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Short Review

RIFM fragrance ingredient safety assessment, 4-hydroxy-3-methyloctanoic acid lactone, CAS Registry Number 39212-23-2

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], F. Siddiqi[a], 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] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *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] *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] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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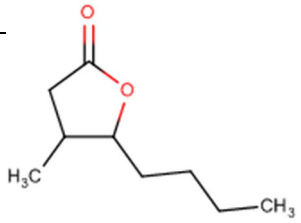
Name: 4-Hydroxy-3-methyloctanoic acid lactone CAS Registry Number: 39212-23-2



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, 2017bib_Comiskey_et_al_2015; Safford et al., 2015a, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_Comiskey_et_al_2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice

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

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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, 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.
4-Hydroxy-3-methyloctanoic acid lactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog (±) 3-methyl-γ-decalactone (CAS # 67663-01-8) show that 4-hydroxy-3-methyloctanoic acid lactone is not expected to be genotoxic. Data on read-across analog γ-hexalactone (γ-caprolactone; CAS # 695-06-7) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 4-hydroxy-3-methyloctanoic acid lactone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for 4-hydroxy-3-methyloctanoic acid lactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-hydroxy-3-methyloctanoic acid lactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-hydroxy-3-methyloctanoic acid lactone 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, 2010; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 333.33 mg/kg/day.	(ECHA REACH Dossier: Nonan-4-olide; ECHA, 2013)
Reproductive Toxicity: Developmental Toxicity: NOAEL = 1000 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC.	(ECHA Dossier: Nonan-4-olide; ECHA, 2013)
Skin Sensitization: Not a sensitization concern under the current, declared levels of use.	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: 98% (OECD 301D)	RIFM (1996)
Bioaccumulation: Screening-level: 9.7 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 210.7 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 210.7 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.2107 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 4-Hydroxy-3-methyloctanoic acid lactone
2. **CAS Registry Number:** 39212-23-2
3. **Synonyms:** 5-Butyldihydro-4-methylfuran-2(3H)-one; 2(3H)-Furanone, 5-butyldihydro-4-methyl-; 3-Methyl-1,4-octalactone; β-Methyl-γ-octalactone; Oaklactone; Octanoic acid, 4-hydroxy-3-methyl-, lactone; Whisky lactone; 5-Butyl-4-methyldihydrofuran-2(3H)-one; 4-Hydroxy-3-methyloctanoic acid lactone
4. Molecular Formula: $C_9H_{16}O_2$
5. Molecular Weight: 156.22
6. RIFM Number: 5122
7. Stereochemistry: Isomer not specified. Two chiral centers and 4 total stereoisomers possible

2. Physical data

1. **Boiling Point:** 260.63 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{OW}:** 2 (EPI Suite)
4. **Melting Point**: 6.29 °C (EPI Suite)
5. **Water Solubility:** 1387 mg/L (EPI Suite)
6. **Specific Gravity:** Not available
7. **Vapor Pressure:** 0.00958 mm Hg @ 20 °C (EPI Suite v4.0), 0.0154 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):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.011% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00025 mg/kg/day or 0.020 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00034 mg/kg/day (RIFM, 2014)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017bib_Comiskey_et_al_2015; Safford, 2015, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_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, 2015, 2017bib_Comiskey_et_al_2015; Safford, 2015, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_Comiskey_et_al_2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

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

2. Analogs Selected:
   a. **Genotoxicity:** (±) 3-methyl-γ-decalactone (CAS # 67663-01-8)
   b. **Repeated Dose Toxicity:** γ-Hexalactone (γ-caprolactone; CAS # 695-06-7)
   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.

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

4-Hydroxy-3-methyloctanoic acid lactone is reported to occur in the following foods by the VCF*:

Grape brandy
Sherry
Whiskey
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

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4-hydroxy-3-methyloctanoic acid lactone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of 4-hydroxy-3-methyloctanoic acid lactone; however, read-across can be made to (±) 3-methyl-γ-decalactone (CAS # 67663-01-8; see Section V). 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, 2010). 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, 2015). 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, and this can be extended to 4-hydroxy-3-methyloctanoic acid lactone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.2. Repeated dose toxicity

The MOE for 4-hydroxy-3-methyloctanoic acid lactone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose data on 4-hydroxy-3-methyloctanoic acid lactone. Read-across material γ-caprolactone (CAS # 695-06-7; see Section V) has sufficient repeated dose toxicity data. An OECD 407 gavage 28-day study was conducted on a group of 5 Crl:CD (SD)IGS BR strain rats/sex/group. The animals (5 per sex/dose) were administered the test material γ-caprolactone through oral gavage at doses of 0 (water), 30, 100, 300, and 1000 mg/kg/day. A separate recovery group of 5 rats/sex/group were maintained for 14 days at doses of 0 and 1000 mg/kg/day. No treatment-related effects were observed for mortality, food consumption, ophthalmology, hematology, urinalysis, behavior, or histopathology. Low-incidence, treatment-related findings observed immediately after dosing with 1000 mg/kg/day included clear, yellow/red test material around areas such as the mouth, urogenital area, and forelimbs in both sexes. At 100 and 300 mg/kg/day, body weights increased in females for 3 weeks; however, no changes in body weight were observed at the highest dose of 1000 mg/kg/day in females or at all tested doses in males. In the recovery group females, 1000 mg/kg/day treatment decreased mean corpuscular hemoglobin concentration during the recovery period. These findings were not observed in males or prior to the recovery period in females. At the 1000 mg/kg/day dose, blood cholesterol levels were decreased in both sexes. In females, increased blood levels of sodium, albumin, total protein, urea nitrogen, and calcium were observed at a dose of 1000 mg/kg/day. Males treated with the 1000 mg/kg/day dose had increased blood aspartate aminotransferase (AST) as well as decreased chloride at 100 and 300 mg/kg/day doses. Absolute (in females) and relative (both sexes) liver weights were increased in the 1000 mg/kg/day dose group. Conversely, during the recovery period, no changes in absolute or relative liver weights were observed in either sex from the recovery groups. During treatment at the highest dose, pale livers were observed in both sexes as well as increased glycogen granules, lipid content, and lysosomes (males). Additionally, in both sexes, the highest dose increased cytoplasmic vacuolization in the liver. These findings were reversed in either sex during the recovery period. Hence, the liver changes identified during the study were generally considered to be adaptive in nature. Thus, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day based on the reversibility of the liver changes following the 14-day recovery period ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 407 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.

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

Therefore, the 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone, 333.33/0.00034 or 980382.

In addition, the total systemic exposure to 4-hydroxy-3-methyloctanoic acid lactone (0.34 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/19.

10.1.3. Reproductive Toxicity

The MOE for 4-hydroxy-3-methyloctanoic acid lactone is adequate for the developmental toxicity endpoint at the current level of use.

There are no fertility data on 4-hydroxy-3-methyloctanoic acid lactone or on any read-across materials. The total systemic exposure to 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone. 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 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone, 1000/0.00034 or 2941176.

In addition, the total systemic exposure to 4-hydroxy-3-methyloctanoic acid lactone (0.34 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on 4-hydroxy-3-methyloctanoic acid lactone or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to 4-hydroxy-3-methyloctanoic acid lactone (0.34 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 11/02/18.

10.1.4. Skin sensitization

Based on the existing data, 4-hydroxy-3-methyloctanoic acid lactone does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on existing data, 4-hydroxy-3-methyloctanoic acid lactone is not considered a skin sensitizer. The chemical structures of the material indicate that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.1). In a guinea pig maximization test, 4-hydroxy-3-methyloctanoic acid lactone did not present reactions indicative of sensitization up to 100 and 20%, respectively (RIFM, 1988a).

Based on the weight of evidence (WoE) from structural analysis and an animal study, 4-hydroxy-3-methyloctanoic acid lactone 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: 09/24/18.

10.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis spectra, 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone 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, 2009). Based on the lack of absorbance, 4-hydroxy-3-methyloctanoic acid lactone 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/14/18.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone. Based on the Creme RIFM Model, the inhalation exposure is 0.020 mg/day. This exposure is 70 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 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 4-hydroxy-3-methyloctanoic acid lactone was performed following the RIFM Environmental Framework (Salvito, 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, 4-hydroxy-3-methyloctanoic acid lactone 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 4-hydroxy-3-methyloctanoic acid lactone 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, 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), 4-hydroxy-3-methyloctanoic acid lactone presents no risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1996: The biodegradability of the test material was evaluated according to ISO method 9434 D. Under the conditions of this study, biodegradation of 100% was observed after 28 days.

10.2.4. Ecotoxicity

No data available.

10.2.5. Other available data

4-Hydroxy-3-methyloctanoic acid lactone has been registered under REACH with no additional data available at this time.

10.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	210.7			1000000	0.2107	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.0	2.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
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 0.2107 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.2020.111226.

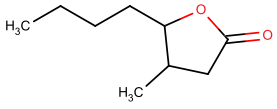
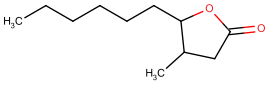
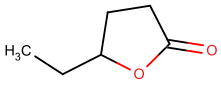
Appendix

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). 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	4-Hydroxy-3-methyloctanoic acid lactone	(±) 3-Methyl-γ-decalactone	γ-Hexalactone (γ-caprolactone)
CAS No.	39212-23-2	67663-01-8	695-06-7
Structure			
Similarity (Tanimoto Score)		0.97	0.67
Read-across Endpoint		• Genotoxicity	• Repeated Dose Toxicity • Developmental toxicity
Molecular Formula	$C_9H_{16}O_2$	$C_{11}H_{20}O_2$	$C_6H_{10}O_2$
Molecular Weight	156.22	184.27	114.14
Melting Point (°C, EPI Suite)	6.29	26.92	−18.00
Boiling Point (°C, EPI Suite)	260.63	292.69	215.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.05	0.368	22.00
Log K_{OW} (KOWWIN v-1.68 in EPI Suite)	2.00	2.98	0.60
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1387.00	148.2	3.219e+004
J_{max} (μg/cm^2/h, SAM)	62.89	6.23	354.00
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.29E+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 ≫ Alkylation	• 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 ≫ Alkylation	
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 v-1.1)	• No alert found	• No alert found	

***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus, IS-S)**	• Oxolane	• Oxolane	
Oncologic Classification	• Lactone Type Reactive Functional Groups	• Lactone Type Reactive Functional Groups	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Clofibrate (Hepatotoxicity) Alert|Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert
Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.-6)	• Non-toxicant (low reliability)		• Non-toxicant (low reliability)
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 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2). 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 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) for the genotoxicity endpoints.
  - 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 the 3-position.
  - o The key difference between the target material and the read-across analog is the length of the aliphatic branch; the target material is a γ-octalactone, whereas the read-across analog is a γ-decalactone. 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 $\leq$80% and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While 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 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 material as well as in the read-across analog is 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.
  - 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 4-hydroxy-3-methyloctanoic acid lactone (CAS # 39212-23-2) for the repeated dose and developmental toxicity endpoints.
  - 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.
  - o The key difference between the target material and the read-across analog is the length of the aliphatic branch; the target material is a γ-octalactone, whereas the read-across analog is a γ-hexalactone. In addition, the target has a methyl group at C-3. 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 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 read-across analog has a hepatotoxicity alert by HESS categorization. The data described in the repeated dose toxicity section confirms that the MOE is adequate at the current level of use. Therefore, the predictions are 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.

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 alpha,beta-unsaturated lactone? No
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for a detailed explanation)? Y
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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