Food and Chemical Toxicology 122 (2018) S192–S200

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, ethyl phenylacetate, CAS Registry Number 101-97-3

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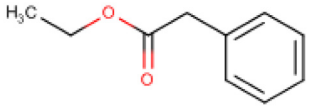
Version: 050418. This version replaces any previous versions.

Name: Ethyl phenylacetate
CAS Registry Number: 101-97-3



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https://doi.org/10.1016/j.fct.2018.08.050
Received 4 May 2018; Received in revised form 10 July 2018; Accepted 22 August 2018
Available online 24 August 2018
0278-6915/

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
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
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 phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data on ethyl phenylacetate and read-across analog methyl phenylacetate (CAS# 101-41-7) show that ethyl phenylacetate is not expected to be genotoxic. The repeated dose, reproductive and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to ethyl phenylacetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data on ethyl phenylacetate and read-across analog methyl benzoate (CAS# 93-58-3) show that ethyl phenylacetate does not present a safety concern under the current, declared levels of use for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; ethyl phenylacetate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl phenylacetate 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 genotoxic. (RIFM, 2001; RIFM, 2015b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns under the current, declared levels of use. (ECHA REACH Dossier: methyl benzoate, accessed 6/14/17)
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: Critical Measured Value: 79% (EEC Method C.4-E) (RIFM, 2000)
Bioaccumulation: Screening-level: 14.8 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 81.35 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: 81.35 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.08135 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Ethyl phenylacetate
2. **CAS Registry Number:** 101-97-3
3. **Synonyms:** Benzeneacetic acid, ethyl ester; Ethyl α-toluate; Ethyl benzeneacetate; ﾌｪﾆﾙｱﾙｶﾝ酸(C = 2 ~ 5)ｱﾙｷﾙ(C = 1 ~ 8); Ethylphenylacetat; Ethyl phenylacetate
4. **Molecular Formula:** $C_{10}H_{12}O_2$
5. **Molecular Weight:** 164.2
6. **RIFM Number:** 450

2. Physical data

1. **Boiling Point:** 275 °C (FMA), 234.31 °C (EPI Suite)
2. **Flash Point:** > 100 °C (GHS), > 212 °F (FMA)
3. **Log K_{ow}:** 2.57 (EPI Suite)
4. **Melting Point**: 10.6 °C (EPI Suite)
5. **Water Solubility:** 739.4 mg/L (EPI Suite)
6. **Specific Gravity:** 1.027–1.032 (FMA), 1.029–1.034 (FMA)
7. **Vapor Pressure:** 0.0596 mm Hg @ 20 °C (EPI Suite), 0.08 mm Hg 20 °C (FMA), 0.0913 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:** Arctander Volume I 1969: Colorless liquid. Powerful, sweet, honey-like, slightly animal and quite persistent odor with a fruity undertone. Sweet and fruity, honey-like taste at concentrations lower than 10 ppm (Arctander, 1969).

3. Exposure

1. **Volume of Use (worldwide band):** 10 to 100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0028% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00010 mg/kg/day or 0.0074 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0011 mg/kg/day (RIFM, 2017)

*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:** Methyl phenylacetate (CAS # 101-41-7)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Methyl benzoate (CAS # 93-58-3)
   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)

Ethyl phenylacetate is reported to occur in the following foods*:

Acerola (*Malpighia*)
Apple brandy (*Calvados*)
Apple processed (*Malus* species)
Artocarpus species.
Beer
Beli, bael (Aegle marmelos Correa)
Bilberry wine
Capers (Capparis spinoza)
Ceriman, pinanona (Monstera deliciosa Liebm.)
Chinese quince (Pseudocydonia sinensis Schneid)
Cider (Apple wine)
Citrus fruits
Cocoa category
Crispbread

Fig (Ficus carica L.)
Grape brandy
Guava and feyoa
Guava wine
Honey
Licorice (*Glycyrrhiza* species)
Litchi (Litchi chinensis Sonn.)
Litchi wine
Macadamia nut (Macadamia integrifolia)
Mangifera species
Melon
Miso (soy bean, rice or fish)
Mountain papaya (C. candamarcensis, C. pubescens)
Olive (Olea europaea)
Papaya (Carica papaya L.)
Passion fruit (*Passiflora* species)
Pear brandy
Peas (Pisum sativum L.)
Pineapple (Ananas comosus)
Plum (*Prunus* species)
Plum Brandy
Prickly Pear (Opuntia ficus indica)
Rambutan (Nephelium lappaceum L.)
Sake
Sherry
Shoyu (fermented soya hydrolysate)
Soybean (*Glycine max*. L. merr.)
Strawberry Wine
Tapereba, Caja Fruit (*Spondias lutea* L.)
Tea
Tequila (Agave tequilana)
Vinegar
Wheaten bread
Whisky
Wine

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

8. IFRA standard

None.

9. REACH dossier

Ethyl phenylacetate, available, accessed 06/15/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, ethyl phenylacetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no studies assessing the mutagenicity of ethyl phenylacetate. The mutagenic activity of read-across material methyl phenylacetate (CAS # 101-41-7; see Section 5) 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 TA97a, TA98, TA100, TA1535, and TA102 were treated with methyl phenylacetate 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 in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, methyl phenylacetate was not mutagenic in the Ames test, and this can be extended to ethyl phenylacetate.

The clastogenic activity of ethyl phenylacetate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with ethyl phenylacetate in DMSO at concentrations up to 1642.0 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (RIFM, 2015b). Under the conditions of the study, ethyl phenylacetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the available data, ethyl phenylacetate does not present a concern for genotoxic potential.

Additional References: Ishidate et al., 1984 Yoo, 1986; Oda et al., 1978 RIFM, 2016b.

Literature Search and Risk Assessment Completed On: 06/19/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on ethyl phenylacetate or any read-across materials. The total systemic exposure to ethyl phenylacetate 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 phenylacetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl phenylacetate (1.1 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: 06/05/2017.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on ethyl phenylacetate or any read-across materials. The total systemic exposure to ethyl phenylacetate 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 phenylacetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl phenylacetate (1.1 μg/kg/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: 06/05/2017.

10.1.4. Skin sensitization

Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3), ethyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for ethyl phenylacetate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section 5), ethyl phenylacetate does not present a safety concern for skin

sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they could possibly react with skin proteins with little to no reaction under physiological conditions. Ethyl phenylacetate was found to be negative in the *in vitro* human Cell Line Activation Test (h-CLAT) (RIFM, 2016c). In guinea pigs, an open epicutaneous test did not present reactions indicative of sensitization in ethyl phenylacetate (Klecak, 1979, 1985). In a murine local lymph node assay, read-across methyl benzoate was found to be negative up to the maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 2.98 (ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17). In guinea pigs, an open epicutaneous test and Freund's complete adjuvant test with read-across material methyl benzoate did not present reactions indicative of sensitization (Klecak, 1979, 1985; Hausen et al., 1995). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm^2 ethyl phenylacetate in petrolatum (RIFM, 1973). In a human maximization test with read-across methyl benzoate, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 in petrolatum (RIFM, 1970).

Based on weight of evidence from structural analysis, human studies and read-across methyl benzoate, ethyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 6/15/2017.

10.1.5. Phototoxicity/Photoallergenicity

Based on the available UV/Vis spectra, ethyl phenylacetate 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 phenylacetate 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 phenylacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/25/17.

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 phenylacetate 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 phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0074 mg/day. This exposure is 189 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: 6/28/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl phenylacetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, ethyl phenylacetate 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 v4.1 did not identify ethyl phenylacetate 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.2.1. Biodegradation. RIFM, 2000**:** The biodegradability of the test material was determined using the Closed Bottle Test following Council Directive 92/69 EEC method C.4-E. Under the conditions of the study, biodegradation of 79% was observed.

10.2.2.2. Ecotoxicity. RIFM, 2000**:** A *Daphnia magna* acute toxicity study was conducted according to the Council Directive 92/601/EEC C.2 method under static conditions. The 48-hour EC50 was reported to be 45.5 mg/L.

RIFM, 2016a**:** A fish (Zebra fish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-hour LC50 was reported to be 8.18 mg/L.

RIFM, 2015a**:** An algae growth inhibition test was conducted according to the OECD 201 method. The 72-hour EC50 was reported to be

44.8 mg/L and 30.5 mg/L for growth rate and yield, respectively.

10.2.2.3. Other available data. Ethyl phenylacetate has been registered under REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Since ethyl phenyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

	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>81.35</u>			1,000,000	0.08135	

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	2.5	2.5
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.08135 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: 6/15/17.

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.050.

Appendix

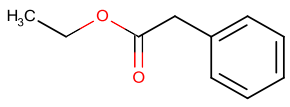
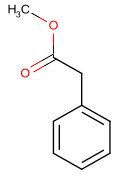
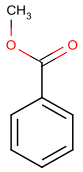
Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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, 2012).

- 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 (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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- 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 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 material	Read-across material	
Principal Name	Ethyl phenylacetate	Methyl phenylacetate	Methyl benzoate
CAS No.	101-97-3	101-41-7	93-58-3
Structure			
Similarity (Tanimoto score)		0.91	0.77
Read-across endpoint		• enotoxicity	• Skin sensitization
Molecular Formula	$C_{10}H_{12}O_2$	$C_9H_{10}O_2$	$C_8H_8O_2$
Molecular Weight	164.21	150.18	136.15
Melting Point (°C, EPI Suite)	10.60	−0.50	−11.87
Boiling Point (°C, EPI Suite)	234.31	215.57	195.93
Vapor Pressure (Pa @ 25°C, EPI Suite)	12.2	20.9	50.6
Log Kow (KOWWIN v1.68 in EPI Suite)	2.28	1.83	2.12
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	739.4	2072	2100
J_{max} (mg/cm^2/h, SAM)	44.26	78.176	77.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.88E-005	1.43E+000	3.47E-005
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-Carcinogen (moderate reliability)	• Non-Carcinogen (moderate reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Skin Sensitization			
Protein binding by OASIS v1.1	• No alert found		• Acylation
Protein binding by OECD	• No alert found		• No alert found
Protein binding potency	• Not possible to classify		• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found		• No alert found
Skin Sensitization reactivity domains (ToxTree v2.6.13)	• No alert found		• No alert found

Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the ethyl phenylacetate (CAS # 101-97-3). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, methyl phenylacetate (CAS # 101-41-7) and methyl benzoate (CAS # 93-58-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Methyl phenylacetate (CAS # 101-41-7) was used as a read-across analog for the target material ethyl phenylacetate (CAS # 101-97-3) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic esters.
  - o The target substance and the read-across analog share an aromatic group on the acid portion of the ester moiety.
  - o The key difference between the target substance and the read-across analog is that the target substance has an ethyl substitution on the alcohol portion of the ester and the read-across analog has a methyl substitution on the alcohol portion of the ester. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties**.**
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog has a DNA binding alert by OECD. This shows that the read-across analog and the target substance have comparable reactivity. The data described in the genotoxicity section show that the read-across analog does not pose a concern for this endpoint. Therefore, the alert will be superseded by the available data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoint.
- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material ethyl phenylacetate (CAS # 101-97-3) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic esters.
  - o The target substance and the read-across analog share an aromatic group on the acid portion of the ester moiety.
  - o The key difference between the target substance and the read-across analog is that the target substance has an ethyl substitution on the alcohol portion of the ester and the read-across analog has a methyl substitution on the alcohol portion of the ester. In addition, the acid portion on the target substance has a carboxylic acid insulated by 1 carbon from the aromatic moiety while the carboxylic acid in the read-across analog has a carboxylic acid conjugated with the aromatic moiety. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoint.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog is predicted to have a protein binding alert by OASIS. The data described in the skin sensitization section above show that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the available data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoint.

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