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Short Review

RIFM fragrance ingredient safety assessment, ethyl *trans*-2-decenoate, CAS Registry Number 7367-88-6

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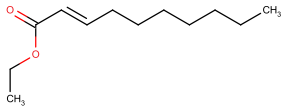

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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.

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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, 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 *trans*-2-decenoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) show that ethyl *trans*-2-decenoate 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 *trans*-2-decenoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across material isobutyl 2-butenoate (CAS # 589-66-2) show that there are no safety concerns for ethyl *trans*-2-decenoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; ethyl *trans*-2-decenoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl *trans*-2-decenoate 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, 2017a; RIFM, 2016)

Repeated Dose Toxicity: No NOAEL was determined. Material was cleared using TTC.

Reproductive Toxicity: No NOAEL was determined. Material was cleared using TTC.

Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. RIFM (2013)

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 3.20 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 487 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 1.52 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 1.52 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.00152 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe (No VoU): Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Ethyl *trans*-2-decenoate
2. **CAS Registry Number:** 7367-88-6
3. **Synonyms:** 2-Decenoic acid, ethyl ester, (E)-; Ethyl dec-2-enoate; Ethyl *trans*-2-decenoate
4. **Molecular Formula:** $C_{12}H_{22}O_2$
5. **Molecular Weight:** 198.3
6. **RIFM Number:** 498
7. **Stereochemistry:** *trans* Isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 90 °C @ 3 mm Hg (Fragrance Materials Association [FMA]), 253.11 °C (EPI Suite)
2. **Flash Point:** 230 °C (FMA)
3. **Log K_{OW}:** 4.58 (EPI Suite)
4. **Melting Point**: 11.61 °C (EPI Suite)
5. **Water Solubility:** 5.496 mg/L (EPI Suite)
6. **Specific Gravity:** 0.88 (FMA)
7. **Vapor Pressure:** 0.0231 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

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 v1.0)

1. **95**th **Percentile Concentration in Shampoo:** 0.008% (RIFM, 2017b)

   (No reported use in hydroalcoholics).

2. **Inhalation Exposure*:** < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2017b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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, 2015, 2017; Safford, 2015, 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 v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Isobutyl 2-butenoate (CAS # 589-66-2)
   e. **Phototoxicity/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 (discrete chemical) or composition (NCS)

Ethyl *trans*-2-decenoate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species)
Pear (*Pyrus communis* L.)
Pear brandy

*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

Pre-registered for 2010; no dossier available as of 04/13/20.

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 and use levels, ethyl *trans*-2-decenoate does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of ethyl *trans*-2-decenoate; however, read-across can be made to ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7; see Section VI). The mutagenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 ethyl *trans*-2,*cis*-4-decadienoate 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, 2017a). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl *trans*-2,*cis*-4-decadienoate 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 ethyl *trans*-2,*cis*-4-decadienoate in DMSO at concentrations up to 1960 μg/mL in a dose range finding (DRF) study. Micronuclei analysis in the main study was conducted up to 500 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Ethyl *trans*-2,*cis*-4-decadienoate 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, 2016). Under the conditions of the study, ethyl *trans*-2,*cis*-4-decadienoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl *trans*-2,*cis*-4-decadienoate does not present a concern for genotoxic potential and this can be extended to ethyl *trans*-2-decenoate).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/08/19.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on ethyl *trans*-2-decenoate or any read-across materials. The total systemic exposure to ethyl *trans*-2-decenoate 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 ethyl *trans*-2-decenoate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl *trans*-2-decenoate (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 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: 11/12/19.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on ethyl *trans*-2-decenoate or any read-across materials. The total systemic exposure to ethyl *trans*-2-decenoate 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 *trans*-2-decenoate or on any read-across materials that can be used

to support the reproductive toxicity endpoint. The total systemic exposure to ethyl *trans*-2-decenoate (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) 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: 11/12/19.

11.1.4. Skin sensitization

There is insufficient evidence to designate ethyl *trans*-2-decenoate as a non-sensitizer based on available data. Based on the read-across material isobutyl 2-butenoate (CAS # 589-66-2), ethyl *trans*-2-decenoate does not present a skin sensitization concern under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for ethyl *trans*-2-decanoate. Based on the read-across material isobutyl 2-butenoate (CAS # 589-66-3; see Section VI), ethyl *trans*-2-decenoate does not present a concern for skin sensitization under the current, declared level of use. Additional data are needed to complete the safety assessment for skin sensitization. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.2). However, in a human repeat insult patch test (HRIPT) with 105 subjects, the read-across material isobutyl 2-butenoate did not induce sensitization reactions at 3.8% or 2093 μg/cm^2 in 1:3 ethanol:diethyl phthalate (RIFM, 2013). In another HRIPT with 38 subjects, the read-across material isobutyl 2-butenoate did not induce sensitization reactions at 2.5% or 1937 μg/cm^2 in alcohol SDA 40 (RIFM, 1971).

Due to the absence of predictive tests in animal models, the reported exposure was benchmarked utilizing the No Observed Effect Level (NOEL) value from the confirmatory HRIPT of the read-across material isobutyl 2-butenoate. The current exposure from the 95th percentile concentration is below this NOEL from the HRIPT when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for ethyl *trans*-2-decenoate that present no appreciable risk for skin sensitization based on the NOEL. These concentrations are not limits; they represent maximum acceptable concentrations based on the NOEL obtained from a confirmatory HRIPT.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/23/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl *trans*-2-decenoate 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 *trans*-2-decenoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, ethyl *trans*-2-decenoate 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 significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/26/19.

11.1.6. Local Respiratory Toxicity

The margin of exposure (MOE) could not be calculated due to a lack of appropriate data. The exposure level for ethyl *trans*-2-decenoate 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 *trans*-2-decenoate. 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, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/05/19.

Table 1
Maximum acceptable concentrations for ethyl *trans*-2-decenoate that present no appreciable risk for skin sensitization based on a NOEL obtained from a confirmatory HRIPT of the read-across material, isobutyl 2-butenoate.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on a NOEL	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.15%	NRU[b]
2	Products applied to the axillae	0.046%	NRU[b]
3	Products applied to the face using fingertips	0.92%	NRU[b]
4	Fine fragrance products	0.86%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.22%	NRU[b]
6	Products with oral and lip exposure	0.51%	NRU[b]
7	Products applied to the hair with some hand contact	1.8%	NRU[b]
8	Products with significant ano-genital exposure	0.090%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	1.7%	0.0080%
10	Household care products with mostly hand contact	6.0%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	3.3%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	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.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl *trans*-2-decenoate was performed following the RIFM Environmental Framework (Salvito, 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 *trans*-2-decenoate 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 *trans*-2-decenoate 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, 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 *trans*-2-decenoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

Ethyl *trans*-2-decenoate has been pre-registered for REACH with no additional data available at this time.

11.2.5. 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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>1.52</u>			1000000	0.00152	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.58	4.58
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	No VoU	< 1
Risk Characterization: PEC/PNEC	**NA**	**< 1**

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

The RIFM PNEC is 0.00152 μg/L. The revised PEC/PNECs for EU (No VoU) 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.

Literature Search and Risk Assessment Completed On: 07/23/19.

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**
- **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
- **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 04/13/20.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111461.

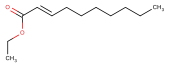
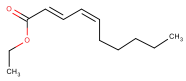
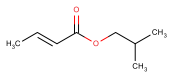
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemicals 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 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 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 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).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	Ethyl *trans*-2-decenoate	Ethyl *trans*-2,*cis*-4-decadienoate	Isobutyl 2-butenoate
CAS No.	7367-88-6	3025-30-7	589-66-2
Structure			
Similarity (Tanimoto Score)		0.39	0.32
Read-across Endpoint		• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{12}H_{22}O_2$	$C_{12}H_{20}O_2$	$C_8H_{14}O_2$
Molecular Weight	198.30	196.29	142.19
Melting Point (°C, EPI Suite)	11.61	10.62	−44.52
Boiling Point (°C, EPI Suite)	253.11	258.41	163.76
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.07974	2.30647	279.976
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.58	4.36	2.54
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.496	8.588	555.2
J_{max} (μg/cm^2/h, SAM)	0.777	3.248	193.182
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.01E+002	7.64E+001	3.43E+001
	• No alert found	• No alert found	

DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)			
DNA Binding (OECD QSAR Toolbox v4.2)	• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ Alpha, beta- unsaturated esters	• Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ Alpha, beta-unsaturated esters	
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	
Oncologic Classification	• Acrylate Reactive Functional Groups	• Acrylate Reactive Functional Groups	
Repeated Dose (HESS)	• Not categorized		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure		
Developmental Toxicity (CAESAR v2.1.6)	• Non-Toxicant (moderate reliability)		
Protein Binding (OASIS v1.1)	• Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds		• Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds
Protein Binding (OECD)	• Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters		• Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters
Protein Binding Potency	• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)		• Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds		• Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron-withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Alert for Michael acceptor		• Alert for Michael acceptor
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on ethyl *trans*-2-decenoate (CAS # 7367-88-6). 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, ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) and isobutyl 2-butenoate (CAS # 589-66-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was used as a read-across analog for the target material ethyl *trans*-2-decenoate (CAS # 7367-88-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of crotonate esters.
  - o The target material and the read-across analog share an ethanol alcohol branch.
  - o The key difference between the target material and the read-across analog is that the target material has an α,β-unsaturated straight C12 acid branch whereas the read-across has an α,β,γ-conjugated straight C12 acid branch. This structural difference is toxicologically insignificant.
  - o 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.
  - 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 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 material and the read-across analog present several genotoxic alerts. Both materials are esters with an α,β-unsaturated acid branch, which may undergo Michael Addition upon nucleophilic attack of a DNA nucleotide at the acid β-carbon. Additionally, both materials have an Acrylate Reactive Functional Groups alert for the Oncologic Classification QSAR Model. This alert, however, can be ignored because neither the target material or the read-across analog is part of the training set. The data described in the genotoxicity section show that the MOE

is adequate at the current level of use. Therefore, the predictions are 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.

- Isobutyl 2-butenoate (CAS # 589-66-2) was used as a read-across analog for the target material ethyl *trans*-2-decenoate (CAS # 7367-88-6) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of crotonate esters.
  - o The target material and the read-across analog share an α,β-unsaturated acid branch and a saturated alcohol branch.
  - o The key difference between the target material and the read-across analog is that the target material has an α,β-unsaturated straight C12 acid branch and an ethanol alcohol branch whereas the read-across has an α,β-unsaturated straight C4 acid branch and an isobutanol alcohol branch. This structural difference is toxicologically insignificant.
  - o 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.
  - 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 $\leq 40\%$, and J_{max} for the read-across analog corresponds to skin absorption $\leq 80\%$. 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 material and the read-across analog present several genotoxic alerts. Both materials are esters with an α,β-unsaturated acid branch, which may undergo Michael Addition upon nucleophilic attack at the acid β-carbon. As discussed in the skin sensitization section, based on the read-across material isobutyl 2-butenoate (CAS # 589-66-2), ethyl *trans*-2-decenoate does not present a skin sensitization concern under the current, declared levels of use. Therefore, data superseded predictions in this case.
  - 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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