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RIFM fragrance ingredient safety assessment, hexadecanolide, CAS Registry Number 109-29-5

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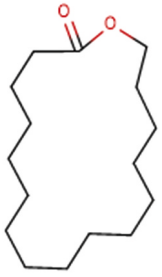
Name: Hexadecanolide

CAS Registry Number: 109-29-5



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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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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 et al., 2015), which should be referred to for clarifications.

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

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

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

Hexadecanolide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that hexadecanolide is not genotoxic. Data on read-across analog oxacyclohexadecen-2-one (CAS # 34902-57-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog ω-pentadecalactone (CAS # 106-02-5) provided hexadecanolide 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) spectra; hexadecanolide 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, and the exposure to hexadecanolide is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; hexadecanolide 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., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 1999c; RIFM, 1999b)
Repeated Dose Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (1998a)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2003c; RIFM, 2003b)
Skin Sensitization: NESIL = 5500 μg/cm^2.	RIFM (2006)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 70% to >100%	(Salvito et al., 2011)
Bioaccumulation: Screening-level: 11260 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: FELS NOEC 0.027 mg/L for oxacyclohexadec-12-en-2-one, (E)	RIFM (2003c)

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Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: FELS NOEC 0.027 mg/L for oxacyclohexadec-12-en-2-one, (E)	RIFM (2003a)
RIFM PNEC is: 2.7 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Hexadecanolide
2. **CAS Registry Number:** 109-29-5
3. **Synonyms:** Cyclohexadecanolide; Dihydro ambrettolide; 16-Hydroxyhexadecanoic acid lactone; Oxacycloheptadecan-2-one; Hexadecanolactone; オキサシクロヘプタデカン-2-オン; ヘキサデカノ - １６ - ラクトン; Hexadecanolide
4. **Molecular Formula:** $C_{16}H_{30}O_2$
5. **Molecular Weight:** 254.41
6. **RIFM Number:** 546
7. **Stereochemistry:** There is no stereocenter possible.

2. Physical data

1. **Boiling Point:** 294 °C (Fragrance Materials Association [FMA]), 377.14 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 6.65 (EPI Suite)
4. **Melting Point**: 30 °C (FMA), 33.75 °C (EPI Suite)
5. **Water Solubility:** 0.04727 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000123 mm Hg at 20 °C (EPI Suite v4.0), 2.48e-005 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 500 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** An opaque crystalline mass that has a tenacious, woody-musky, but rather weak odor

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015).

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.35% (RIFM, 2018b)
2. **Inhalation Exposure*:** 0.00012 mg/kg/day or 0.0086 mg/day (RIFM, 2018b)
3. **Total Systemic Exposure**:** 0.0028 mg/kg/day (RIFM, 2018b)

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

*See the Appendix below for details.

6.2. *Analogs Selected*

a. **Genotoxicity:** None
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:** Macrocyclic Lactone/Lactide SAG

6.3. *Read-across Justification*

See Appendix below

7. Metabolism

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

8. Natural occurrence

Hexadecanolide is reported to occur in the following foods by the VCF*:

Milk and milk products.

*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 11/14/21 (ECHA, 2018).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for hexadecanolide 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 hexadecanolide, the basis was the subchronic reference dose of 10 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).

[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, hexadecanolide does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of hexadecanolide 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, 1999b). Under the conditions of the study, hexadecanolide was not mutagenic in the Ames test.

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, 1999c). Under the conditions of the study, hexadecanolide was considered to be non-clastogenic to human cells.

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

Additional References: RIFM, 1999a.

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

11.1.2. Repeated dose toxicity

The MOE for hexadecanolide 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 on hexadecanolide. Read-across material, oxacyclohexadecen-2-one (CAS # 34902-57-3; 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 the test material 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 via gavage the test material, oxacyclohexadecen-2-one 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 groups and then maintained without treatment for 2 weeks. There were no treatment-related effects up to the highest dose tested; thus, the NOEL for systemic toxicity was considered to be 1000 mg/kg/day (RIFM, 1996).

In another OECD/GLP 407 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 via gavage test material, oxacyclohexadecen-2-one (Globalide) at doses of 0, 100, 300, or 1000 mg/kg/day in 0.8% aqueous hydroxypropyl methylcellulose gel for 28 days. Two recovery groups of 5 rats/sex were added to the control and highest-dose groups 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. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2005).

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

Therefore, the hexadecanolide 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 hexadecanolide, 1000/0.0028, or 357142.

In addition, the total systemic exposure to hexadecanolide (2.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Derivation of subchronic 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, 2020b) and a subchronic reference dose of 10 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for inter-species (10 ×) and intraspecies (10 ×) differences. The subchronic reference dose for hexadecanolide 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: RIFM, 2011a; RIFM, 2011b; RIFM, 1995a.

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

11.1.3. Reproductive toxicity

The MOE for hexadecanolide 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 hexadecanolide. Read-across material oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section VI) has sufficient developmental toxicity data that can be used to support 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, 2003c).

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 to support 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 statistically significantly higher than the controls at day 1 post-partum, 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, 2003b).

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 hexadecanolide 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 hexadecanolide, 1000/0.0028, or 357143.**

In addition, the total systemic exposure to hexadecanolide (2.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 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, 1995a.

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), hexadecanolide is a skin sensitizer with a defined NESIL of 5500 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization data are available on hexadecanolide. Based on existing material-specific data and read-across to ω-pentadecalactone (CAS # 106-02-5; see Section VI), hexadecanolide is considered a skin sensitizer. The chemical structures of these molecules indicate that they would not be expected to react with skin proteins directly (Roberts et al., 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, 2018a). 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, 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 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 sensitizer (RIFM, 1997; RIFM, 1995b). The target material, hexadecanolide, was not found to be sensitizing in a guinea pig open epicutaneous test (OET) (Klecak, 1985). In a Confirmation of No Induction in Humans test (CNIH) with 2% hexadecanolide in dimethyl phthalate, no sensitization reactions were observed in the 54 volunteers (RIFM, 1972). The dose per unit area could not be calculated, as the patch size was not specified in the report. In another CNIH, no sensitization reactions were observed in 40 volunteers when 0.75% (581 μg/cm^2) hexadecanolide in ethanol was used (RIFM, 1964). The CNIHs on the target material were conducted with less than 100 volunteers and therefore were considered insufficient to derive the NESIL. In a CNIH

Table 1
Data Summary for ω-pentadecalactone as a read-across for hexadecanolide.

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.

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, 2006). In another CNIH with 20% ω-pentadecalactone in 1:1 ethanol: diethylphthalate, 1/50 volunteers exhibited sensitization reaction (RIFM, 1998b). The quality of the tested sample was not investigated for the potential presence of impurities. In human maximization tests, hexadecanolide and ω-pentadecalactone were tested at 4% (2760 μg/cm^2) and 10% (6900 μg/cm^2), respectively. No sensitization reactions were observed in these human maximization studies (RIFM, 1974).

The weight of evidence (WoE) from animal and human studies and data from read-across analog ω-pentadecalactone (CAS # 106-02-5), hexadecanolide is a sensitizer with a 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, 2020b) and a subchronic reference dose of 10 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/23/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra, hexadecanolide would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV absorption spectra indicate no absorbance between 290 and 500 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Phototoxicity studies were conducted in guinea pigs and rabbits with 1%, 5%, and 50% hexadecanolide in ethanol (1% and 5%) or DEP (50%). Slightly higher than average scores were observed at 24 h at the irradiated sites in guinea pigs treated with 5% hexadecanolide and at 48 h and 72 h at irradiated sites in rabbits treated with 5% hexadecanolide (RIFM, 1978). However, without proper controls (sites irradiated but not treated with test material), it is impossible to definitively conclude on phototoxicity. Based on the lack of absorbance, hexadecanolide does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV absorption spectra were obtained. The spectra indicate no absorbance in the range of 290–500 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for hexadecanolide 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 hexadecanolide. Based on the Creme RIFM Model, the inhalation exposure is 0.0086 mg/day. This exposure is 162.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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 hexadecanolide was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, hexadecanolide 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 hexadecanolide as being 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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 the current Volume of Use (2015), hexadecanolide presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.3. Other available data

Hexadecanolide has been registered for REACH with the following additional data available at this time (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 64% was observed after 28 days.

The acute fish (*Cyprinus carpio*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on mean measured concentration was reported to be > 0.052 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value for growth rate was reported to be > 0.004 mg/L. This value was above the concentration obtained in a saturated solution prepared at 100 mg/L. This concentration was above the solubility limit of the substance in the test medium (as indicated by the haziness) but could not be measured because it was below the concentration of the lowest calibration solution (i.e., below 0.004 mg/L).

Salvito et al., 2011: A robust summary of available environmental data has been by Salvito et al.

11.3. Risk assessment refinement

Please note: For the macrocyclic lactones/lactides, the lowest acute EC50/LC50 reported (algae, *Daphnia,* or fish) was 0.0425 mg/L (*Danio rerio* lethality study for oxacycloheptadec-11-en-2-one). This material is reported in other studies to be very poorly soluble (the mean limit of solubility reported in its *D. magna* immobilization study is 66 mg/L). This may explain the difference observed in acute toxicity between this material and the other lactones/lactides, where the next lowest acute endpoint reported is an order of magnitude higher (EbC50 in an algae biomass-based inhibition study for o-pentadecalactone). The lowest NOEC from a chronic toxicity study was 0.027 mg/L (fish early life stage study for oxacyclohexadec-12-en-2-one, (E)). Three chronic endpoints are available (algae, *Daphnia*, and fish), and, therefore, an assessment factor of 10 is applied to this NOEC.

Furthermore, the observed biodegradation of macrocyclic lactones/lactides ranged from 70% to >100% (Salvito et al., 2011).

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)**	0.03			1000000	0.00003	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.066	0.083	0.017			Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.014	0.012	0.054	10000	0.0012	Neutral Organics

Tier 3: Measured Data Including Read-across Data

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.1		0.027	10	2.7	
Daphnia		>1.27	0.068			
Algae		0.4	0.26			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.65	6.65
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 the read-across data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 2.7 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: 03/16/21.

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.2022.112920.

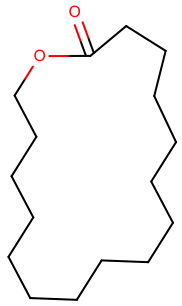
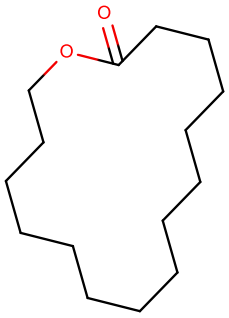
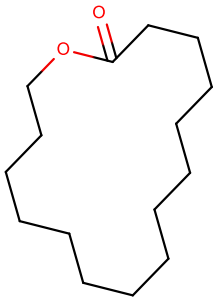
Appendix

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., 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 the *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Hexadecanolide	Oxacyclohexadecen-2-one	ω -Pentadecalactone
CAS No.	109-29-5	34902-57-3	106-02-5
Structure			
Similarity (Tanimoto Score)		0.98	1.00
Endpoint		• Repeated dose toxicity • Reproductive toxicity	• Skin sensitization
Molecular Formula	$C_{16}H_{30}O_2$	$C_{15}H_{28}O_2$	$C_{15}H_{28}O_2$
Molecular Weight	254.41	240.39	240.39
Melting Point (°C, EPI Suite)	33.75	32.00	32.00
Boiling Point (°C, EPI Suite)	377.14	364.47	364.47
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.00	0.01	0.01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	0.05	0.15	0.15
Log K_{OW}	6.65	6.15	6.15
J_{max} (μg/cm^2/h, SAM)	0.01	0.02	0.02
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	312.08	235.07	235.07
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 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	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

Summary

There are insufficient toxicity data on the target material, hexadecanolide (CAS # 109-29-5). 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) and ω-pentadecalactone (CAS # 106-02-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- Oxacyclohexadecen-2-one (CAS # 34902-57-3) was used as a read-across analog for the target material, hexadecanolide (CAS # 109-29-5), for the reproductive toxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog belong to the structural class of macrocyclic lactones.
  - o The target material and the read-across analog share a 15-carbon macrocycle.
  - o The key difference between the target material and the read-across analog is that the target material has a C16 lactone ring, which is a 1-carbon larger macrocycle than in the read-across analog, which has a C15 lactone ring. This structural difference between the target material and the read-across analog does not affect consideration of the toxicity endpoints.

- The similarity between the target material 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the QSAR OECD Toolbox (v4.2), the structural alerts for the toxicity endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- ω-Pentadecalactone (CAS # 106-02-5) was used as a read-across analog for the target material, hexadecanolide (CAS # 109-29-5), for the skin sensitization endpoint.
  - The target material and the read-across analog belong to a class of saturated macrolactones.
  - The target material and the read-across analog share a saturated macrocycle lactone ring.
  - The key difference between the target material and the read-across analog is that the target material has a C16 lactone ring, which is a 1-carbon larger macrocycle than in the read-across analog, which has a C15 lactone ring. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target and read-across materials have a Protein Binding (OECD) acylation alert for acetates. However, neither the target nor the read-across material has a potentially reactive acetate group. As a consequence, all the alerts can be ignored. The predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

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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