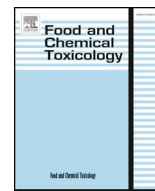




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Short Review

RIFM fragrance ingredient safety assessment, octyl crotonate, CAS Registry Number 22874-79-9



A.M. Api^a, F. Belmonte^a, D. Belsito^b, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, 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, S. La Cava^a, A. Lapczynski^a, M. Lavelle^a, D.C. Lieblerⁱ, M. Na^a, D. O'Brien^a, T.M. Penning^j, G. Ritacco^a, J. Romine^a, N. Sadekar^a, D. Salvito^a, T.W. Schultz^k, 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 Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden

^d Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f Member RIFM 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Wuerzburg, Germany

^h Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Member RIFM 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 RIFM 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

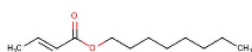
^m Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

Version: 091118. This version replaces any previous versions.

Name: Octyl crotonate CAS Registry Number: 22874-79-9

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
Crete RIFM Model - The Crete 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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association



LOEL - Lowest Observable Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

QRA - Quantitative Risk Assessment

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

* Corresponding author.

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

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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 under the limits 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 use of this material under current conditions is supported by existing information.

Octyl crotonate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) show that octyl crotonate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to octyl crotonate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using DST for reactive materials (64 µg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; octyl crotonate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; octyl crotonate 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, 2017; RIFM, 2016)

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

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

Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM DB)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.2 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 20.5 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 1.785 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: 1.785 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.001785 µg/L

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

1. Identification

1. Chemical Name: Octyl crotonate

2. **CAS Registry Number:** 22874-79-9

3. **Synonyms:** 2-Butenoic acid, octyl ester; Octyl *trans*-2-butenate; Octyl 2-butenate; 2-ブテン酸アルキル (C = 1~8); Octyl but-2-enoate; Octyl crotonate

4. **Molecular Formula:** C₁₂H₂₂O₂

5. **Molecular Weight:** 198.31

6. **RIFM Number:** 88

7. **Stereochemistry:** Isomer not specified. One geometric center present and 2 total geometric isomers possible.

2. Physical data

1. **Boiling Point:** 253.11 °C (EPI Suite)

2. **Flash Point:** Not Available

3. **Log K_{ow}:** 4.58 (EPI Suite)

4. **Melting Point:** 11.61 °C (EPI Suite)

5. **Water Solubility:** 5.496 mg/L (EPI Suite)

6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.0145 mm Hg @ 20 °C (EPI Suite v4.0), 0.0231 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 · cm⁻¹)

9. **Appearance/Organoleptic:** A colorless liquid (RIFM Database)

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)

2. **95th Percentile Concentration in Hydroalcohols:** 0.0014% (RIFM, 2015)

3. **Inhalation Exposure*:** 0.0000056 mg/kg/day or 0.00041 mg/day (RIFM, 2015)

4. **Total Systemic Exposure**:** 0.000077 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; 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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%

2. **Oral:** Assumed 100%

3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v3.2
I	I	I

2. **Analogs Selected:**

a. **Genotoxicity:** Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7)

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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Octyl crotonate is not reported to occur in foods by the VFC*.

*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 available as of 09/11/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, octyl crotonate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of octyl crotonate; however, read-across can be made to ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7; see Section V). The mutagenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 *Escherichia coli* strain WP2uvrA were treated with ethyl *trans*-2,*cis*-4-decadienoate 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, 2017). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 ethyl *trans*-2,*cis*-4-decadienoate in DMSO at concentrations up to 500 µg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Ethyl *trans*-2,*cis*-4-decadienoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl *trans*-2,*cis*-4-decadienoate does not present a concern for genotoxic potential, and this can be extended to octyl crotonate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 5/11/18.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on octyl crotonate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to octyl crotonate (0.077 µg/kg bw/day) is below the TTC (30 µg/kg bw/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: 04/24/18.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on octyl crotonate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to octyl crotonate (0.077 µg/kg bw/day) is below the TTC (30 µg/kg bw/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: 04/24/18.

10.1.4. Skin sensitization

Based on existing data and the application of DST, octyl crotonate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for octyl crotonate. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1978). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for octyl crotonate that present no appreciable risk for skin sensitization based on the reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, octyl crotonate 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 octyl crotonate in experimental models. UV/Vis absorption spectra

Table 1

Maximum acceptable concentrations for octyl crotonate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	0.000% ^b
2	Products applied to the axillae	0.001%	0.000% ^b
3	Products applied to the face using fingertips	0.029%	0.000% ^b
4	Fine fragrance products	0.027%	0.001% ^b
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.007%	0.001% ^b
6	Products with oral and lip exposure	0.016%	0.000% ^b
7	Products applied to the hair with some hand contact	0.056%	0.000% ^b
8	Products with significant ano-genital exposure	0.003%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.000% ^b
10	Household care products with mostly hand contact	0.192%	0.001%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.107%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.018%

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.^b Negligible exposure (< 0.001%).^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, octyl crotonate 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, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry et al., 2009).

Additional References: None.**Literature Search and Risk Assessment Completed On:** 04/11/18.

10.1.6. Local Respiratory Toxicity. The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for octyl crotonate 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 octyl crotonate. Based on the Creme RIFM Model, the inhalation exposure is 0.00041 mg/day. This exposure is 3415 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:** 04/23/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment. A screening-level risk assessment of octyl crotonate 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, octyl crotonate 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 octyl crotonate 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 $\geq 2000 \text{ L/kg}$. 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).

10.2.2. Risk assessment. Based on the current Volume of Use (2015), octyl crotonate does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.**Ecotoxicity:** No data available.10.2.2.1. Other available data

Octyl crotonate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1.785</u>			1,000,000	0.001785	

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	4.5	4.5
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 further assessment is necessary.

The RIFM PNEC is 0.001785 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 4/26/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **NTP:** <http://tools.niehs.nih.gov>
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/>

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.03.012>.

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 Chemical Agency read-across assessment framework ([ECHA, 2016](#)).

- 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 substance 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](#)), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 ([OECD, 2018](#)).

[scifinderExplore.jsf](#)

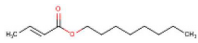
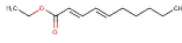
- **PubMed:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>
- **IARC:** <http://monographs.iarc.fr>
- **OECD SIDS:** <http://webnet.oecd.org/hpv/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** <http://www.safe.nite.go.jp/english/db.html>
- **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 are active as of 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

	Target Material	Read-across Material
Principal Name	Octyl crotonate	Ethyl <i>trans</i> -2, <i>cis</i> -4-decadienoate
CAS No.	22874-79-9	3025-30-7
Structure		
Similarity (Tanimoto Score)		0.92
Read-across Endpoint		● Genotoxicity
Formula	C ₁₂ H ₂₂ O ₂	C ₁₂ H ₂₀ O ₂
Molecular Weight	198.31	196.29
Melting Point (°C, EPI Suite)	11.61	10.62
Boiling Point (°C, EPI Suite)	253.11	258.41
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.07	2.31
Log Kow (KOWWIN v1.68 in EPI Suite)	4.58	4.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	5.496	8.588
Jmax (mg/cm ² /h, SAM)	8.453	3.248
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	1.07E+002	7.64E+001
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	● No alert found	● No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	● Michael addition-Polarized	● Michael addition-Polarized
	● Alkenes	● Alkenes
	● α,β-unsaturated esters	● α,β-unsaturated esters
	● Non-carcinogen (low reliability)	● Non-carcinogen (low reliability)
	● No alert found	● No alert found
	● No alert found	● No alert found
	● No alert found	● No alert found
	● Acrylate Reactive Functional Groups	● Acrylate Reactive Functional Groups
Carcinogenicity (ISS)		
DNA Binding (Ames, MN, CA, OASIS v1.1)		
<i>In Vitro</i> Mutagenicity (Ames, ISS)		
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)		
Oncologic Classification		
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 octyl crotonate (CAS # 22874-79-9). 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, ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was used as a read-across analog for the target material octyl crotonate (CAS # 22874-79-9) for the genotoxicity endpoint.
 - The target substance and the read-across analog are structurally similar and are alpha,beta-unsaturated aliphatic esters.
 - The key structural differences between the target substance and the read-across analog is that the read-across analog has diene conjugation alpha to the carbonyl group, whereas the target does not have extended conjugation to the carbonyl group. In addition, the read-across analog is an ethyl ester, and the target material is an octyl ester. These structural differences are toxicologically insignificant.
 - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
 - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
 - The target substance and the read-across analog are Michael acceptors due to the presence of the polarized carbonyl group. The data described in the genotoxicity section show that the read-across analog poses no concern for genetic toxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by data.
 - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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