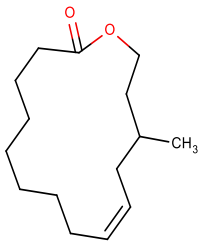
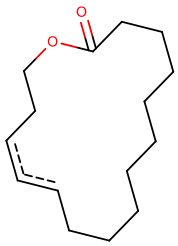
*Read-across justification*

*Methods*

The read-across analog was 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 substance 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 choice of the alert system.

| | Target material | Read-across material |
|---|---|---|
| **Principal Name** | Oxacyclopentadec-10-en-2-one, 13-methyl- | Oxacyclohexadecen-2-one |
| **CAS No.** | 329925-33-9 | 34902-57-3 |
| **Structure** |  |  |
| **Similarity (Tanimoto score)** | | 0.98 |
| **Read-across endpoint** | | • Skin Sensitization<br>• Reproductive toxicity |
| **Molecular Formula** | $C_{15}H_{26}O_2$ | $C_{15}H_{28}O_2$ |
| **Molecular Weight** | 238.37 | 240.39 |
| **Melting Point (°C, EPI Suite)** | 25.81 | 26.06 |
| **Boiling Point (°C, EPI Suite)** | 361.57 | 364.47 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 0.00919 | 0.00689 |
| **Log KOW (KOWWIN v1.68 in EPI Suite)** | 4.81 | 6.15 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 2.148 | 0.1484 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 1.561 | 1.451 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 2.06E+002 | 2.35E+002 |
| ***Reproductive toxicity*** | | |
| **ER Binding by OECD QSAR Tool Box (3.4)** | • Non-binder, without OH or $NH_2$ group | • Non-binder, without OH or $NH_2$ group |
| **Developmental Toxicity Model by CAESAR v2.1.6** | • Non-toxicant (low reliability) | • Non-toxicant (moderate reliability) |
| ***Skin Sensitization*** | | |
| **Protein binding by OASIS v1.1** | • No alert found | • No alert found |
| **Protein binding by OECD** | • Acylation | • Acylation |
| **Protein binding potency** | • Not possible to classify (GSH) | • Not possible to classify (GSH) |
| **Protein binding alerts for skin sensitization by OASIS v1.1** | • No alert found | • No alert found |
| **Skin Sensitization model (CAESAR) (version 2.1.6)** | • Sensitizer (good reliability) | • Sensitizer (good reliability) |
| ***Metabolism*** | | |
| **OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on the oxacyclopentadec-10-en-2-one, 13-methyl- (CAS # 329925-33-9). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, oxacyclohexadecen-2-one (CAS # 34902-57-3) was identified as a read-across material with sufficient data for toxicological evaluation.

*Conclusions*

- Oxacyclohexadecen-2-one (CAS # 34902-57-3) was used as a read-across analog for the target material oxacyclopentadec-10-en-2-one, 13-methyl- (CAS # 329925-33-9) for the skin sensitization and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of macrocyclic lactones.
  - o The target substance and the read-across analog share a carbon macrocyclic ester structure with a double bond.
  - o The key difference between the target substance and the read-across analog is that the target substance has an isolated double bond, an exocyclic methyl substituent, which the read-across analog lacks. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. There are no other protein binding alerts for skin sensitization. The data described in the skin sensitization section show that the read-across analog does not pose a

concern for the skin sensitization endpoint. Therefore, the prediction will be superseded by the availability of the data.

o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

*Explanation of Cramer Classification*

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).

Q1. A 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? **Yes**
Q8. Lactone or cyclic diester? **Yes**
Q9. Lactone, fused to another ring, or 5- or 6-membered alpha,beta-unsaturated lactone? **No**
Q20. Is the structure a linear or simply branched (I) aliphatic (A) compound containing any one or combination of the following functional groups: 4 or less of alcohol, aldehyde, carboxylic acid or esters, and or one or more of the following: acetal, ketone or ketal (not both), mercaptan, sulfide, thioester, polyoxyethylene or primary or tertiary amine? **Yes**
Q21. 3 or more different functional groups? **No**
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No Class I (Class Low)**

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