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RIFM fragrance ingredient safety assessment, ethyl 3,7-dimethylocta-2,6--dienoate, CAS Registry Number 13058-12-3

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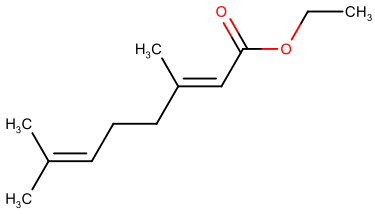
Additional CAS Numbers: 32659-21-5 Ethyl geranate



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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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Ethyl 3,7-dimethylocta-2,6-dienoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *trans*-methylgeranate (CAS # 1189-09-9) show that ethyl 3,7-dimethylocta-2,6-dienoate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to ethyl 3,7-dimethylocta-2,6-dienoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on (ultraviolet/visible) UV/Vis spectra; ethyl 3,7-dimethylocta-2,6-dienoate- is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl 3,7-dimethylocta-2,6-dienoate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2014b; RIFM, 2014c)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 416.7 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1.842 mg/L (RIFM Framework; Salvito et al., 2002)

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Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1.842 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00184 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level	

1. Identification

Chemical Name: Ethyl 3,7-dimethylocta-2,6-dienoate	**Chemical Name:** Ethyl geranate
CAS Registry Number: 13058-12-3	**CAS Registry Number:** 32659-21-5
Synonyms: Geranic acid, ethyl ester; 2,6-Octadienoic acid, 3,7-dimethyl-, ethyl ester; Ethyl geranate; ｼﾞｴﾝ脂肪酸(C = 10 ~ 18)ｱﾙｷﾙ(C = 1 ~ 2); Ethyl 3,7-dimethylocta-2,6-dienoate	**Synonyms:** (E)-3,7-Dimethyl-2,6-octadienoic acid, ethyl ester; 2,6-Octadienoic acid, 3,7-dimethyl-, ethyl ester, (E)-; Ethyl (E)-3,7-dimethylocta-2,6-dienoate; Ethyl 3,7-dimethylocta-2,6-dienoate
Molecular Formula: $C_{12}H_{20}O_2$	**Molecular Formula:** $C_{12}H_{20}O_2$
Molecular Weight: 196.29 g/mol	**Molecular Weight:** 196.29 g/mol
RIFM Number: 5396	**RIFM Number:** 1179
Stereochemistry: Isomer not specified. One geometric center and 2 geometric isomers possible	

2. Physical data

CAS # 13058-12-3	**CAS # 32659-21-5**
Boiling Point: 248.97 °C (EPI Suite)	**Boiling Point:** 120 °C at 15 mm Hg (Fragrance Materials Association [FMA]); 248.97 °C (EPI Suite)
Flash Point: Not Available	**Flash Point:** >200 °F; CC (FMA)
Log K_{ow}: 4.48 (EPI Suite)	**Log K_{ow}:** 4.48 (EPI Suite)
Melting Point: −6.1 °C (EPI Suite)	**Melting Point:** −6.1 °C (EPI Suite)
Water Solubility: 6.885 mg/L (EPI Suite)	**Water Solubility:** 6.885 mg/L (EPI Suite)
Specific Gravity:	**Specific Gravity:**
Vapor Pressure: 0.0182 mm Hg at 20 °C (EPI Suite v4.0), 0.0288 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.0182 mm Hg at 20 °C (EPI Suite v4.0), 0.0288 mm Hg at 25 °C (EPI Suite)
UV Spectra: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	
Appearance/Organoleptic: Arctander, Volume I, 1969: Colorless liquid. Mild, woody-rosy, somewhat green odor.	**Appearance/Organoleptic:** Arctander, Volume I, 1969: Colorless liquid. Mild, woody-rosy, somewhat green odor.

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.0)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0000072% (RIFM, 2020)
2. **Inhalation Exposure****: <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2020)
3. **Total Systemic Exposure*****: 0.0000001 mg/kg/day (RIFM, 2020)

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

**95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

6.1. *Cramer classification*

Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. *Analogs selected*

a. **Genotoxicity:** *trans*-Methylgeranate (CAS # 1189-09-9)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. *Read-across Justification*

See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References.
None.

8. Natural occurrence

Ethyl 3,7-dimethylocta-2,6-dienoate is reported to occur in the following foods by the VCF*:

Beer.

Ethyl geranate 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 that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Ethyl 3,7-dimethylocta-2,6-dienoate has been pre-registered for 2013; ethyl geranate has been pre-registered for 2010; no dossiers available as of 02/10/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, ethyl 3,7-dimethylocta-2,6-dienoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Ethyl 3,7-dimethylocta-2,6-dienoate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic activity of ethyl 3,7-dimethylocta-2,6-dienoate; however, read-across can be made to *trans*-methylgeranate (CAS # 1189-09-9; see Section VI). The mutagenic activity of *trans*-methylgeranate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with *trans*-methylgeranate 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, 2014b). Under the conditions of the study, *trans*-methylgeranate was not mutagenic in the Ames test, and this can be extended to ethyl 3,7-dimethylocta-2,6-dienoate.

There are no studies assessing the clastogenic activity of ethyl 3,7-dimethylocta-2,6-dienoate; however, read-across can be made to *trans*-methylgeranate (CAS # 1189-09-9; see Section VI). The clastogenic activity of *trans*-methylgeranate 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 *trans*-methylgeranate in DMSO at concentrations up to 1825 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h *trans*-Methylgeranate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014c). Under the conditions of the study, *trans*-methylgeranate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ethyl 3,7-dimethylocta-2,6-dienoate.

Based on the data available, ethyl 3,7-dimethylocta-2,6-dienoate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3,7-dimethylocta-2,6-dienoate or any read-across materials. The total systemic exposure to 3,7-dimethylocta-2,6-dienoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3,7-dimethylocta-2,6-dienoate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3,7-dimethylocta-2,6-dienoate (0.0001 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on ethyl 3,7-dimethylocta-2,6-dienoate or any read-across materials. The total systemic exposure to ethyl 3,7-dimethylocta-2,6-dienoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on ethyl 3,7-dimethylocta-2,6-dienoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl 3,7-dimethylocta-2,6-dienoate (0.0001 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.4. Skin sensitization

Based on existing data and the application of DST, ethyl 3,7-dimethylocta-2,6-dienoate does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for ethyl 3,7-dimethylocta-2,6-dienoate. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). However, based on expert judgment, the structural alert is ignored, and the target chemical is not expected to react with skin proteins. In a human maximization test, no skin sensitization reactions were observed at 4% or

Table 1
Maximum acceptable concentrations for 3,7-dimethylocta-2,6-dienoate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	0.011%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	1.5×10^{-5}%
10	Household care products with mostly hand contact	2.7%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	NRU[b]

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

2760 μg/cm^2 of additional material ethyl geranate (RIFM, 1980). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2.5% or 1938 μg/cm^2 of ethyl 3,7-dimethylocta-2,6-dienoate in ethanol, no reactions indicative of sensitization were observed in any of the 37 volunteers tested (RIFM, 1966). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for ethyl 3,7-dimethylocta-2,6-dienoate that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis absorption spectra, ethyl 3,7-dimethylocta-2,6-dienoate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for ethyl 3,7-dimethylocta-2,6-dienoate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, ethyl 3,7-dimethylocta-2,6-dienoate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for ethyl 3,7-dimethylocta-2,6-dienoate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on ethyl 3,7-dimethylocta-2,6-dienoate. Based on the Creme RIFM Model, the inhalation exposure is $<$ 0.0001 mg/day. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 3,7-dimethylocta-2,6-dienoate 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, ethyl 3,7-dimethylocta-2,6-dienoate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl 3,7-dimethylocta-2,6-dienoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), ethyl 3,7-dimethylocta-2,6-dienoate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation**

No data available.

Ecotoxicity

No data available.

Other available data

Ethyl 3,7-dimethylocta-2,6-dienoate has been pre-registered for REACH with no additional information at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.48	4.48
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for both CAS #s.

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

The RIFM PNEC is 0.00184 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/04/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.842			1000000	0.00184	

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/10/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113110.

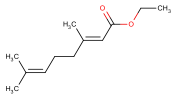
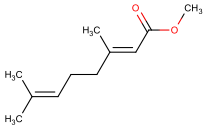
Appendix

Read-across Justification

Methods

The read-across analog(s) was/were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Ethyl 3,7-dimethylocta-2,6-dienoate	*trans*-Methylgeranate
CAS No.	13058-12-3	1189-09-9
Structure		
Similarity (Tanimoto Score)		1.0
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{12}H_{20}O_2$	$C_{11}H_{18}O_2$
Molecular Weight (g/mol)	196.29	182.26
Melting Point (°C, EPI Suite)	−6.10	−16.99
Boiling Point (°C, EPI Suite)	248.97	230.97
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.84	9.91
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.48	3.98
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	6.885	21.24
J_{max} (μg/cm^2/h, SAM)	22.475	38.586
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.31E+002	9.85E+001
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Oncologic Classification	• Acrylate reactive functional group	• Acrylate reactive functional group
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on ethyl 3,7-dimethylocta-2,6-dienoate (CAS # 13058-12-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, *trans*-methylgeranate (CAS # 1189-09-9) was identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- *trans*-Methylgeranate (CAS # 1189-09-9) was used as a read-across analog for the target material ethyl 3,7-dimethylocta-2,6-dienoate (CAS # 13058-12-3) for genotoxicity.
  - o The target material and the read-across belong to the class of aliphatic α,β unsaturated esters.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption ≤10% and J_{max} for the read-across analog corresponds to skin absorption ≤40%. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target and the read-across analog have been classified under the oncologic classification as acrylates – reactive functional group. Acrylates are moderately active animal carcinogens. Most data are from dermal studies with skin as the target organ. The key SAR feature is the presence of unsubstituted, terminal α,β-unsaturated double bond which can bind covalently to DNA and protein via metabolism to epoxide or direct-acting Michael Addition. Irritation may also contribute to the carcinogenic process but is not sufficient by itself. Acrylic acid is highly irritating but not carcinogenic. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity. Therefore, based on structural similarity and the data for read-across analog, the alert is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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