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Short Review

RIFM fragrance ingredient safety assessment, phenethyl propionate, CAS Registry Number 122-70-3

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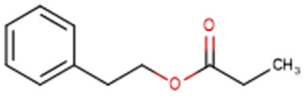

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is here: fragrancematerialsafetyresource.elsevier.com.

Name: Phenethyl propionate

CAS Registry Number: 122-70-3

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
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). Study selection for this safety assessment was 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.

Phenethyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog phenethyl acetate (CAS # 103-45-7) show that phenethyl propionate is not expected to be genotoxic. Data from read-across analogs phenethyl alcohol (CAS # 60-12-8) and propionic acid (CAS # 79-09-4) provide a calculated MOE >100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material; exposure to phenethyl propionate is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for phenethyl propionate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; phenethyl propionate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl propionate 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2002; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day. (Owston et al., 1981)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. (RIFM, 1985b; RIFM, 1986a; RIFM, 1987a; RIFM, 1988a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 50% (ECHA REACH Dossier: Phenethyl Propionate; ECHA, 2017a)
Bioaccumulation: Critical Measured Value: BCF: 46 (ECHA REACH Dossier: Phenethyl Propionate; ECHA, 2017a)
Ecotoxicity: Critical Ecotoxicity Endpoint: Fish LC50: 28.75 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: 28.75 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02875 μg/L

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

1. Identification

1. **Chemical Name:** Phenethyl propionate
2. **CAS Registry Number:** 122-70-3
3. **Synonyms:** Benzylcarbinyl propionate; Phenylethyl propionate; 2-Phenylethyl propionate; 2-Phenylethyl propanoate; Propanoic acid, 2-phenylethyl ester; ｱﾙｶﾝ酸(C = 1～9)ﾌｪﾆﾙｴﾁﾙ; Phenethyl propionate
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23 g/mol
6. **RIFM Number:** 420
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 245 °C (Fragrance Materials Association [FMA]), 252.15 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 3.06 (EPI Suite)
4. **Melting Point**: 21.44 °C (EPI Suite)
5. **Water Solubility:** 136 mg/L (EPI Suite)
6. **Specific Gravity:** 1.08 (FMA)
7. **Vapor Pressure:** 0.02 mm Hg at 20 °C (FMA), 0.0331 mm Hg at 20 °C (EPI Suite v4.0), 0.0514 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00050% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.000050 mg/kg/day or 0.0037 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00025 mg/kg/day (RIFM, 2020b)

*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 V. 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).

5. Derivation of systemic absorption

1. **Dermal:** 77%

RIFM, 2013 (data also available in Ford et al., 1987; Ford, 1990; RIFM, 1986b; RIFM, 1987b; RIFM, 1988b; RIFM, 1988c; RIFM, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA) a hydrolysis product of phenethyl propionate by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg), gavage (430 mg/kg), or dietary (430 mg/kg) administration of PEA to rats, plasma concentrations of PEA were found to be low regardless of the route of administration. The plasma concentrations of phenylacetic acid (PAA, the major metabolite of PEA) greatly exceeded the concentrations of PEA and were highest after gavage, followed by dermal then dietary administration. The pharmacokinetic parameters were compared following topical application of [^{14}]C-labeled PEA to rats, rabbits, and humans (specific activities of dosing solutions: 58–580, 164, and 50 μCi/mL, respectively). In rabbits, the plasma concentration-time profile for PAA was markedly prolonged compared to rats or humans. In humans, only 7.6% of the applied dose of PEA was absorbed, versus 77% in rats and 50% in rabbits. Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation from the human study (87.4% in rats compared to 10.8% in humans).

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Phenethyl acetate (CAS # 103-45-7)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and propionic acid (CAS # 79-09-4)
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

Phenethyl propionate is reported to occur in the following foods by the VCF*:

Apple brandy (Calvados)	Honey
Beer	*Mangifera* species
Blue cheeses	Peanut (*Arachis hypogaea* L.)
Cheese, various types	Rum
Cider (apple wine)	Whisky
Guava and feyoa	

*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.

9. REACH dossier

Available; accessed 06/11/21 (ECHA, 2017a).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, phenethyl propionate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Phenethyl propionate 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, 2014b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equi-reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of phenethyl

propionate; however, read-across can be made to phenethyl acetate (CAS # 103-45-7; see Section VI).

The mutagenic activity of phenethyl acetate 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with phenethyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2002). Under the conditions of the study, phenethyl acetate was not mutagenic in the Ames test, and this can be extended to phenethyl propionate.

The clastogenic activity of phenethyl propionate 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 phenethyl propionate in DMSO at concentrations up to 1783 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1783 μg/mL in the presence and absence of metabolic activation. Phenethyl propionate did not induce binucleated cells with micronuclei when tested up to the cytotoxic or maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, phenethyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, phenethyl acetate does not present a concern for genotoxic potential, and this can be extended to phenethyl propionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for phenethyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenethyl propionate. Phenethyl propionate is expected to hydrolyze to phenethyl alcohol (CAS # 60-12-8; see Section VI) and propionic acid (CAS # 79-09-4; see Section VI).

Phenethyl alcohol was administered at 0.25, 0.5, 1.0, and 2.0 mL/kg/day (250, 500, 1000, and 2000 mg/kg/day) for 90 days in open application to shaved dorsa of Sprague Dawley rats, 15 rats per sex per dose. The NOAEL was determined to be 0.5 mL/kg/day (500 mg/kg/day) based on a reduction in body weight and bodyweight gains among the higher dose group animals (Owston et al., 1981). The metabolite formic acid has an OECD 413 inhalation subchronic 13-week toxicity study conducted on groups of 10 F344/N rats/sex/group. The test material, formic acid, was administered via whole-body inhalation exposure at concentrations of 0, 8, 32, 64, and 128 ppm, equivalent to 0, 4, 17, 34, and 68 mg/kg/day according to standard minute volume and body weight parameters for F344/N rats. The NOAEL was determined to be 128 ppm or 68 mg/kg/day, the highest dose tested (NTP, 1992). The NOAEL of 500 mg/kg/day for phenethyl alcohol was considered for the repeated dose toxicity endpoint. To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013; see Section V) was used to revise the NOAEL of 500 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of the applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 385 mg/kg/day.

In a 90-day dietary study, 20 Sprague Dawley rats/sex/dose were treated with 0, 0.62%, 1.25%, 2.5%, or 5% propionic acid. The concentrations were equal to approximately 0, 312, 625, 1250, or 2500 mg/kg/day. An additional 10 animals were included in the control, 0.62% and 5% groups. The NOAEL for systemic toxicity was determined to be 2500 mg/kg/day (OECD, 2007).

The most conservative NOAEL of 385 mg/kg/day was taken from the 90-day study on phenethyl alcohol.

Therefore, the phenethyl propionate MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to phenethyl propionate, 385/0.00025 or 1540000.

When correcting for skin absorption, the total systemic exposure to phenethyl propionate (0.25 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/23/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on phenethyl propionate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phenethyl propionate (0.25 μg/kg/day) is below the TTC (30 μg/kg/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: 05/23/21.

11.1.4. Skin sensitization

Based on the available material-specific data and read-across to benzyl acetate (CAS # 140-11-4), phenethyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for phenethyl propionate. Based on the available material-specific data and read-across to benzyl acetate (CAS # 140-11-4; see Section VI), phenethyl propionate does not present a concern for skin sensitization. The chemical structure of the target material indicates that it would not be expected to react with skin proteins directly, while the read-across material would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In several guinea pig test methods, no reactions indicative of sensitization were observed with read-across material benzyl acetate (RIFM, 1985a; RIFM, 1985b; RIFM, 1985c; RIFM, 1986a). Phenethyl propionate did not result in reactions indicative of skin sensitization in a guinea pig test (Klecak, 1985). Additionally, in human maximization tests, no reactions indicative of sensitization were observed with phenethyl propionate and read-across material benzyl acetate (RIFM, 1973; Greif, 1967). In several Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9449 $\mu g/cm^2$) of read-across material, benzyl acetate in 3:1 ethanol:diethyl phthalate, no reactions indicative of skin sensitization were observed (RIFM, 1987a; RIFM, 1988a; RIFM, 1988d; RIFM, 1988e; RIFM, 1988f; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across to benzyl acetate, phenethyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/21/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, phenethyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for phenethyl propionate in experimental models. UV/Vis absorption spectra indicate no absorption 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 the lack of absorbance, phenethyl propionate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: 05/26/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenethyl propionate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.7.1. Risk assessment. There are insufficient inhalation data available on phenethyl propionate. Based on the Creme RIFM Model, the inhalation exposure is 0.0037 mg/day. This exposure is 378.4 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: Beroza et al., 1975; Troy (1977); UGCM, 1997; Silver (1992); RIFM, 1997; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; Rogers et al., 2003a; RIFM, 2003d; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004a; Rogers et al., 2005; RIFM, 2014a; Vethanayagam et al., 2013.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenethyl propionate 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, phenethyl propionate 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) identified phenethyl propionate as possibly persistent and not 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 $\geq$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).

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.3. Other available data

Phenethyl propionate has been registered for REACH with the following additional data available at this time (ECHA, 2017a):

A biodegradation study was conducted for 30 days to evaluate the percentage biodegradability of the test material. Biodegradation of 50% was observed after 5 days.

The bioaccumulation study was conducted for estimating the BCF (bioaccumulation factor) value of the test chemical. The bioaccumulation factor (BCF) value was calculated using an estimated log K_{ow} of 3.06 and a regression-derived equation. The BCF (bioaccumulation factor) value of 2-phenylethyl propanoate was determined to be 46.

The 96-h acute fish toxicity test was conducted using *Lepomis macrochirus* under static conditions. The LC50 value based on nominal test concentration was reported to be 12 mg/L.

The 96-h acute fish toxicity test was conducted using Rainbow trout under static conditions. The LC50 value based on nominal test concentration was reported to be > 10 and < 13 mg/L.

The LC50 value of phenethyl propionate in aquatic invertebrates (*Biomphalaria alexandrina*) in a 72-h study on the basis of mortality effect was found to be 296.27 mg/L. The study was conducted under static conditions.

11.2.5. Risk assessment refinement

Since phenethyl propionate 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).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.06	3.06

(*continued on next page*)

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	28.75			1000000	0.02875	

(*continued*)

Exposure	Europe (EU)	North America (NA)
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 additional assessment is necessary.

The RIFM PNEC is 0.02875 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/03/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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 02/14/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.113073.

Appendix

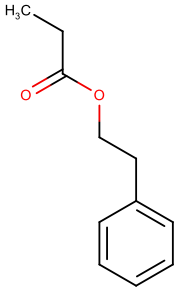
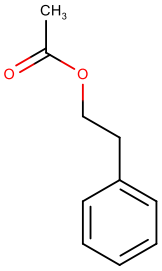
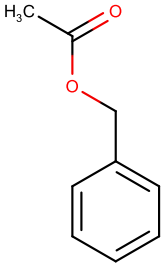
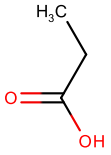
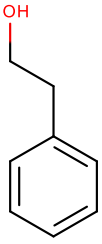
Read-across justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017).

- 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 material 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Phenethyl propionate	Phenethyl acetate	Benzyl acetate	Propionic acid	Phenethyl alcohol
CAS No.	122-70-3	103-45-7	140-11-4	79-09-4	60-12-8
Structure					
Similarity (Tanimoto Score)		0.94	0.39	0.21	0.56
SMILES	CCC(=O)OCCc1ccccc1	CC(=O)OCCc1ccccc1	CC(=O)OCc1ccccc1	CCC(O) = O	OCCc1ccccc1
Endpoint		Genotoxicity	Skin sensitization	Repeated dose toxicity	Repeated dose toxicity
Molecular Formula	$C_{11}H_{14}O_2$	$C_{10}H_{12}O_2$	$C_9H_{10}O_2$	$C_3H_6O_2$	$C_8H_{10}O$
Molecular Weight (g/mol)	178.231	164.204	150.177	74.079	122.167
Melting Point (°C, EPI Suite)	21.44	−31.10	−51.30	−21.10	−27.00
Boiling Point (°C, EPI Suite)	238.00	232.60	213.00	141.10	218.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.85E+00	4.19E+00	2.36E+01	4.71E+02	1.16E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.36E+02	7.11E+02	3.10E+03	1.00E+06	2.22E+04
Log KOW	3.06	2.3	1.96	0.33	1.36
J_{max} (μg/cm^2/h, SAM)	7.22	17.66	64.04	10128.08	355.17
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.52E+00	1.90E+00	1.14E+00	4.51E-02	2.59E-02
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters			
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals| Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Carcinogenicity (ISS)	No alert found	No alert found			
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)	Pethidine (Hepatotoxicity) Alert| Toluene (Renal toxicity) Alert			Carboxylic acids (Hepatotoxicity) No rank|Glycolic acid (Renal Toxicity) Alert	Styrene (Renal Toxicity) Alert| Toluene (Renal toxicity) Alert
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		
Protein Binding (OECD)	No alert found		SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.		Alert for Acyl Transfer agent identified.		
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	N/A*	See Supplemental Data 4

*No metabolites produced. Propionic acid is naturally present in the human body and is metabolized to carbon dioxide and water, which then follow the natural path of clearance.

Summary

There is insufficient toxicity data on phenethyl propionate (CAS # 122-70-3). Hence *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenethyl acetate (CAS # 103-45-7), benzyl acetate (CAS # 140-11-4), propionic acid (CAS # 79-09-4), and phenethyl alcohol (CAS # 60-12-8) were identified as read-across materials with data for their respective toxicity endpoints.

Metabolism

The metabolism of the target material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). Phenethyl propionate (CAS # 122-70-3) is metabolized to propionic acid (CAS # 79-09-4) and phenethyl alcohol (CAS # 60-12-8) in the first step with 0.95 intrinsic probability. Hence, propionic acid and phenethyl alcohol can be used as read-across for phenethyl propionate (CAS # 122-70-3). Phenethyl alcohol (CAS # 60-12-8) was out of domain for the *in vivo* rat and *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided in the Conclusions section.

Conclusions

- Phenethyl acetate (CAS # 103-45-7) was used as a structurally similar read-across analog for the target material phenethyl propionate (CAS # 122-70-3) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog have a phenyl fragment common among them.
  - o The key difference is that the target has a propionate, while the analog has an isovalerate part.
  - o The Tanimoto score is mainly driven by the phenylethyl fragment. The differences in the structure which are responsible for Tanimoto scores <1 are not relevant from a toxicology endpoint perspective.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.

- QSAR OECD model for DNA binding shows Michael addition alert for the target material and the read-across analog. The target material and the read-across analog do not have other DNA binding alerts for genotoxicity. The data described in the genotoxicity endpoint section shows that the read-across analog does not pose a concern. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the alert will be superseded by the availability of the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the genotoxicity endpoint between the metabolites of the read-across analog and the target material are consistent.
- The structural differences between the target material and the read-across analog are deemed to be toxicologically significant.

- Benzyl acetate (CAS # 140-11-4) was used as a structurally similar read-across analog for the target material phenethyl propionate (CAS # 122-70-3) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of esters.
  - The target material and the read-across analog have phenylethyl fragments common among them.
  - The key difference is that the target is propionate, while the analog is a dimethyl propanoate.
  - The Tanimoto score is mainly driven by the phenylethyl fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxicology endpoint perspective.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - There are several SN2 reaction *in silico* alerts by different models for skin sensitization endpoint. The data on the read-across analog confirms it does not pose a concern for skin sensitization under current levels of use. Therefore, the alert will be superseded by the availability of the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the skin sensitization endpoint between the metabolites of the read-across analog and the target material are consistent.
  - The structural differences between the target material and the read-across analog are deemed to be toxicologically significant.
- Phenethyl alcohol (CAS # 60-12-8) and propionic acid (CAS # 79-09-4) are used as read-across analogs for phenethyl propionate (CAS # 122-70-3) for the repeated dose toxicity endpoint.
  - The read-across materials are analogs of the major metabolites of the target material.
  - The structural difference between the target material and the read-across analogs can be mitigated by the fact that the target material could be metabolically hydrolyzed to the analogs of read-across analogs used here. Therefore, the toxicity profile of the target material is expected to be that of the metabolites.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v4.2), structural alerts for the repeated dose, reproductive, and respiratory toxicity endpoints are consistent between the target material and the read-across analog.
  - Both the target material and read-across analogs are predicted to have renal toxicity alert (Repeated Dose (HESS)). The availability of data for the read-across superseded this prediction. The MOE for phenethyl propionate is adequate for the repeated dose toxicity endpoint at the current level of use.
  - The structural differences between the target material and the read-across analogs are deemed to be toxicologically insignificant for the repeated dose toxicity endpoint.

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