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Short Review

RIFM fragrance ingredient safety assessment, 2-octenoic acid, 4-ethyl-, (2E)-, CAS Registry Number 60308-76-1

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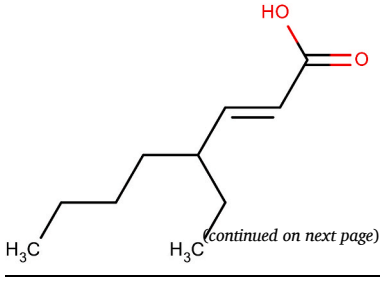
Name: 2-Octenoic acid, 4-ethyl-, (2E)- CAS Registry Number: 60308-76-1



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(*continued*)

Additional CAS #: 60308-75-0; 2-Octenoic acid, 4-ethyl-, (2Z)-* No Reported Use
*included because the materials are isomers

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; Safford et al., 2015a; 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
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.

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

2-Octenoic acid, 4-ethyl-, (2E)- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-octenoic acid, 4-ethyl-, (2E)- is not 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 2-octenoic acid, 4-ethyl-, (2E)- is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog 2-butenoic acid, (2E)- (CAS # 107-93-7) show that there are no safety concerns for 2-octenoic acid, 4-ethyl-, (2E)- for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-octenoic acid, 4-ethyl-, (2E)- is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; 2-octenoic acid, 4-ethyl-, (2E)- 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 (VoU) 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, 2017a; RIFM, 2017b; RIFM, 2021)
Repeated Dose Toxicity: No NOAEL available.	Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available.	Exposure is below the TTC.
Skin Sensitization: No concern for skin sensitization.	(ECHA REACH Dossier: trans-Crotonic acid; ECHA, 2013)
Photoirritation/ Photoallergenicity: Not expected to be photoirritating/ 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: 3.5 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 7.18 mg/L	(RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 7.18 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00718 μg/L
•**Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

Chemical Name: 2-Octenoic acid, 4-ethyl-, (2E)-	**Chemical Name:** 2-Octenoic acid, 4-ethyl-, (2Z)-
CAS Registry Number: 60308-76-1	**CAS Registry Number:** 60308-75-0
Synonyms: (E)-4-ethyl-oct-2-enoic acid; 4-Ethyloct-2-enoic acid; Costasid; 2-Octenoic acid, 4-ethyl-, (2E)-	**Synonyms:** 2-Octenoic acid, 4-ethyl-, (Z)-; 2-Octenoic acid, 4-ethyl-, (Z)-; 4-Ethyloct-2-enoic acid; 2-Octenoic acid, 4-ethyl-, (2Z)-
Molecular Formula: $C_{10}H_{18}O_2$	**Molecular Formula:** $C_{10}H_{18}O_2$
Molecular Weight: 170.25 g/mol	**Molecular Weight:** 170.25 g/mol
RIFM Number: 6626	**RIFM Number:** 6627
Stereochemistry: E isomer specified. One stereocenter and 2 total stereoisomers are possible.	**Stereochemistry:** Z isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

CAS # 60308–76–1	CAS # 60308–75–0
Boiling Point: 274.01 °C (EPI Suite)	**Boiling Point:** 274.01 °C (EPI Suite)
Flash Point: Not Available	**Flash Point:** Not Available
Log K_{OW}: 3.73 (EPI Suite)	**Log K_{OW}:** 3.73 (EPI Suite)
Melting Point: 58.08 °C (EPI Suite)	**Melting Point:** 58.08 °C (EPI Suite)
Water Solubility: 99.93 mg/L (EPI Suite)	**Water Solubility:** 99.93 mg/L (EPI Suite)
Specific Gravity: Not Available	**Specific Gravity:** Not Available
Vapor Pressure: 0.00209 mm Hg at 20 °C (EPI Suite v4.0), 0.00378 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 0.00209 mm Hg at 20 °C (EPI Suite v4.0), 0.00378 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})	**UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (103 L • mol^{-1} • cm^{-1} for basic condition) is below the benchmark (1000 L • mol^{-1} • cm^{-1})
Appearance/Organoleptic: Not available	**Appearance/Organoleptic:** Not available

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00024% (RIFM, 2020)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000005 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.0000002 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, 2015, 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, 2015, 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

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Butenoic acid, (2E)- (CAS # 107-93-7)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
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

2-Octenoic acid, 4-ethyl-, (2E)- and 2-octenoic acid, 4-ethyl-, (2Z)- are 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

2-Octenoic acid, 4-ethyl-, (2E)- and 2-octenoic acid, 4-ethyl-, (2Z)- have been pre-registered for 2010; no dossiers available as of 10/12/22.

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, 2-octenoic acid, 4-ethyl-, (2E)- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Octenoic acid, 4-ethyl-, (2E)- was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). The mutagenic activity of 2-octenoic acid, 4-ethyl-, (2E)- has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-octenoic acid, 4-ethyl-, (2E)- in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. A dose-dependent increase in the mean number of revertant colonies was observed in WP2uvrA in the presence and absence of S9 in the initial and confirmatory assays. Although less than 3-fold, a compound-related increase in the mean number of revertant colonies was also observed in TA1537 at 5000 μg/mL in the presence of S9 in the initial and the confirmatory assays. No increases in the mean number of revertant colonies were observed at any other strains in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, 2-octenoic acid, 4-ethyl-, (2E)- was mutagenic in the Ames test.

The clastogenic activity of 2-octenoic acid, 4-ethyl-, (2E)- 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 2-octenoic acid, 4-ethyl-, (2E)- in DMSO at concentrations up to 1704 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 692 μg/mL in the presence and absence of metabolic activation. 2-

Octenoic acid, 4-ethyl-, (2E)- did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 2-octenoic acid, 4-ethyl-, (2E)- was considered to be non-clastogenic in the *in vitro* micronucleus test.

In order to verify the biological relevance of the results observed in both the Ames and *in vitro* micronucleus tests (MNT), *in vivo* COMET, and micronucleus studies were conducted. The mutagenic and clastogenic activity of 2-octenoic acid, 4-ethyl-, (2E)- was evaluated in a combined *in vivo* micronucleus and COMET test conducted in compliance with GLP regulations and in accordance with OECD TG 474 and 489, respectively. The test material was administered in corn oil via oral gavage to groups of male and female CD-1 mice. Doses of 250, 500, or 1000 mg/kg were administered. Mice from each dose level were euthanized at 3–4 h after the last dose (day 4 dosing), and the peripheral blood was collected and examined for polychromatic erythrocytes. For the COMET assay, a liver sample was collected 3–4 h after the last dose (day 4 dosing). The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes and/or a statistically significant increase in the % DNA tail intensity in the *in vivo* study (RIFM, 2021). Under the conditions of the study, 2-octenoic acid, 4-ethyl-, (2E)- was considered to be non-genotoxic the *in vivo* study. Additionally, 3D skin COMET and 3D skin micronucleus studies (RIFM, 2021) were conducted using skin tissue, which is the primary route of exposure for fragrance materials, which produced positive and negative results, respectively.

As an additional WoE, a structurally similar material, *trans*-2-hexenoic acid, was concluded to be negative in both Ames (RIFM, 2016a) and *in vitro* MNT (RIFM, 2016b). Also, the exposure for this material for use in fragrances is 0.0000002 mg/kg/day, which is less than the genotoxicity TTC value (<0.0025 mg/kg/day).

Taken together, it can be concluded that 2-octenoic acid, 4-ethyl-, (2E)- may not possess any genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/22.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 2-octenoic acid, 4-ethyl-, (2E)- or any read-across materials. The total systemic exposure to 2-octenoic acid, 4-ethyl-, (2E)- 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 2-octenoic acid, 4-ethyl-, (2E)- or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-octenoic acid, 4-ethyl-, (2E)- (0.0002 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: 05/06/22.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 2-octenoic acid, 4-ethyl-, (2E)- or any read-across materials. The total systemic exposure to 2-octenoic acid, 4-ethyl-, (2E)- is below the TTC for the repeated dose 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 2-octenoic acid, 4-ethyl-, (2E)- or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-octenoic acid, 4-ethyl-, (2E)- (0.0002 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: 05/06/22.

11.1.4. Skin sensitization

Based on the existing data and read-across material 2-butenoic acid, (2E)- (CAS # 107-93-7), 2-octenoic acid, 4-ethyl-, (2E)- presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 2-octenoic acid, 4-ethyl-, (2E)-. Therefore, read-across material 2-butenoic acid, (2E)- (CAS # 107-93-7; see Section VI) was used for the risk assessment of 2-octenoic acid, 4-ethyl-, (2E)-. The data on the read-across material are summarized in Table 1 (See Table 1 for a summary of existing data on the read-across material.). Based on the existing data on the read-across material, 2-octenoic acid, 4-ethyl-, (2E)- is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0). In a murine local lymph node assay (LLNA), read-across material 2-butenoic acid (2E)- did not induce contact sensitization up to 50% (12,500 $\mu g/cm^2$) (ECHA, 2013). Additionally, in 3 Confirmation of No Induction in Humans tests (CNIH) with 0.1% or 77.52 $\mu g/cm^2$ of 2-octenoic acid, 4-ethyl-, (2E)- in alcohol SDA 39C, 0.1% or 77.52 $\mu g/cm^2$ of 2-octenoic acid, 4-ethyl-, (2E)- in petrolatum, and 0.02% or 15.50 $\mu g/cm^2$ of 2-octenoic acid, 4-ethyl-, (2E)- in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of 42, 44, and 35 subjects, respectively (RIFM, 1975a; RIFM, 1975b; RIFM, 1975c).

Based on the weight of evidence (WoE) from structural analysis, animal study, and human studies on the read-across material as well as the target material, 2-octenoic acid, 4-ethyl-, (2E)- does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis spectra, 2-octenoic acid, 4-ethyl-, (2E)- would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for 2-octenoic acid, 4-ethyl-, (2E)- 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 photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-octenoic acid, 4-ethyl-, (2E)- does not present a concern for photoirritation 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 photoirritating effects, 1000 $L \bullet mol^{-1} \bullet cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/12/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-octenoic acid, 4-ethyl-, (2E)- 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 2-

Table 1
Summary of existing data on 2-butenoic acid, (2E)- as a read-across for 2-octenoic acid, 4-ethyl-, (2E)-.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	NA	NA	NA	NA	12500	NA	NA
	***In vitro* Data[f]**			***In silico* protein binding alerts (OECD Toolbox v4.5)**			
	KE 1	**KE 2**	**KE 3**	**Target Material**	**Autoxidation simulator**	**Metabolism simulator**	
	NA	NA	NA	No alert found	No alert found	No alert found	

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

octenoic acid, 4-ethyl-, (2E)-. Based on the Creme RIFM Model, the inhalation exposure is 0.0000005 mg/day. This exposure is 2800000times 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: 05/19/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-octenoic acid, 4-ethyl-, (2E)- 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-octenoic acid, 4-ethyl-, (2E)- 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 2-octenoic acid, 4-ethyl-, (2E)- 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, 2017a). 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 VoU (2019), 2-octenoic acid, 4-ethyl-, (2E)- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. 2-Octenoic acid, 4-ethyl-, (2E)- has been pre-registered for REACH, with no additional information available 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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.73	3.73
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.00718 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 volumes of use.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	7.18			1000000	0.00718	

Literature Search and Risk Assessment Completed On: 05/16/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/17/23.

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.2023.113651.

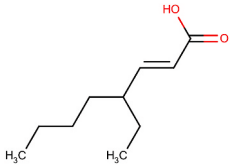
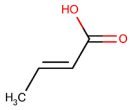
Appendix

Read-across Justification

Methods

The read-across analog was 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, 2017b).

- 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 the OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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 v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	2-Octenoic acid, 4-ethyl-, (2E)-	2-Butenoic acid, (2E)-
CAS No.	60308-76-1	107-93-7
Structure		
Similarity (Tanimoto Score)		0.38
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_{10}H_{18}O_2$	$C_4H_6O_2$
Molecular Weight (g/mol)	170.25	86.09
Melting Point (°C, EPI Suite)	58.08	72.00
Boiling Point (°C, EPI Suite)	274.01	185.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.504	43.330
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.73	0.72
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	9.99E+01	8.60E+04
J_{max} (μg/cm^2/h, SAM)	85.717	1220.519
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.51E-01	6.75E-03
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	• See Supplemental Data	• No metabolism products

Summary

There are insufficient toxicity data on 2-octenoic acid, 4-ethyl-, (2E)- (CAS # 60308-76-1). 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, 2-butenoic acid, (2E)- (CAS # 107-93-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Butenoic acid, (2E)- (CAS # 107-93-7) was used as a read-across analog for the target material, 2-octenoic acid, 4-ethyl-, (2E)- (CAS # 60308-76-1), for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated acids.
    - oThe target material and the read-across analog share an α,β-vinylene acid group.
    - oThe key difference between the target material and the read-across analog is that the target material is an unsaturated, branched C10 aliphatic acid, whereas the read-across analog is an unsaturated C4 straight chain acid. This structural difference is toxicologically insignificant.
    - oThe similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
    - oThe physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
    - oThe read-across analog has a Toxicant alert for the developmental toxicity (CAESAR) characterization scheme. The data described in the reproductive toxicity section show that the MOE is adequate at the current level of use. The predictions are superseded by the data.
    - oAccording to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
    - oThe target material has an alert for valproic acid (hepatotoxicity) by HESS categorization. This is due to 4 ethyl branching, which forms a valproic acid sub-structure. The key difference is that the target material has an additional carbon and a vinylene bond between this branching and carboxylic acid functional group, which differentiates the structure and activity of the target material from valproic acid. Therefore, this alert can be ignored.
    - oThe target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
    - oThe structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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