Short Review

RIFM fragrance ingredient safety assessment, γ-methyldecalactone, CAS Registry Number 7011-83-8

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Version: 121018. This version replaces any previous versions.

Name: γ-Methyldecalactone
CAS Registry Number: 7011-83-8
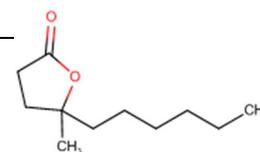
Abbreviation/Definition List:

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

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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
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-Methyldecalactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog (±) 3-methyl-γ-decalactone (CAS # 67663-01-8) show that γ-methyldecalactone is not expected to be genotoxic. Data on read-across analogs (±) 3-methyl-γ-decalactone (CAS # 67663-01-8) and γ-hexalactone (γ-caprolactone; CAS # 695-06-7) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints, respectively. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to γ-methyldecalactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for γ-methyl-ldecalactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; γ-methyldecalactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; γ-methyldecalactone 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, 2002; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day. | RIFM (2015a)
Reproductive Toxicity: Developmental Toxicity: NOAEL = 1000 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC. | (ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013)
Skin Sensitization: Not a sensitization concern under the current, declared levels of use. | (RIFM, 1984a; ECHA REACH Dossier: 5-Hexyldihydro-5-methylfuran-2(3H)-one; ECHA, 2016a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. | (UV Spectra, RIFM Database; RIFM, 1984b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence:
Critical Measured Value: 82% (301 F) | (ECHA REACH Dossier: 5-Hexyldihydro-5-methylfuran-2(3H)-one; ECHA, 2016a)

Bioaccumulation:
Screening-level: 45.71 L/kg | (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC_{50}: 50.06 mg/L | (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

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Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 | (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC_{50}: 50.06 mg/L | (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.05006 μg/L
● **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe

1. Identification

1. **Chemical Name:** γ-Methyldecalactone
2. **CAS Registry Number:** 7011-83-8
3. **Synonyms:** Dihydrojasmone lactone; 2(3H)-Furanone, 5-hex-yldihydro-5-methyl-; 5-Hexyldihydro-5-methylfuran-2(3H)-one; 4-Methyldecanolide; γ-アルキルラクトン(C=0〜14); 5-Hexyl-5-methyldihy-drofuran-2(3H)-one; Lactojasmone; γ-Methyldecalactone
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.27 g/mol
6. **RIFM Number:** 913
7. **Stereochemistry:** Isomer not specified. 1 chiral center and total 2 enantiomers possible

2. Physical data

1. **Boiling Point:** 135 ˚C @ 5 mm Hg (FMA Database), 289.07 ˚C (EPI Suite), 285.0 ˚C at 1013 hPa (RIFM, 2016a)
2. **Flash Point:** 230 ˚F; CC (FMA Database), 110 ˚C (GHS), 144.0 ˚C (average corrected and rounded down to the nearest multiple of 0.5 ˚C) (RIFM, 2016b)
3. **Log K_{OW}:** 2.8 (RIFM, 2013b), 3.02 (EPI Suite)
4. **Melting Point**: 32.34 ˚C (EPI Suite), −14.2 ˚C at 1008 hPa (RIFM, 2016a)
5. **Water Solubility:** 138.1 mg/L (EPI Suite)
6. **Specific Gravity:** 0.95 (FMA Database)
7. **Vapor Pressure:** 0.00165 mm Hg @ 20 ˚C (EPI Suite v4.0), 0.399 Pa @ 25 ˚C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A faintly straw-colored or almost colorless oily liquid with a heavy floral but also fatty (coconut-fatty) and waxy odor

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.033% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0095 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00085 mg/kg/day (RIFM, 2014)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015, 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, 2015, 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*	III	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:** (±) 3-Methyl-γ-decalactone (CAS # 67663-01-8)
   b. **Repeated Dose Toxicity:** (±) 3-Methyl-γ-decalactone (CAS # 67663-01-8)
   c. **Reproductive Toxicity:** γ-Hexalactone (γ-caprolactone; CAS # 695-06-7)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

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

Licorice (*Glycyrrhiza* species).

*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. REACH dossier

Available; accessed 03/17/20.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

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

10.1.1.1. Risk assessment
γ-Methyldecalactone was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of γ-methyldecalactone 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-methyldecalactone 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, 2002). Under the conditions of the study, γ-methyldecalactone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of γ-methyl-decalactone; however, read-across can be made to (±) 3-methyl-γ-decalactone (CAS # 67663-01-8; see Section V). The clastogenicity of (±) 3-methyl-γ-decalactone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with (±) 3-methyl-γ-decalactone in DMSO at concentrations up to 1894 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (RIFM, 2015b). Under the conditions of the study, (±) 3-methyl-γ-decalactone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to γ-methyldecalactone.

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

Additional References: RIFM, 2010.

Literature Search and Risk Assessment Completed On: 11/21/18.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for γ-methyldecalactone 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-methylde-calactone. Read-across material (±) 3-methyl-γ-decalactone (CAS 67663-01-8; see section V) has sufficient repeated dose toxicity data on (±) 3-Methyl-γ-decalactone. In an OECD 407 and GLP-compliant study, Sprague Dawley (Crl:CD[SD]) rats (5 animals/sex/group) were administered (±) 3-methyl-γ-decalactone through oral gavage at doses of 0, 62.5, 250, and 1000 mg/kg/day for 28 days. No mortality was observed during the study at all tested doses. Moreover, no treatment-related effects were reported for body weight, food consumption, functional observations, urinalysis, necropsy, and histopathology in both sexes at all tested doses. Increased salivation due to test material palatability was observed at all doses (1M and 1F at 62.5 mg/kg/day, all animals at 25 and 1000 mg/kg/day). One male and all females receiving the highest dose demonstrated irregular respiration; however, no histopathological changes in lungs were reported. During clinical chemistry evaluation, a dose-dependent (no statistical significance) decrease in male platelet counts was reported; in contrast, females demonstrated a significant increase in platelets at 62.5 mg/kg/day without a dose response, and thus, the increase was considered incidental. In both sexes, prothrombin time was unaltered at all doses. Additionally, a dose-dependent decrease (without statistical significance) in ALP, ALT, and AST was reported in both sexes. At 1000 mg/kg/day, GGT levels were increased in males and total protein levels were increased in females. In both sexes, a dose-dependent increase in absolute liver weights was reported, but the changes were statistically significant only in females in the 1000 mg/kg/day group. In contrast, relative liver weight increased significantly in both sexes at 250 and 1000 mg/kg/day doses. Histopathological findings supporting the alterations of liver weight and enzyme concentrations were not observed. Due to a lack of any histopathological evidence of hepato-toxicity, the reported changes of liver weights in both sexes were considered adaptive. In addition, the increase in absolute brain weight in

females of the 250 mg/kg/day group was considered incidental because these changes were not supported by any histopathological changes, did not demonstrate a dose response, and were observed only in females. Thus, based on the absence of treatment-related adverse effects, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day (RIFM, 2015a; NICNAS report on (±) 3-Methyl-γ-decalactone; NICNAS, 2017).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333.33 mg/kg/day.

Therefore, the γ-methyldecalactone MOE for the repeated dose toxicity endpoint can be calculated by dividing the (±) 3-methyl-γ-decalactone NOAEL in mg/kg/day by the total systemic exposure to γ-methyldecalactone 333.33/0.00085 or 392153.

In addition, the total systemic exposure to γ-methyldecalactone (0.85 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) of a Cramer Class I material for the repeated dose toxicity endpoint at the current level of use.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/06/19.

10.1.3. Reproductive toxicity

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

There are no fertility data on γ-methyldecalactone or on any read-across materials. The total systemic exposure to γ-methyldecalactone is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment

There are no developmental toxicity data on γ-methyldecalactone. 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-methyldecalactone 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-

methyldecalactone, 1000/0.00085 or 1176471.

In addition, the total systemic exposure to γ-methyldecalactone (0.85 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 no fertility data on γ-methyldecalactone or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to γ-methyldecalactone (0.85 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/07/18.

10.1.4. Skin sensitization

Based on the existing data, γ-methyldecalactone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment

Based on the existing data, γ-methyldecalactone is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, γ-methyldecalactone did not present reactions indicative of sensitization at 100% (RIFM, 1984a; ECHA, 2016a). In a human maximization test, no skin sensitization reactions were observed with γ-methyldecalactone at 2% (1380 μg/cm^2) (RIFM, 1976).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, γ-methyldecalactone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1984b; RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 11/09/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available *in vivo* study data and UV/Vis spectra, γ-methyldecalactone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment

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). In a study conducted in guinea pigs, 25% γ-methyldecalactone in ethanol did not result in phototoxic or photoallergenic skin reactions (RIFM, 1984b). Based on the lack of absorbance and the available *in vivo* study data, γ-methyldecalactone 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}·cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/18.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment

There are no inhalation data available on γ-methyldecalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.0095 mg/day. This exposure is 147.4 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: 11/13/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of γ-methyldecalactone 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-methyldecalactone was identified as a fragrance material with the potential to no 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-methyldecalactone 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), γ-methyldecalactone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key studies
10.2.2.1.1. *Biodegradation.* RIFM, 2012: The ready biodegradability of the test material was evaluated according to the OECD 301F method.

After 28 days, biodegradation of 73% was observed.

10.2.2.1.2. Ecotoxicity. RIFM, 2016c: An algae growth inhibition study was conducted according to the OECD 201 method. The 72-hour EC_{50} and NOEC based on the growth rate was 29.5 mg/L and 0.825 mg/L, respectively.

10.2.2.1.3. Other available data. γ-Methyldecalactone ether has been registered for REACH, and the following data is available:

The ready biodegradability of the test material was evaluated according to the OECD 301F method. After 28 days, biodegradation of 82% was observed (ECHA, 2016a).

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-hour EC_{50} was reported to be 2.98 mg/L (ECHA, 2016a).

10.2.3. Risk assessment refinement

Since γ-methyldecalactone 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.

	LC_{50} (Fish)	EC_{50} (*Daphnia*)	EC_{50} (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	<u>50.06 mg/L</u>			1000000	0.05006 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.8	2.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.05006 μg/L. The revised PEC/PNECs for EU and North America are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/19/18.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111336.

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 Chemicals Agency read-across assessment framework (ECHA, 2016b).

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
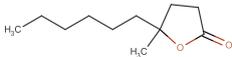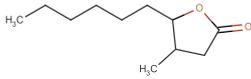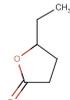- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

- First, the materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	γ-Methyldecalactone	(±) 3-Methyl-γ-decalactone	γ-Hexalactone (γ-caprolactone)
CAS No. Structure	7011-83-8	67663-01-8	695-06-7
Similarity (Tanimoto Score)		0.86	0.71
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity	• Developmental toxicity
Molecular Formula	$C_{11}H_{20}O_2$	$C_{11}H_{20}O_2$	$C_6H_{10}O_2$
Molecular Weight	184.27	184.27	114.14
Melting Point (°C, EPI Suite)	32.34	26.92	−18
Boiling Point (°C, EPI Suite)	289.07	292.69	215.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.399	0.368	22
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.02	2.98	0.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	138.1	148.2	3.219e+004
J_{max} (μg/cm^2/h, SAM)	19.25	6.23	354.0
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.56E+001	7.56E+001	1.83E+001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Michael-type addition on alpha, beta-unsaturated carbonyl compounds|AN2 ≫ Michael-type addition on alpha, beta-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylatio	• AN2|AN2 ≫ Michael-type addition on alpha, beta-unsaturated carbonyl compounds|AN2 ≫ Michael-type addition on alpha, beta-unsaturated carbonyl compounds ≫ Four- and Five-Membered Lactones|SN2|SN2 ≫ Alkylation, ring opening SN2 reaction|SN2 ≫ Alkylatio	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• Oxolane	• Oxolane	
Oncologic Classification	• Lactone Type Reactive Functional Groups	• Lactone Type Reactive Functional Groups	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH_2 group		• Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)
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

Summary

There are insufficient toxicity data on γ-methyldecalactone (CAS # 7011-83-8). 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) 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-methyldecalactone (CAS # 7011-83-8) for the genotoxicity and repeated dose toxicity endpoints.
  ○ The target material and the read-across analog are structurally similar and belong to a class of γ-lactones.
  ○ The target material and the read-across analog share isomeric γ-decalactone structures with one branched methyl group.
  ○ The key difference between the target material and the read-across analog is that the methyl group in the target material is in position 2, whereas the methyl group in the read-across analog is in position 3. This structural difference is toxicologically insignificant.
  ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  ○ Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption ≤80% and J_{max} for the read-across analog corresponds to skin absorption ≤40%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  ○ The target material 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 rings in both the target material and the read-across analog are saturated. After ring opening, the resulting carbonyl in the structure will not be activated (α,β-unsaturated), which reduces the possibility of acting as a nucleophile and involving a DNA-binding reaction. Based on the read-across analog data described in the genotoxicity section, the target does not present a concern for genetic toxicity under the current, declared levels of use. Therefore, the predictions are superseded by data.
  ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- γ-Hexalactone (CAS # 695-06-7) was used as a read-across analog for the target material γ-methyldecalactone (CAS # 7011-83-8) for the developmental toxicity endpoint.
  ○ The target material and the read-across analog are structurally similar and belong to a class of γ-lactones.
  ○ The target material and the read-across analog share a γ − lactone moiety.
  ○ The key difference between the target material and the read-across analog is the length of the aliphatic branch; i.e., the target material is a γ-decalactone while the read-across analog is a γ-hexalactone. The target material has 1 branched methyl group in position 2, which is not present in the read-across analog. These structural differences are toxicologically insignificant.
  ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  ○ *In silico* alerts are consistent with the data.
  ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
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 a detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories) No. Class I (Class Low)

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