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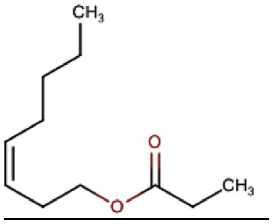
Short review

RIFM fragrance ingredient safety assessment, *cis*-3-octenyl propionate, CAS Registry Number 94134-03-9

A.M. Api[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], M. Francis[a], A.D. Fryer[h], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], A. Patel[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, 58109, 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, Würzburg, 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: 033018. This version replaces any previous versions.
Name: *cis*-3-Octenyl propionate
CAS Registry Number: 94134-03-9



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

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe 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.

cis-3-Octenyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *cis*-3-hexenyl formate (CAS# 33467-73-1) show that *cis*-3-octenyl propionate is not expected to be genotoxic. The repeated dose and reproductive toxicity endpoints were cleared using data from read-across analog *cis*-3-hexen-1-yl acetate (CAS# 3681-71-8), which provided an MOE > 100. Data from read-across analog 3-methyl-2-butenyl acetate (CAS# 1191-16-8) show that there are no safety concerns for *cis*-3-octenyl propionate for skin sensitization under the current declared levels of use. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to *cis*-3-octenyl propionate is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; *cis*-3-octenyl propionate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *cis*-3-octenyl propionate 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, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA Dossier: (Z)-hex-3-enyl acetate)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA Dossier: (Z)-hex-3-enyl acetate)
Skin Sensitization: No safety concerns for skin sensitization under the current declared levels of use.	(RIFM, 2013a; RIFM, 2014)
Phototoxicity/Photoallergenicity: Not 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: 231 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 4.521 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: 4.521 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.004521 µg/L

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

1. Identification

1. **Chemical Name:** *cis*-3-Octenyl propionate
2. **CAS Registry Number:** 94134-03-9
3. **Synonyms:** Pearlate; 3-Octen-1-ol, propanoate, (Z)-; *cis*-3-Octenyl propionate
4. **Molecular Formula**: $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.28
6. **RIFM Number**: 6902
7. **Stereochemistry:** Cis Isomer specified.

2. Physical data

1. **Boiling Point:** 252.00–254.00 °C @ 760.00 mm Hg*
2. **Flash Point:** 211.00 °F TCC (99.44 °C)*
3. **Log K_{OW}:** 0.765 (est)*
4. **Melting Point**: Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** 0.880–0.890 (Private communication to FEMA); 1.15100 to 1.17200 @ 20.00 °C*
7. **Vapor Pressure:** 0.0382 mm Hg @ 20 °C (EPI Suite 4.0); 0.019000 mm Hg @ 25.00 °C. (est)*
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:** Colorless to pale yellow clear liquid with a fresh fruity odor.*

*http://www.thegoodscentscompany.com/data/rw1486221.html, 10/09/17.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Scented Candles:** 0.00054% (RIFM, 2017)
   No reported use in hydroalcoholics
3. **Inhalation Exposure*:** 0.0000027 mg/kg/day or 0.00019 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0000026 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey, 2015, 2017; Safford, 2015, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 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 v 3.2 (OECD, 2012)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** *cis*-3-Hexenyl formate (CAS # 33467-73-1)
   b. **Repeated Dose Toxicity:** *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8)
   c. **Reproductive Toxicity:** *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8)
   d. **Skin Sensitization:** 3-Methyl-2-butenyl acetate (CAS # 1191-16-8)
   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)

cis-3-Octenyl propionate is not reported to occur in foods by the VCF.*

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 03/23/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, *cis*-3-octenyl propionate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. *cis*-3-Octenyl propionate was assessed in the

BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013c). There are no studies assessing the mutagenic activity of *cis*-3-octenyl propionate; however, read-across can be made to *cis*-3-hexenyl formate (CAS # 33467-73-1; see Section V). The mutagenic activity of *cis*-3-hexenyl formate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (OECD, 2015) using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *cis*-3-hexenyl formate 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, 2016a). Under the conditions of the study, *cis*-3-hexenyl formate was not mutagenic in the Ames test and this can be extended to *cis*-3-octenyl propionate.

There are no studies assessing the clastogenic activity of *cis*-3-octenyl propionate, however, read-across can be made to *cis*-3-hexenyl formate (CAS # 33467-73-1; see Section V). The clastogenic activity of *cis*-3-hexenyl formate 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 *cis*-3-hexenyl formate in DMSO at concentrations up to 1280 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h *cis*-3-Hexenyl formate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the presence or absence of S9 activation (Bowles, 2016; RIFM, 2016b). Under the conditions of the study, *cis*-3-hexenyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to *cis*-3-octenyl propionate.

Based on the data available, *cis*-3-hexenyl formate does not present a concern for genotoxic potential, and this can be extended to *cis*-3-octenyl propionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/18/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for *cis*-3-octenyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on *cis*-3-octenyl propionate. Read-across material *cis*-3-hexenyl acetate (CAS # 3681-71-8; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 422/GLP oral gavage repeated dose toxicity study with a reproduction/developmental screening test was conducted in Wistar rats. Groups of 11 rats/sex/dose were administered via oral gavage test material *cis*-3-hexenyl acetate at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks, while the females were dosed for approximately 7 weeks. There were no observable treatment-related adverse effects with body weights, hematological and clinical chemistry parameters, or organ weight differences. Macroscopic and microscopic findings were within the range of normal background alterations in animals of this strain and age and thus were not considered related to treatment with the test material. The NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: (Z)-hex-3-enyl acetate).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the *cis*-3-octenyl propionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to *cis*-3-octenyl propionate, 333/0.0000026 or 128076923.

In addition, the total systemic exposure to *cis*-3-octenyl propionate (0.0026 μg/kg/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.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/20/17.

10.1.3. Reproductive toxicity

The margin of exposure for *cis*-3-octenyl propionate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on *cis*-3-octenyl propionate. Read-across material *cis*-3-hexenyl acetate (CAS # 3681-71-8; see Section V) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. An OECD 422/GLP oral gavage repeated dose toxicity study with reproduction/developmental screening test was conducted in Wistar rats. Groups of 11 rats/sex/dose were administered via oral gavage test material *cis*-3-hexenyl acetate at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks while the females were dosed for approximately 7 weeks. In addition to systemic toxicity, the fertility and developmental toxicity parameters were also assessed. There were no effects observed in male and female reproductive function and performance (estrous cycling and sperm measures). The mean precoital time, fertility index, gestation index, conception rate, and implantation rate were not affected by the treatment with the test material. There were no toxicologically significant differences in the mean numbers of corpora lutea per dam, and no impact on the post implantation loss was observed. There were no treatment-related alterations on the development of the pups (body weights, macroscopic or histopathological findings, birth and viability indices, and sex ratio) observed during the first litter check and on day 4 post-partum. Thus the NOAEL for maternal toxicity, developmental toxicity, and fertility was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: (Z)-hex-3-enyl acetate).

Therefore, the *cis*-3-octenyl propionate MOE for the reproductive toxicity endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to *cis*-3-octenyl propionate, 1000/0.0000026 or 384615384.

In addition, the total systemic exposure to *cis*-3-octenyl propionate (0.0026 μg/kg/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: 09/20/17.

10.1.4. Skin sensitization

Based on the read-across material 3-methyl-2-butenyl acetate (CAS# 1191-16-8), *cis*-3-octenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for *cis*-3-octenyl propionate. Based on the read-across material 3-methyl-2-butenyl acetate (CAS# 1119-16-8; see Section V), *cis*-3-octenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use. cis-3-Octenyl propionate is not predicted to be reactive to skin proteins directly; however, read-across material 3-methyl-2-butenyl acetate may be protein reactive (Toxtree 2.6.13; OECD toolbox v3.4). Read-across material 3-methyl-2-butenyl acetate was found to be negative in an *in*

vitro Direct Peptide Reactivity Assay (DPRA), and positive in the LuSens and U937-CD86 tests (RIFM, 2012a; RIFM, 2013b; RIFM, 2012b). However, in a murine local lymph node assay (LLNA), read-across material 3-methyl-2-butenyl acetate was found to be non-sensitizing up to 100% (BASF, 2013C; RIFM, 2013a). In a Buehler test, read-across material 3-methyl-2-butenyl acetate at 100% did not present reactions indicative of sensitization (BASF, 2012f; RIFM, 2014). In a human maximization test, no skin sensitization reactions were observed with 20% of read-across material 3-methyl-2-butenyl acetate (RIFM, 1977). Additionally, in confirmatory human repeat insult patch tests (HRIPT) with 2326 μg/cm2 of read-across material 3-methyl-2-butenyl acetate in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 9 or 35 volunteers (RIFM, 1971; RIFM, 1972). Based on the weight of evidence from structural analysis and read-across material 3-methyl-2-butenyl acetate, *cis*-3-octenyl propionate does not present a safety concern for skin sensitization under the current declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/20/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *cis*-3-octenyl propionate 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 *cis*-3-octenyl propionate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, *cis*-3-octenyl propionate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/19/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material *cis*-3-octenyl propionate exposure level 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 *cis*-3-octenyl propionate. Based on the Creme RIFM Model, the inhalation exposure is 0.00019 mg/day. This exposure is 7368 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.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/30/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *cis*-3-octenyl propionate 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, *cis*-3-octenyl propionate 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).

Bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), *cis*-3-octenyl propionate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Biodegradation

No data available.

10.2.4. Ecotoxicity

No data available.

10.2.5. Other available data

cis-3-Octenyl propionate has been pre-registered for REACH with no additional data at this time.

10.2.6. 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.

	(mg/L)	(Daphnia) (mg/L)	(mg/L)			
RIFM Framework Screening-level (**Tier 1**)	<u>4.521</u>			1,000,000	0.004521	

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

Exposure	Europe	North America
Log K_{ow} used	4.0	4.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.004521 μg/L. The revised PEC/PNECs for EU and NA: Not applicable, cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 9/13/17.

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/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/oppthpv/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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.042.

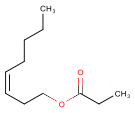
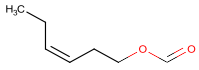
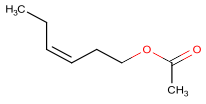
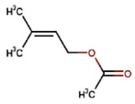
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 was 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- 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 v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	*cis*-3-Octenyl propionate	*cis*-3-Hexenyl formate	*cis*-3-Hexen-1-yl acetate	3-Methyl-2-butenyl acetate
CAS No.	94134-03-9	33467-73-1	3681-71-8	1191-16-8
Structure				
Similarity (Tanimoto Score)		0.70	0.79	0.57
Read-across Endpoint		• Genotoxicity	• Repeated dose	

			• Reproductive	• Skin sensitization
Molecular Formula	$C_{11}H_{20}O_2$	$C_8H_{14}O_2$	$C_8H_{14}O_2$	$C_7H_{12}O_2$
Molecular Weight	184.28	142.20	142.20	128.17
Melting Point (°C, EPI Suite)	0.78	−33.28	−33.28	−53.90
Boiling Point (°C, EPI Suite)	235.33	176.55	176.55	149.15
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.89	152	152	556
Log Kow (KOWWIN v1.68 in EPI Suite)	4.09	2.07	2.7[1]	2.1[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	16.97	1607	480.5	1289
J_{max} (mg/cm^2/h, SAM)	19.398	79.09	206.005	636.746
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.49E-003	6.36E-004	6.36E-004	5.65E-004
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found		
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Non-Carcinogen (moderate reliability)	• Non-Carcinogen (low reliability)		
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	• Aldehyde type compound		
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-Toxicant (moderate reliability)		• Toxicant (good reliability)	
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found			• SN2 reaction
Protein Binding (OECD)	• No alert found			• SN2 reaction
Protein Binding Potency	• Not possible to classify			• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found			• SN2 reaction
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found			• SN2 reaction
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	94134-03-9.pdf	33467-73-1 pdf	3681-71-8 pdf	1191-16-8 pdf

Summary

There are insufficient toxicity data on *cis*-3-octenyl propionate (CAS # 94134-03-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, *cis*-3-hexenyl formate (CAS # 33467-03-9), *cis*-3-hexen-1-yl acetate (CAS # 3681-71-8), and 3-methyl-2-butenyl acetate (CAS # 1191-16-8) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- *cis*-3-Hexenyl formate (CAS # 33467-03-9) was used as a read-across analog for the target material *cis*-3-octenyl propionate (CAS # 94134-03-9) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a common unsaturated aliphatic alcohol on the ester.
  - o The key difference between the target substance and the read-across analog is the aliphatic chain length on both the acid and alcohol portions of the ester. These structural differences are insignificant for the genotoxic endpoint
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the aliphatic ester moiety. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o 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 v3.4, 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 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.

- *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8) was used as a read-across analog for the target material *cis*-3-octenyl propionate (CAS # 94134-03-9) for the repeated dose and reproductive toxicity endpoints.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - The target substance and the read-across analog share a common unsaturated aliphatic alcohol on the ester.
  - The key difference between the target substance and the read-across analog is the aliphatic chain length on both the acid and alcohol portions of the ester. These structural differences are insignificant for the repeated dose and reproductive toxicity endpoints.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the aliphatic ester moiety. 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.
  - The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity, while the target substance is predicted to be a non-toxicant. The data described in the developmental toxicity section above show that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the 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.
- 3-Methyl-2-butenyl acetate (CAS # 1191-16-8) was used as a read-across analog for the target material *cis*-3-octenyl propionate (CAS # 94134-03-9) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of alipahtic esters.
  - The target substance and the read-across analog share a common unsaturated aliphatic alcohol on the ester.
  - The key difference between the target substance and the read-across analog is the aliphatic chain length on both the acid and alcohol portions of the ester. These structural differences are toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the aliphatic ester moiety. 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.
  - The read-across analog is predicted to have protein binding alerts by OECD for skin sensitization. The data described in the skin sensitization section above show that the read-across analog does not pose a concern for skin sensitization endpoint. Therefore, the alert will be superseded by the availability of the 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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