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RIFM fragrance ingredient safety assessment, 2-phenylethyl valerate, CAS Registry Number 7460-74-4

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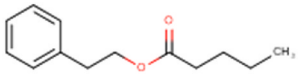

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Name: 2-Phenylethyl valerate

CAS Registry Number: 7460-74-4

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; Safford et al., 2015; Safford et al., 2017; Comiskey 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). 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.

2-Phenylethyl valerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs phenethyl acetate (CAS # 103-45-7) and phenethyl propionate (CAS # 122-70-3) show that 2-phenylethyl valerate is not expected to be genotoxic. Data on read-across analogs phenethyl alcohol (CAS # 60-12-8) and acetic acid (CAS # 64-19-7) 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, and the exposure to 2-phenylethyl valerate is below the TTC (0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from the read-across analog benzyl acetate (CAS # 140-11-4) show that this material is not a concern for skin sensitization. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 2-phenylethyl valerate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-phenylethyl valerate 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: Screening-level: 3.129 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 216.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 4.581 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: 4.581 mg/L	(RIFM Framework; Salvito et al, 2002)

RIFM PNEC is: 0.004581 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Phenylethyl valerate
2. **CAS Registry Number:** 7460-74-4
3. **Synonyms:** Pentanoic acid, 2-phenylethyl ester; 2-Phenethyl valerate; 2-Phenylethyl pentanoate; 2-Phenylethyl valerate
4. **Molecular Formula:** $C_{13}H_{18}O_2$
5. **Molecular Weight:** 206.28 g/mol
6. **RIFM Number:** 6852
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 285.11 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.05 (EPI Suite)
4. **Melting Point**: 42.34 °C (EPI Suite)
5. **Water Solubility:** 14.26 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00164 mm Hg at 20 °C (EPI Suite v4.0), 0.00298 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 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000077% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.0000009 mg/kg/day or 0.000060 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00020 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%, read-across from phenethyl alcohol (CAS # 60-12-8)

RIFM, 2013a (data also available in RIFM, 1986b; RIFM, 1987b; RIFM, 1988b; RIFM, 1988c; RIFM, 1990; Ford et al., 1987; Ford, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA) 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); phenethyl propionate (CAS # 122-70-3)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8); acetic acid (CAS # 64-19-7)
   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

2-Phenylethyl valerate is reported to occur in the following foods by the VCF*:

Cider (Apple wine)
Mentha oils.
Rum.
Sea buckthorn (*Hippophaë rhamnoides* L.)

*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 on 02/10/22.

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, 2-phenylethyl valerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Phenylethyl valerate 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, 2013b). 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 2-phenylethyl valerate; 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 2-phenylethyl valerate.

There are no studies assessing the clastogenicity of 2-phenylethyl valerate; however, read-across can be made to phenethyl propionate (CAS # 122-70-3; see Section VI).

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 dimethyl sulfoxide (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, and this can be extended to 2-phenylethyl valerate.

Based on the data available, phenethyl acetate and phenethyl propionate do not present a concern for genotoxic potential, and this can be extended to 2-phenylethyl valerate.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for 2-phenylethyl valerate 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 2-phenylethyl valerate. 2-Phenylethyl valerate is expected to hydrolyze to phenethyl alcohol (CAS # 60-12-8; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI).

Acetic acid has been reviewed by EFSA (EFSA, 2012), NICNAS (NICNAS, 2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR (CIR, 2010) for its use in cosmetics. Results from repeated oral, inhalation, and dermal exposure of humans to acetic acid under occupational conditions have been reported with effects on the gastrointestinal tract, digestive disorders including heartburn and constipation, chronic inflammation of the respiratory tract, pharyngitis, catarrhal bronchitis, darkening of the skin, skin dermatitis, and erosion of the exposed front teeth enamel. In addition, skin on the palms of hands was reported to become dry, cracked, and hyperkeratotic. These observed effects were not associated with any systemic findings, suggesting the effects observed could be due to the material's local corrosive activity. The NICNAS review concluded that acetic acid is not considered to cause serious damage to health from repeated oral exposure nor is it likely to be a carcinogen (NICNAS, 2013). Based on the available data, the CIR panel concluded that acetic acid is safe under the present practices of use and concentrations (CIR, 2010). Acetic acid is recognized as GRAS by the US FDA and is estimated to be consumed by humans at about 1 gm/day for centuries without any adverse effects. Furthermore, estimations of the daily intake of acetic acid have also been reported to vary from about 1 to 2.1 g per day for subjects older than 2 years (NICNAS, 2013).

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 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, 2013a; 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.

Therefore, the 2-phenylethyl valerate 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 2-phenylethyl valerate, 385/0.00020 or 1925000.

When correcting for skin absorption, the total systemic exposure to 2-phenylethyl valerate (0.20 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 2-phenethyl valerate or any read-across materials. The total systemic exposure to 2-phenethyl valerate 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 2-phenethyl valerate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-phenethyl valerate (0.20 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 read-across benzyl acetate (CAS # 140-11-4), 2-phenylethyl valerate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 2-phenylethyl valerate. Based on read-across to benzyl acetate (CAS # 140-11-4; see Section VI), 2-phenylethyl valerate 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 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, 1985b; RIFM, 1986a; RIFM, 1985a; RIFM, 1985c; RIFM, 1985a; RIFM, 1985c). Additionally, in a human maximization test, no reactions indicative of sensitization were observed with read-across material benzyl acetate (Greif, 1967). In Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9449 μg/cm^2) of read-across material, benzyl acetate in 3:1 ethanol:diethylphthalate, no reactions indicative of skin sensitization were observed (RIFM, 1987a; RIFM, 1988a; RIFM, 1975e; RIFM, 1988d; RIFM, 1988e; RIFM, 1988f; RIFM, 1975d; RIFM, 1975c; RIFM, 1975b; RIFM, 1975a).

Based on the weight of evidence (WoE) from structural analysis and read-across to benzyl acetate, 2-phenylethyl valerate 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, 2-phenylethyl valerate 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 2-phenylethyl valerate 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, 2-phenylethyl valerate 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 2-phenylethyl valerate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 2-phenylethyl valerate. Based on the Creme RIFM Model, the inhalation exposure is 0.000060 mg/day. This exposure is 23,333 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: Troy (1977); The Union of German Candle Manufacturers, 1997; Silver (1992); RIFM, 1997; RIFM, 2003b; RIFM, 2003c; Rogers et al, 2003a; RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola et al, 2004a; Rogers et al, 2005; RIFM, 2014; Vethanayagam et al, 2013.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenylethyl valerate was performed following the RIFM Environmental Framework (Salvito, 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, 2-phenylethyl valerate 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 2-phenylethyl valerate 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 $\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), 2-phenylethyl valerate 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.

11.2.2.1.3. Other available data. 2-Phenylethyl valerate has been registered for REACH with no additional data at this time.

11.2.3. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.05	4.05
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	Not Reported
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.004581 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the 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

	(mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	4.581			1000000	0.004581	

- **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 02/10/22.

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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113056.

Appendix

Read-across Justification

Methods

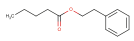
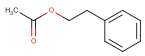
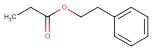
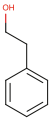
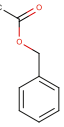
The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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 (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Read-across Material
Principal Name	2-Phenylethyl valerate	Phenethyl acetate	Phenethyl propionate		Acetic acid	Benzyl acetate

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
				Phenethyl alcohol		
CAS No.	7460-74-4	103-45-7	122-70-3	60-12-8	64-19-7	140-11-4
Structure						
Similarity (Tanimoto Score)		0.59	0.70	0.35	N/A	0.89
Endpoint		Genotoxicity	Genotoxicity	Repeated dose toxicity	Repeated dose toxicity	Skin sensitization
Molecular Formula	$C_{13}H_{18}O_2$	$C_{10}H_{12}O_2$	$C_{11}H_{14}O_2$	$C_8H_{10}O$	$C_2H_4O_2$	$C_9H_{10}O_2$
Molecular Weight (g/mol)	206.28	164.20	178.23	122.17	60.052	150.18
Melting Point (°C, EPI Suite)	42.34	−31.10	21.44	−27.00	16.64	−51.30
Boiling Point (°C, EPI Suite)	285.11	232.60	238.00	218.20	117.90	213.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.40	4.19	6.85	11.57	2.09E+03	23.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	14.26	710.80	136.00	22200.00	1.00E+06	3100.00
Log K_{OW}	4.05	2.30	3.06	1.36	−0.17	1.96
J_{max} (μg/cm^2/h, SAM)	1.33	17.66	7.22	355.17	6282.71	64.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.46	1.90	2.52	0.03	1.45E-02	1.14
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	No alert found			
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	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			
Carcinogenicity (ISS)	No alert found	No alert found	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found			
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found	No alert found			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found	No alert found			
Oncologic Classification	Not classified	Not classified	Not classified			
Repeated Dose Toxicity						
Repeated Dose (HESS)	Not categorized			Styrene (Renal Toxicity) Alert| Toluene (Renal toxicity) Alert	Acetamide (Renal Toxicity) Alert| Carboxylic acids (Hepatotoxicity) No rank	
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	See Supplemental Data 4	No metabolite possible	See Supplemental Data 5

Summary

There are insufficient toxicity data on the target material 2-phenylethyl valerate (CAS # 7460-74-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenylethyl acetate (CAS # 103-45-7), phenylethyl propionate (CAS # 122-70-3), phenethyl alcohol (CAS # 60-12-8), acetic acid (CAS # 64-19-7), and benzyl acetate (CAS # 140-11-4) were identified as read-across materials with data for their respective toxicity endpoints.

Metabolism

Metabolism of the target material was not considered for the risk assessment, and therefore metabolism data were not reviewed, except where it may pertain in specific endpoint sections above. Metabolism of the target material 2-phenylethyl valerate (CAS # 7460-74-4) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to metabolize into phenethyl alcohol (CAS # 60-12-8) and valeric acid (CAS # 109-52-4) in the first step with a 0.95 pre-calculated probability. Acetic acid (CAS # 64-19-7) is structurally similar to valeric acid (CAS # 109-52-4). Hence, phenethyl alcohol and acetic acid can be used as read-across analogs for the target material. Benzyl alcohol was out of domain for the *in vivo* 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.

Conclusion

- Phenylethyl acetate (CAS # 103-45-7) was used as a read-across analog for the target material 2-phenylethyl valerate (CAS # 7460-74-4) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of esters.

- The key difference between the target material and the read-across analog is that the target material is a pentanoate ester while the read-across analog is an acetate ester. This structural difference is toxicologically insignificant.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- There is a Michael addition alert for both target and read-across materials (OECD QSAR Toolbox v4.2). This alert is due to the presence of an aromatic ring on the alcohol end of the ester. A P450 mediated epoxidation followed by conversion to a reactive quinone has been postulated as the primary cause of benzene derivatives' ability to bind to biological nucleophiles (via a Michael addition mechanism). However, under the conditions of the mutagenic study, read-across analog was not mutagenic in the Ames test, and this can be extended to the target material.
- 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Phenylethyl propionate (CAS # 122-70-3) was used as a read-across analog for the target material 2-phenylethyl valerate (CAS # 7460-74-4) for the genotoxicity endpoint.
  - The target material and the read-across analog belong to a class of esters.
  - The key difference between the target material and the read-across analog is that the target material is a pentanoate ester while the read-across analog is a propionate ester. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There is Michael addition alert for both target and read-across materials (OECD QSAR Toolbox v4.2). This alert is due to the presence of an aromatic ring on the alcohol end of the ester. A P450 mediated epoxidation followed by conversion to a reactive quinone has been postulated as the primary cause of benzene derivatives' ability to bind to biological nucleophiles (via a Michael addition mechanism). However, under the conditions of the mutagenic study, read-across analog was not mutagenic in the Ames test, and this can be extended to the target material.
  - 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Benzyl acetate (CAS # 140-11-4) was used as a read-across analog for the target material 2-phenylethyl valerate (CAS # 7460-74-4) for the skin sensitization endpoint.
  - The target material and the read-across analog belong to a class of esters.
  - The key difference between the target material and the read-across analog is that the target material is a pentanoate ester while the read-across analog is an acetate ester. Moreover, the target has a phenylethyl fragment on the alcohol side, whereas the read-across analog has a benzyl fragment on the alcohol side. These structural differences are toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - There is an S_N2 reaction alert for the read-across analog. The S_N2 mechanism occurring at the activated carbon has been suggested to be responsible for the protein reactivity of such alkyl esters. However, based on read-across benzyl acetate (CAS # 140-11-4), 2-phenylethyl valerate does not present a concern for skin sensitization under the current, declared levels of use.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Phenethyl alcohol (CAS # 60-12-8) and acetic acid (CAS # 64-19-7) were used as read-across analogs for the target material 2-phenylethyl valerate (CAS # 7460-74-4) for the repeated dose toxicity endpoint.
  - The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - The target material is an ester formed from the read-across analog alcohol and the read-across analog acid.
  - Structural differences between the target material and the ester read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the alcohol read-across analog. Therefore, the toxicity profile of the target is expected to be similar to that of metabolites.
  - The target material and the ester read-across analogs have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analog do not affect consideration of the toxic endpoints.
  - According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity endpoints are consistent between the target material and the read-across analogs.

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