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Short Review

RIFM fragrance ingredient safety assessment, ethyl 3-phenylpropionate, CAS Registry Number 2021-28-5

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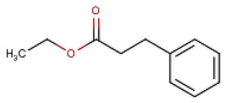
Version: 073118. This version replaces any previous versions.

Name: Ethyl 3-phenylpropionate

CAS Registry Number: 2021-28-5



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

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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 3-phenylpropionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog methyl phenylacetate (CAS # 101-41-7) show that ethyl 3-phenylpropionate is not expected to be genotoxic. Data from read-across analog methyl benzoate (CAS # 93-58-3) show that ethyl 3-phenylpropionate is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. Data from read-across analog methyl phenylacetate (CAS # 101-41-7) provided a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material and the exposure to ethyl 3-phenylpropionate is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl 3-phenylpropionate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; ethyl 3-phenylpropionate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2001; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 67 mg/kg/day.	(ECHA Dossier: Methyl phenylacetate)
Reproductive Toxicity: NOAEL = 200 mg/kg/day.	(ECHA Dossier: Methyl phenylacetate)
Skin Sensitization: No safety concerns under the current, declared levels of use.	(ECHA REACH Dossier: Methyl benzoate, accessed 11/20/17)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.9 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 29.39 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 28-.76 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 28-.76 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02876 µg/L	

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical name:** ethyl 3-phenylpropionate
2. **CAS Registry Number:** 2021-28-5
3. **Synonyms:** Benzenepropanoic acid, ethyl ester; Ethyl dihydrocinnamate; Ethyl hydrocinnamate; Ethyl 3-phenylpropanoate; Ethyl 3-phenylpropionate
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23
6. **RIFM Number:** 6726
7. Stereochemistry:

2. Physical data

1. **Boiling Point:** 240 °C (FMA), 252.15 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{ow}:** 3.06 (EPI Suite)
4. **Melting Point**: 21.44 °C (EPI Suite)
5. **Water Solubility:** 261.8 mg/L (EPI Suite)
6. **Specific Gravity:** 1.020 (FMA)
7. **Vapor Pressure:** 0.0201 mm Hg @ 20 °C (EPI Suite v4.0), 0.05 mm Hg 20 °C (FMA), 0.0316 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor 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, somewhat oily liquid. Sweet, very light fruity, honey-like odor. Sweet, fresh-fruity-floral taste with a honey-like note.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00039% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.0000019 mg/kg/day or 0.00014 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000037 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:** Methyl phenylacetate (CAS # 101-41-7)
   b. **Repeated Dose Toxicity:** Methyl phenylacetate (CAS # 101-41-7)
   c. **Reproductive Toxicity:** Methyl phenylacetate (CAS # 101-41-7)

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

No relevant data available for inclusion in this safety assessment.

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

Ethyl 3-phenylpropionate is reported to occur in the following foods*:

Alpinia species Apple brandy (*Calvados*)Beer Cashew apple (*Anacardium occidentale*)Cashew apple wine Citrus fruits Durian (*Durio zibethinus*)Grape Brandy Guava wine Melon Passionfruit (*Passiflora* Species)Pear Brandy Plum brandy Rum Sugar molasses Tapereba, caja fruit (*Spondias lutea* L.) Tequila (*Agave tequilana*) 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 07/31/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, ethyl 3-phenylpropionate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Ethyl 3-phenylpropionate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

There are no studies assessing the mutagenicity of ethyl 3-phenylpropionate. The mutagenic activity of read-across material methyl phenylacetate (CAS # 101-41-7; see Section V) 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 an S9 activation system (RIFM, 2001). Under the conditions of the study, methyl phenylacetate was not mutagenic in the Ames test, and this can be extended to ethyl 3-phenylpropionate.

There are no studies assessing the clastogenicity of ethyl 3-phenylpropionate. The clastogenic activity of read-across material methyl phenylacetate 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 methyl phenylacetate in DMSO at concentrations up to 1500 μg/mL in the presence and absence of an S9 metabolic activation system for 4 and 24 h. Methyl phenylacetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration either in the presence or absence of S9 metabolic activation (RIFM, 2015). Under the conditions of the study, methyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to ethyl 3-phenylpropionate.

Based on the available data, ethyl 3-phenylpropionate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/16/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for ethyl 3-phenylpropionate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on ethyl 3-phenylpropionate. Read-across material methyl phenylacetate (CAS # 101-41-7; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered methyl phenylacetate via oral gavage at doses of 0, 50, 200, or 800 mg/kg/day in corn oil. Males were dosed for 2 weeks prior to mating and continued through the day before euthanasia (at least 50 days), while females were dosed for 2 weeks prior to mating and continued through lactation day (LD) 13. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose group (but not mated) and served as the 14-day treatment-free recovery groups. Three females were subjected to unscheduled euthanasia on gestation day (GD) 27 due to non-parturition (dose not specified), with no evidence of treatment-related macroscopic or microscopic findings. There was a statistically significant decrease in bodyweight gain among males and females (76% and 69% of control, respectively) of the high-dose group during treatment days 1–50. Hematological, clinical chemistry, and organ weight changes were observed among animals of the high-dose group; however, these alterations were not considered to be adverse as there were no associated histopathological correlates and the finding were reversible after the recovery period. The NOAEL for repeated dose toxicity was considered to be 200 mg/kg/day, based on decreased bodyweight gain among high-dose group animals (ECHA Dossier: Methyl phenylacetate).

In another OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test, groups of 13 Wistar rats/sex/dose were administered via oral gavage test material methyl phenylacetate at doses of 0, 308, 556, or 1000 mg/kg/day in corn oil for 63 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. There were no treatment-related adverse effects observed up to the highest dose. The NOAEL was considered to be 1000 mg/kg/day (ECHA Dossier: Methyl phenylacetate). The most conservative NOAEL of 200 mg/kg/day was selected for the repeated dose toxicity endpoint. A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 200/3 or 67 mg/kg/day.

Therefore, the ethyl 3-phenylpropionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl phenylacetate NOAEL in mg/kg/day by the total systemic

exposure to ethyl 3-phenylpropionate, 67/0.000037 or 1810811.

In addition, the total systemic exposure to ethyl 3-phenylpropionate (0.037 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/10/17.

10.1.3. Reproductive toxicity

The margin of exposure for ethyl 3-phenylpropionate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on ethyl 3-phenylpropionate. Read-across material, methyl phenylacetate (CAS # 101-41-7; see Section V) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered methyl phenylacetate via oral gavage at doses of 0, 50, 200, or 800 mg/kg/day in corn oil. Males were dosed for 2 weeks prior to mating and continued through the day before euthanasia (at least 50 days), while females were dosed for 2 weeks prior to mating and continued through LD 13. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose group (but not mated) and served as the 14-day treatment-free recovery groups. Three females were subjected to unscheduled euthanasia on GD 27 due to non-parturition (dose not specified), with no evidence of treatment-related macroscopic or microscopic findings. At 800 mg/kg/day, there was an increase in the number of dead or cannibalized pups and statistically significant increases in gestation period and perinatal deaths were observed. A decrease in the regularity of estrus cycle (75%) was also observed in high-dose dams. Furthermore, statistically significant decreases in live litter size and viability index were observed in high-dose animals. There was a significant decrease in body weight of male and female pups observed on PND 0 (down to 83% of control) and PND 13 (90% of control). One dead fetus was observed in the uterus of 1 high-dose dam, which was considered to be toxicologically significant since treatment-related systemic (decreased bodyweight gain among high-dose parental animals), fertility and developmental (increased perinatal death and decreased live litter size) adverse effects were observed at 800 mg/kg/day. The NOAEL for fertility and developmental toxicity was considered to be 200 mg/kg/day, based on decreases in the regularity of estrus cycle, live litter size, viability index, and body weights in F1 pups and increases in gestation period and perinatal deaths observed among high-dose group dams (ECHA Dossier: Methyl phenylacetate).

In another OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 13 Wistar rats/sex/dose were administered methyl phenylacetate via oral gavage at doses of 0, 308, 556, or 1000 mg/kg/day in corn oil for 63 days. Additional groups of 5 rats/sex/dose were assigned to the control and high-dose group to serve as the 14-day treatment-free recovery groups. Mid- and high-dose dams showed prolonged diestrous (i.e., more than 3 days with total estrous cycle period of 6 days or more before mating period), while the control and low-dose groups showed regular cyclicity (i.e., 3–5 days estrous cycle). The pregnancy indices were 92.3%, 84.62%, 84.62%, and 61.54% for the control, low-, mid-, and high-dose groups, respectively. There was no statistically significant difference between the control and treatment groups in maternal and pups parameters (e.g., gestational length, litter size, number and sex of pups, stillbirths, live births, post-implantation loss and post-natal loss) except for decreased fertility index in high-dose dams, which was considered to be treatment-related. Pups that died among the control and treatment groups during the course of the study revealed various lesions. These findings (e.g., external: emaciated carcass, cannibalism, tearing of neck muscle, and internal: absence of milk in stomach, blood clot in thoracic cavity, reddish discoloration of the brain and lungs, paleness of the liver, congested intestine, and autolytic changes were observed in all treatment groups) were not considered treatment-related when examined externally and internally. The NOAEL was considered to be 556 mg/kg/day, based on decreased fertility index among high-dose group females (ECHA Dossier: Methyl phenylacetate). The most conservative NOAEL of 200 mg/kg/day was selected for the reproductive toxicity endpoint.

Therefore, the ethyl 3-phenylpropionate MOE for the reproductive toxicity endpoint can be calculated by dividing the methyl phenylacetate NOAEL in mg/kg/day by the total systemic exposure to ethyl 3-phenylpropionate, 200/0.000037 or 5405405.

In addition, the total systemic exposure to ethyl 3-phenylpropionate (0.037 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/10/17.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for ethyl 3-phenylpropionate. Based on the existing data and read-across analog methyl benzoate (CAS # 93-58-3; see Section V), ethyl 3-phenylpropionate 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 would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay, read-across analog 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 11/20/17). In guinea pigs, an open epicutaneous test and a Freund's complete adjuvant test with read-across analog 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 4% or 2760 μg/cm^2 read-across analog methyl benzoate in petrolatum (RIFM, 1970).

Based on weight of evidence from structural analysis, animal and human studies, and read-across analog methyl benzoate, ethyl 3-phenylpropionate 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: 11/20/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl 3-phenylpropionate 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 3-phenylpropionate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical

range, ethyl 3-phenylpropionate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for ethyl 3-phenylpropionate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/20/17.

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 3-phenylpropionate 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 3-phenylpropionate. Based on the Creme RIFM Model, the inhalation exposure is 0.00014 mg/day. This exposure is 10000 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: 12/01/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 3-phenylpropionate 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 3-phenylpropionate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl 3-phenylpropionate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). 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 3-phenylpropionate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Ethyl 3-phenylpropionate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	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>28.76</u>			1,000,000	0.02876	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.06	3.06
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

assessment is necessary.

The RIFM PNEC is 0.02876 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/28/17.

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. The links listed above were active as of 07/31/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.018.

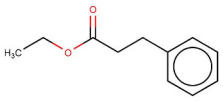
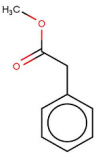
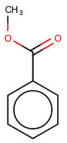
Appendix

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, 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 (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	Read-across Material
Principal Name	Ethyl 3-phenylpropionate	Methyl phenylacetate	Methyl benzoate
CAS No.	2021-28-5	101-41-7	93-58-3
Structure			
Similarity (Tanimoto Score)			
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity	• Skin sensitization
Molecular Formula	$C_{11}H_{14}O_2$	$C_9H_{10}O_2$	$C_8H_8O_2$
Molecular Weight	178.23	150.18	136.15
Melting Point (°C, EPI Suite)	21.44	−0.50	−11.87
Boiling Point (°C, EPI Suite)	252.15	215.57	195.93
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.22	20.9	50.6
Log Kow(KOWWIN v1.68 in EPI Suite)	2.73	1.83	2.12

Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	220	2072	2100
J_{max} (mg/cm^2/h, SAM)	7.454	78.176	77.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.53E + 000	1.43E + 000	3.52E + 000
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition	• Michael addition	
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, OH or NH2	• Non-binder, OH or NH2	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	•No alert found		•Acylation
Protein Binding (OECD)	•No alert found		•No alert found
Protein Binding Potency	•Not possible to classify		•Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	•No alert found		•No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	•No alert found		•No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on ethyl 3-phenylpropionate (CAS # 2021-28-5). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, methyl phenylacetate (CAS # 101-41-7), and methyl benzoate (CAS # 93-58-3) were identified as read-across materials 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 3-phenylpropionate (CAS # 2021-28-5) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of aromatic esters.
  - ○ The target substance and the read-across analog share an alkyl aromatic acid portion.
  - ○ The key structural difference between the target substance and the read-across analog is that the target substance has a phenylpropionic acid moiety, and the read-across analog has a phenyl acetic acid moiety. This structural difference is toxicologically insignificant.
  - ○ Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the alkyl aromatic acid portion. 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.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog have a Michael addition alert by the DNA binding model by OECD. According to these predictions, the target substance and the read-across analog are expected to have comparable reactivity. As described in the genotoxicity section above, based on current existing data, the read-across analog does not pose a concern for genotoxicity. Therefore, data superseded predictions in this case.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material ethyl 3-phenylpropionate (CAS # 2021-28-5) for the skin sensitization endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of aromatic esters.
  - ○ The target substance and the read-across analog share an alkyl moiety as alcohol portion.
  - ○ The key structural difference between the target substance and the read-across analog is that the target substance has a phenylpropionic acid moiety and the read-across analog has a benzoic acid moiety. This structural difference is toxicologically insignificant.
  - ○ Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the methyl moiety as alcohol portion. 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.
  - ○ Differences are predicted for J_{max}, which estimates skin absorption. $J_{max} \leq 40\%$ for the target substance and $\leq 80\%$ for the read-across analog.

While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.

- ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- ○ The read-across analog has a protein binding alert by the OASIS model. The target substance does not have any such alert. According to these predictions, the read-across analog is expected to be more reactive compared to the target substance. As described in the skin sensitization section above, the read-across analog does not present a safety concern for skin sensitization under the current, declared levels of use. Therefore, data superseded predictions in this case.
- ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- ○ The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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