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Short Review

RIFM fragrance ingredient safety assessment, ethyl *trans*-2-butenoate, CAS Registry Number 623-70-1

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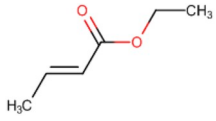
Version 091218. This version replaces any previous versions.

Name: Ethyl *trans*-2-butenoate CAS Registry Number: 623-70-1

Additional CAS Numbers*:

10544-63-5 Ethyl *trans*-2-butenoate

*Included because they are the same material.



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., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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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
QRA - Quantitative Risk Assessment
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 under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment 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 use of this material under current conditions is supported by existing information.

Ethyl *trans*-2-butenoate 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-butenoate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to ethyl *trans*-2-butenoate 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 isobutyl 2-butenoate (CAS # 589-66-2) show that there are no safety concerns for ethyl *trans*-2-butenoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl *trans*-2-butenoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl *trans*-2-butenoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2017; RIFM, 2016)
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 current, declared levels of use. RIFM (2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 5.54 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 323.10 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: 323.1 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.323 µg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

Chemical Name: Ethyl *trans*-2-butenoate
CAS Registry Number: 623-70-1
Chemical Name: Ethyl *trans*-2-butenoate
CAS Registry Number: 10544-63-5
Synonyms: 2-Butenoic acid, ethyl ester, (2E)-; 2-Butenoic acid, ethyl ester, (E)-; Ethyl *trans*-2-butenoate; Ethyl crotonate
Molecular Formula: $C_6H_{10}O_2$
Molecular Weight: 114.14
RIFM Number: 6998
RIFM Number: 1014

Stereochemistry: E isomer specified. One geometric center present and a total of 2 geometric isomers possible.

2. Physical data*

1. **Boiling Point:** 132.84 °C (EPI Suite)
2. **Flash Point:** 34 °C (GHS)
3. **Log K_{ow}:** 1.63 (EPI Suite)
4. **Melting Point:** −57.31 °C (EPI Suite)
5. **Water Solubility:** 4259 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 5.47 mm Hg @ 20 °C (EPI Suite v4.0), 7.46 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} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless mobile liquid which has a powerful and diffusive, sour-caramellic-fruity odor, reminiscent of unripe berries. (1196)

*Because both CAS numbers refer to the same material, they have identical physical data.

3. Exposure to fragrance ingredient***

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0060% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.0000096 mg/kg/day or 0.00069 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; 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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

***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 hydroalcoholics, inhalation exposure, and total exposure.

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

6. Metabolism

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

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

Ethyl *trans*-2-butenoate is reported to occur in the following foods by the VCF*:
Acerola (*Malpighia*)
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Babaco fruit (*Carica pentagona* Heilborn)
Cashew apple (*Anacardium occidentale*)
Cashew apple wine.
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cherimoya (*Annona cherimolia* Mill.)
Chinese quince (*Pseudocydonia sinensis* Schneid)
Citrus fruits.
Cocoa.
Custard apple, atemoya (*Annona atemoya*)
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)
Durian (*Durio zibethinus*)
Fish.
Grape (*Vitis* species)
Grape brandy.
Guava and feyoa
Guava wine.
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*)
Licorice (*Glycyrrhiza species*)
Mangifera species.
Melon.
Mountain papaya (*C. candamarcensis, C. pubescens*)
Mussel.
Naranjilla fruit (*Solanum quitoense* Lam.)
Papaya (*Carica papaya* L.)
Passion fruit (*passiflora* species)
Pawpaw (*Asimina triloba* Dunal.)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Plum brandy.
Prickly pear (*Opuntia ficus indica*)
Quince, marmelo (*Cydonia oblonga* Mill.)
Rambutan (*Nephelium lappaceum* L.)
Soursop (*Annona muricata* L.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Wine.
Wood apple (*Feronia limonia*)
*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.

8. IFRA standard

None.

9. REACH dossier

Both CAS numbers for this material have been pre-registered for 2010; no dossier available as of 09/11/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, ethyl *trans*-2-butenoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of ethyl *trans*-2-butenoate; however, read-across can be made to ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7; see Section V). 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, 2017). 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 500 μg/mL in the presence and absence of metabolic activation (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-butenoate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/11/18.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on ethyl *trans*-2-butenoate or on any read-across materials. The total systemic exposure to ethyl *trans*-2-butenoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on ethyl *trans*-2-butenoate 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-butenoate (0.14 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on ethyl *trans*-2-butenoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl *trans*-2-butenoate (0.14 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.1.4. Skin sensitization

Based on the read-across material isobutyl 2-butenoate (CAS # 589-66-2), ethyl *trans*-2-butenoate does not present a safety concern under current, declared levels of use.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for ethyl *trans*-2-butenoate. Based on the existing data and read-across material isobutyl 2-butenoate (CAS # 589-66-2; see Section V), ethyl *trans*-2-butenoate does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.1).

In confirmatory human repeat insult patch tests (HRIPT) with 2093 μg/cm^2 and 1937 μg/cm^2 of read-across material isobutyl 2-butenoate, no reactions indicative of sensitization was observed in any of the 105 and 38 volunteers, respectively (RIFM, 2013; RIFM, 1971).

Based on weight of evidence (WoE) from structural analysis and read-across material isobutyl 2-butenoate, ethyl *trans*-2-butenoate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/2018.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl *trans*-2-butenoate would not be expected to present a concern for phototoxicity or

photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for ethyl *trans*-2-butenoate 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 et al., 2009). Based on lack of absorbance, ethyl *trans*-2-butenoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. Key studies. There are no studies available on ethyl *trans*-2-butenoate in experimental models.

10.1.5.3. 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 $L\,mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for ethyl *trans*-2-butenoate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on ethyl *trans*-2-butenoate. Based on the Creme RIFM Model, the inhalation exposure is 0.00069 mg/day. This exposure is 2029 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: 05/29/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl *trans*-2-butenoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers 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-butenoate 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-butenoate 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).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), ethyl *trans*-2-butenoate does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

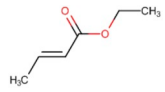
Other available data

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

10.2.3. 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	1.63	1.63
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use 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 0.323 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 4/11/2018.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.024.

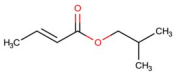
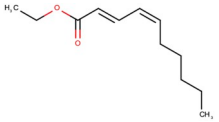
Appendix

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 Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox 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 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	
Principal Name	Ethyl *trans*-2-butenoate	Isobutyl 2-butenoate	Ethyl *trans*-2,*cis*-4-decadienoate
CAS No.	623-70-1	589-66-2	3025-30-7
Structure			
Similarity (Tanimoto Score)		0.62	0.31
Read-across Endpoint		• Skin sensitization	• Genotoxicity
Formula	$C_6H_{10}O_2$	$C_8H_{14}O_2$	$C_{12}H_{20}O_2$
Molecular Weight	114.15	142.20	196.29
Melting Point (°C, EPI Suite)	−57.31	−44.52	10.62
Boiling Point (°C, EPI Suite)	132.84	163.76	258.41
Vapor Pressure (Pa @ 25 °C, EPI Suite)	994	280	2.31
Log Kow (KOWWIN v1.68 in EPI Suite)	1.63	2.54	4.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4259	555.2	8.588
J_{max} (mg/cm^2/h, SAM)	246.677	193.182	3.248
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	1.95E+001	3.44E+001	7.64E+001
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found		• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition- Polarized • Alkenes • Alpha,beta-unsaturated esters		• Michael addition -Polarized • Alkenes • Alpha,beta- unsaturated esters
Carcinogenicity (ISS)	• NON-carcinogen (low reliability)		• NON-carcinogen (low reliability)
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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	323.10			1,000,000	0.323	

Skin Sensitization			
Protein Binding (OASIS v1.1)	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	
Protein binding (OECD)	• Michael addition - Polarized alkene - esters	• Michael addition -Polarized alkene - esters	
Protein Binding Potency	• Moderately reactive (GSH)	• Moderately reactive (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	• Michael addition on conjugated systems with electron withdrawing group • Alpha,beta-carbonyl compounds with polarized double bond	
Skin Sensitization Reactivity Domains (-Toxtree v2.6.13)	• Michael acceptor alert	• Michael acceptor alert	
Metabolism			
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-butenoate (CAS # 623-70-1). 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, isobutyl 2-butenoate (CAS # 589-66-2) and ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Isobutyl 2-butenoate (CAS # 589-66-2) was used as a read-across analog for the target material ethyl *trans*-2-butenoate (CAS # 623-70-1) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and are alpha,beta-unsaturated aliphatic esters.
  - The key difference between the target substance and the read-across analog is that the read-across is an isobutyl ester, whereas the target is an ethyl ester of butenoic acid. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target and the read-across analog are predicted to be Michael acceptors due to the presence of a polarized carbonyl functional group in them. The data for the read-across analog show that the material is not a concern for skin sensitization. Therefore based on structural similarity between the target substance and the read-across analog, and the data for read-across analog, the alerts will be superseded by the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Ethyl *trans*-2,*cis*-4-decadienoate (CAS # 3025-30-7) was used as a read-across analog for the target material ethyl *trans*-2-butenoate (CAS # 623-70-1) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and are alpha,beta-unsaturated aliphatic esters.
  - The key difference between the target substance and the read-across analog is that the read-across is a decadienoate ethyl ester with extended conjugation to alpha,beta-unsaturation, whereas the target is a butenoate ethyl ester. These structural differences are would increase the reactivity of the read across material.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target and the read-across analog are predicted to be Michael acceptors in DNA binding and are classified as acrylate reactive functional groups due to the presence of a polarized carbonyl functional group in them. The data for the read-across analog show that the material is not a concern for genetic toxicity. Therefore, based on structural similarity between the target substance and the read-across analog, and the data for read-across analog, the alerts will be superseded by the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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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