Food and Chemical Toxicology 110 (2017) S670–S678

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

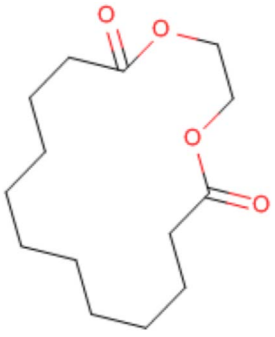
RIFM fragrance ingredient safety assessment, ethylene dodecanedioate, CAS registry number 54982-83-1

A.M. Api[a,*], D. Belsito[b], D. Botelho[a], D. Browne[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], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], R. Parakhia[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], Y. Thakkar[a], E.H. Theophilus[a], A.K. Tiethof[a], Y. Tokura[m], S. Tsang[a], J. Wahler[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: 091917. This version replaces any previous versions.

Name: Ethylene dodecanedioate
CAS Registry Number: 54982-83-1



* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

http://dx.doi.org/10.1016/j.fct.2017.10.050
Received 2 October 2017; Accepted 27 October 2017
Available online 02 November 2017

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; Safford et al., 2017; Comiskey et al., 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
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
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 - Ultra Violet/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 RIFM's Criteria Document (Api et al., 2015) and 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 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 guidance relevant to human health and environmental protection.

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

The material (ethylene dodecanedioate) was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that ethylene dodecanedioate is not genotoxic and provided a MOE > 100 for the repeated dose toxicity endpoint. Data from the read across analog oxacyclohexadecane-2,13-dione (CAS # 38223-29-9) show that ethylene dodecanedioate does not present a concern for skin sensitization. The developmental, reproductive and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on ethylene dodecanedioate. The environmental endpoints were evaluated, ethylene dodecanedioate 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 genotoxic. (RIFM, 1999c; RIFM, 1999d)

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

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

Skin Sensitization: Not a concern for skin sensitization. (RIFM, 2000a; RIFM, 1982b; RIFM, 1997e; RIFM, 1983; RIFM, 1982a; RIFM, 1975)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1981)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 100% (RIFM, 2000b)

Bioaccumulation: Screening-Level: 283.2 L/kg (US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 96-hr Fish LC50: 0.88 mg/L (RIFM, 1997b)

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: 96-hr Fish LC50: 0.88 mg/L (RIFM, 1997b)

RIFM PNEC is: 0.88 µg/L

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

1. Identification

1. **Chemical Name:** Ethylene dodecanedioate
2. **CAS Registry Number:** 54982-83-1
3. **Synonyms:** Arova 16; Cyclic ethylene dodecanedioate; 1,4-Dioxacyclohexadecane-5,16-dione; Musk 144; Musk C-14; Zenolide; 1,4-ｼﾞｵｷｻｼｸﾛﾍｷｻﾃﾞｶﾝ-5,16-ｼﾞｵﾝ; Ethylene dodecanedioate
4. **Molecular Formula:** $C_{14}H_{24}O_4$
5. **Molecular Weight:** 256.35
6. **RIFM Number:** 7

2. Physical data

1. **Boiling Point:** 421.78 °C [US EPA, 2012a]
2. **Flash Point:** 178.00 °F. TCC (81.11 °C)*
3. **Log K_{ow}:** 3.65 at 20 °C [RIFM, 1999b], 4.22 [US EPA, 2012a]
4. **Melting Point:** 63.39 °C [US EPA, 2012a]
5. **Water Solubility:** 7.5 × 10^{-2} g/L at 20 °C [RIFM, 1999b], (calculated) 5.417 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 1.048–1.068 @ 25/25 °C [RIFM]
7. **Vapor Pressure:** < 0.001 mm Hg 20 °C [FMA database], 0.028 Pa at 25 °C [RIFM, 1999b], (calculated) 0.00000129 mm Hg @ 20 °C [US EPA, 2012a], (calculated) 2.44e-006 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** Minor absorption in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1}).
9. **Organoleptic:** A colorless to pale yellowish oily liquid with a natural mild musk odor.

*http://www.thegoodscentscompany.com/data/rw1001991.html, retrieved 5/19/2015.

3. Exposure

1. **Volume of Use (Worldwide Band):** 100–1000 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 1.2% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.0013 mg/kg/day or 0.098 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.029 mg/kg/day (RIFM, 2014)

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I*	I	III

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further detail.

2. Analogs selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Oxacyclohexadecane-2,13-dione (CAS # 38223-29-9)
   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)

Ethylene dodecanedioate 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 that 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 03/24/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, ethylene dodecanedioate does not present a concern for genotoxicity.

10.1.2. Risk assessment

The mutagenic potential of ethylene dodecanedioate was assessed in an Ames assay conducted in compliance with GLP regulations in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535,

TA1537, TA1538, TA98 and TA100 and *Escherichia coli* strain WP2 uvrA were treated with ethylene dodecanedioate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No substantial increases in revertant colony numbers of the test strains were observed, following treatment with the test material at any dose levels in the presence or absence of S9 mix (RIFM, 1999d). Under the conditions of the study, ethylene dodecanedioate was not considered to be mutagenic in the Ames test.

The clastogenicity of ethylene dodecanedioate was assessed in an *in vitro* chromosome aberration assay conducted in compliance with GLP regulations and in accordance with OECD 473. Human peripheral blood lymphocytes (HPBL) were treated with ethylene dodecanedioate in DMSO at the concentrations of 15.6, 31.3, 62.5, 125, 250, 500, 1000 and 2000 μg/mL in the presence and absence of metabolically active microsomal mixture (S9 mix). No significant increase in the number of cells with chromosomal aberrations was observed at any concentration tested, in the presence and absence of S9 mix (RIFM, 1999c). Under the conditions of the study, ethylene dodecanedioate was considered non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, ethylene dodecanedioate does not present a concern for genotoxicity.

Additional References: Abramsson-Zetterberg and Slanina, 2002.

Literature Search and Risk Assessment Completed on: 03/15/2017.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are sufficient repeated dose toxicity data on ethylene dodecanedioate for the repeated toxicity dose endpoint. In an OECD 407 gavage 28-day subchronic toxicity study with a 2-week recovery period, groups of 5 Sprague-Dawley Crl:CD BR VAF PLUS(TM) rats/sex/dose were administered via gavage test material, ethylene dodecanedioate at doses of 0, 15, 150, 400 and 1000 mg/kg/day in corn oil. Additional groups of 5 rats/sex from the control and high dose groups were subjected to the 4-week treatment period, followed by a 2-week recovery period. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, as there were no adverse treatment-related findings up to the highest dose tested (RIFM, 2000c).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day 407 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 ethylene dodecanedioate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethylene dodecanedioate NOAEL in mg/kg/day by the total systemic exposure to ethylene dodecanedioate, 333/0.029 or 11483.

In addition, the total systemic exposure to ethylene dodecanedioate (29 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: 03/14/2017.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on ethylene dodecanedioate or any read across materials. The total systemic exposure to ethylene dodecanedioate is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on ethylene dodecanedioate or any read across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to ethylene dodecanedioate (29 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on ethylene dodecanedioate or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethylene dodecanedioate (29 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.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/14/2017.

10.1.7. Skin sensitization

Based on existing data and read across to oxacyclohexadecane-2,13-dione (CAS # 38223-29-9), ethylene dodecanedioate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on available data and read across to oxacyclohexadecane-2,13-dione (CAS # 38223-29-9; see Section V), ethylene dodecanedioate does not present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react with skin proteins (Toxtree 2.6.13, OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read across material, oxacyclohexadecane-2,13-dione was found to be negative up to a maximum tested level of 30% (w/v) in acetone (RIFM, 1997e). In a guinea pig test method, ethylene dodecanedioate and read across analog oxacyclohexadecane-2,13-dione did not exhibit the potential to induce skin sensitization (RIFM, 1975; RIFM, 1982a; RIFM, 1983). In a confirmatory human repeat patch test with 25% or 13,778 μg/cm^2 ethylene dodecanedioate in 3:1 alcohol SD 39C:diethyl phthalate, no sensitization reactions were observed (RIFM, 2000a). In a human maximization test, no reactions were observed when 20% or 13,800 μg/cm^2 ethylene dodecanedioate in petrolatum was used for induction and challenge (RIFM, 1978). Similarly, in a confirmatory human repeat patch test with 20% oxacyclohexadecane-2,13-dione in white petrolatum applied under semi-occlusive covering, no reactions indicative of sensitization (0/50) were observed in any of the subjects (RIFM, 1982b). Based on the weight of evidence from structural analysis, animal and human data, as well as read across to oxacyclohexadecane-2,13-dione, ethylene dodecanedioate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/14/2013.

10.1.9. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra and existing *in vivo* data, ethylene dodecanedioate would not be expected to present a concern for phototoxicity or photoallergenicity at the current level of use.

10.1.10. Risk assessment

UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). In a guinea pig phototoxicity study, barely perceptible erythema was observed at both irradiated and unirradiated sites, and well-defined erythema was observed in one animal at 24 h, at sites treated with 30% ethylene dodecanedioate, which is well above the current use level. The reactions were no longer present at 48 h. There were no reactions seen at sites treated with 5 or 10% ethylene dodecanedioate (RIFM, 1981). Based on the lack of absorbance and i*n vivo* data, ethylene dodecanedioate does not present a concern for phototoxicity or photoallergenicity at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/12/2017.

10.1.11. Local respiratory toxicity

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

10.1.12. Risk assessment

There are no inhalation data available on ethylene dodecanedioate. Based on the Creme RIFM model, the inhalation exposure is 0.098 mg/day. This exposure is 14.3 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: 03/21/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethylene dodecanedioate was performed following the RIFM Environmental Framework (Salvito et al., 2002) that 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; US EPA, 2012b) 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, which is considered proprietary information, 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 dodecanedioate was identified as a fragrance material with 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) identified ethylene dodecanedioate as not persistent and not 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 EPI Suite v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), ethylene dodecanedioate presents a risk to the aquatic compartment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1997a:The biodegradability of the test material was evaluated using a modified Sturm test conducted according to the OECD 301B method. The total biodegradation of ethylene dodecanedioate in the two tests was 80% and 78%.

RIFM, 1999a: The biodegradability of ethylene dodecanedioate was determined according to the OECD 301C method. The average biodegradation rate was 73% by BOD measurement, and 100% by gas chromatography analysis, therefore ethylene dodecanedioate was considered readily biodegradable.

RIFM, 2000b: The biodegradability of ethylene dodecanedioate was evaluated using the OECD 301B method. Greater than a 100% biodegradation was observed after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 1997d: A 48-h *Daphnia magna* acute toxicity test was conducted under static renewal conditions according to the OECD 202 method. The test material did not induce acute immobilization of *Daphnia magna* at 14 mg/L after 48 h of exposure (NOEC). The 48-h EC50 was > 14 mg/L.

RIFM, 1997b: The acute toxicity of ethylene dodecanedioate to Rainbow trout was evaluated in a 96-h acute test according to the OECD 203 method. The 96-h LC50 was calculated to be 0.88 mg/L.

RIFM, 1997c: A study was conducted according to the OECD 201 method to determine the 72-h EC50 of the test material to *Scenedesmus capricornutum*. The EC50 for biomass was 1.9 mg/L test material. The EC50 for growth rate was 17 mg/L test material. The NOEC for inhibition of growth rate and inhibition of biomass at 72 h was 0.61 mg/L.

10.2.3.3. Other available data. Ethylene dodecanedioate has been registered under REACH with no additional data.

10.2.4. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	12.98 mg/L			1,000,000	0.0126 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.727 mg/L	6.492 mg/L	2.128 mg/L	10,000	0.2128 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.94 mg/L	4.591 mg/L	6.42 mg/L			Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.88 mg/L			1000	0.88 µg/L	
Daphnia		14 mg/L				
Algae		1.9 mg/L				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.65	3.65
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.88 µg/L. The revised PEC/PNECs for EU and NA are < 1 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: 03/15/2017.

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/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/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=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-arsQS324GwBg&ved=0CBQQ1S4

*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.2017.10.050.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.050.

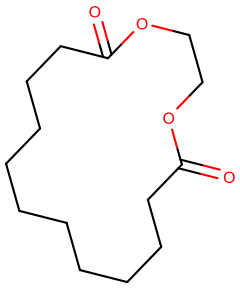
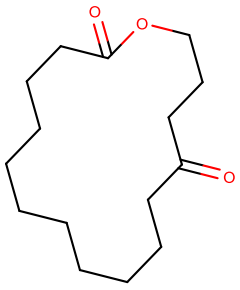
Appendix

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
Principal Name	Ethylene dodecanediaote	Oxacyclohexadecane-2,13-dione
CAS No.	54982-83-1	38223-29-9
Structure		
Similarity (Tanimoto score)		0.89
Read across endpoint		• Skin Sensitization
Molecular Formula	$C_{14}H_{24}O_4$	$C_{15}H_{26}O_3$
Molecular Weight	256.35	254.37
Melting Point (°C, EPISUITE)	63.39	89.31
Boiling Point (°C, EPISUITE)	421.78	397.20
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.000326	0.000312
Log Kow (KOWWIN v1.68 in EPISUITE)	3.65[1]	4.11[2]
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	75[1]	80[3]
J_{max} (mg/cm^2/h, SAM)	1.597	3.414
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.39E-001	8.96E-002
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• Acylation	• Acylation
Protein binding potency	• Not possible to classify (GSH)	• Not possible to classify (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2

1. RIFM, 1999b.
2. RIFM, 1990a.
3. RIFM, 1990b.

Summary

There are insufficient toxicity data on the ethylene dodecanediaote (CAS # 54982-83-1). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, oxacyclohexadecane-2,13-dione (CAS # 38223-29-9) was identified as a read across material with data for the skin sensitization endpoint.

Conclusion/Rationale

- Oxacyclohexadecane-2,13-dione (CAS # 38223-29-9) was used as a read across analog for the target material ethylene dodecanediaote (CAS # 54982-83-1) for the skin sensitization endpoint.
  - o The target material and the read across analog are structurally similar and belong to the structural class of macrocyclic lactones.
  - o The target material and the read across analog share a carbon macrocyclic ester structure.
  - o The key difference between the target material and the read across analog is that the target material has one less carbon in its macrocycle compared to the read across analog. The carbonyl at the 13 position in the read across analog replaces an ester at the same position in the target. These structural differences between the target material and the read across analog do not affect consideration of the toxicological endpoint.
  - o Similarity between the target material and the read across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical-chemical properties of the target material and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoint are consistent between the target material and the read across analog.
  - o The target material and the read across analog are predicted to be sensitizers by the CAESAR model for skin sensitization. There are no other protein binding alerts for skin sensitization. The data described in the skin sensitization section show that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the prediction is superseded by the availability of data.
  - o The target material and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

Explanation of cramer classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Note: As ethylene dodecanedioate is a cyclic diester, Cramer classification on the hydrolysis products (HOCH2CH2OH and HO2C(CH2)10CO2H) was performed, and if they have different classes assigned, the higher of the two to the parent compound was used. So, after No to question 9, it should be treated as hydrolysis product.

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, and 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 alpha,beta-unsaturated lactone? **No**
Q19. Open chain? **Yes**
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? **Yes**
Q21. 3 or more different functional groups? **No**
Q18. One of the list: (a) a vicinal diketone; or a ketone or ketal of a ketone attached to a terminal vinyl group (b) a secondary alcohol or ester of a secondary alcohol attached to a terminal vinyl group (c) allyl alcohol or its acetal, ketal or ester derivative (d) allyl mercaptan, an allyl sulphide, an allyl thioester or allyl amine (e) acrolein, a methacrolein or their acetals (f) acrylic or methacrylic acid (g) an acetylenic compound (h) an acyclic aliphatic ketone, ketal or keto alcohol with no other functional groups and with four or more carbons on either side of the keto group (i) a substance in which the functional groups are all sterically hindered? (see Cramer et al., 1978 for detailed explanation on list of categories)? **No**
Class I (Class Low)

References

Abramsson-Zetterberg, L., Slanina, P., 2002. Macrocyclic musk compounds - an absence of genotoxicity in the Ames Test and the in vivo micronucleus assay. Toxicol. Lett. 135, 155–163.

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

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

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

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

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

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

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

ECHA, 2016. Read across assessment framework (RAAF). Retrieved from. www.echa.

europa.eu/documents/10162/13628/raaf_en.pdf.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
OECD, 2012. The OECD QSAR Toolbox, v. 3.4. Retrieved from. http://www.qsartoolbox.org/.
OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
RIFM (Research Institute for Fragrance Materials, Inc), 1975. Contact Hypersensitivity Test of Ethylene Dodecanedioate in Guinea Pigs. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM report number 37765 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1978. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1787 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1981. Primary Skin Irritation Study and Phototoxicity Study in Guinea Pigs of Musk C-14. Unpublished report from Takasago International Corporation. RIFM report number 32953 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1982a. Delayed Contact Hypersensitivity Study of Guinea Pigs of Ethylene Dodecanedioate (Musk C-14). Unpublished report from Takasago International Corporation. RIFM report number 32952 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1982b. Repeated Insult Patch Test/photosensitization Study of Oxacyclohexadecane-2,13-dione in Human Subjects. Unpublished report from Firmenich Incorporated. RIFM report number 38906 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1983. Magnusson and Kligman Maximization Study: Determination of the Contact Sensitization Potential of Oxacyclohexadecane-2,13-dione (12-ketopentadecanolide) in the Guinea Pig. Unpublished report from Symrise. RIFM report number 59232 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc)., 1990a. Determination of the Partition Coefficient (N-octanol/water of Oxacyclohexadecane-2,13-dione (12-ketopentadecanolide). Unpublished report from Symrise. RIFM report number 59235 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1990b. Determination of the Water Solubility of Oxacyclohexadecane-2,13-dione (12-ketopentadecanolide). Unpublished report from Symrise. RIFM report number 59249 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1997a. Determination of Ready Biodegradability: Carbon Dioxide (CO2) Evolution Test (Modified Sturm Test) with Musk C-14. Unpublished report from Takasago International Corporation. RIFM report number 32955 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1997b. The Acute Toxicity of Ethylene Dodecanedioate to Rainbow Trout. Unpublished report from International Flavors and Fragrances. RIFM report number 48563 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1997c. The Acute Toxicity of Ethylene Dodecanedioate to the Green Alga Selenastrum Capricornutum. Unpublished report from International Flavors and Fragrances. RIFM report number 48564 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1997d. The Acute Toxicity of Ethylene Dodecanedioate to Daphnia Magna. Unpublished report from International Flavors and Fragrances. RIFM report number 48565 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1997e. Oxacyclohexadecane-2,13-dione (12-ketopentadecanolide): Local Lymph Node Assay. Unpublished report from Symrise. RIFM report number 59258 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1999a. Test on Biodegradability of Ethylene Dodecanedioate by Microorganisms. Unpublished report from Takasago International Corporation. RIFM report number 40189 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1999b. Ethylene Dodecanedioate: Physicochemical Properties. Unpublished report from IFF Incorporated. RIFM report number 47318 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1999c. Ethylene Dodecanedioate: in Vitro Mammalian Chromosome Aberration Test in Human Lymphocytes. Unpublished report from IFF Incorporated. RIFM report number 47320 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 1999d. Ethylene Dodecanedioate: Bacterial Mutation Assay. Unpublished report from IFF Incorporated. RIFM report number 47321 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 2000a. Repeat Insult Patch Test with Ethylene Dodecanedioate. Unpublished report from IFF Incorporated. RIFM report number 47317 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 2000b. Ethylene Dodecanedioate: Determination of Ready Biodegradability (CO2 Evolution Test). Unpublished report from IFF Incorporated. RIFM report number 47319 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 2000c. Ethylene Dodecanedioate: Toxicity Study by Oral Administration to CD Rats for 4 Weeks Followed by a 2 Week Recovery Period. Unpublished report from IFF Incorporated. RIFM report number 47323 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc), 2014. Use Level Survey, September 2014.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
US EPA, 2012a. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.0-v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft® Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.