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Short review

RIFM fragrance ingredient safety assessment, ethylene brassylate, CAS Registry Number 105-95-3

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ABSTRACT

Summary: : The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using ethylene dodecanedioate (CAS # 54982-83-1) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra along with data on the target material. The environmental endpoint was completed as described in the RIFM Framework along with data on the suitable read across analog oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2).

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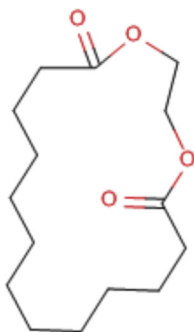
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Version: 082216. This version replaces any previous versions.

Name: Ethylene brassylate

CAS Registry Number: 105-95-3



Abbreviation 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; Safford et al., 2015) 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

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

RIFM- Research Institute for Fragrance Materials

RQ- Risk Quotient

TTC- Threshold of Toxicological Concern

UV/Vis Spectra- Ultra Violet/Visible spectra

VCF- Volatile Compounds in Food

VoU- Volume of Use

vPvB- (very) Persistent, (very) Bioaccumulative

WOE- Weight of Evidence

RIFM's Expert Panel* 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 reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

(continued)

Summary: The use of this material under current conditions is supported by existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic nor does it have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using ethylene dodecanedioate (CAS # 54982-83-1) as a suitable read across analog, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra along with data on the target material. The environmental endpoint was completed as described in the RIFM Framework along with data on the suitable read across analog oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2).

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (ECHA REACH Dossier; Abramsson-Zetterberg and Slanina, 2002)

Repeated Dose Toxicity: NOAEL = 333 mg/kg/day. (RIFM, 2000)

Developmental and Reproductive Toxicity: NOEL = 1000 mg/kg/day. (RIFM, 2003a,b,c,d,e)

Skin Sensitization: Not sensitizing. (RIFM, 1995a, 1995b; RIFM, 1997a,b,c,d; RIFM, 2004)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1983; Ogoshi et al., 1980; Ohkoshi et al., 1981)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 100% (RIFM, 1997a,b,c,d)

Bioaccumulation: Screening Level: 597.3 l/kg (EPISUITE ver 4.1)

Ecotoxicity: Critical Ecotoxicity Endpoint: Based on read-across to oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2), 33 days; Fish chronic; NOEC: 0.027 mg/l (RIFM, 2003a,b,c,d,e)

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: Based on read-across to oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2), 33 days; Fish chronic; NOEC: 0.027 mg/l (RIFM, 2003a,b,c,d,e)

RIFM PNEC is: 2.7 µg/L

- Revised PEC/PNECs (2011 IFRA VoU): North America and Europe < 1

1. Identification

- 1. Chemical Name:** Ethylene brassylate
- 2. CAS Registry Number:** 105-95-3
- 3. Synonyms:** Astratone; Cyclo-1,13-ethylenedioxytridecan-1,13-dione; 1,4-Dioxacycloheptadecane-5,17-dione; Ethylene brassylate; Ethylene glycol brassylate, cyclic diester; Ethylene undecane dicarboxylate; Musk T; Tridecanedioic acid cyclic ethylene glycol diester; 1,4-ジ オキサ-5,17-ジ オキサヘプタデカン; Ethylene-tridecane-dioate; Cyclic ethylene glycol tridecanedioate
- 4. Molecular Formula:** C₁₅H₂₆O₄
- 5. Molecular Weight:** 270.37
- 6. RIFM Number:** 392

2. Physical data

- 1. Boiling Point:** 330 °C [FMA database], (calculated) 434.44 °C [EPI Suite]
- 2. Flash Point:** >212 °F; CC [FMA database]

3. **Log Kow:** 4.7 @ 24 °C [RIFM, 1993], 4.71 [EPI Suite]
4. **Melting Point:** 71.08 °C [EPI Suite]
5. **Water Solubility:** 1.719 mg/L [EPI Suite]
6. **Specific Gravity:** 1.042–1.049 [FMA database], 1.040–1.047 [FMA database], 1.042 g/ml [RIFM, 1993]
7. **Vapor Pressure:** <0.001 mm Hg 20 °C [FMA database], (calculated) 0.000000199 mm Hg @ 20 °C [EPI Suite 4.0], (calculated) 4.38e-007 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorption in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹).
9. **Appearance/Organoleptic:** An almost colorless, viscous liquid which has a sweet-musky, somewhat oily odor of outstanding tenacity (Arctander, 1969).

3. Exposure

1. **Volume of Use (worldwide band):** >1000 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcohols:** 3.5% (RIFM, 2013)
3. **Inhalation Exposure*:** 0.0030 mg/kg/day or 0.21 mg/day (RIFM, 2013)
4. **Total Systemic Exposure**:** 0.079 mg/kg/day (RIFM, 2013)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al, 2015 and Safford et al, 2015).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al, 2015).

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
I*	I	III

*See Appendix below for explanation.

2. Analogs Selected:

- a. **Genotoxicity:** None
- b. **Repeated Dose Toxicity:** Ethylene dodecanedioate (CAS # 54982-83-1)
- c. **Developmental and Reproductive Toxicity:** oxacyclohexadec-12-en-2-one, (E)-(CAS # 111879-80-2)Skin Sensitization: None

- d. **Phototoxicity/Photoallergenicity:** None
 - e. **Local Respiratory Toxicity:** None
 - f. **Environmental Toxicity:** Macrocytic Lactones/Lactides SAC
3. **Read-across Justification:** See Appendix below

6. Metabolism

Not relevant for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

Ethylene brassylate is not reported to occur in food 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, contains 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

Available; accessed on 8/27/2013.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, ethylene brassylate does not present a concern for genetic toxicity.

10.1.2. Risk assessment

The mutagenic potential of ethylene brassylate was evaluated in an Ames test conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA were tested with ethylene brassylate up to 5000 µg/plate with and without metabolic activation (ECHA REACH Dossier). Under the conditions of the study, ethylene brassylate was concluded not mutagenic in bacteria.

The clastogenicity of ethylene brassylate was assessed in an *in vivo* micronucleus test conducted using procedures similar to those outlined in OECD 474. Ethylene brassylate was administered by a single intraperitoneal dose to groups of male CD-1 and female NMRI mice (3/sex/dose) up to 1600 mg/kg in male (CD-1 mice) and 1400 mg/kg (female NMRI mice). Ethylene brassylate did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the peripheral blood of CD-1 male or NMRI female mice. The treated animals showed no adverse effects at any of the doses tested (Abramsson-Zetterberg and Slanina, 2002). Under the conditions of the study, ethylene brassylate was considered not clastogenic in the *in vivo* micronucleus assay.

Based on the available data, ethylene brassylate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/30/13.

10.1.3. Repeated dose toxicity

The margin of exposure for Ethylene brassylate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.4. Risk assessment

The repeated dose toxicity data on ethylene brassylate are insufficient. Read across material ethylene dodecanedioate (CAS # 54982-83-1; see Section 5) has an OECD 407 gavage 28-day sub-chronic toxicity study in rats which determined the NOAEL to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2000).

A default safety factor of 3 was used when deriving a NOAEL from the 28 day or OECD 422/421/407 studies. The safety factor has been approved by RIFM's Independent Expert Panel*.

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

Therefore, the MOE is equal to the ethylene dodecanedioate NOAEL in mg/kg/day divided by the total systemic exposure, 333/0.079 or 4215.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: McGinty et al., 2011a; Belsito et al., 2011; RIFM, 1974; Bitsch et al., 2002; RIFM, 1990; McGinty et al., 2011b; McGinty et al., 2011c, 2011d; RIFM, 1999a,b; RIFM, 1998a,b; RIFM, 1995a,b; RIFM, 1996a; RIFM, 1998a,b; RIFM, 2003a,b.

Literature Search and Risk Assessment Completed on: 07/30/13.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for Ethylene brassylate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on ethylene brassylate. Read across material oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2; see Section 5) has an OECD 414 gavage developmental toxicity study in rats which determined the NOAEL to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2003a). **Therefore, the MOE for developmental toxicity is equal to the oxacyclohexadec-12-en-2-one, (12E)- NOEL in mg/kg/day divided by the total systemic exposure, 1000/0.079 or 12658.**

There are no reproductive toxicity data on ethylene brassylate. Read across material oxacyclohexadec-12-en-2-one, (12E)- (CAS # 111879-80-2) has an OECD 415 gavage 1-generation reproductive toxicity study in rats which determined the NOAEL to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2003b). **Therefore, the MOE for reproductive toxicity is equal to the oxacyclohexadec-12-en-2-one, (12E)- NOEL in mg/kg/day divided by the total systemic exposure, 1000/0.079 or 12658.**

Additional References: McGinty et al., 2011a; Belsito et al., 2011; RIFM, 1974; Bitsch et al., 2002; RIFM, 1990; McGinty et al., 2011b; McGinty et al., 2011c, 2011d; RIFM, 1999a,b; RIFM, 1998a,b; RIFM, 1995a,b; RIFM, 1996a; RIFM, 1998a,b; RIFM, 2003a,b.

Literature Search and Risk Assessment Completed on: 07/30/13.

10.1.7. Skin sensitization

Based on the existing data, ethylene brassylate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data, ethylene brassylate is not considered to present as a concern for skin sensitization. While ethylene

brassylate is predicted by *in silico* methods to be potentially protein reactive, experimental *in chemico* studies have shown that the material lacks significant reactivity to cysteine based peptides (OECD Toolbox V3.1; Natsch et al., 2007; Roberts and Natsch, 2009). Ethylene brassylate was negative in the LLNA and guinea pig sensitization tests (RIFM, 1997b; RIFM, 1997c; and RIFM, 2004). In the HRIPT, no reactions indicative of sensitization to ethylene brassylate were observed in human repeated insult patch tests (data summarized in Belsito et al., 2011).

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/30/13.

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, ethylene brassylate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

The UV spectra for ethylene brassylate indicate no significant absorption in the range of 290–700 nm, and a corresponding molar absorption coefficient below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ cm⁻¹ (Henry et al., 2009). In phototoxicity studies conducted in guinea pigs and rabbits, ethylene brassylate (up to 50%) was not found to be phototoxic (Ohkoshi et al., 1981; RIFM, 1978; Ogoshi et al., 1980; RIFM, 1983). In another study, Guinea Pigs RIFM, 1983) with 5 and 10% ethylene brassylate in acetone did not exhibit phototoxic skin reactions, while application of 30% ethylene brassylate resulted in phototoxic reactions in all 5 guinea pigs tested (RIFM, 1981). Based on UV/Vis spectra and weight of evidence from existing *in vivo* studies, ethylene brassylate would not be expected to present a concern for phototoxicity or photoallergenicity at the current levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/19/16.

10.1.10.1. Local Respiratory Toxicity. The margin of exposure could not be calculated due to lack of appropriate data. The material, ethylene brassylate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.11. Risk assessment

There is limited inhalation data available on ethylene brassylate. Based on the Creme RIFM model, the inhalation exposure is 0.21 mg/day. This exposure is 6.7 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: Gilbert and Kemp, 1996; Fukayama et al., 1999.

Literature Search and Risk Assessment Completed on: 7/20/2016.

10.2. Environmental endpoint summary

10.2.1. Analogs identified/justification

Within the RIFM Database there are a number of microcyclic lactone/lactides materials that are structurally related and can be used for read-across purposes. A robust summary of available environmental data has been published in "Macrocylic fragrance materials – A screening level environmental assessment using chemical categorization" (Salvito et al., 2011).

10.2.2. Screening-level assessment

A screening level risk assessment of ethylene brassylate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework ethylene brassylate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify ethylene brassylate as being possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.3. Risk assessment

Based on current Volume of Use (2011), ethylene brassylate presents a risk to the aquatic compartment in the screening level assessment.

10.2.4. Key studies

10.2.4.1. Biodegradation. RIFM, 1994: Biodegradation was evaluated by the sealed vessel test. 10 mg/l of ethylene brassylate was incubated at for 28 days. The rate of degradation after 28 days was 78.1%.

RIFM, 1999a,b: The biodegradability of ethylene brassylate was evaluated using the Manometric Respiratory Test according to OECD guideline 301F. Ethylene brassylate (100 mg/l) was added to flasks containing mineral medium inoculated with activated sludge 28 days. Biodegradation reached 71% at the end of the 10-day window and was 83% after 28 days.

RIFM, 1996b: A 28 day study was conducted to assess the biodegradability of the test material with the BOD test for insoluble substances (BODIS). Under the condition of this study, the test material showed an average degradation rate of 66% after 28 days.

RIFM, 1998a,b: The biodegradability of ethylene brassylate was evaluated using the Manometric Respiriometry Test according to OECD guideline 301F. Ethylene brassylate (50 mg/l) was added to flasks containing mineral salts medium inoculated with activated

sludge for 28 days. Oxygen consumption was equivalent to 61% of the Theoretical Oxygen Demand (ThOD) after 7 days and 89% after 28 days.

RIFM, 1996c: The biodegradability of ethylene brassylate was evaluated using the Manometric Respiriometry Test according to OECD guideline 301F. Ethylene brassylate (50 mg/l) was added to flasks containing mineral salts medium inoculated with activated sludge for 28 days. Oxygen consumption was equivalent to 61% of the Theoretical Oxygen Demand (ThOD) after 7 days and 89% after 28 days.

RIFM, 1996d: The biodegradability of ethylene brassylate was evaluated using the Manometric Respiratory Test according to OECD guideline 301F. Ethylene brassylate (100 mg/l) was added to mineral medium inoculated with activated sludge for 28 days. The degradation level was 77% at 28 days.

RIFM, 1996e: A closed bottle degradation test was conducted and ethylene brassylate (3.64 mg/l) was classified as "not readily biodegradable" (40%).

RIFM, 1997d: Biodegradation was evaluated in accordance to OECD guidelines 301C. Ethylene brassylate (100 mg/l) was added to glass vessels containing basal culture medium, and the vessels were incubated for 28 days.

RIFM, 1997a: The biodegradability of ethylene brassylate was evaluated using the carbon dioxide evolution test (modified Sturm test). A biodegradation of 100% was observed within 28 days.

10.2.4.2. Ecotoxicity. RIFM, 1996f: A 48 h *Daphnia magna* acute test was conducted with the test material. A geometrics mean of EC₀/EC₁₀₀ of 3.65 mg/l was reported.

RIFM, 1996g: A 96-h acute toxicity study was conducted with 10 Zebra fish. A geometrics mean of EC₀/EC₁₀₀ of 1.23 mg/l was reported.

RIFM, 1996h: A 72 h algae acute test was conducted according to the Directive 67/548/EEC guidelines. Under the conditions of this study, the EC₅₀ values for integral biomass and growth rate were 5.2 and > 6.94 mg/l (measured concentration), respectively.

10.2.5. Other available data

Salvito et al., 2011: Ethylene brassylate has been pre-registered for REACH with no additional data. A robust summary of available environmental data has been published in "Macrocyclic fragrance materials – A screening level environmental assessment using chemical categorization".

10.2.6. Risk assessment refinement

Please note: For the macrocyclic lactones/lactides, the lowest acute EC₅₀/LC₅₀ reported (algae, daphnia or fish) was 0.0425 mg/L (*Danio rerio* lethality study for oxacycloheptadec-11-en-2-one). This material is reported in other studies to be very poorly soluble (mean limit of solubility reported in its *D. magna* immobilization study is 66 mg/L). This may explain the difference observed in acute toxicity between this material and the other lactones/lactides where the next lowest acute endpoint reported is an order of magnitude higher (EbC₅₀ in an algae biomass based inhibition study for *o*-pentadecalactone). The lowest NOEC from a chronic toxicity study was 0.027 mg/L (fish early life stage study for oxacyclohexadec-12-en-2-one, (E)). Three chronic endpoints are available (algae, daphnia, and fish), therefore an assessment factor of 10 is applied to this NOEC.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (fish)	EC50 (daphnia)	EC50 (algae)	AF	PNEC	Chemical class
RIFM framework screening level (Tier 1)	<u>4.632 mg/l</u>			1,000,000	0.00163 µg/l	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	0.942 mg/l	1.465 mg/l	<u>0.406 mg/l</u>	10,000	0.362 µg/l	Esters
ECOSAR acute endpoints (Tier 2) Ver 1.11	0.814 mg/l	0.594 mg/l	<u>1.246 mg/l</u>			Neutral Organics
Tier 3: Measured Data Including Read-across data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.23 mg/l		<u>0.027 mg/l</u>	10	2.7 µg/l	
Daphnia		3.65 mg/l				
Algae		5.2 mg/l				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.7	4.7
Biodegradation factor used	1	1
Dilution factor	3	3
Regional volume of use tonnage band	>1000	100–1000
Risk characterization: PEC/PNEC	<1	<1

Based on the read-across data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 2.7 µg/L. The revised PEC/PNECs for EU and NA are < 1.

Literature Search and Risk Assessment Completed on: 07/30/13.

11. Literature Search^a

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: <http://echa.europa.eu/>
- NTP: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- 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://www.chem.unep.ch/irptc/sids/oecd/sids/sidspub.html>
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jspx?_afPfm=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: <http://www.epa.gov/hpv/hpvis/index.html>
- US EPA Robust Summary: <http://cfpub.epa.gov/hpv-s/>
- Japanese NITE: <http://www.safe.nite.go.jp/english/db.html>
- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: <https://www.google.com/webhp?tab=ww&ei=KMSOUpiQK-arsQ324GwBg&ved=0CBQQ1S4>

^a Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2016.09.032>.

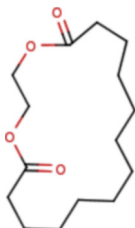
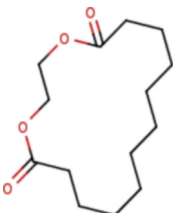
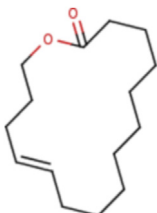
Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2016.09.032>.

Appendix

Methods:

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{\max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using

	Target material	Read across material	
Principal name	Ethylene brassylate	Ethylene dodecanedioate	Oxacyclohexadec-12-en-2-one, (12E)-
CAS no.	105-95-3	54982-83-1	111879-80-2
Structure			
3D structure	http://www.thegoodscentscompany.com/opl/105-95-3.html	http://www.thegoodscentscompany.com/opl/54982-83-1.html	http://www.thegoodscentscompany.com/opl/111879-80-2.html
Read-across endpoint		•Repeated Dose	•Devel/Repro
Molecular formula	C15H26O4	C14H24O4	C15H26O2
Molecular weight	270.37	256.35	238.37
Melting point (°C, EPISUITE)	71.08	63.39	26.84
Boiling point (°C, EPISUITE)	434.44	421.78	366.00
Vapor pressure (Pa @ 25°C, EPISUITE)	5.84E-005	0.0003253	0.007053
Log Kow (KOWWIN v1.68 in EPISUITE)	4.71	4.22	4.88
Water solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	1.719	5.417	1.859
J_{\max} (mg/cm ² /h, SAM)	3.011319647	5.271013012	1.450995146
Henry's Law (Pa·m ³ /mol, Bond method, EPISUITE)	0.317046	0.238823	206.399025
Similarity (Tanimoto score) ¹		100% ²	75%
In silico results for target and analog			
Repeated dose toxicity			
Repeated dose (HESS)	Not categorized	Not categorized	
Developmental and reproductive toxicity			
ER binding (OECD)	Non binder, without OH or NH2 group		Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (moderate reliability)		NON-Toxicant (moderate reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

¹ Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. Rogers and Hahn, 2010.

² The Tanimoto coefficient is calculated by determining the number of common fragments in target and the analog. A Tanimoto score of 100% means that two chemical structures are very similar but not necessarily identical.

Summary:

There are insufficient toxicity data on ethylene brassylate (RIFM # 392, CAS # 105-95-3). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

- OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Ethylene dodecanedioate (analog) was used as a read-across analog for Ethylene brassylate (target) based on:
 - The target and analogs belong to the generic class of macrocyclic lactones and lactides.
 - They have two ester groups and similar numbers of ring members.
 - The only difference is that the target has a larger macrocyclic ring than the analog. The difference between structures does not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
 - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
 - The target and analog show similar alerts for protein binding.
 - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- Oxacyclohexadec-12-en-2-one, (12E)- (analog) was used as a read-across analog for Ethylene brassylate (target) based on:
 - The target and analogs belong to the generic class of macrocyclic lactones and lactides.
 - They have ester groups and similar numbers of ring members.
 - The key difference is that the target has two ester groups while the analog only have one ester group. Besides, the analog has an unsaturated vinyl group within the macrocyclic ring. The difference between structures does not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
 - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
 - The target and analog show similar alerts for protein binding.
 - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Environmental analogs identified/justification:

- Within the RIFM Database there are a number of microcyclic lactone/lactides materials that are structurally related and can be used for read-across purposes. A robust summary of available environmental data has been published in "Macrocyclic fragrance materials – A screening level environmental assessment using chemical categorization" (Salvito et al., 2011).

Explanation of cramer class:

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., 1976).

Q1. Normal constituent of the body? **No**

Q2. Contains functional groups associated with enhanced toxicity? **No**

Q3. Contains elements other than C,H,O,N,divalent S? **No**

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**

Q6. Benzene derivative with certain substituents? **No**

Q7. Heterocyclic? **Yes**

Q8. Lactone or cyclic diester? **Yes**

Q9. Lactone, fused to another ring, or 5- or 6-membered, a,b-unsaturated lactone? **No**

Q20. Aliphatic with some functional groups? **Yes**

Q21. 3 or more different functional groups? **No**

Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No** Class Low (Class I)

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