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Short Review

RIFM fragrance ingredient safety assessment, ω-pentadecalactone, CAS Registry Number 106-02-5

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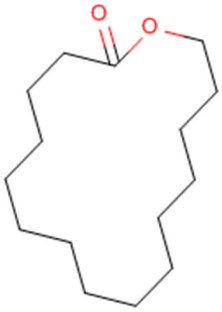
Conflicts of interest

The authors declare that they have no conflicts of interest.

Version: 040,820. This version replaces any previous versions.

Name: ω-Pentadecalactone
CAS Registry Number: 106-02-5



Abbreviation/Definition List:

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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., 2015, 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

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LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

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

ω-Pentadecalactone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog ethylene dodecanedioate (CAS # 54,982-83-1) show that ω-pentadecalactone is not expected to be genotoxic. Data provided a No Expected Sensitization Induction Level (NESIL) of 5500 μg/cm^2 for the skin sensitization endpoint. Data from read-across analog oxacyclohexadecen-2-one (CAS # 34,902-57-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to ω-pentadecalactone is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; ω-pentadecalactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ω-pentadecalactone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2001; RIFM, 1999; Abramsson-Zetterberg, 2002)
Repeated Dose Toxicity: NOAEL = 250 mg/kg/day.	RIFM (1998a)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2003a; RIFM, 2003b)
Skin Sensitization: NESIL = 5500 μg/cm^2.	RIFM (2006)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; Forbes, 1977; Ogoshi, 1980; Ohkoshi, 1981; RIFM, 1978a; RIFM, 1974)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 93% (OECD 301 B)	RIFM (1996b)
Bioaccumulation: Screening-level: 3024 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.068 mg/L	RIFM (1996d)
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: 21-day *Daphnia magna* NOEC: 0.068 mg/L	RIFM (1996d)
RIFM PNEC is: 1.36 μg/L	
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

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1. Identification

1. **Chemical Name:** ω-Pentadecalactone
2. **CAS Registry Number:** 106-02-5
3. **Synonyms:** Cyclopentadecanolide; Cyclopentadecanolid Supra; Exaltolide; 15-Hydroxypentadecanoic acid, ω-lactone; Oxacyclohexadecan-2-one; Pentadecanolide; Pentalide; Thibetolide; Exaltex; Macrolide; Pentadecalactone; ω-ﾋﾄﾞﾛｷｼｱﾙｶﾝ(C = 12–15)酸ﾗｸﾄﾝ; Muskalactone; Macrolide supra; ω-Pentadecalactone
4. **Molecular Formula:** $C_{15}H_{28}O_2$
5. **Molecular Weight:** 240.38
6. **RIFM Number:** 502

2. Physical data

1. **Boiling Point:** 364.47 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA Database)
3. **Log K_{OW}:** Log10 Pow = 5.78 (RIFM, 2013), >6.0 at 35 °C (RIFM, 2004), 6.15 (EPI Suite)
4. **Melting Point**: 26.06 °C (EPI Suite)
5. **Water Solubility:** 0.1484 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0002 torr (Vuilleumier, 1995), <0.001 mm Hg 20 °C (FMA Database), (calculated) 0.0000261 mm Hg @ 20 °C (EPI Suite v4.0), (calculated) 5.17e-005 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorption between 290 and 400 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Organoleptic:** Colorless solid with needle like crystals. Due to high odor, it is recommended to smell in a 10.00% solution or less. The odor is overall musk animal powdery natural fruity. It is also described as, tobacco, coumarin, heliotropine, powdery, licorice, and brown. The taste is like vanilla bean, powdery heliotropine, creamy, and licorice*

*This information was retrieved from: http://www.thegoodscentscompany.com/data/rw1004211.html, 3/23/17.

3. Volume of use (band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.094% (RIFM, 2015)
2. Inhalation Exposure*: 0.00081 mg/kg/day or 0.059 mg/day (RIFM, 2015)
3. Total Systemic Exposure**: 0.016 mg/kg/day (RIFM, 2015)

*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 v 2.6	OECD QSAR Toolbox v 3.2
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 details.

2. Analogs Selected:
   a. **Genotoxicity:** Ethylene dodecanedioate (CAS # 54,982-83-1)
   b. **Repeated Dose Toxicity:** Oxacyclohexadecen-2-one (CAS # 34,902-57-3: 99,219-32-6, 111,879-79-9, 111,879-80-2, 111,879-81-3 mixture)
   c. **Developmental and Reproductive Toxicity:** Oxacyclohexadecen-2-one (CAS # 34,902-57-3: 99,219-32-6, 111,879-79-9, 111,879-80-2, 111,879-81-3 mixture)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

ω-Pentadecalactone is reported to occur in the following foods by the VCF* and is found in some natural complex substances (NCS):

Angelica (Angelica archangelica L.)

*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; accessed 08/15/19 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for ω-pentadecalactone are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.42
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
5 A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.60
5 B	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
10 A	Household care products with mostly hand contact (hand dishwashing detergent)	4.6
10 B	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	Not Restricted

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 ω-pentadecalactone, the basis was the reference dose of 2.5 mg/kg/day, a predicted skin absorption value of 10% 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, ω-pentadecalactone does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic potential of ω-pentadecalactone was assessed in an Ames assay conducted in compliance with

GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA98, and TA100 were treated with of ω-pentadecalactone in dimethyl sulfoxide (DMSO) up to 5000 μg/plate in the presence and absence of a metabolically-active microsomal mixture (S9 mix). No substantial increases in the revertant colony numbers of the tester strains were observed following treatment with the test material at any dose level in the presence or absence of S9 mix in either mutation test (RIFM, 2001). Under the conditions of the study, ω-pentadecalactone was considered not mutagenic in the Ames test.

The clastogenicity of read-across analog ethylene dodecanedioate (CAS # 54,982-83-1; see Section VI) 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 ethylene dodecanedioate in DMSO at concentrations of 15.6, 31.3, 62.5, 125, 250, 500, 1000, and 2000 μg/mL in the presence and absence of S9 mix. No significant increase in the number of cells with chromosomal aberrations was observed in the presence or absence of S9 mix (RIFM, 1999). In addition, ω-pentadecalactone was tested *in vivo* in a mouse micronucleus study. Although the study was not conducted in compliance with GLP regulations, it was conducted using the procedures outlined in the OECD protocol (Abramsson-Zetterberg, 2002). Under the conditions of the studies, ethylene dodecanedioate and ω-pentadecalactone did not induce chromosome aberrations both *in vitro* and *in vivo*.

Based on the available data, ω-pentadecalactone does not present a concern for genotoxic potential.

Additional References: Aeschbacher (1989); RIFM, 1978b; RIFM, 1995b; RIFM, 2001.

Literature Search and Risk Assessment Completed On: 08/14/13.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for ω-pentadecalactone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on ω-pentadecalactone. Read-across material oxacyclohexadecen-2-one (CAS # 34,902-57-3; see Section VI) has sufficient repeated dose toxicity data. 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. Two males treated with 1000 mg/kg/day were found dead on days 34 and 85, and the cause of death was considered to be due to mal-dosing. However, there were no signs of mal-dosing during histopathology. The NOAEL was considered to be 250 mg/kg/day, based on mortality reported among high-dose group animals (RIFM, 1998a). In a 4-week gavage toxicity study conducted in rats with a 2-week recovery period, 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 the highest dose group and then maintained without treatment for 2 weeks. There were no treatment-related effects up to the highest dose tested. The NOEL for systemic toxicity was considered to be 1000 mg/kg/day (RIFM, 1996a). In another OECD 407/GLP gavage 28-day toxicity study conducted in rats with a 2-week recovery period, 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 hydroxypropylmethyl cellulose gel for 28 days. Two recovery groups of 5 rats/sex were added to the control and the 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 treatment 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, 2005b). The NOAEL of 250 mg/kg/day from the OECD 408 study was considered for this safety assessment. **Therefore, the ω-pentadecalactone 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 ω-pentadecalactone, 250/0.016 or 15,625.**

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. These factors can be refined based on availability of data. Due to insufficient intraspecies susceptibility data for ω-pentadecalactone, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences respectively (Renwick, 1993).

11.1.2.1.1. Derivation of reference dose (RfD). 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 2.5 mg/kg/day.

The RfD for ω-pentadecalactone was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 250 mg/kg/day by the uncertainty factor, 100 = 2.5 mg/kg/day.

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

Literature Search and Risk Assessment Completed On: 03/22/17.

11.1.3. Developmental and reproductive toxicity

The MOE for ω-pentadecalactone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on ω-pentadecalactone. Read-across material oxacyclohexadecen-2-one (CAS # 34,902-57-3; 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, or 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, 2003a). **Therefore, the ω-pentadecalactone 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 ω-pentadecalactone, 1000/0.016 or 62,500.**

There are no reproductive toxicity data on ω-pentadecalactone. Read-across material oxacyclohexadecen-2-one (CAS # 34,902-57-3; see Section VI) has sufficient reproductive toxicity 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 the pre-mating, mating, gestation, and lactation periods. 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, or mating performance up to the highest dose tested. The NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003b). **Therefore, the ω-pentadecalactone 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 ω-pentadecalactone, 1000/0.016 or 62, 500.**

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

Literature Search and Risk Assessment Completed On: 03/22/17.

11.1.4. Skin sensitization

Based on the available data, ω-pentadecalactone is considered to be a weak skin sensitizer with a defined NESIL of 5500 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, ω-pentadecalactone is considered to be a weak skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.13; OECD Toolbox v3.4). In guinea pig studies, ω-pentadecalactone did not result in reactions classifiable as sensitization (RIFM, 1995e; RIFM, 1997). However, in a murine local lymph node assay (LLNA), a range of EC3 values were observed with various qualities of the sample (RIFM, 2009a; RIFM, 2010a; RIFM, 2010b; RIFM, 2009b). 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 material, no sensitization potential was observed up to the highest tested concentration of 50% or 12,500 μg/cm^2 (RIFM, 2010b). In a human repeated insult patch test (HRIPT), 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, 2006). The Expert Panel for Fragrance Safety concluded that given that the impurities remain unidentified, a NESIL based on the HRIPT results of the commercial material should be adopted. The available data demonstrate that ω-pentadecalactone is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 5500 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 2.5 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/14/13.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, ω-pentadecalactone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In phototoxicity studies, application of 10% ω-Pentadecalactone did not result in skin reactions in guinea pigs (Ogoshi, 1980; Ohkoshi, 1981). Application of neat ω-pentadecalactone did not result in phototoxic reactions in mice or pigs (RIFM, 1974; Forbes, 1977). In a phototoxicity study (RIFM, 1978a), there were slightly greater average reactions at 24 h and 72 h in rabbits treated with 10% ω-pentadecalactone and guinea pigs treated with 50% ω-pentadecalactone and irradiated compared to the unirradiated test group (individual scores not provided). However, the study did not include an irradiated, untreated control group, making it impossible to determine if the reactions were phototoxic in nature. Based on the lack of absorbance and *in vivo* study data, ω-pentadecalactone does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectral analysis. The available UV spectra indicate no absorbance in the range of 290–400 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: 04/27/17.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for ω-pentadecalactone 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 ω-pentadecalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.059 mg/day. This exposure is 23.7 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: The Union of German Candle Manufacturers, 1997; Pinching (1974); Gilbert (1996).

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ω-pentadecalactone 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

Table 1
Data Summary for ω-pentadecalactone.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (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; HRIPT = Human Repeat Insult Patch 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 HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

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, ω-pentadecalactone 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 ω-pentadecalactone as not persistent, but possibly bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on current Vuilleumier et al. (1995), ω-pentadecalactone presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 1998b: A study was conducted to assess the ready degradability of the test material in the CO_2 evolution test (Modified Sturm Test) according to the OECD 301 B method. Biodegradation of 82% was observed after 28 days.

RIFM, 1996b: A biodegradation study was conducted using a CO_2 evolution test according to the OECD 301 B method. Biodegradation of 93% was observed after 28 days.

RIFM, 2005a: A biodegradation study was conducted using activated sludge in a manometric respirometry test according to the OECD 301 F method. In the study, 100 mg of the test material was incubated for 28 days. Biodegradation of 71% was observed.

RIFM, 1995d: A biodegradation study was conducted using a manometric respirometer according to the method C.4-D. The test material achieved 90% biodegradation in 28 days.

11.2.3.2. Ecotoxicity. RIFM, 1995c: A 48-h acute *Daphnia magna* test was conducted according to the Directive 67/548/EEC method. Under the conditions of this study, the EC0 values at 24 and 48 h were ≥2.2 mg/L (nominal concentration) and ≥1.27 mg/L (measured concentration), respectively.

RIFM, 1994: A 96-h acute toxicity test to fish (*Brachydanio rerio*) was conducted according to the (C.1) Directive 67/548/EEC method. Under the conditions of this study, the LC0 value was ≥0.11 mg/L.

RIFM, 1996c: An algae growth inhibition test was conducted according to the (C.3), Directive 67/548/EEC method was. The 72-h EC50 was reported to be 0.47 mg/L and 0.4 mg/L for growth rate and biomass, respectively. The 48-h NOEC was reported to be 0.26 mg/L.

RIFM, 1996d: A *Daphnia magna* 21-day reproduction test was conducted according to the OECD 211 guidelines. The geometric mean determined for immobilization based on measured concentration was 0.093 mg/L. The EC50 (reproduction) was determined to be > 0.068 and < 0.127 mg/L, and the NOEC (reproduction) was 0.068 mg/L.

11.2.4. Other available data

The material, ω-pentadecalactone, has been registered under REACH with no additional data at this time.

Risk Assessment Refinement:

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on the available data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 1.36 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 volumes of use.

Literature Search and Risk Assessment Completed On: 03/13/19.

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**
- **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/

		(mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	0.166			1000000	0.00016	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.121	0.161	0.035			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.037	0.031	0.111	10000	0.0031	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.11					
Daphnia		>1.27	0.068	50	1.36	
Algae		0.4	0.26			

12.1. 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 01/22/19.

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.2020.111762.

Appendix

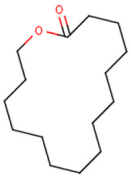
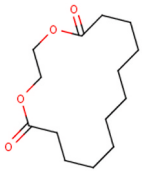
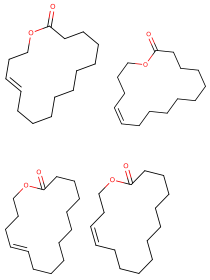
Read-across Justification

Methods

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

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- The J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were estimated using OECD QSAR Toolbox v3.1 (OECD, 2012).
- ER binding and repeat dose toxicity categorization were estimated using OECD QSAR Toolbox v3.1 (OECD, 2012).

- Developmental toxicity was estimated using CAESAR v.2.1.6 (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox v3.1 (OECD, 2012).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.1 (OECD, 2012).

	Target Material	Read-across Material	
Principal Name	ω-Pentadecalactone	Ethylene dodecanedioate	E− and Z-Oxacyclohexadec-12 (+13)-en-2-one (mixture of Oxacyclohexadec-13-en-2-one, (13 E)-, Oxacyclohexadec-12-en-2-one, (12Z)-, E-Oxacyclohexadec-12-en-2-one, and (Z)-Oxacyclohexadec-13-en-2-one)
CAS No.	106-02-5	54,982-83-1	34,902-57-3 (99,219-32-6, 111,879-79-9, 111,879-80-2, 111,879-81-3 mixture)
Structure			
Read-across endpoint		•Genotoxicity	•Repeated dose toxicity •Developmental and reproductive toxicity
Molecular Formula	$C_{15}H_{28}O_2$	$C_{14}H_{24}O_4$	$C_{15}H_{26}O_2$
Molecular Weight	240.39	256.35	238.37
Melting Point (°C, EPI Suite)	26.06	63.39	26.84
Boiling Point (°C, EPI Suite)	364.47	421.78	366.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.006893	0.0003253	0.00705
Log Kow (KOWWIN v1.68 in EPI Suite)	6.15	4.22	4.88
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.1484	5.417	1.859
J_{max} (μg/cm^2/h, SAM)	0.939	5.271	1.451
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.34 E+002	2.39E-001	2.06 E+002
Similarity (Tanimoto score)		77%	72%
In silico Results for Target and Analog			
Genotoxicity			
DNA binding (OASIS v1.1)	•No alert found	•No alert found	
DNA binding (OECD)	•No alert found	•No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	•No alert found	
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found	•No alert found	
***In vitro* mutagenicity (Ames test) alerts (ISS)**	•No alert found	•No alert found	
***In vivo* mutagenicity (Micronucleus) alerts (ISS)**	•H-acceptor-path3-H-acceptor	•H-acceptor-path3-H-acceptor	
Oncologic classification (OECD)	•Lactone Type Reactive Functional Groups	•Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized	Not categorized	
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non-binder, without OH or NH2 group		Non-binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Non-Toxicant (moderate reliability)		Non-Toxicant (moderate reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3 See Supplemental Data 4

Summary

There are insufficient toxicity data on ω-pentadecalactone (CAS # 106-02-5). Hence, *in silico* evaluation was conducted to determine the read-across analogs. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, the above shown read-across analogs were identified as materials with sufficient data for toxicological evaluation for the respective endpoints.

Conclusions

- Ethylene dodecanedioate was used as a read-across analog for ω-pentadecalactone for the genotoxicity endpoint based on the following:
  - o The target material and analog belong to the generic class of macrocyclic lactones and lactides.

- They have similar lactones and number of ring carbons.
- The key difference is that the read-across analog has 2 lactone groups while the target only has 1 lactone group. The difference between structures does not essentially change the physical–chemical properties or raise any additional structural alerts; therefore, the toxicity profiles are expected to be similar.
- The target material and analog show similar alerts for DNA binding, mutagenicity, genotoxicity, and oncologic classification.
- The target material and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular initiating event analogous to protein binding.
- The target material and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

- E− and Z-Oxacyclohexadec-12 (+13)-en-2-one (mixture of oxacyclohexadec-13-en-2-one, (13 E)-, oxacyclohexadec-12-en-2-one, (12Z)-, E-oxacyclohexadec-12-en-2-one, and (Z)-oxacyclohexadec-13-en-2-one) was used as a read-across analog for ω-pentadecalactone for the repeated dose toxicity and the developmental and reproductive toxicity endpoints based on the following:
  - The target material and analogs belong to the generic class of macrocyclic lactones and lactides.
  - They have similar lactone groups and numbers of ring carbons.
  - The only difference is that the analog has an unsaturated vinyl group within the macrocyclic ring. The difference between structures does not essentially change the physical–chemical properties or raise any additional structural alerts; therefore, the toxicity profiles are expected to be similar.
  - The target material and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular initiating event analogous to protein binding.
  - The target material and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer Class. 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. Normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, 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 a,b-unsaturated lactone? **No**
Q20. Aliphatic with some functional groups? **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 Low (Class I)

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