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Short review

RIFM fragrance ingredient safety assessment, δ-undecalactone, CAS Registry Number 710-04-3

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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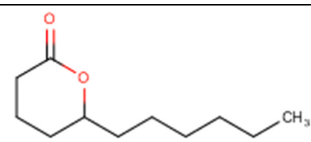


Abbreviation/Definition List:

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., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

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

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is

(*continued on next column*)

(*continued*)

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.

δ-Undecalactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hydroxynonanoic acid, δ-lactone (CAS # 3301-94-8) show that δ-undecalactone is not expected to be genotoxic. Data on read-across analog δ-decalactone (CAS # 705-86-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog δ-octalactone (CAS # 698-76-0) show that there are no safety concerns for δ-undecalactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; δ-undecalactone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; δ-undecalactone 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.	(RIFM, 2014a; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Decan-5-olide; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity: 1000 mg/kg/day Fertility: 1000 mg/kg/day.	(ECHA REACH Dossier: Decan-5-olide; ECHA, 2013)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: Tetrahydro-6-propyl-2H-pyran-2-one; ECHA, 2019b)

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: 80% (OECD 301F)	(ECHA REACH Dossier: 6-Hexyltetrahydro-2H-pyran-2-one; ECHA, 2019a)
Bioaccumulation:	
Screening-level: 48.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 33.53 mg/L	(RIFM Framework; Salvito, 2002)

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: Fish LC50: 33.53 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.03353 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** δ-Undecalactone
2. **CAS Registry Number:** 710-04-3
3. **Synonyms:** 5-n-Hexyl-5-hydroxypentanoic acid lactone; δ-n-Hexyl-δ-valerolactone; 2H-Pyran-2-one, 6-hexyltetrahydro-; Undeca-1,5-lactone; δ-ｵｷｼｱﾙｶﾝ酸(C = 9～18)δ-ﾗｸﾄﾝ; 6-Hexyltetrahydro-2H-pyran-2-one; 5-Hydroxyundecanoic acid lactone; δ-Undecalactone
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.27
6. **RIFM Number:** 702
7. **Stereochemistry:** Isomer not specified. One chiral center present and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 298.4 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (Fragrance Materials Association [FMA] Database), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.9 and 3.0 (RIFM, 2014b), 3.06 (EPI Suite)
4. **Melting Point**: 28.95 °C (EPI Suite)
5. **Water Solubility:** 128.3 mg/L (EPI Suite)
6. **Specific Gravity:** 0.96 (FMA Database)
7. **Vapor Pressure:** 0.00107 mm Hg at 20 °C (EPI Suite v4.0), 0.00196 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Arctander Volume II 1969: Colorless, very viscous liquid. Powerful, creamy-fatty, and in dilution pronounced peach-like odor of excellent tenacity. At concentrations below 10 ppm, the flavor is more typical peach-like and less grassy than that of γ-undecalactone. The minimum perceptible is well below 0.1 ppm

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 v3.0.4)

1. **95th Percentile Concentration in Fine Fragrance:** 0.035% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.011 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
I	II	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 the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Hydroxynonanoic acid, δ-lactone (CAS # 3301-94-8)
   b. **Repeated Dose Toxicity:** δ-Decalactone (CAS # 705-86-2)
   c. **Reproductive Toxicity:** δ-Decalactone (CAS # 705-86-2)
   d. **Skin Sensitization:** δ-Octalactone (CAS # 698-76-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

δ-Undecalactone is reported to occur in the following foods by the VCF*:

Ceriman, pinanona (Monstera deliciosa Liebm.)	Mentha oils
Chicken	Milk and milk products
Coconut (Cocos nucifera L.)	Rambutan (Nephelium lappaceum L.)
Melon	Raspberry, blackberry, and boysenberry
	Starfruit (Averrhoa carambola 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 08/13/20 (ECHA, 2019a).

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, δ-undecalactone does not present a concern for genotoxicity.

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

There are no studies assessing the mutagenic and clastogenic activity of δ-undecalactone; however, read-across can be made to hydroxynonanoic acid, δ-lactone (CAS # 3301-94-8; see Section VI).

The mutagenic activity of hydroxynonanoic acid, δ-lactone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with hydroxynonanoic acid, δ-lactone 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 concentration in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, hydroxynonanoic acid, δ-lactone was not mutagenic in the Ames test, and this can be extended to δ-undecalactone.

The clastogenic activity of hydroxynonanoic acid, δ-lactone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with hydroxynonanoic acid, δ-lactone in DMSO at concentrations up to 1562.3 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1562.3 μg/mL in the presence and absence of metabolic activation. Hydroxynonanoic acid, δ-lactone did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, hydroxynonanoic acid, δ-lactone was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to δ-undecalactone.

Based on the data available, hydroxynonanoic acid, δ-lactone does not present a concern for genotoxic potential, and this can be extended to δ-undecalactone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

The MOE for δ-undecalactone 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 δ-undecalactone. Read-across material δ-decalactone (CAS # 705-86-2) has sufficient data to support the repeated dose toxicity endpoint. In a GLP/OECD 407-compliant subchronic study, 6 Sprague Dawley rats/sex/dose were administered δ-decalactone via gavage at doses of 0, 250, 500, and 1000 mg/kg/day for 28 days. An additional 6 Sprague Dawley rats/sex/dose at 0 and 1000 mg/kg/day were maintained as recovery groups for 2 weeks after the treatment period. No mortality occurred throughout the study period. No treatment-related effects were observed on clinical signs, body weights, bodyweight gains, food consumption, ophthalmology, hematology, clinical biochemistry, urinalysis, behavior, organ weights, gross pathology, or histopathology. Based on no toxicologically relevant effects seen up to the highest dose, the NOAEL for this study was determined to be 1000 mg/kg/day (ECHA, 2013).

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

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

Therefore, the δ-undecalactone MOE for the repeated dose toxicity endpoint can be calculated by dividing the δ-decalactone NOAEL in mg/kg/day by the total systemic exposure to δ-undecalactone, 333/0.0012, or 277500.

In addition, the total systemic exposure to δ-undecalactone (1.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/14/20.

11.1.3. Reproductive toxicity

The MOE for δ-undecalactone is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on δ-undecalactone. Read-across material δ-decalactone (CAS # 705-86-2) has sufficient data to support the reproductive toxicity endpoint. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material δ-decalactone via oral gavage in corn oil at doses of 0, 250, 500, or 1000 mg/kg/day. Males were dosed for 37 days (2 weeks prior to mating, through the mating period, and until termination), while females were dosed for approximately 62 days (2 weeks prior to mating, during mating, during post-coitum, and up to lactation day 13). No treatment-related mortality was observed in any dose group. No changes were observed in mean body weights and organ weights (both relative and absolute). No treatment-related effects were seen with respect to any fertility parameters for males and females. Pups did not show any clinical signs or external anomalies throughout the lactation period. No treatment-related changes in pup weights or ano-genital distance ratio were observed in any group. The NOAEL for developmental toxicity and fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). **Therefore, the δ-undecalactone MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the δ-decalactone NOAEL in mg/kg/day by the total systemic exposure to δ-undecalactone, 1000/0.0012, or 833333.**

In addition, the total systemic exposure to δ-undecalactone (1.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/20.

11.1.4. Skin sensitization

Based on the existing data and read-across to δ-octalactone (CAS # 698-76-0), δ-undecalactone presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for δ-undecalactone. Based on read-across material δ-octalactone (CAS # 698-76-0; see Section VI), δ-undecalactone is not considered a skin sensitizer. The chemical structure of these materials indicate that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material δ-octalactone was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test (ECHA, 2019b). In a guinea pig maximization test, the read-across material did not present reactions indicative of sensitization (RIFM, 1981). In human maximization tests, no skin sensitization reactions were observed with δ-undecalactone and read-across material δ-octalactone (RIFM, 1975; RIFM, 1977).

Based on weight of evidence (WoE) from structural analysis, human studies, and read-across material δ-octalactone, δ-undecalactone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, δ-undecalactone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for δ-undecalactone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, δ-undecalactone does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for δ-undecalactone 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 δ-undecalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.011 mg/day. This exposure is 127.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of δ-undecalactone was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, δ-undecalactone was identified as a fragrance material with no 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 δ-undecalactone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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), δ-undecalactone presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key Studies

11.2.2.1.1. ***Biodegradation.*** RIFM, 2013a: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 78% was observed after 28 days.

11.2.2.1.2. ***Ecotoxicity.*** No data available.

11.2.2.1.3. ***Other available data.*** δ-Undecalactone has been registered for REACH, with the following additional data available at this time (ECHA, 2019a):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 80% was observed after 28 days.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on mean measured test concentration was reported to be 21 mg/L (95% CI: 19–24 mg/L).

The algae growth inhibition test was conducted according to the OECD 202 guideline under static conditions. The 72-h EC50 value based on time-weighted average concentration for growth rate was reported to be 27 mg/L (95% CI: 25–29 mg/L).

11.2.3. Risk Assessment Refinement

Since δ-undecalactone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.0	3.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.03353 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 09/11/20.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	33.53	X	X	1000000	0.03353	X

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 02/10/21.

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.2021.112208.

Appendix

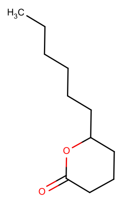
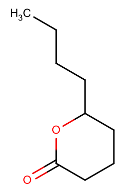
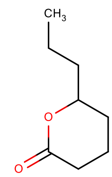
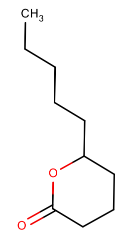
Read-across Justification

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

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	δ-Undecalactone	Hydroxynonanoic acid, δ-lactone	δ-Octalactone	δ-Decalactone
CAS No.	710-04-3	3301-94-8	698-76-0	705-86-2
				
Similarity (Tanimoto Score)		0.97	0.94	1.00
Endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{11}H_{20}O_2$	$C_9H_{16}O_2$	$C_8H_{14}O_2$	$C_{10}H_{18}O_2$
Molecular Weight	184.279	156.225	142.198	170.252
Melting Point (°C, EPI Suite)	28.95	8.52	−2.09	18.86
Boiling Point (°C, EPI Suite)	298.40	267.02	249.98	283.16
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.61E-01	1.45E+00	3.64E+00	6.33E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.28E+02	1.20E+03	3.63E+03	3.94E+02
Log K_{OW}	3.06	2.08	1.59	2.57
J_{max} (μg/cm^2/h, SAM)	6.01	25.79	50.62	12.71
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.56E+01	4.29E+01	3.23E+01	5.69E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found		
Oncologic Classification	Lactone Type Reactive Functional Groups	Lactone Type Reactive Functional Groups		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Not categorized			Not categorized
Reproductive Toxicity				
	Non-binder, without OH or NH2 group			

(continued on next page)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
ER Binding (OECD QSAR Toolbox v4.2)				Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)			Non-toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents		Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents	
Protein Binding (OECD)	Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates		Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents		Acylation|Acylation ≫ Ring opening acylation|Acylation ≫ Ring opening acylation ≫ Active cyclic agents	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on δ-undecalactone (CAS # 710-04-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, hydroxynonanoic acid, δ-lactone (CAS # 3301-94-8), δ-octalactone (CAS # 698-76-0), and δ-decalactone (CAS # 705-86-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Hydroxynonanoic acid, δ-lactone (CAS # 3301-94-8) was used as a read-across analog for the target material δ-undecalactone (CAS # 710-04-3) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of δ-lactones.
  - o The target material and the read-across analog share a δ-lactone substructure.
  - o The key difference between the target material and the read-across analog is that the target material has methyl substitution on the 4 position, which the read-across analog lacks. One more structural difference is that the target material is a lactone of undecanoic acid, while the read-across analog is a lactone of nonanoic acid. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog and the target material have an alert of containing lactone type reacting functional group under the oncologic classification scheme by OECD QSAR Toolbox. Lactones are cyclic esters that may open to serve as an acylating agent. In general, the ability to open the ring is dependent on the size of the ring. Gamma and δ-lactones are considerably weaker acylating agents with some carcinogenicity potential, only if unsaturation is present in the ring α-β to the carbonyl group. The ring in the target material, as well as the read-across analog, is saturated. The data on the read-across analog confirm that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog, and the data present on the read-across analog, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- δ-Octalactone (CAS # 698-76-0) was used as a read-across analog for the target material δ-undecalactone (CAS # 710-04-3) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of δ-lactones.
  - o The target material and the read-across analog share a δ-lactone substructure.
  - o The key difference between the target material and the read-across analog is that the target material has methyl substitution on the 4 position, which the read-across analog lacks. One more structural difference is that the target material is a lactone of undecanoic acid, while the read-across analog is a lactone of octanoic acid. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog and the target material have an alert of direct acylating agent for skin sensitization endpoint by several models. Lactones are cyclic esters that may open to serve as an acylating agent. The chemical may have an assumptive weak sensitization effect as a result of protein acylation by lactones. In general, the ability to open the ring is dependent on the size of the ring. Gamma and δ-lactones are considerably weaker acylating agents, only if unsaturation is present in the ring α-β to the carbonyl group. The ring in the target material, as well as the read-across analog, is saturated. The data on the read-across analog confirm that the material does not pose a concern for skin sensitization. Therefore, based on the structural similarity between the target material and the read-across analog, and the data present on the read-across analog, the predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- δ-Decalactone (CAS # 705-86-2) was used as a read-across analog for the target material δ-undecalactone (CAS # 710-04-3) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of δ-lactones.
  - o The target material and the read-across analog share a δ-lactone substructure.
  - o The key difference between the target material and the read-across analog is that the target material has methyl substitution on the 4 position, which the read-across analog lacks. One more structural difference is that the target material is a lactone of undecanoic acid, while the read-across analog is a lactone of decanoic acid. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the target material and the read-across analog for repeated dose toxicity and reproductive toxicity. Therefore, the predictions are consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1 A normal constituent of the body? No.
Q2 Contains functional groups associated with enhanced toxicity? No.
Q3 Contains elements other than C, H, O, N, and divalent S? No.
Q43 Possibly harmful divalent sulfur? No.
Q5 Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6 Benzene derivative with certain substituents? No.
Q44 Possibly harmful analog of benzene? No.
Q7 Heterocyclic? No.
Q8 Lactone or cyclic diester? Yes.
Q9 Lactone, fused to another ring, or 5- or 6-membered α,β-unsaturated lactone? No.
Q20 Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
Q21 Three or more different functional groups? No.
Q44 Free α-β, unsaturated heteroatom? No.
Q18 One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No. Class I (Class low)

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