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Short Review

RIFM fragrance ingredient safety assessment, 4-hydroxy-3-pentenoic acid lactone, CAS Registry number 591-12-8

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Expert Panel for Fragrance Safety, 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*
[f] *Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239 USA*
[h] *Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Expert Panel for Fragrance Safety, 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*
[j] *Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Expert Panel for Fragrance Safety, 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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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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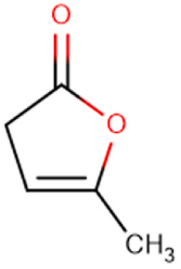
Name: 4-Hydroxy-3-pentenoic acid lactone
CAS Registry Number: 591-12-8



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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
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.

4-Hydroxy-3-pentenoic acid lactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data on the target material and read-across analog 4,6-dimethyl-2H-pyran-2-one (CAS # 675-09-2) show that 4-hydroxy-3-pentenoic acid lactone is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data provide 4-hydroxy-3-pentenoic acid lactone a No

(*continued on next page*)

(*continued*)

Expected Sensitization Induction Level (NESIL) of 230 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on target data and ultraviolet/visible (UV/Vis) spectra for read-across analog 2-nonenoic acid γ-lactone (CAS # 21963-26-8); 4-hydroxy-3-pentenoic acid lactone is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 4-hydroxy-3-pentenoic acid lactone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.	
Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 1982; RIFM, 2021a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	
Skin Sensitization: NESIL = 230 μg/cm^2.	RIFM (2017b)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1988; RIFM, 2001b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.12 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 6848 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: 6848 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 6.848 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 4-Hydroxy-3-pentenoic acid lactone
2. **CAS Registry Number:** 591-12-8
3. **Synonyms:** α-Angelica lactone; 2(3H)-Furanone, 5-methyl-; 5-Methyl-2(3H)-furanone; Pent-3-en-1,4-lactone; 5-Methylfuran-2(3H)-one; 4-Hydroxy-3-pentenoic acid lactone
4. **Molecular Formula:** $C_5H_6O_2$
5. **Molecular Weight:** 98.1 g/mol
6. **RIFM Number:** 6157
7. **Stereochemistry:** No stereocenter is present, and therefore, no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 55 °C at 12 mm Hg (Fragrance Materials Association [FMA]), 198.32 °C (EPI Suite v4.11)
2. **Flash Point:** 68 °C (Globally Harmonized System)
3. **Log K_{OW}:** 0.03 (EPI Suite v4.11)
4. **Melting Point**: −23.56 °C (EPI Suite v4.11)
5. **Water Solubility:** 112400 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 1.092 (FMA)
7. **Vapor Pressure:** 0.266 mm Hg at 20 °C (EPI Suite v4.0), 2.4 mm Hg 20 °C (FMA), 0.392 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 0.s1 to 1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Scented Candles:** 0.048% (RIFM, 2021b)
   (No reported use in Fine Fragrance).
2. **Inhalation Exposure*:** 0.000083 mg/kg/day or 0.0052 mg/day (RIFM, 2021b)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2021b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; Safford, 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	III	III

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** 4,6-Dimethyl-2H-pyran-2-one (CAS # 675-09-2)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** 2-Nonenoic acid γ-lactone (CAS # 21963-26-8)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Grape (*Vitus* species)	Soybean (*Glycine max.* L. merr)
Licorice (*Glycyrrhiza* species)	Tamarind (*Tamarindus indica* L.)
Passionfruit (*Passiflora* species)	*Vaccinum* species
Raspberry, Blackberry, and Boysenberry	Wheaten Bread

*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.

9. REACH Dossier

4-Hydroxy-3-pentenoic acid lactone has been pre-registered for 2010; no dossier available as of 09/08/22.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 4-hydroxy-3-pentenoic acid lactone are detailed below.

IFRA Category[b]	Descript[a]on of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.018
2	Products applied to the axillae	0.0053
3	Products applied to the face/body using fingertips	0.11
4	Products related to fine fragrances	0.099
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.025
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.025
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.025
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.058
7	Products applied to the hair with some hand contact	0.20
8	Products with significant ano-genital exposure (tampon)	0.010
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.19
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.69
10B	Aerosol air freshener	0.69
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substra[a]e (feminine hygiene pad)	0.38
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note.
[a] Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concen[b]rations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 4-hydrox[c]-3-pentenoic acid lactone, the basis was a skin sensitization NESIL of 230 μg/cm^2.
[b] For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c] Calculations by Creme RIFM Aggregate Exposure Model v3.2.6.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of 4-hydroxy-3-pentenoic acid lactone; however, read-across can be made to 4,6-dimethyl-2H-pyran-2-one (CAS # 675-09-2; see Section VI).

The mutagenic activity of 4,6-dimethyl-2H-pyran-2-one 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 TA1538 were treated with 4,6-dimethyl-2H-pyran-2-one in ethanol at concentrations up to 50 mg/plate (50000 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, 1982). Under the conditions of the study, 4,6-dimethyl-2H-pyran-2-one was not mutagenic in the Ames test, and this can be extended to 4-hydroxy-3-pentenoic acid lactone.

The clastogenic activity of 4-hydroxy-3-pentenoic acid lactone was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4-hydroxy-3-pentenoic acid lactone in dimethyl sulfoxide (DMSO) at concentrations up to 981 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 981 μg/mL in the presence and absence of metabolic activation. 4-Hydroxy-3-pentenoic acid lactone did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2021a). Under the conditions of the study, 4-hydroxy-3-pentenoic acid lactone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4-hydroxy-3-pentenoic acid lactone does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

Table 1
Data summary for 4-hydroxy-3-pentenoic acid lactone.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[4]	Buehler[4]
Moderate	236	NA	NA	230	250	Negative	NA
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		No alert found	No alert found	Nucleophilic addition

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Studies conducted according to the OECD TG 406 are included in the table.
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 4-hydroxy-3-pentenoic acid lactone or any read-across materials. The total systemic exposure to 4-hydroxy-3-pentenoic acid lactone is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4-hydroxy-3-pentenoic acid lactone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.14 µg/kg/day) is below the TTC for 4-hydroxy-3-pentenoic acid lactone (30 µg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/09/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 4-hydroxy-3-pentenoic acid lactone or any read-across materials. The total systemic exposure to 4-hydroxy-3-pentenoic acid lactone is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-hydroxy-3-pentenoic acid lactone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.14 µg/kg/day) is below the TTC for 4-hydroxy-3-pentenoic acid lactone (30 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/08/21.

11.1.4. Skin sensitization

Based on the existing data, 4-hydroxy-3-pentenoic acid lactone is considered a skin sensitizer with a defined NESIL of 230 µg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section 10.

11.1.4.1. Risk assessment. Based on the existing data, 4-hydroxy-3-

pentenoic acid lactone is considered a skin sensitizer (Table 1). The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), 4-hydroxy-3-pentenoic acid lactone was found to be sensitizing with an EC3 value of 1% (250 μg/cm^2) (RIFM, 2017a). In a guinea pig maximization test, 4-hydroxy-3-pentenoic acid lactone did not lead to skin sensitization reactions up to 30% in liquid paraffin (RIFM, 2001a). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 0.2% or 236 μg/cm^2 of 4-hydroxy-3-pentenoic acid lactone in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2017b).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 4-hydroxy-3-pentenoic acid lactone is a moderate sensitizer with a WoE NESIL of 230 μg/cm^2 (Table 1). Section 10 provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020).

Additional References: RIFM, 1988.

Literature Search and Risk Assessment Completed On: 09/27/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vivo* study data for the target material and UV/Vis absorption spectra for the structurally related read-across material, 2-nonenoic acid γ-lactone (CAS # 21963-26-8), 4-hydroxy-3-pentenoic acid lactone would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra for 4-hydroxy-3-pentenoic acid lactone were not available. UV/Vis absorption spectra for the structurally related material, 2-nonenoic acid γ-lactone (CAS # 21963-26-8) indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). *In vivo* photoirritation study data were available and demonstrated that in guinea pigs treated with 4-hydroxy-3-pentenoic acid lactone at concentrations up to 50% (the highest dose tested), photoirritation was not observed (RIFM, 1988; RIFM, 2001b). Based on the available *in vivo* study data for the target material and the lack of absorbance for the structurally related analog, 4-hydroxy-3-pentenoic acid lactone does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were not available for 4-hydroxy-3-pentenoic acid lactone. UV/Vis absorption spectra for the structurally related material, 2-nonenoic acid γ-lactone (CAS # 21963-26-8) indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 4-hydroxy-3-pentenoic acid lactone is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 4-hydroxy-3-pentenoic acid lactone. Based on the Creme RIFM Model, the inhalation exposure is 0.0052 mg/day. This exposure is 269.2 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: 07/19/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-hydroxy-3-pentenoic acid lactone 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 VoU 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-pentenoic 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-pentenoic 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 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, 2017a). 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	6848			1000000	6.848	

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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), 4-hydroxy-3-pentenoic acid lactone presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. Biodegradation:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. 4-Hydroxy-3-pentenoic acid lactone has been pre-registered for REACH with no additional information available at this time.

11.2.2. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.03	0.03
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	Not Reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 6.848 μg/L. The revised PEC/PNECs for EU and NA (No VoU) 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 VoU.

Literature Search and Risk Assessment Completed On: 09/09/22.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 09/27/22.

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.2023.114228.

Appendix

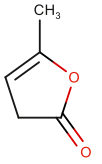
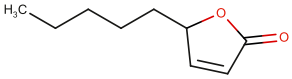
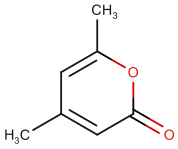
Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).

- The physical–chemical properties of the target 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	4-Hydroxy-3-pentenoic acid lactone	2-Nonenoic acid γ-lactone	4,6-Dimethyl-2H-pyran-2-one
CAS No.	591-12-8	21963-26-8	675-09-2
Structure			
Similarity (Tanimoto Score)		0.30	0.07
SMILES	CC1OC(=O)CC = 1	CCCCCC1OC(=O)C═C1	CC1OC(=O)C═C(C)C = 1
Endpoint		Photoirritation/photoallergenicity	Genotoxicity
Molecular Formula	$C_5H_6O_2$	$C_9H_{14}O_2$	$C_7H_8O_2$
Molecular Weight (g/mol)	98.101	154.209	124.139
Melting Point (°C, EPI Suite)	18.00	10.85	51.50
Boiling Point (°C, EPI Suite)	198.32	267.68	245.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.23E+01	1.40E+00	2.61E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.00E+04	1.87E+03	1.82E+04
Log KOW	0.03	1.86	0.85
J_{max} (μg/cm^2/h, SAM)	159.53	29.77	118.20
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.64E+01	2.01E+01	7.66E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found		No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found		No alert found
Carcinogenicity (ISS)	No alert found		No alert found
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)**	No alert found		No alert found
Oncologic Classification	Lactone-type Reactive Functional Groups		Not classified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	N/A*	See Supplemental Data 2

*Not applicable for the endpoint under consideration.

Summary

There are insufficient toxicity data on 4-Hydroxy-3-pentenoic acid lactone (CAS # 591-12-8). 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, 2-nonenoic acid γ-lactone (CAS # 21963-26-8) and 4,6-dimethyl-2H-pyran-2-one (CAS # 675-09-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 4,6-Dimethyl-2H-pyran-2-one (CAS # 675-09-2) was used as a read-across analog for the target material 4-hydroxy-3-pentenoic acid lactone (CAS # 591-12-8) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a structural class of lactones.
  - o The target material and the read-across analog share a γ-lactone ring.
  - o The key difference between the target material and the read-across analog is that the target material is a methyl-substituted γ-lactone, while the read-across analog is a dimethyl-substituted δ lactone. Both the target material and the read-across analog can undergo ring-opening and subsequent keto-enol tautomerization with equal probability. The α, β-unsaturation in the read-across analog has a β methyl substitution. Therefore, it is unable to perform any Michael addition reactions. Therefore, the reactive features between the 2 structures are well matched. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 a 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 target material has an alert of lactone-type reactive groups. The data on the read-across analog confirms that the substance does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog, and the data on the read-across analog, the structural *in silico* alert is superseded.
- 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.

- 2-Nonenoic acid γ-lactone (CAS # 21963-26-8) was used as a read-across analog for the target material 4-hydroxy-3-pentenoic acid lactone (CAS # 591-12-8) for the photoirritation/photoallergenicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a structural class of cyclic lactones.
  - o The target material and the read-across analog share a γ-lactone ring.
  - o The key difference between the target material and the read-across analog is that the target material is a methyl-substituted γ-lactone while the read-across analog is a 5-carbon chain substituted γ-lactone which has α,β-unsaturation. This structural difference does not alter the chromophore and light-absorbing properties of the molecule in the region of concern.
  - 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 a 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 target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the photoirritation/photoallergenicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

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 detailed explanation)? Yes.
Q21	Three 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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