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RIFM fragrance ingredient safety assessment, 13-methyloxacyclopentadecan-2-one, CAS Registry Number 868846-58-6

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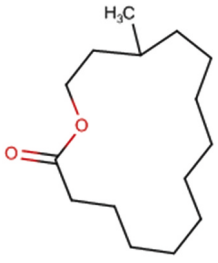

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 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.

13-Methyloxacyclopentadecan-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data and read-across to hexadecanolide (CAS # 109-29-5) show that 13-methyloxacyclopentadecan-2-one is not expected to be genotoxic. Data on read-across oxacyclohexadecen-2-one (CAS 34902-57-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog ω-pentadecalactone (CAS # 106-02-5) provide 13-methyloxacyclopentadecan-2-one a No Expected Sensitization Induction Level (NESIL) of 5500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV/Vis) spectra; 13-methyloxacyclopentadecan-2-one is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). For the hazard assessment based on the screening data, 13-methyloxacyclopentadecan-2-one is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 13-methyloxacyclopentadecan-2-one was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2006c; RIFM, 1999a; RIFM, 1999b)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (1998a)
Reproductive Toxicity: Developmental toxicity NOAEL: 1000 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	(RIFM, 2003b; RIFM, 2003a)
Skin Sensitization: NESIL = 5500 μg/cm^2.	(RIFM, 2006a; RIFM, 1983)
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: 83% (OECD 301C)	RIFM (2006b)

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Bioaccumulation:
Screening-level: 4774 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Not applicable
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards
Risk Assessment:
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** 13-Methyloxacyclopentadecan-2-one
2. **CAS Registry Number:** 868846-58-6
3. **Synonyms:** Oxacyclopentadecan-2-one, 13-methyl-; 13-Methyloxacyclopentadecan-2-one
4. **Molecular Formula:** $C_{15}H_{28}O_2$
5. **Molecular Weight:** 240.38 g/mol
6. **RIFM Number:** 7328
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 360.04 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 6.08 (EPI Suite)
4. **Melting Point**: 25.03 °C (EPI Suite)
5. **Water Solubility:** 0.1715 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 7.61E-005 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <1.0 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.000099 mg/kg/day or 0.0071 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2019)

*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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low* (Expert Judgment)

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

*See Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** Hexadecanolide (CAS # 109-29-5)
   b. **Repeated Dose Toxicity:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
   c. **Reproductive Toxicity:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
   d. **Skin Sensitization:** ω-Pentadecalactone (CAS # 106-02-5)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

13-Methyloxacyclopentadecan-2-one 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

Not pre-registered; no dossier available as of 12/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for

13-methyloxacyclopentadecan-2-one 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)	0.42
2	Products applied to the axillae	0.13
3	Products applied to the face/body using fingertips	2.5
4	Products related to fine fragrances	2.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.60
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.60
5D	Baby cream, oil, talc	0.20
6	Products with oral and lip exposure	1.4
7	Products applied to the hair with some hand contact	4.8
8	Products with significant ano-genital exposure (tampon)	0.20
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.6
10A	Household care products with mostly hand contact (hand dishwashing detergent)	17
10B	Aerosol air freshener	17
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.20
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 13-methyloxacyclopentadecan-2-one, the basis was the subchronic reference dose of 10 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 5500 μg/cm^2.

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

[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, 13-methyloxacyclopentadecan-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 13-methyloxacyclopentadecan-2-one has been evaluated in a bacterial reverse mutation assay conducted using the preincubation method with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2006c). Under the conditions of the study, 13-methyloxacyclopentadecan-2-one was not mutagenic in the Ames test.

As an additional weight of evidence (WoE), the mutagenic activity of read-across hexadecanolide (CAS # 109-29-5) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with hexadecanolide in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1999a). Under the conditions of the study, hexadecanolide was not mutagenic in the Ames test, and this can be extended to 13-methyloxacyclopentadecan-2-one.

There are no studies assessing the clastogenic activity of 13-methyloxacyclopentadecan-2-one; however, read-across can be made to hexadecanolide (CAS # 109-29-5; see Section VI).

The clastogenicity of hexadecanolide was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with hexadecanolide in DMSO at concentrations up to 2000 μg/mL in the presence and absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test material, either with or without S9 metabolic activation (RIFM, 1999b). Under the conditions of the study, hexadecanolide was considered to be non-clastogenic to human cells, and this can be extended to 13-methyloxacyclopentadecan-2-one.

Based on the data available, hexadecanolide does not present a concern for genotoxic potential, and this can be extended to 13-methyloxacyclopentadecan-2-one.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for 13-methyloxacyclopentadecan-2-one is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data for 13-methyloxacyclopentadecan-2-one. Read-across material oxacyclohexadecen-2-one (CAS 34902-57-3; see Section VI) has sufficient data for the repeated dose toxicity endpoint. An OECD 408 gavage 90-day subchronic toxicity study was conducted in rats. Groups of 15 Sprague Dawley Crl:CD 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 for 90 days. Two recovery groups of 10 rats/sex were gavaged with 0 or 1000 mg/kg/day for 90 days and then maintained without treatment for a further 28 days. There were no treatment-related mortalities or toxicologically significant changes in any of the parameters measured during the study. One male rat treated with 1000 mg/kg/day was found dead on day 34 and another at the same dose on day 85. The NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 1998a).

In a 4-week gavage toxicity study followed by a 2-week recovery period conducted in rats, groups of 6 Crl:CD(SD)BR strain (VAF plus) rats/sex/dose were administered oxacyclohexadecen-2-one via gavage at doses of 0, 500, 750, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose. Two recovery groups of 6 rats/sex were added to the control and highest-dose group and then maintained without treatment for 2 weeks. There were no treatment-related effects up to the highest dose tested; therefore, the NOEL for systemic toxicity was considered to be 1000 mg/kg/day (RIFM, 1996).

In another OECD 407/GLP gavage 28-day toxicity study followed by a 2-week recovery period conducted in rats, groups of 5 Crl:CD rats/sex/dose were administered oxacyclohexadecen-2-one (Globalide) via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in 0.8% aqueous hydroxypropylmethylcellulose gel for 28 days. Two recovery groups of 5 rats/sex were added to the control and highest-dose group and then maintained without treatment for 2 weeks. Salivation was observed in males and females treated at 1000 mg/kg/day, which began 3 min after test material administration and lasted for 30 min. Apart from salivation, no other effects on functional, hematological, clinical, and pathological parameters were observed. The NOAEL for systemic toxicity was

considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2005).

A NOAEL of 1000 mg/kg/day from the OECD 408 study was considered for this safety assessment.

Therefore, the 13-methyloxacyclopentadecan-2-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to 13-methyloxacyclopentadecan-2-one, 1000/0.0053, or 188679.

In addition, the total systemic exposure to 13-methyloxacyclopentadecan-2-one (5.3 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.

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 subchronic reference dose (RfD) of 10 mg/kg/day.

11.1.2.1. Derivation of subchronic RfD. The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for 13-methyloxacyclopentadecan-2-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 1000 mg/kg/day by the uncertainty factor, 100 = 10 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/24/21.

11.1.3. Reproductive toxicity

The MOE for 13-methyloxacyclopentadecan-2-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on 13-methyloxacyclopentadecan-2-one. Read-across material oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section VI) has sufficient developmental toxicity data that can be used for the developmental toxicity endpoint. An OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley CD rats. Groups of 24 rats/dose were administered oxacyclohexadecen-2-one via oral gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose from gestations days (GDs) 5–19. Pregnant females were euthanized on GD 20, and their uterine content was examined. No mortality was reported during the study. There were no treatment-related adverse effects observed for body weight, food consumption, clinical observations, or gravid uterus and placental weight; no significant changes were reported for the number of pregnancies, corpora lutea, implantations, or litter size. At 1000 mg/kg/day, there was a non-statistically significant and non-dose-dependent increase in pre-implantation loss when compared to controls, and without any effects on post-implantation loss or live litter size at any of the tested doses, this finding was not considered to be adverse. Fetal body weights were dose-dependently increased and reached statistical significance at 1000 mg/kg/day when compared to controls. There were no treatment-related changes in fetal viability, growth, and development, including the type of incidences of visceral or skeletal anomalies, observed. Therefore, the increased fetal body weight at the highest dose was not considered to be adverse since subsequent fetal evaluations (particularly the evaluation of skeletal development) did not indicate any significant precocious development of fetuses. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003b).

There are no fertility data on 13-methyloxacyclopentadecan-2-one. Read-across material oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section VI) has sufficient fertility data that can be used for the fertility endpoint. An OECD 415/GLP 1-generation reproduction study was conducted in Sprague Dawley Crl:CD(SD) IGS BR strain rats. Groups of 28 rats/sex/dose were administered oxacyclohexadecen-2-one via oral gavage at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose. Males and females were dosed for 72 and 16 days, respectively, prior to pairing and continued throughout mating, gestation, and lactation. At weaning of pups on day 21, all parental animals and pups were euthanized and examined macroscopically, whereas reproductive organs and tissues of control and high-dose group parental animals were examined microscopically. Two mid-dose males were found dead during the mating/post-mating period. Macroscopic examination of the 2 deceased males revealed changes in the lungs that were attributed to dosing trauma. At 1000 mg/kg/day, pup body weight was significantly higher than the controls at day 1 postpartum, and the group mean time to completion of incisor eruption was statistically significantly lower than the controls but were within 10% of control values. Additionally, pup body weights from the high-dose group animals were similar to controls and all treatment groups by days 7–21 postpartum. Therefore, these findings were not considered to be treatment-related. There were no treatment-related adverse effects observed in parental body weights, food consumption, mating performance, fertility, gestation, parturition, litter size at birth, viability, and subsequent growth and development of pups. The NOAEL for fertility effects and on the development of pups was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003a).

Since both OECD 414 and 415 studies did not indicate any treatment-related effects observed in the mating performance (OECD 415 study only) and growth and development of pups up to the highest dose tested, the reproductive toxicity NOAEL was considered to be 1000 mg/kg/day. **Therefore, the 13-methyloxacyclopentadecan-2-one MOE for the reproductive toxicity endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to 13-methyloxacyclopentadecan-2-one, 1000/0.0053, or 188679.**

In addition, the total systemic exposure to 13-methyloxacyclopentadecan-2-one (5.3 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: 03/24/21.

11.1.4. Skin sensitization

Based on the existing data on the read-across material, ω-pentadecalactone (CAS # 106-02-5), 13-methyloxacyclopentadecan-2-on, is a skin sensitizer with a defined NESIL of 5500 μg/cm^2.

11.1.4.1. Risk assessment. No skin sensitization studies are available for oxacyclotridecan-2-one. Based on the data on the read-across material ω-pentadecalactone (CAS # 106-02-5; see Section VI), 13-methyloxacyclopentadecan-2-one is a skin sensitizer. The chemical structures of these molecules indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; OECD Toolbox v4.2; Toxtree v3.1.0). Read-across material ω-pentadecalactone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the human cell line activation test (h-CLAT) (RIFM, 2016a; RIFM, 2016b; RIFM, 2018). In a murine local lymph node assay (LLNA) with the read-across material, a range of EC3 values were observed with various qualities of the sample (RIFM, 2009b; RIFM, 2010b; RIFM, 2010a; RIFM, 2009a). The positive results in the LLNA may be due to unidentified impurities that have the potential to induce sensitization. In an LLNA carried out on a purified read-across material, no sensitization potential was observed up to the highest tested concentration of 50% or 12500 μg/cm^2 (RIFM, 2010a). In 2 guinea pig maximization tests, the read-across material was not predicted to be a

Table 1
Data Summary for ω-pentadecalactone as a read-across for 13-methyloxacyclopentadecan-2-one.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>12,500 [a]	Weak	5500	6900	NA	5500

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.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

sensitizer (RIFM, 1997; RIFM, 1995). In a Confirmation of No Induction in Human test (CNIH) with the read-across material, no reactions indicative of sensitization were observed when 10% or 5510 μg/cm^2 ω-pentadecalactone in 3:1 ethanol:diethyl phthalate was used for induction and challenge (RIFM, 2006a). In another CNIH with 20% ω-pentadecalactone in 1:1 ethanol:diethylphthalate, 1/50 volunteers exhibited a sensitization reaction (RIFM, 1998b). The quality of the tested sample was not investigated for the potential presence of impurities. In a human maximization test with 10% ω-pentadecalactone (6900 μg/cm^2), no sensitization reactions were observed (RIFM, 1974).

The Expert Panel for Fragrance Safety concluded that given that the impurities remain unidentified in the read-across material, a NESIL based on the CNIH results of the commercial material should be adopted. The available data on the read-across material demonstrates it is a sensitizer with a Weight of Evidence (WoE) NESIL of 5500 μg/cm^2 (Table 1), and the same NESIL is applied for the target material, 13-methyloxacyclopentadecan-2-one. 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 10 mg/kg/day.

Additional References: None.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 13-methyloxacyclopentadecan-2-one 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 13-methyloxacyclopentadecan-2-one 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 absorbance, 13-methyloxacyclopentadecan-2-one 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: 05/03/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 13-methyloxacyclopentadecan-2-one 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 13-methyloxacyclopentadecan-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0071 mg/day. This exposure is 197.2 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: 04/19/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 13-methyloxacyclopentadecan-2-one 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, 13-methyloxacyclopentadecan-2-one was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 13-methyloxacyclopentadecan-2-one as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in

the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Not Applicable.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2006b: The ready biodegradability of the test material was evaluated using the modified MITI test according to the OECD 301 C guideline. Biodegradation of 85% was observed after 28 days.

11.2.2.2. Ecotoxicity. Not available.

11.2.2.3. Other available data. 13-Methyloxacyclopentadecan-2-one has not been registered for REACH.

11.2.2.4. Risk assessment refinement. Not applicable.

Literature Search and Risk Assessment Completed On: 04/20/21.

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 12/10/21.

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.2022.112916.

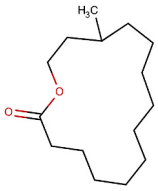
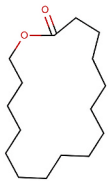
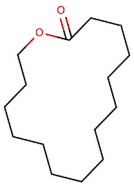
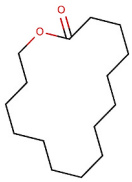
Appendix

Read-across Justification

Methods

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

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

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	13-Methyloxacyclopentadecan-2-one	Hexadecanolide	*ω*-Pentadecalactone	Oxacyclohexadecen-2-one
CAS No.	868846-58-6	109-29-5	106-02-5	34902-57-3
Structure				
Similarity (Tanimoto Score)		0.56	0.56	0.56
Endpoint		• Genotoxicity	• Skin sensitization	• Reproductive toxicity • Repeated dose toxicity
Molecular Formula	$C_{15}H_{28}O_2$	$C_{16}H_{30}O_2$	$C_{15}H_{28}O_2$	$C_{15}H_{28}O_2$
Molecular Weight (g/mol)	240.39	254.41	240.39	240.39
Melting Point (°C, EPI Suite)	25.03	33.75	32.00	32.00
Boiling Point (°C, EPI Suite)	360.04	377.14	364.47	364.47
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.01	0.00	0.01	0.01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.17	0.05	0.15	0.15
Log K_{OW}	6.08	6.65	6.15	6.15
J_{max} (μg/cm^2/h, SAM)	0.03	0.01	0.02	0.02
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	235.07	312.08	235.07	235.07
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	Lactone Type Reactive Functional Groups	Lactone Type Reactive Functional Groups		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Perhexiline (Hepatotoxicity) Alert			Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group			Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)			Non-toxicant (moderate reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found		No alert found	
Protein Binding (OECD)	Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates		Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	
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)	No alert found		No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 13-methyloxacyclopentadecan-2-one (CAS # 868846-58-6). 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,

hexadecanolide (CAS # 109-29-5), ω-pentadecalactone (CAS # 106-02-5), and oxacyclohexadecen-2-one (CAS # 34902-57-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Hexadecanolide (CAS # 109-29-5) was used as a read-across analog for the target material 13-methyloxacyclopentadecan-2-one (CAS # 868846-58-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of macrocyclic lactones.
  - o The main difference between the target material and read-across analog is that the target has a methyl substituent at the C-13 position. Moreover, the macrocycle in the target material is 2 carbons shorter than that of the read-across analog. These structural differences are irrelevant from a toxicological point of view.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- ω-Pentadecalactone (CAS # 106-02-5) was used as a read-across analog for the target material 13-methyloxacyclopentadecan-2-one (CAS # 868846-58-6) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of macrocyclic lactones.
  - o The main difference between the target material and read-across analog is that the target has a methyl substituent at the C-13 position and is 1 carbon shorter. This structural difference is irrelevant from a toxicological point of view.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There is an acylation alert (Protein Binding [OECD]) for both the target material and read-across analog. This alert is due to the presence of an ester group in both the target material and read-across analog. However, based on the data, the read-across analog does not present any concern and hence, can be used to clear the target chemical.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Oxacyclohexadecen-2-one (CAS # 34902-57-3) was used as a read-across analog for the target material 13-methyloxacyclopentadecan-2-one (CAS # 868846-58-6) for the repeated dose and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to a class of macrocyclic lactones.
  - o The main difference between the target material and read-across analog is that the macrocycle in the target material is a carbon shorter than in the read-across analog. This structural difference is irrelevant from a toxicological point of view.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o 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 (Cramer et al., 1978).

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
Q43. Possibly harmful divalent sulfur (not detected via Q3) No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q42. Possibly harmful analog of benzene No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? Yes
Q18. One of the list? (see Cramer et al., 1978 for detailed explanation on list of categories) No, Low (Class I)

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