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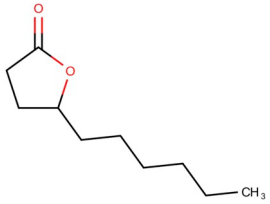
Short Review

RIFM fragrance ingredient safety assessment, γ-decalactone, CAS Registry Number 706-14-9

A.M. Api[a], F. Belmonte[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

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

Version: 052219. This version replaces any previous versions.
Name: γ-Decalactone
CAS Registry Number: 706-14-9



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
EU - Europe/European Union

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

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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
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: Existing information supports the use of this material as described in this safety assessment.

γ-Decalactone 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 analogs γ-octalactone (CAS # 104-50-7) and γ-nonalactone (CAS # 104-61-0) show that γ-decalactone is not expected to be genotoxic. Data on read-across material 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; exposure is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from the target material and read-across analogs 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-decalactone for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; γ-decalactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; γ-decalactone 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.	(RIFM, 2000; 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 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: 82% (OECD 301F)	RIFM (1995a)
Bioaccumulation: Screening-level: 28.95 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 8.08 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: 8.08 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.808 μg/L	
● Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1	

1. Identification

1. **Chemical Name:** γ-Decalactone
2. **CAS Registry Number:** 706-14-9
3. **Synonyms:** Decan-4-olide; 2(3H)-Furanone, 5-hexyldihydro-; 4-n-Hexyl-4-hydroxybutanoic acid lactone; 4-Hydroxydecanoic acid, γ-lactone; γ-アルキルラクトン(C = 0 ~ 14); 5-Hexyldihydrofuran-2(3H)-one; γ-Decalactone
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.25

6. **RIFM Number:** 620
7. **Stereochemistry:** Isomer not specified. One stereocenter present and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 281 °C (FMA Database), 281.72 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database), 136 °C (GHS)
3. **Log K_{OW}:** 3.0 at 25 °C (RIFM, 1995b), 2.57 (EPI Suite)
4. **Melting Point**: 20.2 °C (EPI Suite)
5. **Water Solubility:** 291.6 mg/L (EPI Suite)
6. **Specific Gravity:** 0.955 (FMA Database)
7. **Vapor Pressure:** 0.00317 mm Hg @ 20 °C (EPI Suite v4.0), 0.008 mm Hg 20 °C (FMA Database), 0.00512 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, oily liquid with pleasant, fruity, peach-like or refined, oily-peach odor

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.064% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00057 mg/kg/day or 0.042 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.0039 mg/kg/day (RIFM, 2015)

*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 4. 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. ERIVATION 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:** γ-octalactone (CAS # 104-50-7); γ-nonalactone (CAS # 104-61-0)
   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-Decalactone is reported to occur in the following foods by the VCF*:

Acerola (*Malpighia*).
Apple brandy (Calvados).
Apricot (*Prunus armeniaca* L.)
Babaco fruit (*Carica Pentagona* Heilborn).
Beef.
Beer.
Bilberry wine.
Blue cheeses.
Cape gooseberry (*Physalis peruviana* L.)
Cashew apple (*Anacardium occidentale*).
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cheddar cheese.
Cheese, various types.
Cherry (*prunus avium* [sweet], *pr. Cerasus* [sour])
Chicken.
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cider (apple wine).
Citrus fruits.
Cloves (*Eugenia caryophyllata* Thunberg).
Cocoa category.
Coconut (*Cocos nucifera* L.)
Elderberry (*Sambucus nigra* L.)
Grape brandy.
Guava and feyoa
Guava wine.
Honey.
Lamb and mutton.
Licorice (*Glycyrrhiza* species).
Litchi (*Litchi chinensis* Sonn.)
Lobster.
Malt.
Mangifera species.
Mate (*Ilex paraguayensis*).
Melon.
Mentha oils.
Milk and milk products.
Mushroom.
Nectarine.
Olive (*Olea europaea*).
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*).
Plum (Prunus species).
Plum wine.
Pork.
Potato (*Solanum tuberosum* L.)
Prickly pear (*Opuntia ficus indica*).
Quince, marmelo (*Cydonia oblonga* Mill.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry, blackberry, and boysenberry.
Rice (*Oryza sativa* L.)
Rum.
Sherry.
Shrimps (prawn).
Soybean (*Glycine max*. L. Merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species).
Strawberry wine.
Sugar molasses.
Tarragon (*Artemisia dracunculus* L.)
Tea.
Vaccinium species.
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 and use levels, γ-decalactone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. γ-Decalactone was assessed in the BlueScreen assay and found negative for genotoxicity with S9 and found positive for genotoxicity without S9. These positive results were observed at cytotoxic concentrations (positive: < 80% relative cell density) (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human derived gene expression. While the BlueScreen assay on the target material showed positive results, data from additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic activity of γ-decalactone; however, read-across can be made to γ-octalactone (CAS # 104-50-7; see Section 5). The mutagenic activity of γ-octalactone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with γ-octalactone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000). Under the conditions of the study, γ-octalactone was not mutagenic in the Ames test, and this can be extended to γ-decalactone.

There are no studies assessing the clastogenic activity of γ-decalactone; however, read-across can be made to γ-nonalactone (CAS # 104-61-0; see Section 5). 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 the test material for 24 or 48 h. Mice from each dose level were euthanized at 24 h. Additional samples were taken at 48 h in the high-dose group only. The 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, and this can be extended to γ-decalactone.

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

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for γ-decalactone 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-decalactone. Read-across material γ-caprolactone (CAS # 695-06-7; see Section 5) 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-decalactone 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-decalactone, 333.3/0.0039, or 85461.

In addition, the total systemic exposure to γ-decalactone (3.9 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: RIFM, 1961.

Literature Search and Risk Assessment Completed On: 05/01/18.

10.1.3. Developmental and Reproductive Toxicity

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

There are insufficient reproductive toxicity data on γ-decalactone or on any read-across materials. The total systemic exposure to γ-decalactone 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-decalactone. Read-across material γ-caprolactone (CAS # 695-06-7; see Section 5) 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-decalactone 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-decalactone, 1000/0.0039 or 256410.

In addition, the total systemic exposure to γ-decalactone (3.9 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-decalactone or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to γ-decalactone (3.9 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: 05/01/18.

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-decalactone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for γ-decalactone. Based on the existing data and read-across materials 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2; see Section 5) and (±) 3-methyl-γ-decalactone (CAS # 67663-01-8; see Section 5), γ-decalactone does not present a concern for skin sensitization under the 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-decalactone 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 10% γ-decalactone (RIFM, 1975).

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

Additional References: RIFM, 1988b.

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

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for γ-decalactone 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-decalactone does not present a concern for phototoxicity or photoallergenicity.

10.2. 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.

10.2.1. Local Respiratory Toxicity

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

10.2.1.1. Risk assessment. There are insufficient inhalation data available on γ-decalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.042 mg/day. This exposure is 33.3 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.

10.3. Environmental endpoint summary

10.3.1. Screening-level assessment

A screening-level risk assessment of γ-decalactone 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-decalactone 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-decalactone 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.

10.3.2. Risk assessment

Based on the current VoU (2015), γ-decalactone presents a risk to the aquatic compartment in the screening-level assessment.

10.3.2.1. Biodegradation. RIFM, 1995a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. γ-Decalactone underwent 82% biodegradation after 28 days in the test conditions.

10.3.2.2. Ecotoxicity. No data available.

10.3.3. Other available data

γ-Decalactone has been registered under REACH, and the following additional data is available:

A 96-h fish (*Leuciscus idus*) acute toxicity study was conducted according to the OECD 203 method under static conditions. The LC50 was reported to be 21.5 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 (geometric mean) was reported to be 37.2 mg/L based on the growth rate and 12.2 mg/L based on the yield.

10.3.4. Risk assessment refinement

Since γ-decalactone 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>30.98</u>			1,000,000	0.03093	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	10.61	20.76	<u>8.08</u>	10,000	0.808	Esters
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	43.28	25.89	23.95			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.0	3.0
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 0.808 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: 10/9/18.

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 05/28/19.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

☒ 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.2019.110722.

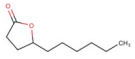
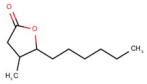
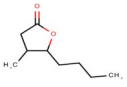
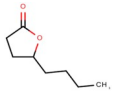
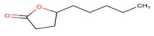
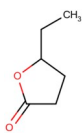
Appendix

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	Read-across Material	Read-across Material
Principal Name	γ-Decalactone	(±) 3-Methyl-γ-decalactone	4-Hydroxy-3-methyloctanoic acid lactone	γ-Octalactone	γ-Nonalactone	γ-Hexalactone (γ-caprolactone)
CAS No.	706-14-9	67663-01-8	39212-23-2	104-50-7	104-61-0	695-06-7
Structure						
Similarity (Tanimoto Score)		0.85	0.78	0.68	0.83	0.78
Read-across Endpoint		• Skin Sensitization	• Skin Sensitization	• Genotoxicity	• Genotoxicity	• Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{10}H_{18}O_2$	$C_{11}H_{20}O_2$	$C_9H_{16}O_2$	$C_8H_{14}O_2$	$C_9H_{16}O_2$	$C_6H_{10}O_2$
Molecular Weight	170.25	184.27	156.22	142.19	156.22	114.14
Melting Point (°C, EPI Suite)	20.20	26.92	6.29	−0.80	9.83	−18
	281.72	292.69	260.63	248.37	265.50	215.5

Boiling Point (°C, EPI Suite)						
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.683	0.368	2.05	8.46	1.57	22
Log Kow (KOWWIN v1.68 in EPI Suite)	2.72	2.98	2.00	1.59	2.08	0.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	291.6	148.2	1387	3632	1201	3.219e+004
Jmax (μg/cm^2/h, SAM)	12.785	6.231	62.889	94.569	45.653	353.995
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.69E+001	7.56E+001	4.29E+001	3.23E+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 ≫ Michael-type addition on α, β-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylation			• AN2|AN2 ≫ Michael-type addition on α, β-unsaturated carbonyl compounds|AN2 ≫ Michael-type addition on α, β-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylation	• AN2|AN2 ≫ Michael-type addition on α, β-unsaturated carbonyl compounds|AN2 ≫ Michael-type addition on α, β-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylation	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found			• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)			• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found			• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found			• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• Oxolane			• Oxolane	• Oxolane	
Oncologic Classification	• Lactone Type Reactive Functional Groups			• 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 (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 v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5	See Supplemental Data 6

Summary

There are insufficient toxicity data on γ-decalactone (CAS # 706-14-9). 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), γ-octalactone (CAS # 104-50-7), γ-nonalactone (CAS # 104-61-0), 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-decalactone (CAS # 706-14-9) 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 read-across analog has 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.
- 4-Hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) was used as a read-across analog for the target material γ-decalactone (CAS # 706-14-9) 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 hexyl 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-Octalactone (CAS # 104-50-7) was used as a read-across analog for the target material γ-decalactone (CAS # 706-14-9) for the genotoxicity 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 hexyl substitution on the 5 position while the read-across analog has a butyl substitution. 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 AN2 reaction alerts and oxolane alerts for *in vivo* mutagenicity by the ISS model. Both substances are classified as lactones in oncologic classification. The lactone ring in the target substance as well as in the read-across material is saturated. After ring opening, the resulting carbonyl in the structure will not be activated (α,β-unsaturated), which reduces the possibility of it acting as a nucleophile and involving a DNA binding reaction. Based on the read-across analog data described in the genotoxicity section, the read-across analog does not present a concern for genetic toxicity under the current, declared levels of use. 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-Nonalactone (CAS # 104-61-0) was used as a read-across analog for the target material γ-decalactone (CAS # 706-14-9) for the genotoxicity 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 hexyl substitution on the 5 position while the read-across analog has a pentyl substitution. 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.

- The physical–chemical properties of the target substance 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 substance and the read-across analog.
- The target substance and the read-across analog have AN2 reaction alerts and oxolane alerts for *in vivo* mutagenicity by the ISS model. Both substances are classified as lactones in oncologic classification. The lactone ring in the target substance as well as in the read-across material is saturated. After ring opening, the resulting carbonyl in the structure will not be activated (α,β-unsaturated), which reduces the possibility of it acting as a nucleophile and involving a DNA binding reaction. Based on the read-across analog data described in the genotoxicity section, the read-across analog does not present a concern for genetic toxicity under the current, declared levels of use. Therefore, the predictions are superseded by data.
- The target substance 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-decalactone (CAS # 706-14-9) for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target substance and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - The key difference between the target substance and the read-across analog is that the target substance has a hexyl substitution on the 5 position while the read-across analog has an ethyl substitution. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target substance 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 substance and the read-across analog.
  - The target substance and the read-across analog have AN2 reaction alerts and oxolane alerts for *in vivo* mutagenicity by the ISS model. Both substances are classified as lactones in oncologic classification. The lactone ring in the target substance as well as in the read-across material is saturated. After ring opening, the resulting carbonyl in the structure will not be activated (α,β-unsaturated), which reduces the possibility of it acting as a nucleophile and involving a DNA binding reaction. Based on the read-across analog data described in the genotoxicity section, the read-across analog does not present a concern for genetic toxicity under the current, declared levels of use. Therefore, the predictions are superseded by data.
  - The target substance 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? 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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