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Short review

# RIFM fragrance ingredient safety assessment, γ-nonalactone, CAS Registry Number 104-61-0

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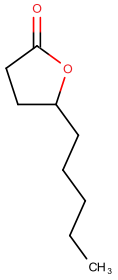
**Version: 052219. This version replaces any previous versions.**

**Name**: γ-Nonalactone
**CAS Registry Number**: 104-61-0




**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; Safford et al., 2015a; Safford et al., 2017; Comiskey 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
**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

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**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
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence

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

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

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

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

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

γ-Nonalactone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that γ-nonalactone is not genotoxic. Data on read-across analog γ-caprolactone (CAS # 695-06-7) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to γ-valerolactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from the target material and read-across materials 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) and ( ± ) 3-methyl-γ-decalactone (CAS # 67663-01-8) show that there are no safety concerns for γ-nonalactone for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; γ-nonalactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; γ-nonalactone 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 genotoxic | (ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013; RIFM, 2009) |
| **Repeated Dose Toxicity:** NOAEL = 333.3 mg/kg/day | ECHA REACH Dossier: Nonan-4-olide; ECHA (2013) |
| **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 (2013) |
| **Skin Sensitization:** Not a concern for 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: 91% (OECD 301B) | (RIFM, 1994) |
| **Bioaccumulation:** Screening-level: 10.8 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** Screening-level: 96-h Algae EC50: 16.34 mg/L | (ECOSAR; US EPA, 2012b) |
| **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards | |
| **Risk Assessment:** | |
| **Screening-level**: PEC/PNEC (North America and Europe) > 1 | (RIFM Framework; Salvito et al., 2002) |
| **Critical Ecotoxicity Endpoint:** 96-h Algae EC50: 16.34 mg/L | (ECOSAR; US EPA, 2012b) |
| **RIFM PNEC is:** 1.634 μg/L | |
| • Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1 | |

## 1. Identification

1. **Chemical Name:** γ-Nonalactone
2. **CAS Registry Number:** 104-61-0
3. **Synonyms:** Abricolin; Aldehyde C-18 (so called); γ-Amyl butyrolactone; 4-n-Amyl-4-hydroxybutyric acid lactone; Coconut aldehyde; 2(3H)-Furanone, dihydro-5-pentyl-; 4-Hydroxynonanoic acid, γ-lactone; γ-Pelargolactone; Prunolide; γ-アルキルラクトン(C = 0–14); 5-Pentyldihydrofuran-2(3H)-one; Aldehyde C-18; γ-Nonalactone
4. **Molecular Formula:** $C_9H_{16}O_2$
5. **Molecular Weight:** 156.22
6. **RIFM Number:** 305
7. **Stereochemistry:** Isomer not specified. One stereocenter present and 2 total stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 214 °C (FMA Database), 265.5 °C (EPI Suite)
2. **Flash Point:** > 212 °F; CC (FMA Database), 126 °C (GHS)
3. **Log $K_{OW}$:** 2.5 at 25 °C (RIFM, 1995), 2.08 (EPI Suite)
4. **Melting Point**: 9.83 °C (EPI Suite)
5. **Water Solubility:** 1201 mg/L (EPI Suite)
6. **Specific Gravity:** 0.958–0.966 (FMA Database), 0.962 (FMA Database), 0.960–0.968 (FMA Database)
7. **Vapor Pressure:** 0.0073 mm Hg @ 20 °C (EPI Suite v4.0), 0.02 mm Hg 20 °C (FMA Database), 0.0118 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to yellow liquid with coconut odor

## 3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.17% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.0013 mg/kg/day or 0.094 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0082 mg/kg/day (RIFM, 2017)

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

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

## 4. Derivation of systemic absorption

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

## 5. Computational toxicology evaluation

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

| Expert Judgment | Toxtree v 2.6 | 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 Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** γ-Caprolactone (CAS # 695-06-7)
   c. **Developmental and Reproductive Toxicity:** γ-Caprolactone (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

## 6. Metabolism

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

## 7. Natural occurrence (discrete chemical) or composition (NCS)

γ-Nonalactone is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*).
Apple brandy (calvados).
Apricot (*Prunus armeniaca* L.)
Asparagus (*Asparagus officinalis* L.)
Avocado (*Persea americana* Mill.)
Beans.
Beef.
Beer.
Black currants (*Ribes nigrum* L.)
Brown algae.
Buckwheat.
Cashew apple (*Anacardium occidentale*).
Cheddar cheese.
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.)
Chicken.
Chinese liquor (baijiu).
Citrus fruits.
Cocoa category.
Crispbread.
Elderberry (*Sambucus nigra* L.)
Fenugreek (*Trigonella foenum-graecum* L.)
Filbert, hazelnut (*Corylus avellano*).
Grape (*Vitis* species).
Grape brandy.
Guava and feyoa
Guava wine.
Honey.
Kumazasa (sasa albo-marginata).
Lamb and mutton.
Licorice (*Glycyrrhiza* species).
Litchi (*Litchi chinensis* Sonn.)
Macadamia nut (*Macadamia integrifolia*).
Malt.
*Mangifera* species.
Mate (*Ilex paraguayensis*).
Melon.
Milk and milk products.
Mountain papaya (*C. candamarcensis, C. pubescens*).
Mushroom.
Mustard (*Brassica* species).
Nectarine.
Oats (*Avena sativa* L.)
Olive (*Olea europaea*).
Origanum (Spanish) (*Coridothymus cap*. (L.) *Rchb*.)
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species).
Peach (*Prunus persica* L.)
Pear (*Pyrus communis* L.)
Pear brandy.
Pecan (*Carya illinoensis koch*).
Pineapple (*Ananas comosus*).
Pistachio nut (*Pistacia vera*).
Plum (*Prunus* species).
Plum wine.
Pork.
Potato (*Solanum tuberosum* L.)
Prickly pear (*Opuntia ficus indica*).
Pumpkin seed oil.
Rambutan (*Nephelium lappaceum* L.)
Rapeseed.
Raspberry, blackberry, and boysenberry.
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*).
Rum.
Sherry.
Shrimps (prawn).
Soybean (*Glycine max*. L. Merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species).
Sugar molasses.
Sweet grass oil (*Hierochloe odorata*).
Tamarind (*Tamarindus indica* L.)
Tea.
Tequila (agave tequilana).
Tomato (*Lycopersicon esculentum* Mill.)
Truffle.
Vanilla.
Wheaten bread.
Whisky.
Wine.

*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.

## 8. IFRA standard

None.

## 9. REACH dossier

Available; accessed 11/01/18.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

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

*10.1.1.1. Risk assessment.* γ-Nonalactone was assessed in the BlueScreen assay and found negative for both cytotoxicity (reduced the relative cell density to less than 80%) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of γ-nonalactone has been evaluated in a bacterial reverse mutation assay conducted similar to OECD TG 471 using the standard plate incorporation. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with γ-nonalactone in dimethyl sulfoxide (DMSO) at concentrations up to 37500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Heck et al., 1989). Under the conditions of the study, γ-nonalactone was not mutagenic in the Ames test. Since this assay deviated from current OECD 471 guidelines for the Ames test, additional weight of evidence was made with negative results in a mammalian cell gene mutation assay conducted according to GLP regulations and OECD 476 guidelines. Mouse lymphoma L5178Y cells were treated with γ-nonalactone in acetone at concentrations up to 1562 μg/mL for 3 h or 24 h in the absence of metabolic activation or 3 h in the presence of S9. No increases in the frequency of mutant colonies were observed with any concentration of the test item, either with or without metabolic activation (ECHA, 2013). Under the conditions of the study, γ-nonalactone was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of γ-nonalactone was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 500, 1000, or 2000 mg/kg body weight were administered for 24 or 48 h. Mice from each dose level were euthanized at 24 h. Additional samples were taken at the high dose only at 48 h. Bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2009). Under the conditions of the study, γ-nonalactone was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: Ha and Reineccius, 1988.

**Literature Search and Risk Assessment Completed On:** 10/10/2018.

#### 10.1.2. Repeated dose toxicity

The margin of exposure for γ-nonalactone is adequate for the repeated dose toxicity endpoint at the current level of use.

*10.1.2.1. Risk assessment.* There are insufficient repeated dose toxicity data on γ-nonalactone. Read-across material γ-caprolactone (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-caprolactone 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. Based on the absence of systemic toxic effects, a NOAEL of 1000 mg/kg/day was selected for the repeated dose toxicity endpoint (ECHA, 2013).

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-nonalactone MOE for the repeated dose toxicity endpoint can be calculated by dividing the γ-caprolactone NOAEL in mg/kg/day by the total systemic exposure to γ-nonalactone, 333.3/0.0082, or 40646.

In addition, the total systemic exposure to γ-nonalactone (8.2 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**: Oser et al., 1965; Bar and Griepentrog, 1967.

**Literature Search and Risk Assessment Completed On**: 05/02/18.

#### 10.1.3. Development and reproductive toxicity

The margin of exposure for γ-nonalactone is adequate for the developmental toxicity endpoint at the current level of use.

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

*10.1.3.1. Risk assessment.* There are insufficient developmental toxicity data on γ-nonalactone. Read-across material γ-caprolactone (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-caprolactone 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, 2013).

Therefore, the γ-nonalactone MOE for the developmental toxicity endpoint can be calculated by dividing the γ-caprolactone NOAEL in mg/kg/day by the total systemic exposure to γ-nonalactone, 1000/0.0082 or 121951.

In addition, the total systemic exposure to γ-nonalactone (8.2 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-nonalactone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to γ-nonalactone (8.2 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:** Oser et al., 1965; Hagan et al., 1967; RIFM, 1961.

**Literature Search and Risk Assessment Completed On:** 05/02/2018.

*10.1.4. 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-nonalactone does not present a concern for skin sensitization.

*10.1.4.1. Risk assessment.* Limited skin sensitization studies are available for γ-nonalactone. 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-nonalactone 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 2.6.13; OECD toolbox v4.1). No predictive *in chemico* or *in vitro* skin sensitization studies are available on γ-nonalactone or read-across materials 4-hydroxy-3-methyloctanoic acid lactone and ( ± ) 3-methyl-γ-decalactone in the literature. In guinea pig maximization tests, 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). In human maximization tests, no skin sensitization reactions were observed with γ-nonalactone (RIFM, 1976; RIFM, 1972).

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-nonalactone does not present a concern for skin sensitization under current, declared levels of use.

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

**Literature Search and Risk Assessment Completed On:** 10/10/18.

*10.1.5. Phototoxicity/photoallergenicity*

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

*10.1.5.1. Risk assessment.* There are no phototoxicity studies available for γ-nonalactone 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 lack of absorbance, γ-nonalactone does not present a concern for phototoxicity or photoallergenicity.

*10.1.5.2. 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:** 04/11/18.

*10.1.6. Local Respiratory Toxicity*

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

*10.1.6.1. Risk assessment.* There are insufficient inhalation data available on γ-nonalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.094 mg/day. This exposure is 14.9 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:** 09/25/18.

*10.2. Environmental endpoint summary*

*10.2.1. Screening-level assessment*

A screening-level risk assessment of γ-nonalactone 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-nonalactone was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify γ-nonalactone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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.

*10.2.1.1. Risk assessment.* Based on the current Volume of Use (2015), γ-nonalactone presents a risk to the aquatic compartment in the screening-level assessment.

*10.2.1.2. Biodegradation.* RIFM, 1994: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B method. Biodegradation of 91% was observed after 28 days.

RIFM, 1991: The ready biodegradability of the test material was determined by the Respirometric Method (modified MITI Test) according to the OECD 301C method. After 28 days, biodegradation of 80% was observed.

RIFM, 1999: The biological degradation of the test material was evaluated using a closed bottle method according to the OECD 301D guidelines. Under the conditions of the study, biodegradation of 71% was observed.

*10.2.1.3. Ecotoxicity.* RIFM, 1999: A *Daphnia magna* acute immobilization test was conducted according to the 92/69/EEC C.4 method under static conditions. The geometric mean of EC0/EC100 was reported to be 52 mg/L.

*10.2.1.4. Other available data.* γ-Nonalactone has been registered under REACH and the following additional data is available:

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on the growth rate was reported to be 63.5 mg/L.

*10.2.1.5. Risk assessment refinement.* Since γ-nonalactone 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.

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | <u>77.38</u> | | | 1,000,000 | 0.07738 | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 18.85 | 38.87 | <u>16.34</u> | 10,000 | 1.634 | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 109.6 | 62.69 | 48.08 | | | Neutral Organic |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 2.5 | 2.5 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 100–1000 | 100–1000 |
| **Risk Characterization: PEC/PNEC** | **< 1** | **< 1** |

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

The RIFM PNEC is 1.634 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 10/8/18.

## 11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 05/24/19.

## 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.2019.110905.

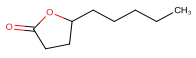
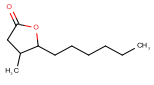
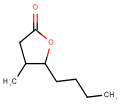
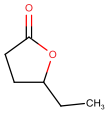
## Appendix

*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 substance 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).
- 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 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 |
|---|---|---|---|---|
| **Principal Name** | γ-Nonalactone | ( ± ) 3-Methyl-γ-decalactone | 4-Hydroxy-3-methyloctanoic acid lactone | γ-Hexalactone (γ-Caprolactone) |
| **CAS No.** | 104-61-0 | 67663-01-8 | 39212-23-2 | 695-06-7 |
| **Structure** |  |  |  |  |
| **Similarity (Tanimoto Score)** | | 0.71 | 0.86 | 0.78 |
| **Read-across Endpoint** | | • Skin Sensitization | • Skin Sensitization | • Repeated dose toxicity<br>• Developmental toxicity |
| **Molecular Formula** | $C_9H_{16}O_2$ | $C_{11}H_{20}O_2$ | $C_9H_{16}O_2$ | $C_6H_{10}O_2$ |
| **Molecular Weight** | 156.23 | 184.28 | 156.23 | 114.14 |
| **Melting Point (°C, EPI Suite)** | 9.83 | 26.92 | 6.29 | −22.87 |
| **Boiling Point (°C, EPI Suite)** | 265.50 | 292.69 | 260.63 | 211.41 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 1.57 | 0.368 | 2.05 | 22 |
| **Log Kow (KOWWIN v1.68 in EPI Suite)** | 2.08 | 2.98 | 2.00 | 0.60 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 1201 | 148.2 | 1387 | 3.219E+004 |
| **$J_{max}$ (μg/cm²/h, SAM)** | 45.653 | 6.231 | 62.889 | 353.995 |
| **Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)** | 4.29E+001 | 7.56E+001 | 4.29E+001 | 1.83E+001 |
| ***Repeated Dose Toxicity*** | | | | |
| **Repeated Dose (HESS)** | • Not categorized | | | • Not categorized |
| ***Developmental 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 (low 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 | • Acylation | |
| **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 v-4.2)** | Supplemental Data 1 | Supplemental Data 2 | Supplemental Data 3 | Supplemental Data 4 |

*Summary*

There are insufficient toxicity data on γ-nonalactone (CAS # 104-61-0). 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, ( ± ) 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*

- ( ± ) 3-Methyl-γ-decalactone (CAS # 67663-01-8) was used as a read-across analog for the target material γ-nonalactone (CAS # 104-61-0) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The key difference between the target substance and the read-across analog is that the target substance has a pentyl substitution at the 5 position while the read-across analog has a pentyl substitution at the 5 position and a methyl substitution at 4 the position. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance 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 substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for $J_{max}$, which estimates skin absorption. $J_{max}$ for the target substance 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.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have acylation alerts. Based on the limited data on the target and data on the read-across analog, it is confirmed that the substances do not present a concern for skin sensitization. Therefore, the predictions are superseded by data.
  - o The target substance 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.
- 4-Hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) was used as a read-across analog for the target material γ-nonalactone (CAS # 104-61-0) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The key difference between the target substance and the read-across analog is that the target substance has a pentyl substitution at the 5 position while the read-across analog has a butyl substitution at the 5 position and a methyl substitution at the 4 position. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance 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 substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have acylation alerts. Based on the limited data on the target and data on the read-across analog, it is confirmed that the substances do not present a concern for skin sensitization. Therefore, the predictions are superseded by data.
  - o The target substance 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.
- γ-Hexalactone (CAS # 695-06-7) was used as a read-across analog for the target material γ-nonalactone (CAS # 104-61-0) for the developmental toxicity and repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The key difference between the target substance and the read-across analog is the target substance has an amyl substitution on the 5 position while the read-across analog has an ethyl substitution on the same position. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance 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 substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.

- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o The target substance 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 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? No
Q8. Lactone or cyclic diester? No
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)? Yes
Q21.3 or more different functional groups? No
Q18. One of the list? No (see Cramer et al., 1978 for detailed explanation on list of categories) Yes, Class I (Class Low)

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