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Short Review

RIFM fragrance ingredient safety assessment, γ-undecalactone, CAS Registry Number 104-67-6

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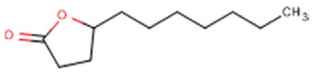
Version: 020719. This version replaces any previous versions.

Name: γ-Undecalactone **CAS Registry Number:** 104-67-6



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
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
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose

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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.

γ-Undecalactone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog γ-nonalactone (CAS # 104-61-0) show that γ-undecalactone is not expected to be genotoxic. Data on read-across material γ-hexalactone (CAS # 695-06-7) provide a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints. Based on the existing data and read-across materials 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) and (±) 3-methyl-γ-decalactone (-CAS # 67663-01-8), γ-undecalactone does not present a concern for skin sensitization. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; γ-undecalactone is not expected to be phototoxic/photoallergenic. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to γ-undecalactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). The environmental endpoints were evaluated; γ-undecalactone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(Heck et al., 1989; #8904; ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013a)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day.	(ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013a)
Developmental and Reproductive Toxicity: Developmental Toxicity: NOAEL = 1000 mg/kg/day. Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	(ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(RIFM, 2002; RIFM, 1988a)
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: 99.7% (OECD 301B)	RIFM (1994)

Bioaccumulation:

Critical Measured Value: 48.4 L/kg	(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.138 mg/L	ECHA REACH Dossier: Undecan-4-olide; ECHA (2013b)

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: 21-day *Daphnia magna* NOEC: 0.138 mg/L	ECHA REACH Dossier: Undecan-4-olide; ECHA (2013b)

RIFM PNEC is: 2.76 μg/L

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

1. Identification

1. **Chemical Name:** γ-Undecalactone
2. **CAS Registry Number:** 104-67-6
3. **Synonyms:** Aldehyde C-14 pure (so called); 2(3H)-Furanone, 5-heptyldihydro-; γ-n-Heptyl butyrolactone; 4-Hydroxyundecanoic acid, γ-lactone; Peach aldehyde (so called); Peche pure; Undecanolide-1,4; Undecylene methyl lactone; γ-Undecyl lactone; γ-Heptylbutyrolactone; 5-Heptyldihydro-2(3H)-furanone; 4-Undecanolide; Peach Pure; γ-アルキルラクトン(C = 0～14); 5-Heptyldihydrofuran-2(3H)-one; γ-Undecalactone
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.28
6. **RIFM Number:** 205
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 297 °C (FMA), 297.04 °C (EPI Suite)
2. **Flash Point:** 145 °C (GHS), > 200 °F; CC (FMA)
3. **Log K_{OW}:** 3.6 at 25C (RIFM, 1995), 3.06 (EPI Suite)
4. **Melting Point**: 10.66 °C (EPI Suite)
5. **Water Solubility:** 128.3 mg/L (EPI Suite)
6. **Specific Gravity:** 0.94 (RIFM, 1994), 0.942–0.945 (FMA), 0.944–0.947 (FMA)
7. **Vapor Pressure:** 0.00252 mm Hg @ 20 °C (EPI Suite v4.0), 0.002 mm Hg 20 °C (FMA), 0.00409 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Arctander Volume II 1969: Almost colorless or very pale straw-colored, slightly viscous liquid. Sweet, oily-fruity, peach-like taste in concentrations lower than 20 ppm. The effect at higher concentrations is not unpleasant, but strongly fruity, supporting other fruity notes, necessarily present at a high concentration of the lactone.

3. Exposure

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0013% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.0010 mg/kg/day or 0.073 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2018)

*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 IV. 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 I, Low (Expert Judgment)

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I*	II	III

*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. See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** γ-Nonalactone (CAS # 104-61-0)
   b. **Repeated Dose Toxicity:** γ-Hexalactone (CAS # 695-06-7)
   c. **Developmental and Reproductive Toxicity:** γ-Hexalactone (CAS # 695-06-7)
   d. **Skin Sensitization:** 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2), (±) 3-methyl-γ-decalactone (CAS # 67663-01-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

γ-Undecalactone is reported to occur in the following foods*:
Apricot (*Prunus armeniaca* L.)
Beef.
Chicken.
Macadamia nut (*Macadamia integrifolia*).
Milk and milk products.
Peach (*Prunus persica* L.)
Plum (*Prunus* species).
Pork.
Rambutan (*Nephelium lappaceum* L.)
Raspberry, blackberry and boysenberry.
Rice (*Oryza sativa* L.)
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. This is a partial list.

9. IFRA standard

None.

10. REACH dossier

Available, accessed 02/08/19.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, γ-undecalactone does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of γ-undecalactone; however, read-across can be made to γ-nonalactone (CAS # 104-61-0; see Section V). The mutagenicity of γ-nonalactone was assessed in an *in vitro* mammalian cell gene mutation assay conducted in compliance with GLP, in accordance with OECD TG 476. Mouse lymphoma L5178Y cells were treated with γ-nonalactone in acetone at concentrations up to 1562 mg/mL (10 mM) in the presence and absence of metabolic activation. No increase in the mean mutant frequencies of the test groups compared to controls (ECHA, 2013a). Under the conditions of the study, γ-nonalactone was considered non-mutagenic.

The clastogenic activity of γ-undecalactone was assessed in an *in vitro* chromosome aberration test conducted equivalent to OECD TG 473. Chinese hamster fibroblast cell line (CHL) were treated with γ-undecalactone in DMSO at concentrations up to 500 μg/mL in the presence and the absence of metabolic activation. No significant increases in the numbers of chromosome breaks were observed (Ishidate et al., 1984). Under the conditions of the study, γ-undecalactone was considered not clastogenic.

For weight of evidence, the clastogenic potential of read-across material γ-nonalactone (CAS # 104-61-0) was investigated in an *in vivo* bone marrow micronucleus assay, performed according to OECD Guideline 474 and in compliance with GLP. Groups of male and female NMRI mice were administered a single oral dose of γ-nonalactone in corn oil at concentrations of 0, 500, 1000, and 2000 mg/kg. No statistically significant increases in the frequency of micronucleated polychromatic erythrocytes were observed at any doses tested (ECHA, 2013a). Under the test conditions, γ-nonalactone is not considered to be clastogenic in the mouse bone marrow micronucleus, and this can be extended to γ-undecalactone.

Based on the available data, γ-nonalactone does not present a concern for genotoxic potential, and this can be extended to γ-undecalactone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/07/19.

11.1.2. Repeated dose toxicity

The MOE is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data for γ-undecalactone. The available repeated dose toxicity data on γ-undecalactone is in a subacute single dose study (Oser et al., 1965). Due to the lack of robust experimental design, that study is considered as weight of evidence in this safety assessment. In a non-guideline and non-GLP-compliant 90-day toxicity study, FDRL rats (Control: 60 rats/sex; Treatment: 15 rats/sex) were fed diets containing γ-undecalactone (purity not reported) at doses of 14.6 mg/kg/day and 16.5 mg/kg/day for males and females, respectively. Necropsy was performed only for

the liver and kidneys. With the exception of reduced leukocyte counts in both the sexes, despite normal differential WBC counts, no treatment-related adverse effects were reported (Oser et al., 1965). Because this is a single dose study, a NOAEL could not be determined from the study.

Read-across material γ-hexalactone (CAS # 695-06-7; see Section V) has sufficient repeated dose toxicity data. In a subchronic toxicity study (GLP and OECD 407–compliant) performed on Crl:CD (Sprague Dawley) IGS BR rats, γ-hexalactone was administered through oral gavage at dose levels of 0 (vehicle control: deionized water), 30, 100, 300, or 1000 mg/kg/day for a period of 28 days. No treatment-related adverse effects were reported up to highest tested dose level; therefore, the NOAEL was considered to be 1000 mg/kg/day (ECHA, 2013a). Based on the absence of systemic toxic effects for the repeated dose endpoint, in both studies, the highest NOAEL of 1000 mg/kg/day was selected from the more robust OECD 407 study.

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

The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333.3 mg/kg/day.

Therefore, the γ-undecalactone MOE for the repeated dose toxicity endpoint can be calculated by dividing the γ-hexalactone NOAEL in mg/kg/day by the total systemic exposure to γ-undecalactone, 333.3/0.0053, or 62887.

In addition, the total systemic exposure to γ-undecalactone (5.3 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.

* 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: Galea et al., 1965; Bar and Griepentrog, 1967.

Literature Search and Risk Assessment Completed On: 02/01/19.

11.1.3. Developmental and Reproductive Toxicity

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

There are insufficient reproductive toxicity data on γ-undecalactone or on any read-across materials. The total systemic exposure to γ-undecalactone is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are insufficient developmental toxicity data on γ-undecalactone. Read-across material γ-hexalactone (CAS # 695-06-7; see Section V) has sufficient developmental toxicity data. In a developmental toxicity study (GLP and OECD 414–compliant) performed on Crl:CD (Sprague Dawley) IGS BR rats (25/sex/dose), γ-hexalactone was administered through oral gavage at dose levels of 0 (vehicle control: deionized water), 100, 300, or 1000 mg/kg/day for a period of 14 days during gestation from days 6–19. No treatment-related changes were reported for dams in clinical signs, body weights, gravid uterine weight, feed consumption, and necropsy examination. A significant decrease in fetal body weight was reported in the high-dose group; however, the decrease in body weight was within the historical control range. At 300 mg/kg/day, external malformations including meningocele were reported in 1 fetus, visceral malformations including malpositioned descending aorta were reported in another fetus, and a skeletal malformation (a vertebral centra anomaly: the right half of lumbar centrum number 2 was absent and the right half of lumbar centrum no. 1 was malpositioned) was reported in 1 fetus. However, these changes were reported in only 3 of 365 fetuses examined at this dose level and were not present at any other dose level. Other soft tissue and skeletal malformations and variants were reported in a single fetus, but they did not occur in a dose-related manner. In addition, the skeletal variants reported in all treated groups were within the historical control data and therefore not considered to be treatment-related. The NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg/day, as no treatment-related adverse effects were reported up to the highest dose level tested (ECHA, 2013a). **Therefore, the γ-undecalactone MOE for the developmental toxicity endpoint can be calculated by dividing the γ-hexalactone NOAEL in mg/kg/day by the total systemic exposure to γ-undecalactone, 1000/0.0053 or 188679.**

In addition, the total systemic exposure to γ-undecalactone (5.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are insufficient reproductive toxicity data on γ-undecalactone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to γ-undecalactone (5.3 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, 1961.

Literature Search and Risk Assessment Completed On: 01/21/19.

11.1.4. Skin sensitization

Based on the existing data and read-across materials 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) and (±) 3-methyl-γ-decalactone (CAS # 67663-01-8), γ-undecalactone does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for γ-undecalactone. Based on the existing data and read-across materials 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2; see Section V) and (±) 3-methyl-γ-decalactone (CAS # 67663-01-8; see Section V), γ-undecalactone does not present a concern for skin sensitization under current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive *in chemico* or *in vitro* skin sensitization studies are available on the target material, γ-undecalactone, or the read-across materials, 4-hydroxy-3-methyloctanoic acid lactone and (±) 3-methyl-γ-decalactone, in the literature. Although limited details were provided in the report, no skin reactions were reported in a guinea pig open cutaneous test with γ-undecalactone (Klecak, 1985). In the guinea pig maximization tests, the read-across materials 4-hydroxy-3-methyloctanoic acid lactone and (±) 3-methyl-γ-decalactone did not present reactions indicative of sensitization up to 10% and 20%, respectively (RIFM, 1988a; RIFM, 2002). Based on weight of evidence (WoE) from structural analysis, human and animal studies, and read-across materials 4-hydroxy-3-methyloctanoic acid lactone and (±) 3-methyl-γ-decalactone, γ-undecalactone does not present a concern for skin sensitization under current, declared levels of use.

Additional References: RIFM, 1962; RIFM, 1988b.

Literature Search and Risk Assessment Completed On: 01/22/19.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, γ-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 γ-undecalactone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity

(Henry et al., 2009). Based on the lack of absorbance, γ-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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/05/19.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on γ-undecalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.073 mg/day. This exposure is 19.18 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: 01/28/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of γ-undecalactone ether 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, γ-undecalactone 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 did not identify γ-undecalactone as either being 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 ≥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 VoU (2015), γ-undecalactone presents a risk to the aquatic compartment in the screening-level assessment.

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

RIFM, 1999b: Biodegradability was evaluated by the closed bottle test according to the OECD 301D method. 2.7 mg/L of γ-undecalactone was incubated with local wastewater for 28 days. The biodegradation rate was 82% after the 28-day incubation period.

RIFM, 1994: Biodegradation was evaluated by the sealed vessel test according to the OECD 301B method. 10 mg/L of γ-undecalactone was incubated with filtered activated sludge for 28 days. The rate of degradation after 28 days was 99.7%.

RIFM, 1991: The ready biodegradability of the test material was determined by the Respirometric Method (modified MITI Test) according to the OECD 301C method. Biodegradation of 74% was observed after 28 days.

Ecotoxicity:

RIFM, 1999a: A 48-hour *Daphnia magna* acute toxicity study was conducted with the test material. Geometric mean (EC0/EC100) based on 48-hour data was reported to be 4.0 mg/L.

RIFM, 2013a: A 48-hour *Daphnia magna* acute test was conducted according to the OECD 202 guidelines under flow-through conditions. The EC50 was reported to be 6.1 mg/L.

RIFM, 2013b: A 96-hour algae (*Pseudokirchneriella subcapitata*) acute test was conducted according to the OECD 201 guidelines. The 96-hour EbC50 (area under the growth curve) and ErC50 (growth rate) were reported to be 1.3 mg/L and 1.6 mg/L, respectively. The 0–96-h NOEC based on the growth curve and yield was reported to be less than 0.47 mg/L.

RIFM, 2013c: A 96-hour Fathead minnow (*Pimephales promelas*) acute test was conducted according to the OECD 203 guidelines under flow-through conditions. The LC50 was reported to be 7.3 mg/L.

Other available data:

γ-Undecalactone has been registered under REACH, with following additional data.

The *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC for reproduction was reported to be 0.138 mg/L based on mean geometric measured concentration (ECHA, 2013b).

The algae (*Pseudokirchneriella subcapitata*) acute test was conducted according to the OECD 201 guidelines. The 48-hour ErC50 (growth rate) was reported to be 5.94 mg/L and the NOEC was reported to be 0.779 mg/L (ECHA, 2013b).

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.08			1000000	0.01008	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.937	11.02	3.966	10000	0.397	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	16.97	10.62	11.85			Neutral Organic SAR (Baseline toxicity)
Tier 3: Measured Data (including REACH data)						
	LC50 (mg/L)	EC50 (mg/L)	NOEC	AF	PNEC (μg/L)	Comments
Fish	7.3					
Daphnia		6.1	0.138	50	2.76	
Algae		1.3	0.47			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.6	3.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	> 1000
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 2.76 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/24/19.

Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research

Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111101.

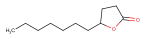
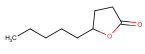
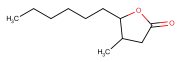
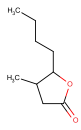
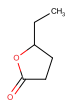
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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) (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization 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).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	γ-Undecalactone	γ-Nonalactone	(±) 3-Methyl-γ-decalactone	4-Hydroxy-3-methyloctanoic acid lactone	γ-Hexalactone
CAS No.	104-67-6	104-61-0	67663-01-8	39212-23-2	695-06-7
Structure					
Similarity (Tanimoto Score)		1	0.83	0.81	0.78
Read-across Endpoint		• Genotoxicity	• Skin Sensitization	• Skin Sensitization	• Repeated Dose Toxicity • Developmental Toxicity
Molecular Formula	$C_{11}H_{20}O_2$	$C_9H_{16}O_2$	$C_{11}H_{20}O_2$	$C_9H_{16}O_2$	$C_6H_{10}O_2$
Molecular Weight	184.27	156.22	184.27	156.22	114.14
Melting Point (°C, EPI Suite)	10.66	9.83	26.92	6.29	−18
Boiling Point (°C, EPI Suite)	286	265.50	292.69	260.63	215.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.545	1.57	0.368	2.05	22
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.06	2.08	2.98	2.00	0.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	128.3	1201	148.2	1387	3.219e+004
J_{max} (μg/cm^2/h, SAM)	11.348	45.653	6.23	62.889	353.995
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.56E+001	4.29E+001	7.56E+001	4.29E+001	1.83E+001
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Michael-type addition on α,β-unsaturated carbonyl compounds|AN2 ≫	• AN2|AN2 ≫ Michael-type addition on α,β-unsaturated carbonyl			

	Michael-type addition on alpha, beta-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylation, ring opening SN2 reaction ≫ Four- and Five-Membered Lactones	compounds|AN2 ≫ Michael-type addition on alpha, beta-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylation, ring opening SN2 reaction ≫ Four- and Five-Membered Lactones			
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found			
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)			
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)	• Oxolane	• Oxolane			
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 (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group				• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)				• Non-toxicant (low reliability)
Skin Sensitization					
Protein Binding (OASIS v1.1)	• No alert found		• 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	• 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)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found	• No alert found	
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	See Supplemental Data 5

Summary

There are insufficient toxicity data on γ-undecalactone (CAS # 104-67-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, γ-nonalactone (CAS # 104-61-0), (±) 3-methyl-γ-decalactone (CAS # 67663-01-8), 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2), and γ-hexalactone (CAS # 695-06-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- γ-Nonalactone (CAS # 104-61-0) was used as a read-across analog for the target material γ-undecalactone (CAS # 104-67-6) for the genotoxicity endpoints.

  - The target material and the read-across analog are structurally similar and belong to a class of γ-lactone.
  - The target material and the read-across analog share a γ-lactone ring with a straight chain saturated aliphatic substituents at position 4.
  - The key difference between the target material and the read-across analog is that the target material has a straight chain C7 substituent at position 4 while its read-across analog has a straight chain C5 substituent at position 4. This structural difference is toxicologically insignificant.
  - 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 target and read-across materials show several alerts due to the γ-lactone ring. Saturated γ-Lactones are known for being considerably weaker acylating agents compared to other lactones. Additionally, γ-lactones are reported to be totally inactive to DNA alkylation. In consequence, all the alerts can be ignored.
  - 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.

- (±) 3-Methyl-γ-decalactone (CAS # 67663-01-8) was used as a read-across analog for the target material γ-undecalactone (CAS # 104-67-6) for the skin sensitization endpoint.

  - The target material and the read-across analog are structurally similar and belong to a class of γ-lactone.
  - The target material and the read-across analog share a γ-lactone ring with a straight chain aliphatic substituent at the 4-position.
  - The key difference between the target material and the read-across analog is that the target material has a straight chain C7 substituent at the 4-position while its read-across analog has a chain C6 substituent at the 4-position and a methyl group in position 3. This structural difference is toxicologically insignificant.
  - 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.
  - Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq 80\%$ and J_{max} for the read-across analog corresponds to skin absorption $\leq 40\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - 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 target and read-across materials a Protein Binding (OECD) acylation alert for acetates. However, neither the target nor the read-across materials have a potentially reactive acetate group. In consequence, all the alerts can be ignored. The predictions are superseded by 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.

- 4-Hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) was used as a read-across analog for the target material γ-undecalactone (CAS # 104-67-6) for the skin sensitization endpoint.

  - The target material and the read-across analog are structurally similar and belong to a class of γ-lactone.
  - The target material and the read-across analog share a γ-lactone ring with a straight chain aliphatic substituent at the 4-position.
  - The key difference between the target material and the read-across analog is that the target material has a straight chain C7 substituent at position 3 while its read-across analog has a straight chain C4 substituent at the 4-position and a methyl group in position 3. This structural difference is toxicologically insignificant.
  - 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 target and read-across materials a Protein Binding (OECD) acylation alert for acetates. However, neither the target nor the read-across materials have a potentially reactive acetate group. In consequence, all the alerts can be ignored. The predictions are superseded by 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.

- γ-Hexalactone (CAS # 695-06-7) was used as a read-across analog for the target material γ-undecalactone (CAS # 104-67-6) for the repeated dose toxicity and developmental toxicity endpoint.

- The target material and the read-across analog are structurally similar and belong to a class of γ-lactone.
- The target material and the read-across analog share a γ-lactone ring with a straight chain aliphatic substituents at position 4.
- The key difference between the target material and the read-across analog is that the target material has a straight chain C7 aliphatic substituent at position 4 while its read-across analog has a straight chain C2 substituent at position 4. This structural difference is toxicologically insignificant.
- 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.
- 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
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? Yes
Q8. Lactone or cyclic diester? Yes
Q9. Lactone, fused to another ring, or 5- or 6-membered alpha,beta-unsaturated lactone? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
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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