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Short Review

RIFM fragrance ingredient safety assessment, ethyl benzoate, CAS Registry Number 93-89-0

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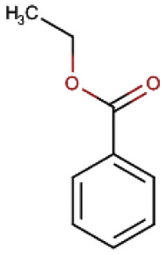
Version: 050418. This version replaces any previous versions.

Name: Ethyl benzoate

CAS Registry Number: 93-89-0



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

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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 as described in this safety assessment.

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Ethyl benzoate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that ethyl benzoate is not genotoxic. Based on the data from ethyl benzoate and read-across analog methyl benzoate (CAS # 93-58-3), this material is not a concern for skin sensitization under the current, declared levels of use. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material and the exposure to ethyl benzoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; ethyl benzoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl benzoate 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, 1991; RIFM, 2014a)
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: 69% (OECD 301D) RIFM (2000)
Bioaccumulation: Screening-level: 25.6 L/kg (EPI Suite, v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 62-.13 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: 6-2.13 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.06213 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe

1. Identification

1. **Chemical Name:** Ethyl benzoate
2. **CAS Registry Number:** 93-89-0
3. **Synonyms:** Benzoic acid, ethyl ester; Ethyl benzene carboxylate; Ethyl benzoate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.18
6. **RIFM Number:** 332

2. Physical data

1. **Boiling Point:** 212 °C (FMA); 215.57 °C (EPI Suite)
2. **Flash Point:** 88 °C (GHS); 190 °F; CC (FMA)
3. **Log K_{OW}**: Log K PDMS–w = 2.400 (n = 12); 2.32 (EPI Suite), 2.59 at 22.8 °C (RIFM, 2014b)
4. **Melting Point**: 0.5 °C (EPI Suite)
5. **Water Solubility:** 421.5 mg/L (EPI Suite)
6. **Specific Gravity:** 1.043–1.046 (FMA); 1.045–1.048 (FMA)
7. **Vapor Pressure:** 0.131 mm Hg @ 20 °C (EPI Suite v4.0); 0.1 mm Hg 20 °C (FMA); 0.197 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 clear, colorless liquid with a sweet, medicinal, green, minty, fruity, birch beer, and wintergreen-like odor.*

*http://www.thegoodscentscompany.com/data/rw1004771.html, retrieved 6/21/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0028% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0078 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00035 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 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).

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:** 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 benzoate is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Acerola (*Malpighia*)
Apple brandy (Calvados)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Babaco fruit (*Carica pentagona heilborn*)
Banana (*Musa sapientum* L.)
Beer
Beli, bael (*Aegle marmelos correa*)
Bilberry wine
Black currants (*Ribes nigrum* L.)
Cape gooseberry (*Physalis peruviana* L.)
Capers (*Capparis spinoza*)
Cashew apple (*Anacardium occidentale*)
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cheese, various types
Cherry (*Prunus avium* (sweet), *Pr. cerasus* (sour))
Cherry brandy
Chinese Liquor (Baijiu)
Chinese quince (*Pseudocydonia sinensis* Schneid)
Cider (apple wine)
Citrus fruits
Cloudberry (*Rubus chamaemorus* L.)
Cloves (*Eugenia caryophyllata* Thunberg)
Cocoa category
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)
Date (*Phoenix dactylifera* L.)
Elderberry (*Sambucus nigra* L.)
Gabiroba (*Campomanesia xanthocarpa*)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Guava wine
Honey
Kiwifruit (*Actinidia chinensis*, syn. *A. Deliciosa*)
Macadamia nut (*Macadamia integrifolia*)
Maize (*Zea mays* L.)
Mangifera species
Melon
Milk and milk products
Miso (soy bean, rice, or fish)
Mountain papaya (*C. candamarcensis, C. pubescens*)
Mushroom
Naranjilla fruit (*Solanum quitoense* Lam.)
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Pimento (allspice) (*Pimenta dioica* L. Merr.)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Plum brandy
Pomegranate juice (*Punica granatum* L.)
Quince, marmelo (*Cydonia oblonga* Mill.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry brandy
Raspberry, blackberry, and boysenberry
Rice (*Oryza sativa* L.)
Rum
Sapodilla fruit (*Achras sapota* L.)
Sea buckthorn (*Hippophaë rhamnoides* L.)
Sherry
Shoyu (fermented soya hydrolysate)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Tamarind (*Tamarindus indica* L.)
Tapereba, caja fruit (*Spondias lutea* L.)
Tea
Vaccinium species
Vanilla
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

Available, accessed 6/21/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, ethyl benzoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Ethyl benzoate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of ethyl benzoate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium*

strains TA98, TA100, TA1535, TA1537, and TA102 were treated with ethyl benzoate 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, 1991). Under the conditions of the study, ethyl benzoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl benzoate 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 benzoate in solvent DMSO at concentrations up to 1502 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Ethyl benzoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014a). Under the conditions of the study, ethyl benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/19/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on ethyl benzoate or any read-across materials. The total systemic exposure to ethyl benzoate 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 benzoate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to ethyl benzoate (0.35 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: 06/05/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on ethyl benzoate or any read-across materials. The total systemic exposure to ethyl benzoate 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 benzoate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to ethyl benzoate (0.35 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: 06/05/17.

10.1.4. Skin sensitization

Based on the existing data and read-across methyl benzoate (CAS # 93-58-3), ethyl benzoate 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 benzoate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section V), ethyl benzoate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they could possibly react with skin proteins with little to no reaction under physiological conditions. In guinea pigs, open epicutaneous tests did not present reactions indicative of sensitization in ethyl benzoate (Klecak, 1985). Read-across material methyl benzoate does not present a concern for skin sensitization. In a murine local lymph node assay, read-across material methyl benzoate was found to be negative up to a 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, open epicutaneous tests and Freund's complete adjuvant tests with read-across material methyl benzoate did not present reactions indicative of sensitization (Klecak, 1985; Hausen et al., 1995). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm^2 ethyl benzoate in petrolatum (RIFM, 1972). In a human maximization test for the read-across material methyl benzoate, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 in petrolatum (RIFM, 1970). Based on the weight of evidence from structural analysis and animal and human studies, ethyl benzoate 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: 6/14/17.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry 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 benzoate 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 benzoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0078 mg/day. This exposure is 179 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: Smyth et al., 1954.

Literature Search and Risk Assessment Completed On: 06/27/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl benzoate 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 benzoate 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 (US EPA, 2012a) did not identify ethyl benzoate 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 benzoate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2000: Ready biodegradability of the test material was evaluated according to the OECD 301D method. Under the conditions of the study, biodegradation of 69% was observed after 28 days.

10.2.2.2. Ecotoxicity. RIFM, 2015a: An algae growth inhibition test was conducted according to the OECD 201 method. The 0–72-h EC50 was reported to be 24.1 mg/L and 6.6 mg/L based on growth rate and yield, respectively.

RIFM, 2015b: A *Daphnia magna* acute toxicity study was conducted according to the OECD 202 method under static conditions in a closed system. The 48-h EC50 was reported to be 27.1 mg/L.

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

10.2.3. Risk assessment refinement

Since ethyl benzoate has passed the screening, measured data has been 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).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	62.13			1,000,000	0.06213	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.59	2.59
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 0.06213 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:** http://tools.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 to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.017.

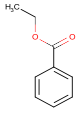
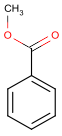
Appendix

Read-across Justification

Methods

The read-across analog was 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, 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 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 benzoate	Methyl benzoate
CAS No.	93-89-0	93-58-3
Structure		
Similarity (Tanimoto score)		0.90
Read-across endpoint		• Skin sensitization
Molecular Formula	$C_9H_{10}O_2$	$C_8H_8O_2$
Molecular Weight	150.18	136.15
Melting Point (°C, EPI Suite)	−0.50	−11.87
Boiling Point (°C, EPI Suite)	215.57	195.93
Vapor Pressure (Pa @ 25°C, EPI Suite)	26.3	50.6
Log Kow(KOWWIN v1.68 in EPI Suite)	2.64	2.12
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	720	2100
J_{max} (mg/cm^2/h, SAM)	39.935	77.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.61E-005	3.47E-005
Skin Sensitization		
Protein binding by OASIS v1.1	• Acylation	• 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)	See Supplemental Data 1	See Supplemental Data 2
	Target material	**Read-across material**
Rat liver S9 metabolism simulator and structural alerts for metabolites		

Summary

There are insufficient toxicity data on the ethyl benzoate (CAS # 93-89-0). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, methyl benzoate (CAS # 93-58-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material ethyl benzoate (CAS # 93-89-0) 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.

- The target substance and the read-across analog share a benzoate fragment.
- The key difference between the target substance and the read-across analog is that the target has an ethyl substitution on the alcohol portion of the ester, while the read-across has a methyl substitution on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
- Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the benzoate fragment. 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 QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
- The read-across analog and the target substance are 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 availability of the data.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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