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RIFM fragrance ingredient safety assessment, 2-phenoxyethyl propionate, CAS Registry Number 23495-12-7

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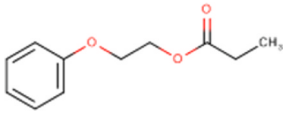
CAS Registry Number: 23495-12-7



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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
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)

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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, 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, 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-Phenoxyethyl propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog phenethyl isobutyrate (CAS # 103-48-0) show that 2-phenoxyethyl propionate is not expected to be genotoxic. Data on read-across analog 2-phenoxyethyl isobutyrate (CAS # 103-60-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint and show that there are no safety concerns for skin sensitization under the current declared levels of use. The reproductive toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material; exposure is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-phenoxyethyl propionate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-phenoxyethyl propionate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2001; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 228.1 mg/kg/day. RIFM (2004)
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. RIFM (2002)
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: 2.87 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 24.01 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 78.76 mg/L (RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 78.76 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.07876 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 2-Phenoxyethyl propionate
2. **CAS Registry Number:** 23495-12-7
3. **Synonyms:** Ethanol, 2-phenoxy-, propanoate; Ethylene glycol monophenyl ether, propionate; ｱﾙｷﾙ(C = 1 ~ 3)ｶﾙﾎﾞﾝ酸ﾌｪﾉｷｼｴﾁﾙ; 2-Phenoxyethyl propanoate; Phenoxyethyl propionate; 2-Phenoxyethyl propionate
4. **Molecular Formula:** $C_{11}H_{14}O_3$
5. **Molecular Weight:** 194.23 g/mol
6. **RIFM Number:** 421
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stere

2. Physical data

1. **Boiling Point:** 269.72 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; closed cup (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 2.6 (EPI Suite)
4. **Melting Point**: 37.69 °C (EPI Suite)
5. **Water Solubility:** 283.6 mg/L (EPI Suite)
6. **Specific Gravity:** 1.080 (FMA)
7. **Vapor Pressure:** 0.00414 mm Hg at 20 °C (EPI Suite v4.0), 0.007 mm Hg 20 °C (FMA), 0.00737 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm under neutral and acidic conditions. Minor absorbance between 290 and 700 nm

under basic conditions; molar absorption coefficient (99 L mol^{-1} • cm^{-1}) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless oily liquid

3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.2.6)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.015% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000013 mg/kg/day or 0.0011 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000020 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 5%, read-across from 2-phenoxyethyl isobutyrate (CAS # 103-60-6)

Hotchkiss (1998): An *in vitro* skin absorption study was conducted using rat and human skin samples. Radio-labeled read-across material 2-phenoxyethyl isobutyrate (CAS # 103-60-6; see Section VI) was applied to human and rat skin using flow-through diffusion cells. Freshly obtained circles of skin from rats or human surgical patients were placed into flow-through diffusion cells, and surface temperature was maintained at 32 °C. The radio-labeled test material was applied to the skin surface, and the skin was either occluded with a Teflon cap or left open to the atmosphere. A buffer or tissue culture medium flowed across the underside of the skin to aid maintenance of skin viability, and this receptor fluid was collected at hourly intervals for up to 72 h and assayed for penetrated parent compound and metabolites by liquid scintillation spectrometry/HPLC. At the end of the experiment, the skin surface was washed to remove unabsorbed material, and the skin was digested to assess residual radioactive material (parent compound and/or metabolites). Forty-six and 41% of the dose were absorbed through occluded and unoccluded rat skin. Five percent of the dose was absorbed through occluded and unoccluded human skin.

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class II, Intermediate* (Expert Judgment).

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

*See the Appendix below for further details.

6.2. Analogs selected

a. **Genotoxicity:** Phenethyl isobutyrate (CAS # 103-48-0)
b. **Repeated Dose Toxicity:** 2-Phenoxyethyl isobutyrate (CAS # 103-60-6)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 2-Phenoxyethyl isobutyrate (CAS # 103-60-6)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

2-Phenoxyethyl propionate is not reported to occur in foods by the VCF*.

*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

2-Phenoxyethyl propionate has been pre-registered for 2010; no dossier available as of 03/24/22.

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 and use levels, 2-phenoxyethyl propionate does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. 2-Phenoxyethyl 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, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on a more 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 and clastogenic activity of 2-phenoxyethyl propionate; however, read-across can be made to phenethyl isobutyrate (CAS # 103-48-0; see Section VI).

The mutagenic activity of phenethyl isobutyrate 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 TA98, TA100, TA1535, TA1537, and TA102 were treated with phenethyl

isobutyrate 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, 2001). Under the conditions of the study, phenethyl isobutyrate was not mutagenic in the Ames test, and this can be extended to 2-phenoxyethyl propionate.

The clastogenic activity of phenethyl isobutyrate 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 isobutyrate in DMSO at concentrations up to 1920 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation. Phenethyl isobutyrate did not induce binucleated cells with micronuclei when in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, phenethyl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-phenoxyethyl propionate.

Based on the data available, phenethyl isobutyrate does not present a concern for genotoxic potential, and this can be extended to 2-phenoxyethyl propionate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

The MOE for 2-phenoxyethyl 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 2-phenoxyethyl propionate. Read-across material 2-phenoxyethyl isobutyrate (CAS # 103-60-6; see Section VI) has a dermal 13-week subchronic toxicity study conducted in rats, which determined the NOAEL to be 1000 mg/kg/day, the highest dosage tested (RIFM, 2004). An *in vivo* dermal absorption study was conducted on 2-phenoxyethanol isobutyrate with rats (RIFM, 2004). At the dosage of 1000 mg/kg/day under semi-occlusion, 22.81% of the applied dose was absorbed. To account for bioavailability following dermal application, these data from the *in vivo* dermal absorption study were used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 22.81% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 228.1 mg/kg/day.

Therefore, the 2-phenoxyethyl propionate MOE is equal to the 2-phenoxyethyl isobutyrate NOAEL in mg/kg/day divided by the total systemic exposure to 2-phenoxyethyl propionate, 228.1/0.000020, or 11405000.

In addition, the total systemic exposure for 2-phenoxyethyl propionate (0.020 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint at the current level of use.

Additional References: RIFM, 2012c; RIFM, 2012d; RIFM, 2012a; RIFM, 1994; Guy (2010); RIFM, 2012b.

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 2-phenoxyethyl propionate or any read-across materials. The total systemic exposure to 2-phenoxyethyl propionate is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-phenoxyethyl propionate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.020 μg/kg/day) is below the TTC for 2-phenoxyethyl propionate (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: RIFM, 2012c; RIFM, 2012d; RIFM, 2012a; RIFM, 1994; Guy (2010); RIFM, 2012b.

Literature Search and Risk Assessment Completed On: 09/30/20.

11.1.4. Skin sensitization

Based on the existing data and read-across to 2-phenoxyethyl isobutyrate (CAS # 103-60-6), 2-phenoxyethyl propionate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-phenoxyethyl propionate. Based on the existing data and read-across material 2-phenoxyethyl isobutyrate (CAS # 103-60-6; see Section VI), 2-phenoxyethyl propionate is not considered a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 2-phenoxyethyl isobutyrate was not found to be sensitizing when tested up to 100% (RIFM, 2002). In human maximization tests, no skin sensitization reactions were observed with 2-phenoxyethyl propionate and read-across material, 2-phenoxyethyl isobutyrate at 10% (6900 μg/cm^2) and 4% (2760 μg/cm^2), respectively (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 388 μg/cm^2 of read-across material 2-phenoxyethyl isobutyrate in ethanol, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1965).

Based on the weight of evidence (WoE) from structural analysis, human study, and read-across material 2-phenoxyethyl isobutyrate, 2-phenoxyethyl propionate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1967; RIFM, 1968.

Literature Search and Risk Assessment Completed On: 09/10/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-phenoxyethyl 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 2-phenoxyethyl propionate in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2-phenoxyethyl 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 between 290 and 700 nm under neutral and acidic conditions. Minor absorbance was observed between 290 and 700 nm under basic conditions; the molar absorption coefficient (99 L mol^{-1} • cm^{-1}) is below the benchmark (1000 L mol^{-1} • cm^{-1}) (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/01/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-phenoxyethyl propionate is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-phenoxyethyl propionate. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 427.3 times lower

than the Cramer Class III* TTC level of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009) and is deemed safe for use at the reported use level.

*As per Carthew et al. (2009), Cramer Class II defaults to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/30/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenoxyethyl propionate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow}, and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor, as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b) (providing chemical class-specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. Following the RIFM Environmental Framework, 2-phenoxyethyl 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) did not identify 2-phenoxyethyl propionate 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2015), 2-phenoxyethyl propionate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

Biodegradation: No data available.

Ecotoxicity: No data available.

11.2.3. Other available data

2-Phenoxyethyl propionate has been pre-registered for REACH with no additional information available at this time.

11.2.3.1. 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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.6	2.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<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 0.07876 μg/L. The revised PEC/PNECs for EU and NA 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 volumes of use.

Literature Search and Risk Assessment Completed On: 09/30/20.

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 03/24/22.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	78.76			1000000	0.07876	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113256.

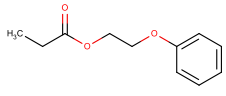
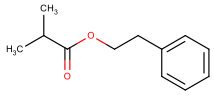
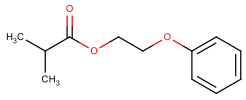
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). 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, 2017b).

- 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
Principal Name	2-Phenoxyethyl propionate	Phenethyl isobutyrate	2-Phenoxyethyl isobutyrate
CAS No.	23495-12-7	103-48-0	103-60-6
Structure			
Similarity (Tanimoto Score)		0.29	0.92
Endpoints		• Genotoxicity	• Skin sensitization • Repeated dose toxicity
Molecular Formula	$C_{11}H_{14}O_3$	$C_{12}H_{16}O_2$	$C_{12}H_{16}O_3$
Molecular Weight (g/mol)	194.23	192.258	208.257
Melting Point (°C, EPI Suite)	37.69	21.57	37.71
Boiling Point (°C, EPI Suite)	269.72	250.00	276.18
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.83E-01	3.63E+00	7.01E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.84E+02	5.10E+01	1.06E+02
Log K_{OW}	2.6	3.48	3.01
J_{max} (μg/cm^2/h, SAM)	5.39	3.41	2.69

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.36E-01	3.35E+00	1.80E-01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	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	
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)**	H-acceptor-path3-H-acceptor	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Pethidine (Hepatotoxicity) Alert		Not categorized
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found		No alert found
Protein Binding (OECD)	No alert found		No alert found
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		No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts 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

Summary

There are insufficient toxicity data on 2-phenoxyethyl propionate (CAS # 23495-12-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, phenethyl isobutyrate (CAS # 103-48-0) and 2-phenoxyethyl isobutyrate (CAS # 103-60-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- Phenethyl isobutyrate (CAS # 103-48-0) was used as a read-across analog for the target material 2-phenoxyethyl propionate (CAS # 23495-12-7) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the target material has an ether linkage while the read-across analog lacks it. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has an alert for Michael addition reaction. This alert is due to the aromatic ring of the read-across analog. The target material does not have the alert due to the ether link attached to the aromatic ring. The structure of the read-across analog is out of the domain for the applicability of the expert rule-based alert due to ester functionality. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alert and predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Phenoxyethyl isobutyrate (CAS # 103-60-6) was used as a read-across analog for the target material 2-phenoxyethyl propionate (CAS # 23495-12-7) for dermal absorption and the repeated dose toxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the read-across analog has an additional methyl group compared to the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o 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.

- o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- o The target material has higher aqueous solubility (in mg/L) than the read-across analog. The partition coefficient (log K_{ow}) of the target material is lower than the read-across analog. The predicted skin absorption (J_{max}) of the read-across analog is less than the target material. With these physical–chemical properties, the read-across analog serves as a conservative option for data gap filling for the skin absorption property.
- o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Class

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? No.
Q23. Aromatic? Yes.
Q27. Rings with substituents? Yes.
Q28. More than one aromatic ring: No.
Q30. Aromatic Ring with complex substituents? Yes.
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No for 'Residue 1′ and '2'
Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below? Yes, Class Intermediate (Class II) for 'Residue 1′ and '2'

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