Food and Chemical Toxicology 161 (2022) 112853

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, 5-hydroxy-7-decenoic acid δ-lactone, CAS Registry Number 25524-95-2

A.M. Api [a], D. Belsito [b], 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], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

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

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

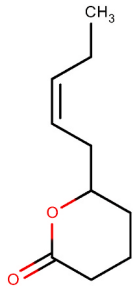
ABSTRACT

The existing information supports the use of this material as described in this safety assessment. 5-Hydroxy-7-decenoic acid δ-lactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across material tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0) show that 5-hydroxy-7-decenoic acid δ-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, and the exposure to 5-hydroxy-7-decenoic acid δ-lactone is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for 5-hydroxy-7-decenoic acid δ-lactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 5-hydroxy-7-decenoic acid δ-lactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 5-Hydroxy-7-decenoic acid δ-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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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

https://doi.org/10.1016/j.fct.2022.112853
Received 6 October 2021; Received in revised form 22 December 2021; Accepted 4 February 2022
Available online 9 February 2022

Version: 100621. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 5-Hydroxy-7-decenoic acid δ-lactone
CAS Registry Number: 25524-95-2
Additional CAS Numbers*: 34686-71-0
Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one
*Included because the materials are isomers

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 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
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,

(*continued on next column*)

(*continued*)

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.

5-Hydroxy-7-decenoic acid δ-lactone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across material tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0) show that 5-hydroxy-7-decenoic acid δ-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, and the exposure to 5-hydroxy-7-decenoic acid δ-lactone is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data show that there are no safety concerns for 5-hydroxy-7-decenoic acid δ-lactone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 5-hydroxy-7-decenoic acid δ-lactone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 5-Hydroxy-7-decenoic acid δ-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 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, 2013a; RIFM, 2013c)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. RIFM, (2020b)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Critical Measured Value: 88% (OECD 301F) RIFM (2012)

Bioaccumulation:

Screening-level: 16.56 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 227 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: 227 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.227 μg/L

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

1. Identification

Chemical Name: 5-Hydroxy-7-decenoic acid δ-lactone
CAS Registry Number: 25524-95-2
Synonyms: 7-Decen-1,5-lactone; (Z)-7-Decen-5-olide; Jasmin lactone; *cis*-5-(2-Pentenyl)pentanolide; 2H-Pyran-2-one, tetrahydro-6-(2-pentenyl)-, (Z); (Z)-Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one; 6-Pent-2-en-1-yltetrahydro-2H-pyran-2-one; Jasmin Lactone Δ; Jasminlactone; 5-Hydroxy-7-decenoic acid δ-lactone
Molecular Formula: $C_{10}H_{16}O_2$

Chemical Name: Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one
CAS Registry Number: 34686-71-0
Synonyms: 5-Hydroxy-7-decenoic acid lactone;.δ.-2-Pentenylvalerolactone; 2H-Pyran-2-one, tetrahydro-6-(2-pentenyl)-; 3,4,5,6-ﾃﾄﾗﾋﾄﾞﾛ-6-(2-ﾍﾟﾝﾃﾆﾙ)-2H-ﾋﾟﾗﾝ-2-ｵﾝ; 6-Pent-2-en-1-yltetrahydro-2H-pyran-2-one; Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one
Molecular Formula: $C_{10}H_{16}O_2$

(*continued on next page*)

(*continued*)

Molecular Weight: 168.23 g/mol **RIFM Number:** 5093 **Stereochemistry:** Z Isomer specified. One chiral center and 1 geometric center present. Total of 4 isomers possible.	**Molecular Weight:** 168.23 g/mol **RIFM Number:** 5670 **Stereochemistry:** Isomer not specified. One chiral center and 1 geometric center present. Total of 4 isomers possible.

2. Physical data

CAS # 25524-95-2 **Boiling Point:** 287.95 °C (EPI Suite) **Flash Point:** >93 °C (Globally Harmonized System) **Log K_{OW}:** 2.0 (RIFM, 2013d); 2.35 (EPI Suite) **Melting Point:** 17.72 °C (EPI Suite) **Water Solubility:** 614.3 mg/L (EPI Suite) **Specific Gravity:** Not Available **Vapor Pressure:** 0.00227 mm Hg at 20 °C (EPI Suite v4.0), 0.00369 mm Hg at 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not Available	CAS # 34686-71-0 **Boiling Point:** 287.95 °C (EPI Suite) **Flash Point:** Not Available **Log K_{OW}:** 2.0 (RIFM, 2013d); 2.35 (EPI Suite) **Melting Point:** 17.72 °C (EPI Suite) **Water Solubility:** 614.3 mg/L (EPI Suite) **Specific Gravity:** Not Available **Vapor Pressure:** 0.00227 mm Hg at 20 °C (EPI Suite v4.0), 0.00369 mm Hg at 25 °C (EPI Suite) **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015).

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.033% (RIFM, 2019)
2. **Inhalation Exposure**:** 0.000037 mg/kg/day or 0.0027 mg/day (RIFM, 2019)
3. **Total Systemic Exposure***:** 0.00093 mg/kg/day (RIFM, 2019)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**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 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 et al., 2015; Safford et al., 2017; and 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	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 the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   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

5-Hydroxy-7-decenoic acid δ-lactone is reported to occur in the following foods by the VCF*:

Cheddar Cheese
Guava and feyoa
Honey
Mangifera species
Mentha oils
Nectarine
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Tetrahydro-6-(2-pentenyl)-2H-pyran-2-one is reported to occur in the following foods by the VCF*:
Tea

*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

5-Hydroxy-7-decenoic acid δ-lactone has been pre-registered for 2010; tetrahydro-6-(2-pentenyl)-2H-pyran-2-one has been pre-registered for 2013; no dossier for either available as of 10/06/21.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 5-hydroxy-7-decenoic acid δ-lactone does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 5-hydroxy-7-decenoic acid δ-lactone was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity with metabolic activation, and positive for both cytotoxicity and genotoxicity without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Whereas the BlueScreen assay on the target material showed positive results, data from additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic and clastogenic activity of 5-hydroxy-7-decenoic acid δ-lactone; however, read-across can be made to tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0; see Section VI).

The mutagenic activity of tetrahydro-6-(3-pentenyl)-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 preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA, were treated with tetrahydro-6-(3-pentenyl)-2H-pyran-2-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small increases in the mean number of revertant colonies were observed at 15 and 150 μg/plate in strain TA100 in the absence of S9 (RIFM, 2013a). However, the maximum increase was only 1.25-fold, there was no dose-dependence observed, the result was not reproducible, and the values were within the historical control limit. Therefore, this result was not considered biologically relevant. Under the conditions of the study, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was not mutagenic in the Ames test, and this can be extended to 5-hydroxy-7-decenoic acid δ-lactone.

The clastogenic activity of tetrahydro-6-(3-pentenyl)-2H-pyran-2-one 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 tetrahydro-6-(3-pentenyl)-2H-pyran-2-one in DMSO at concentrations up to 1680 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1680 μg/mL in the presence and absence of metabolic activation. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013c). Under the conditions of the study, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 5-hydroxy-7-decenoic acid δ-lactone.

Based on the data available, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one does not present a concern for genotoxic potential, and this can be extended to 5-hydroxy-7-decenoic acid δ-lactone.

Additional References: RIFM, 2004.

Literature Search and Risk Assessment Completed On: 12/11/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 5-hydroxy-7-decenoic acid δ-lactone or any read-across materials. The total systemic exposure to 5-hydroxy-7-decenoic acid δ-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 5-hydroxy-7-decenoic acid δ-lactone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 5-hydroxy-7-decenoic acid δ-lactone (0.93 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/25/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 5-hydroxy-7-decenoic acid δ-lactone or any read-across materials. The total systemic exposure to 5-hydroxy-7-decenoic acid δ-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 5-hydroxy-7-decenoic acid δ-lactone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 5-hydroxy-7-decenoic acid δ-lactone (0.93 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/03/20.

11.1.4. Skin sensitization

Existing data do not indicate 5-hydroxy-7-decenoic acid δ-lactone is a sensitizer. Based on the existing data, 5-hydroxy-7-decenoic acid δ-lactone presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Existing data indicate 5-hydroxy-7-decenoic acid δ-lactone presents no concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.2). In a Confirmation of No Induction in Humans test (CNIH) with 0.84% or 992 μg/cm^2 of 5-hydroxy-7-decenoic acid δ-lactone in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2020b). In another CNIH with 1.25% or 969 μg/cm^2 of 5-hydroxy-7-decenoic acid δ-lactone in 98.75% alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1972). Based on the weight of evidence (WoE) from the human studies, 5-hydroxy-7-decenoic acid δ-lactone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/30/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 5-hydroxy-7-decenoic acid δ-lactone would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 5-hydroxy-7-decenoic acid δ-lactone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 5-hydroxy-7-decenoic

acid δ-lactone does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/03/20.

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 5-hydroxy-7-decenoic acid δ-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 5-hydroxy-7-decenoic acid δ-lactone. Based on the Creme RIFM Model, the inhalation exposure is 0.0027 mg/day. This exposure is 518.5 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: 12/10/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 5-hydroxy-7-decenoic acid δ-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 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, 5-Hydroxy-7-decenoic acid δ-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 5-hydroxy-7-decenoic acid δ-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, 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.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 5-hydroxy-7-decenoic acid δ-lactone presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. **RIFM, 2012:** The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F method. Biodegradation of 88% was observed after 43 days.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. 5-Hydroxy-7-decenoic acid δ-lactone has been preregistered 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.

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

*Combined regional Volumes of Use for both CAS #s.

Based on available data, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.227 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 VoU.

Literature Search and Risk Assessment Completed On: 12/04/20.

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
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	227			1000000	0.227	

&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 10/06/21.

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.2022.112853.

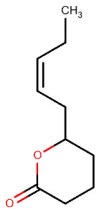
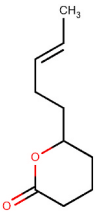
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). 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, 2017).

- 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, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020) 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, 2020).
- 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
Principal Name	5-Hydroxy-7-decenoic acid δ-lactone	Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one
CAS No.	25524-95-2	32764-98-0
Structure		
Similarity (Tanimoto Score)		0.75
Endpoint		• Genotoxicity
Molecular Formula	$C_{10}H_{16}O_2$	$C_{10}H_{16}O_2$
Molecular Weight (g/mol)	168.236	168.236
Melting Point (°C, EPI Suite)	17.72	17.72
Boiling Point (°C, EPI Suite)	287.95	287.95
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.92E-01	4.92E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	6.14E+02	6.14E+02
Log K_{OW}	2.35	2.35
J_{max} (μg/cm^2/h, SAM)	14.95	14.95
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.01E+01	5.01E+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	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25524-95-2). 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, tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (CAS # 32764-98-0) was used as a read-across analog for the target material 5-hydroxy-7-decenoic acid δ-lactone (CAS # 25524-95-2) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of ∂ lactone.
  - o The target material and the read-across analog share a ∂ lactone ring.
  - o The key difference between the target material and the read-across analog is in the position of the vinylene bond. The target has it at 8 position while the read-across analog has it at 7 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an 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 There are no alerts for the target material and the read-across analog for genotoxicity endpoint. *In silico* alerts are consistent with 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? No.
Q9. Lactone, fused to another ring, or 5- or 6-membered α,β-unsaturated lactone? No.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
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)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2020. The OECD QSAR Toolbox, v3.2–4.4. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1972. Repeated Insult Patch Test with Tetrahydro-6-(2-Pentenyl)-2h-Pyran-2-One (Jasmin Lactone). Unpublished Report from International Flavors and Fragrances. RIFM report number 53956. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2004. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one (Jasmolactone): Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. Unpublished report from Firmenich. RIFM report number 67739. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2012. Ready Biodegradability of 5-Hydroxy-7-Decenoic Acid Delta-Lactone and Tetrahydro-6-(2-Pentenyl)-2h-Pyran-2-One (Jasmin Lactone Delta). Unpublished report from Givaudan. RIFM report number 63559. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013a. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one: Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. RIFM report number 65014. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Report on the Testing of 5-Hydroxy-7-Decenoic Acid Delta-Lactone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65147. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013c. Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL) [Amendment attached] RIFM report number 66028. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013d. Partition Coefficient N-Octanol/water of 5-Hydroxy-7-Decenoic Acid Delta-Lactone and Tetrahydro-6-(2-Pentenyl)-2h-Pyran-2-One (Jasmin Lactone Delta). Unpublished report from Givaudan. RIFM report number 66663. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey, 23. January 2019.

RIFM (Research Institute for Fragrance Materials, Inc), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM report number 76272. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2020b. 5-Hydroxy-7-decenoic Acid δ-lactone: Repeated Insult Patch Test (RIPT). RIFM report number 76634. RIFM, Woodcliff Lake, NJ, USA.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.