Food and Chemical Toxicology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment 2-methyl-trans-2-butenoic acid, CAS Registry Number 80-59-1

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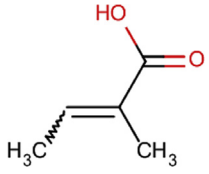
Version: 110317. This version replaces any previous versions.
Name: 2-Methyl-trans-2-butenoic acid
CAS Registry Number: 80-59-1



Abbreviation list:

2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach.

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https://doi.org/10.1016/j.fct.2018.05.048
Received 24 January 2018; Received in revised form 27 March 2018; Accepted 18 May 2018

DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA- North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- Quantitative Risk Assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
Statistically Significant - statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test.
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- 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 reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, *etc*. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
2-Methyl-trans-2-butenoic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-methyl-trans-2-butenoic acid is not genotoxic. Data from read-across analogs trans-crotonic acid (CAS # 107-93-7) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) show that 2-methyl-trans-2-butenoic acid is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to 2-methyl-trans-2-butenoic acid is below the TTC (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 2-methyl-trans-2-butenoic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, and 2-methyl-trans-2-butenoic acid was not found to be PBT as per IFRA environmental standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2016a; RIFM, 2016b)
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.	(ECHA Dossier: Crotonic acid; RIFM, 2013a)
Phototoxicity/Photoallergenicity: Not 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: 3.3 (Biowin 3)	(EPI Suite v4.1)
Bioaccumulation: Screening-Level: 3.2 L/kg	(EPI Suite v4.1)
Ecotoxicity: Screening-Level: Fish LC50: 449.3 mg/L	(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 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 449.3 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.4493 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 2-Methyl-trans-2-butenoic acid
2. **CAS Registry Number:** 80-59-1
3. **Synonyms:** 2-Butenoic acid, 2-methyl-, (E); trans-2-Methylcrotonic acid; Tiglic acid; ｱﾙｹﾆﾙﾓﾉｶﾙﾎﾞﾝ酸(C = 5–23); ﾁｸﾞﾘﾝ酸; 2-Methylbut-2-enoic acid; 2-Methyl-trans-2-butenoic acid
4. **Molecular Formula:** $C_5H_8O_2$
5. **Molecular Weight:** 100.12
6. **RIFM Number:** 999

2. Physical data

1. **Boiling Point:** 199 °C (FMA), 188.47 °C (EPI Suite)
2. **Flash Point:** 102 °C (GHS)
3. **Log K_{ow}:** 1.4 (EPI Suite)
4. **Melting Point:** 60 °C (FMA), 5.45 °C (EPI Suite)
5. **Water Solubility:** 18450 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.275 mmHg @ 20 °C (EPI Suite), 0.05 mm Hg 20C (FMA), 0.448 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:** Triclinic plates, rods from water with a fruity, berry or spicy odor. Arctander Volume II 1969: Slightly soluble in water, soluble in alcohol and oils. Spicy-rooty, sweet-sour herbaceous odor of moderate tenacity. Spicy-warm, slightly sour taste in concentrations near 50 ppm. The acidulous taste fades away at lower concentrations leaving only the pleasant, spicy-rooty taste.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:**0.000070% (RIFM, 2016)
3. **Inhalation Exposure***: 0.00000050 mg/kg/day or 0.000040 mg/day (RIFM, 2016)
4. **Total Systemic Exposure****: 0.000041 mg/kg/day (RIFM, 2016)

*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 4. 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).

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:** None.
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** trans-crotonic acid (CAS # 107-93-7) and 2-Methylpent-2-en-1-oic acid (CAS # 3142-72-1)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

2-Methyl-trans-2-butenoic acid is reported to occur in the following foods*:

Camomile
Celery (*Apium graveolens* l.)
Cocoa category
Katsuobushi (dried bonito)
Mangifera species

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database that contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 01/23/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, 2-methyl-trans-2-butenoic acid does not present a concern for genotoxicity.

10.1.2. Risk assessment

2-Methyl-trans-2-butenoic acid was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013b). The mutagenic activity of 2-methyl-trans-2-butenoic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP and OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2uvrA were treated with 2-methyl-trans-2-butenoic acid 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 dose with or without S9 (RIFM, 2016a). Under the conditions of the study, 2-methyl-trans-2-butenoic acid was not mutagenic in the Ames test.

The clastogenic activity of 2-methyl-trans-2-butenoic acid was evaluated in an in vitro micronucleus test conducted in compliance with GLP and OECD TG 487. Human peripheral blood lymphocytes were treated with 2-methyl-trans-2-butenoic acid in DMSO at concentrations up to 1000 μg/ml in the presence and absence of S9 for 3 and 24 h 2-Methyl-trans-2-butenoic acid did not induce binucleated cells with micronuclei when tested up to cytotoxic levels/the maximum concentration in the presence and absence of S9 (RIFM, 2016b). Under the conditions of the study, trans-2-methyl-trans-2-butenoic acid was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the available data, 2-methyl-trans-2-butenoic acid does not present a concern for genotoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 5/2/2017.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on 2-methyl-trans-2-butenoic acid or any read-across materials that can be used to support the repeated dose toxicity endpoint evaluation. There is an OECD 408 gavage 90-day toxicity study conducted with 2-methylcrotonic acid (2-methyl-trans-2-butenoic acid; tiglic acid). Groups of 10 rats/sex/dose were administered via gavage test material at doses of 0 or 77 mg/kg/day in soybean oil. A NOAEL for systemic toxicity could not be established under the design of this study (Lindecrona et al., 2003).

The total systemic exposure for 2-methyl-trans-2-butenoic acid (0.041 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/02/2017.

10.1.5. Reproductive toxicity

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

10.1.6. Risk assessment

There are no developmental toxicity data on 2-methyl-trans-2-butenoic acid or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 2-methyl-trans-2-butenoic acid (0.041 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on 2-methyl-trans-2-butenoic acid or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to 2-methyl-trans-2-butenoic acid (0.041 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 05/02/2017.

10.1.7. Skin sensitization

Based on the existing data on the target 2-methyl-trans-2-butenoic acid and read-across materials trans-crotonic acid (CAS # 107-93-7) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1), 2-methyl-trans-2-butenoic acid does not present a concern for skin sensitization.

10.1.8. Risk assessment

Limited skin sensitization studies are available for 2-methyl-trans-2-butenoic acid. Based on the existing data on the target (2-methyl-trans-2-butenoic acid) and read-across materials trans-crotonic acid (CAS # 107-93-7) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1); see Section 5), 2-methyl-trans-2-butenoic acid does not present a concern for skin sensitization. The chemical structures of these materials indicate that they could possibly react with proteins, although little or no reaction would likely occur under physiological conditions (Toxtree 2.6.13; OECD Toolbox v3.4). No predictive skin sensitization studies are available for 2-methyl-trans-2-butenoic acid. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1977). In a local lymph node assay, read-across material trans-crotonic acid did not induce sensitization up to 50% (ECHA Dossier: Crotonic acid). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 661 μg/cm2 (1.2%) of 2-methylpent-2-en-1-oic acid in 1:3 ethanol:DEP there were no reactions indicative of sensitization in any of the 107 volunteers (RIFM, 2013a). Based on weight of evidence from structural analysis, human data and read-across to trans-crotonic acid and 2-methylpent-2-en-1-oic acid, 2-methyl-trans-2-butenoic acid does not present a concern for skin sensitization.

Additional References: FCT, 1963.

Literature Search and Risk Assessment Completed on: 5/4/17.

10.1.9. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-methyl-trans-2-butenoic acid would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for 2-methyl-trans-2-butenoic acid in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 2-methyl-trans-2-butenoic acid does not present a concern for phototoxicity or photoallergenicity.

10.1.11. UV spectra analysis

UV/Vis absorption spectra (OECD test guideline 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 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/20/17.

10.1.12. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-methyl-trans-2-butenoic acid, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.13. Risk assessment

There are no inhalation data available on 2-methyl-trans-2-butenoic acid. Based on the Creme RIFM model, the inhalation exposure is 0.000040 mg/day. This exposure is 35000 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: 5/8/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-trans-2-butenoic acid was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-methyl-trans-2-butenoic acid 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 EPISUITE ver 4.1 did not identify 2-methyl-trans-2-butenoic acid as possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI SUITE v4.1).

10.2.2. Risk assessment

Based on current VoU (2011), 2-methyl-trans-2-butenoic acid does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Biodegradation

No data available.

10.2.4. Ecotoxicity

No data available.

10.2.5. Other available data

2 -Methyl-trans-2-butenoic acid has been pre-registered for REACH with no additional data at this time.

10.2.6. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	449.3 mg/L			1,000,000	0.4493 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.4	1.4
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 the available data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.4493 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; 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: 5/3/17.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp

- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.05.048.

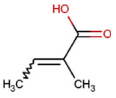
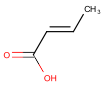
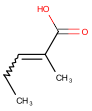
Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reportinga read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD on the reporting of defined approached used within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemical Agency (ECHA) read-across assessment framework or RAAF (ECHA, 2016).

- In essence, materials were first clustered based on their structural similarity. Then, data availability and data quality on the selected cluster was examined. Finally, appropriate read-across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read-across analog were calculated using EPI Suite™ (EPI Suite, 2012).
- Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target	Read-across	
Principal Name	2-Methyl-trans-2-butenoic acid	trans-crotonic acid	2-Methylpent-2-en-1-oic acid
CAS No.	80-59-1	107-93-7	3142-72-1
Structure			
Similarity (Tanimoto Score)		0.74	0.88
Read-across Endpoint		• Skin sensitization	• Skin sensitization
Molecular Formula	$C_5H_8O_2$	$C_4H_6O_2$	$C_6H_{10}O_2$
Molecular Weight	100.2	86.09	114.15
Melting Point (°C, EPI SUITE)	5.45	2.39	16.91
Boiling Point (°C, EPI SUITE)	188.47	173.37	208.44
Vapor Pressure (Pa @ 25 °C, EPISUITE)	59.7	33	23.7
Log Kow (KOWWIN v1.68 in EPI SUITE)	1.4	0.72	1.89
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI SUITE)	18450	8.6E+004	6330
J_{max} (mg/cm^2/h, SAM)	1762.543	1220	903.804
Henry's Law (Pa·m^3/mol, Bond Method, EPI SUITE)	7.09E-007	4.59E-002	9.54E-002
Skin Sensitization			
Protein Binding (OASIS v1.1)	• AN2, Michael addition	• AN2, Michael addition	• AN2, Michael addition
Protein Binding (OECD)	• No alert found	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	• No alert found
Skin Sensitization Model (CAESAR v2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism			
OECD QSAR Toolbox (v3.4) Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites	No metabolites	No metabolites	No metabolites

Summary

There are insufficient toxicity data on the 2-methyl-trans-2-butenoic acid (CAS # 80-59-1). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, analogs trans-crotonic acid (CAS # 107-93-7) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) were identified as read-across materials with data for the respective toxicological endpoints.

Conclusion/Rationale

- trans-Crotonic acid (CAS # 107-93-7) and 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) are used as read-across analogs for target 2-methyl-trans-2-butenoic acid (CAS # 80-59-1) for skin senzitization.
  - ○ The target substance and the read-across analogs are structurally similar and belong to the class of unsaturated carboxylic acids.
  - ○ The target substance and the read-across analog share a carboxylic acid moiety with α-β unsaturation.
  - ○ The key difference between the target substance and the read-across analog is that the α carbon is substituted in the target substance whereas there is no α carbon substitution in the read-across analog trans-crotonic acid (CAS # 107-93-7). The read-across analog 2-methylpent-2-en-1-oic acid (CAS # 3142-72-1) is a C6 molecule whereas the target substance is a C5 molecule. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analogs is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the carboxylic acid moiety with α-β unsaturation. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical-chemical properties of the target substance and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analogs.
  - ○ The read-across analogs and the target substance are predicted to be sensitizers by the CAESAR model for skin sensitization, and they also have a Michael addition alert by the protein binding model by OASIS. This shows that the target substance and the read-across analogs have similar reactivity. The data described in the skin sensitization section above show that the read-across analogs do not pose a concern for the skin sensitization endpoint. Therefore the alert will be superseded by the availability of the data.
  - ○ The target substance and the read-across analogs 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 analogs and the target material.

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