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Short Review

RIFM fragrance ingredient safety assessment, (±) 3-methyl-γ-decalactone, CAS Registry Number 67663-01-8

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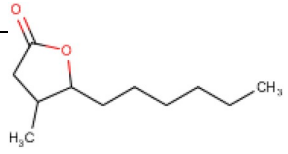

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2015; 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
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.

(±) 3-Methyl-γ-decalactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that (±) 3-methyl-γ-decalactone is not genotoxic. Data on (±) 3-methyl-γ-decalactone and read-across analog 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 (±) 3-methyl-γ-decalactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across material 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) show that there are no safety concerns for (±) 3-methyl-γ-decalactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; (±) 3-methyl-γ-decalactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; (±) 3-methyl-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 genotoxic.	(RIFM, 2010a; RIFM, 2015d)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day.	RIFM (2015c)
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.	(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 301 F)	RIFM (2011)
Bioaccumulation:	
Screening-level: 43.29 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 34.90 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe)	< 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint:: Fish LC50: 34.90 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.0349 µg/L	

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

1. Identification

1. **Chemical Name:** (±) 3-Methyl-γ-decalactone
2. **CAS Registry Number:** 67663-01-8
3. **Synonyms:** 5-Hexyldihydro-4-methylfuran-2(3H)-one; 2(3H)-Furanone, 5-hexyldihydro-4-methyl-(9Cl); 5-Hexyl-4-methyldihydrofuran-2(3H)-one; Peacholide; Aprifloren; (±) 3-Methyl-γ-decalactone
4. **Molecular Formula:** Not available
5. **Molecular Weight:** 184.27
6. **RIFM Number:** 180
7. **Stereochemistry:** (±) isomer specified. Two chiral centers and 4 total stereoisomers possible

2. Physical data

1. **Boiling Point:** 292.69 °C (EPI Suite), 287–289 °C corrected to 1013 hPa (RIFM, 2015a)
2. **Flash Point:** 141.0 °C (corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015b)
3. **Log K_{OW}:** 2.98 (EPI Suite)
4. **Melting Point**: 26.92 °C (EPI Suite), no melting point down to a temperature of −100 °C at 1024 hPa (RIFM, 2015a)
5. **Water Solubility:** 148.2 mg/L (EPI Suite)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.00276 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:** Not available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.06% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00032 mg/kg/day or 0.024 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0016 mg/kg/day (RIFM, 2017)

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

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

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	II	I

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** γ-Caprolactone (CAS # 695-06-7)
   d. **Skin Sensitization:** 4-Hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification: See Appendix below**

6. Metabolism

WHO Food Additives Series: 52 (WHO, 2004; accessed 08/23/18): (±) 3-Methyl-γ-decalactone belongs to the aliphatic lactones group. The metabolic fate of these aliphatic lactones can be predicted based on the known biotransformation pathway of structurally-related lactones. These are expected to hydrolyze to the corresponding hydroxycarboxylic acid, followed by beta-oxidative cleavage to yield metabolites that are completely metabolized via the citric acid cycle. In blood, lactones hydrolyze rapidly to the open-chain hydroxycarboxylic acid.

Additional References: None.

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

(±) 3-Methyl-γ-decalactone is not reported to occur in foods by the VCF*.

*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

Pre-registered; no dossier available as of 12/10/18.

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, (±) 3-methyl-γ-decalactone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of (±) 3-methyl-γ-decalactone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with (±) 3-methyl-γ-decalactone 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, 2010a). Under the conditions of the study, (±) 3-methyl-γ-decalactone was not mutagenic in the Ames test.

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, 2015d). Under the conditions of the study, (±) 3-methyl-γ-decalactone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, (±) 3-methyl-γ-decalactone does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for (±) 3-methyl-γ-decalactone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are 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, this increase was considered to be 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 hepatotoxicity, 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 were 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, 2015c; 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 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 (±) 3-methyl-γ-decalactone, 333.33/0.0016 or 208331.

In addition, the total systemic exposure to (±) 3-methyl-γ-decalactone (0.0016 μg/kg bw/day) is below the TTC (30 μg/kg bw/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 (±) 3-methyl-γ-decalactone is adequate for the developmental toxicity endpoint at the current level of use.

There are no fertility data on (±) 3-methyl-γ-decalactone or on any read-across materials. The total systemic exposure to (±) 3-methyl-γ-decalactone 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 (±) 3-methyl-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 (±) 3-methyl-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 (±) 3-methyl-γ-decalactone, 1000/0.0016 or 625000.

In addition, the total systemic exposure to (±) 3-methyl-γ-decalactone (1.6 μg/kg bw/day) is below the TTC (30 μg/kg bw/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 (±) 3-methyl-γ-decalactone or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to (±) 3-methyl-γ-decalactone (1.6 μg/kg bw/day) is below the TTC (30 μg/kg bw/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: RIFM, 2015c.

Literature Search and Risk Assessment Completed On: 10/23/18.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for (±) 3-methyl-γ-decalactone. Based on the existing data and read-across material 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2; see Section 5), (±) 3-methyl-γ-decalactone is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In guinea pigs, maximization tests with (±) 3-methyl-γ-decalactone and read-across material 4-hydroxy-3-methyloctanoic acid lactone did not present reactions indicative of sensitization up to 20% and 100%, respectively (RIFM, 2002; RIFM, 1988a).

Based on the weight of evidence (WoE) from structural analysis, an animal study, and read-across material 4-hydroxy-3-methyloctanoic acid lactone, (±) 3-methyl-γ-decalactone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1988b.

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

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, (±) 3-methyl-γ-decalactone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for (±) 3-methyl-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 the lack of absorbance, (±) 3-methyl-γ-decalactone does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for (±) 3-methyl-γ-decalactone 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 (±) 3-methyl-γ-decalactone. Based on the Creme RIFM Model, the inhalation exposure is 0.024 mg/day. This exposure is 58.34 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 (±) 3-methyl-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, (±) 3-methyl-γ-decalactone was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify (±) 3-methyl-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.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), (±) 3-methyl-γ-decalactone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2011: The ready biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 301 F. Under the test conditions, biodegradation of 82% was observed in 28 days.

10.2.1.2.2. Ecotoxicity. RIFM, 2010b: A 96-h fish (zebra fish) acute study was conducted according to the OECD 203 method under flow-through conditions, and the LC50 was reported to be 11.5 mg/L.

10.2.1.3. Other available data. (±) 3-Methyl-γ-decalactone has been registered under REACH with no additional data available at this time.

10.2.2. Risk assessment refinement

Since (±) 3-methyl-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)**	34.90			1000000	0.0349	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.98	2.98
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
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 0.0349 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/14/18.

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

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.2019.111105.

Appendix

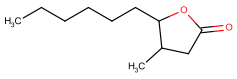
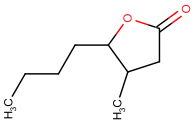
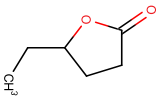
Read-across Justification

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, 2016).

- 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) (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	(±) 3-Methyl-γ-decalactone	4-Hydroxy-3-methyloctanoic acid lactone	γ-Hexalactone
CAS No.	67663-01-8	39212-23-2	695-06-7
Structure			
Similarity (Tanimoto Score)		0.97	0.65
Read-across Endpoint		• Skin Sensitization	• Developmental toxicity
Molecular Formula	$C_{11}H_{20}O_2$	$C_9H_{16}O_2$	$C_6H_{10}O_2$
Molecular Weight	184.27	156.22	114.14
Melting Point (°C, EPI Suite)	26.92	6.29	−18
Boiling Point (°C, EPI Suite)	292.69	260.63	215.5
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.368	2.05	22
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.98	2.00	0.60
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	148.2	1387.00	3.219e+004
J_{max} (μg/cm^2/h, SAM)	6.23	62.89	354.0
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.56E+001	4.29E+001	1.83E+001
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v-4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v-2.1.6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	• Acylation|Acylation ≫ Direct Acylation Involving a Leaving group|Acylation ≫ Direct Acylation Involving a Leaving group ≫ Acetates	
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• 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

Summary

There are insufficient toxicity data on (±) 3-methyl-γ-decalactone (CAS # 67663-01-8). 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, 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) and γ-hexalactone (CAS # 695-06-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 4-Hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) was used as a read-across analog for the target material (±) 3-methyl-γ-decalactone (CAS # 67663-01-8) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The target material and the read-across analog share a γ-lactone structure with a methyl group in position 3.
  - o The key difference between the target material and the read-across analog is that the target material is a γ-decalactone, whereas the read-across analog is a γ-octalactone. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption ≤40% and J_{max}

for the read-across analog corresponds to skin absorption ≤80%. 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.

- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material and the read-across analog have an acylation alert by the protein binding model by OECD. The alert is due to the fact that the substances contain an acetate substructure in the lactone ring. The data described in the skin sensitization section confirms that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert is superseded by the data.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- γ-Hexalactone (CAS # 695-06-7) was used as a read-across analog for the target material (±) 3-methyl-γ-decalactone (CAS # 67663-01-8) for the developmental toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of γ-lactones.
  - o The target material and the read-across analog share a γ − lactone moiety.
  - o 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 3, which is not present in the read-across analog. These structural differences are toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption ≤40% and J_{max} for the read-across analog corresponds to skin absorption ≤80%. 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.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o *In silico* alerts are consistent with the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
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? Yes
Q9. Lactone, fused to another ring, or 5- or 6-membered α,β-unsaturated lactone? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for 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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