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RIFM fragrance ingredient safety assessment, 12-oxahexadecanolide, CAS Registry Number 6707-60-4

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Name: 12-Oxahexadecanolide

CAS Registry Number: 6707-60-4

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

(*continued on next column*)

(*continued*)

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.

12-Oxahexadecanolide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 12-oxahexadecanolide and read-across analog hexadecanolide (CAS # 109-29-5) show that 12-oxahexadecanolide is not expected to be genotoxic. Data on 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 show no safety concerns for 12-oxahexadecanolide for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 12-oxahexadecanolide 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 III material, and the exposure to 12-oxahexadecanolide is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 12-oxahexadecanolide 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 expected to be genotoxic.	(ECHA REACH Dossier: 12-Oxahexadecanolide; ECHA, 2017a; RIFM, 1979; RIFM, 1999c)
Repeated Dose Toxicity: NOAEL = 250 mg/kg/day.	RIFM (1998)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(RIFM, 2003b; RIFM, 2003a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared use levels.	(ECHA REACH Dossier: 12-Oxahexadecan-16-olide; ECHA, 2017a; RIFM, 1977b; Klecak, 1985; RIFM, 1977a)
Phototoxicity/Photoallergenicity: Not phototoxic/not expected to be photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1983; RIFM, 1978a; Ohkoshi et al., 1981)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 96% (OECD 301B)	RIFM, (1996b)
Bioaccumulation:	
Screening-level: 791.1 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96 h Algae EC50: 0.286 mg/L	(ECOSAR; (US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 0.286 mg/L	(ECOSAR; (US EPA, 2012b)

RIFM PNEC is: 0.0286 μg/L

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

1. Identification

1. **Chemical Name:** 12-Oxahexadecanolide
2. **CAS Registry Number:** 6707-60-4
3. **Synonyms:** Cervolide; 1,6-Dioxacycloheptadecan-7-one; Hibiscolide; 16-hydroxy-12-oxahexadecanoic acid, ω lactone; Musk 781; 12-Oxahexadecan-16-olide; 12-Oxahexadecanolide

4. **Molecular Formula:** $C_{15}H_{28}O_3$
5. **Molecular Weight:** 256.38 g/mol
6. **RIFM Number:** 991
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomerism possible.

2. Physical data

1. **Boiling Point:** 380.27 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (Fragrance Materials Association [FMA]), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.9 (EPI Suite)
4. **Melting Point**: 46.8 °C (EPI Suite)
5. **Water Solubility:** 1.433 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00000775 mm Hg at 20 °C (EPI Suite v4.0), 1.58e-005 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Arctander (1969): Colorless viscous liquid. Practically insoluble in water, soluble in alcohol and oils. Sweet tenacious and intensely musky odor.

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.15% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000035 mg/kg/day or 0.0026 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0023 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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; and 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

1. **Cramer Classification:** Class III, High

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

2. Analogs Selected:
   a. **Genotoxicity:** Hexadecanolide (CAS # 109-29-5)
   b. **Repeated Dose Toxicity:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
   c. **Reproductive Toxicity:** Oxacyclohexadecen-2-one (CAS # 34902-57-3)
   d. **Skin Sensitization:** 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.

7.1. Additional References

None

8. NATURAL occurrence (Discrete chemical)

12-Oxahexadecanolide is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 02/02/22 (ECHA, 2017a).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 12-oxahexadecanolide does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 12-Oxahexadecanolide was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 12-oxahexadecanolide has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 12-oxahexadecanolide in saline and dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2017a). Under the conditions of

the study, 12-oxahexadecanolide was not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of 12-oxahexadecanolide. The clastogenicity of read-across material hexadecanolide (CAS # 109-29-5; 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 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, and this can be extended to 12-oxahexadecanolide.

Based on the available data, hexadecanolide does not present a concern for genotoxic potential, and this can be extended to 12-oxahexadecanolide.

Additional References: RIFM, 1999a; RIFM, 1999b.

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

11.1.2. Repeated dose toxicity

The MOE for 12-oxahexadecanolide 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 12-oxahexadecanolide. 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 via gavage the test material, oxacyclohexadecen-2-one 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. Thus, the NOAEL was considered to be 250 mg/kg/day, based on mortality reported among high-dose group animals (RIFM, 1998). 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 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, 1996a). 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 hydroxypropylmethylcellulose 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. The NOAEL for systemic toxicity was considered to be 250 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 12-oxahexadecanolide 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 12-oxahexadecanolide, 250/0.0023, or 108696.**

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

Literature Search and Risk Assessment Completed On: 02/08/21.

11.1.3. Reproductive toxicity

The MOE for 12-oxahexadecanolide 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 12-oxahexadecanolide. Read-across material oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section VI) has sufficient developmental toxicity data. An OECD 414/GLP gavage developmental toxicity study was conducted in rats. Groups of 24 mated Sprague Dawley CD strain female rats/dose were administered via gavage the test material oxacyclohexadecen-2-one at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose from days 5–19 of gestation. There were no significant treatment-related effects on fetal viability, growth, and developmental toxicity up to the highest dose tested. The NOAEL for developmental toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003b). **Therefore, the 12-oxahexadecanolide 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 12-oxahexadecanolide, 1000/0.0023, or 434783.**

There are no fertility data on 12-oxahexadecanolide. Read-across material, oxacyclohexadecen-2-one (CAS # 34902-57-3; see Section VI), has sufficient fertility data. An OECD 415/GLP gavage 1-generation reproductive toxicity study was conducted in rats. Groups of 28 Sprague Dawley Crl:CD(SD) IGS BR strain rats/sex/dose were administered via gavage test material, oxacyclohexadecen-2-one at doses of 0, 50, 250, or 1000 mg/kg/day in 0.5% carboxymethyl cellulose daily, throughout pre-mating, mating, gestation, and lactation. The males were dosed for 72 days, and females were dosed for 16 days prior to mating. There were no effects on the reproductive organs, fertility, or mating performance up to the highest dose tested. Thus, the NOAEL for fertility was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2003a). **Therefore, the 12-oxahexadecanolide MOE for the fertility endpoint can be calculated by dividing the oxacyclohexadecen-2-one NOAEL in mg/kg/day by the total systemic exposure to 12-oxahexadecanolide, 1000/0.0023, or 434783.**

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

Literature Search and Risk Assessment Completed On: 02/08/21.

11.1.4. Skin Sensitization

Based on existing data, 12-oxahexadecanolide is not considered to be a skin sensitizer.

11.1.4.1. Risk assessment. Based on the existing data, 12-oxahexadecanolide is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Toxtree v3.1.0; OECD Toolbox v4.2). 12-Oxahexadecanolide was not predicted to react with skin proteins in an *in vitro* direct peptide reactivity assay (DPRA) (ECHA, 2017a). Also, it was not predicted to be a skin sensitizer in KeratinoSens (ECHA, 2017a). In guinea pig studies, 12-oxahexadecanolide did not result in reactions classifiable as sensitization (RIFM, 1977b; Klecak, 1985). In a human maximization test, no sensitization reactions were observed in response to 10% (6900 μg/cm^2) 12-oxahexadecanolide (RIFM, 1977a).

Based on the weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies, 12-oxahexadecanolide does not present a concern for skin sensitization under the current, declared

levels of use.

Additional References: RIFM, 1978b.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra and existing *in vivo* data, 12-oxahexadecanolide does not present a concern for phototoxicity. Based on lack of absorbance, 12-oxahexadecanolide does not present a concern for photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). In multiple *in vivo* phototoxicity studies with 12-oxahexadecanolide, there were no reactions indicative of phototoxicity (RIFM, 1978a; Ogoshi et al., 1980; Ohkoshi et al., 1981; RIFM, 1983). Based on the existing *in vivo* data and lack of absorbance, 12-oxahexadecanolide does not present a concern for phototoxicity. Based on the lack of absorbance, 12-oxahexadecanolide does not present a concern for photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/10/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 12-oxahexadecanolide is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 12-oxahexadecanolide. Based on the Creme RIFM Model, the inhalation exposure is 0.0026 mg/day. This exposure is 180.8 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 12-oxahexadecanolide 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, 12-oxahexadecanolide 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) did not identify 12-oxahexadecanolide as possibly persistent or bioaccumulative based on its structure and physical−chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 12-oxahexadecanolide presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. ***Biodegradation***

RIFM, 1996b: Biodegradation was evaluated by the sealed vessel test according to the OECD 301F method. Filtered activated sludge and 10 mg/L of 12-oxahexadecanolide were incubated for 28 days. The rate of degradation after 28 days was 96%.

Ecotoxicity

No data available.

Other available data

12-Oxahexadecanolide has been registered for REACH with the following additional data available (ECHA, 2017a).

A *Daphnia magna* immobilization test was conducted according to the OECD 202 guideline under semi-static conditions. The 48-h EC50 value based on geometric mean measured concentration was reported to be 10.3 mg/L (95% CI: 6.7–16 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 values based on geometric mean measured concentration for growth rate and yield were reported to be 1.2 mg/L and 0.51 mg/L, respectively.

11.2.3. 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.9	4.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

	(mg/L)	(*Daphnia*) (mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	1.037			1000000	0.001037	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.697	1.062	0.286	10000	0.0286	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.527	0.391	0.880			Neutral Organics SAR

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

The RIFM PNEC is 0.0286 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

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

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 02/02/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113162.

Appendix

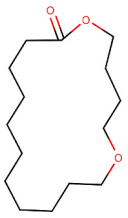
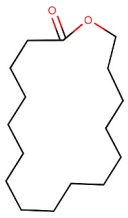
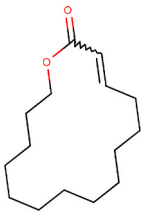
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). 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, 2017b).

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

	Target Material	Read-across Material	Read-across Material
Principal Name	12-Oxahexadecanolide	Hexadecanolide	Oxacyclohexadecen-2-one
CAS No.	6707-60-4	109-29-5	34902-57-3
Structure			
Similarity (Tanimoto score)		0.91	0.98
Read-across endpoint		• Genotoxicity	• Repeated Dose • Reproductive toxicity
Molecular Formula	$C_{15}H_{28}O_3$	$C_{16}H_{30}O_2$	$C_{15}H_{28}O_2$
Molecular Weight (g/mol)	256.39	254.42	240.39
Melting Point (°C, EPI Suite)	46.80	33.75	26.06
Boiling Point (°C, EPI Suite)	380.27	377.14	364.47
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.0021	0.0033	0.00689
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.9	6.65	6.15
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.433	0.04727	0.1484
J_{max} (μg/cm^2/h, SAM)	6.093	0.382	1.451
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.07E+000	3.12E+002	2.35E+002
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (4.2)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found	
***In vivo* Mutagenicity (Micronucleus) alerts by ISS**	• No alert found	• No alert found	
Oncologic Classification	• Lactone-type Reactive Functional Groups	• Lactone-type Reactive Functional Groups	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Reproductive Toxicity			
ER Binding by OECD QSAR Tool Box (4.2)	• Non-binder, without OH or NH_2 group		• Non-binder, without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (good reliability)		• Non-toxicant (moderate reliability)
Metabolism			
OECD QSAR Toolbox (4.2) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 12-oxahexadecanolide (CAS # 6707-60-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, hexadecanolide (CAS # 109-29-5) and oxacyclohexadecen-2-one (CAS # 34902-57-3) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusion

- Hexadecanolide (CAS # 109-29-5) was used as a read-across analog for the target material 12-oxahexadecanolide (CAS # 6707-60-4) for the genotoxicity endpoint.
  - o The target material and the read-across analogs belong to the structural class of macrocyclic lactones.
  - o The key difference between the target material and the read-across analog hexadecanolide (CAS # 109-29-5) is that the target material has an ether functional group in the macrocyclic ring and has 1 less carbon compared to the read-across analog. This structural difference between the target material and the read-across analogs does not affect consideration of the toxicity endpoint.
  - o The similarity between the target material and the read-across analogs 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 endpoint.
  - o The physical−chemical properties of the target material and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analogs.
  - o The target and the read-across analogs have been classified as Lactone-type Reactive Functional Groups in oncologic classification. There are no other classification alerts. The data described in the genotoxicity section show that the read-across analogs do not pose a concern for the genotoxicity endpoint. Therefore, this prediction will be superseded by the availability of the data.
  - o The target material and the read-across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.
- Oxacyclohexadecen-2-one (CAS # 34902-57-3) was used as a read-across analog for the target material 12-oxahexadecanolide (CAS # 6707-60-4) for the reproductive toxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of macrocyclic lactones.
  - o The key difference between the target material and the read-across analog is that the target has an ether functional group in the macrocyclic ring, whereas the read-across analog has a double bond at the 2,3 position. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoints.
  - o 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.
  - o The physical−chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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