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RIFM fragrance ingredient safety assessment, phenethyl phenylacetate, CAS Registry Number 102-20-5

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Fostadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel for Fragrance Safety, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *Member Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

A R T I C L E I N F O

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A B S T R A C T

The existing information supports the use of this material as described in this safety assessment. Phenethyl phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenethyl phenylacetate is not genotoxic. Data provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog benzyl benzoate (CAS # 120-51-4) provide an MOE >100 for the developmental toxicity endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to phenethyl phenylacetate is below the TTC (0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from analog benzyl phenylacetate (CAS # 102-16-9) show that there are no safety concerns for phenethyl phenylacetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; phenethyl phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl phenylacetate 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.

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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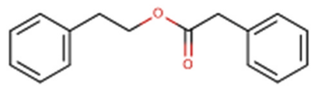


Version: 100821. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

Name: Phenethyl phenylacetate CAS Registry Number: 102-20-5

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2020)
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 (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).

(*continued on next column*)

(*continued*)

*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 phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenethyl phenylacetate is not genotoxic. Data provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across analog benzyl benzoate (CAS # 120-51-4) provide an MOE >100 for the developmental toxicity endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to phenethyl phenylacetate is below the TTC (0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from analog benzyl phenylacetate (CAS # 102-16-9) show that there are no safety concerns for phenethyl phenylacetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; phenethyl phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl phenylacetate was found not to be PBT as per the IFRA Environmental Standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2001a; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day.	(Hagan et al., 1967)
Reproductive Toxicity: Developmental toxicity: NOAEL = 194.3 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC.	(Morita et al., 1980)
Skin Sensitization: Not a concern for skin sensitization at the current declared levels of use.	(RIFM, 2005; RIFM, 1970; RIFM, 2004; RIFM, 1971c; RIFM, 1971b)
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: 104% (OECD 301F)	RIFM (1999a)
Bioaccumulation: Screening-level: 309 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 72-h Algae EbC50: 1.27 mg/L	RIFM (2016b)
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: 72-h Algae EbC50: 1.27 mg/L	RIFM (2016b)
RIFM PNEC is: 1.27 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Phenethyl phenylacetate
2. **CAS Registry Number:** 102-20-5
3. **Synonyms:** Benzeneacetic acid, 2-phenylethyl ester; Benzylcarbinyl phenylacetate; Phenethyl-α-toluate; Phenylethyl phenylacetate; 2-Phenylethyl phenylacetate; 2-Phenylethyl α-toluate; ﾌｴﾆﾙ酸ﾌｴﾆﾙｴﾁﾙ; Phenylethylphenylacetat; Phenethyl phenylacetate
4. **Molecular Formula:** $C_{16}H_{16}O_2$
5. **Molecular Weight:** 240.3
6. **RIFM Number:** 196
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 324 °C (Fragrance Materials Association [FMA]), 343.16 °C (EPI Suite)
2. **Flash Point:** 124 °C (Globally Harmonized System), >200 °F; CC (FMA), 181.0 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015b)
3. **Log K_{OW}:** 3.8 at 35 °C (RIFM, 1999b), 4.28 (EPI Suite)
4. **Melting Point**: 89.4 °C (EPI Suite)
5. **Water Solubility:** 5.921 mg/L (EPI Suite)
6. **Specific Gravity:** 1.081–1.084 (FMA), 1.08 g/mL (RIFM, 1994), 1.079–1.082 (FMA)
7. **Vapor Pressure:** 0.0000966 mm Hg at 20 °C (EPI Suite v4.0), 0.000186 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:** A clear, colorless to pale yellow liquid having a flowery, balsamic odor. May solidify on standing (Arctander, 1969)

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. 95th **Percentile Concentration in Fine Fragrance:** 0.15% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00045 mg/kg/day or 0.033 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0031 mg/kg/day (RIFM, 2020b)

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

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
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:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Benzyl benzoate (CAS # 120-51-4)
   d. **Skin Sensitization:** Benzyl phenylacetate (CAS # 102-16-9)
   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.
Additional References: None.

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

Phenethyl phenylacetate 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

Available; accessed 09/24/21

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, phenethyl phenylacetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Phenethyl phenylacetate 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. Additional assays were considered to fully assess the potential mutagenic and clastogenic effects of the target material.

The mutagenic activity of phenethyl phenylacetate 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 TA1535, TA1537, TA98, TA100, and TA102 were treated with phenethyl phenylacetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2001b). Under the conditions of the study, phenethyl phenylacetate was not mutagenic in the Ames test.

The clastogenic activity of phenethyl phenylacetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with phenethyl phenylacetate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of S9 for 4 and 20 h. Increases in micronucleated cells were observed in the 4-h treatment with metabolic activation; however, these increases were within historical laboratory controls and were considered to be biologically not relevant. Phenethyl phenylacetate did not induce binucleated cells with micronuclei in any other test condition when tested up to the maximum dose in either non-activated or S9-activated test systems

(RIFM, 2016a). Under the conditions of the study, phenethyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, phenethyl phenylacetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/04/21.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for phenethyl phenylacetate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on phenethyl phenylacetate. In a dietary 17-week chronic toxicity study, groups of 10 rats/sex/dose were administered 0, 1000, 2500, or 10000 ppm phenethyl phenylacetate (equivalent to 0, 50, 125, or 500 mg/kg/day) in the diet for 17 weeks. No treatment-related alterations were observed among the treated animals. Thus, the NOAEL was considered to be 10000 ppm or 500 mg/kg/day, the highest dose tested, as per the conversion factor for rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives (Hagan et al., 1967). **Therefore, the phenethyl phenylacetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl phenylacetate NOAEL in mg/kg/day by the total systemic exposure to phenethyl phenylacetate, 500/0.0031, or 161290.**

Additional References: Lehman (1955); Draize et al., 1948; Migally (1979); RIFM, 1980; Ornellas (1965); Bar and Griepentrog, 1967

Literature Search and Risk Assessment Completed On: 01/05/21.

11.1.3. Reproductive toxicity

The MOE for phenethyl phenylacetate is adequate for the developmental toxicity endpoint at the current level of use.

There are no fertility data on phenethyl phenylacetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phenethyl phenylacetate 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 developmental toxicity data on phenethyl phenylacetate. Read-across material benzyl benzoate (CAS # 120-51-4; see Section VI) has sufficient developmental toxicity data. Groups of 21 pregnant Wistar rats were administered diets supplemented with 0.04% and 1% test material, benzyl benzoate. Of the 21 females per group, 14 animals were terminated at day 20, and 7 were retained for a 21-day postpartum phase. For the low-dose group (0.04%), the mean total diet consumption was 153.4 mg/rat, equivalent to 7.7 mg/kg/day benzyl benzoate; and for the high-dose group (1%), the mean total consumption was 3886.7 mg/rat, equivalent to 194.3 mg/kg/day. No treatment-related maternal effects were reported. Fetal abnormalities reported include mandibular defects and the absence of a tongue or a cleft palate in 1 high-dose group fetus, but there was no significant difference in incidence when compared to controls. No effects were apparent in the low-dose treatment group. The visceral observations revealed bilateral heterotaxia in 1 high-dose group fetus, but there was no significance when compared to controls. Other abnormalities reported include dilation of the renal pelvis (seen in 1 fetus in the low-dose group), dilation of the renal pelvis (2 fetuses), and bisection of the apex (1 fetus) observed in the high-dose group. During the postpartum phase, the fetal bodyweight gains were decreased by days 14 and 21 among the treated dams. However, the effect was not dose-dependent. Overall, even with reports of minor abnormalities among treatment groups, but with no significant differences when compared to controls, the study concluded that benzyl benzoate was not teratogenic. Therefore, the NOAEL for developmental toxicity was considered to be 194.3 mg/kg/day, the highest dose tested (Morita et al., 1980). **Therefore, the phenethyl phenylacetate MOE for the developmental toxicity endpoint can be calculated by dividing the benzyl benzoate NOAEL in mg/kg/day by the total systemic exposure to phenethyl phenylacetate, 194.3/0.0031, or 62677.**

In addition, the total systemic exposure to phenethyl phenylacetate (3.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint for a Cramer Class I material at the current level of use.

There are insufficient fertility data on phenethyl phenylacetate or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to phenethyl phenylacetate (3.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint for a Cramer Class I material at the current level of use.

Additional References: Lehman (1955); Draize et al., 1948; Migally (1979); RIFM, 1980; Ornellas (1965).

Literature Search and Risk Assessment Completed On: 02/10/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to benzyl phenylacetate (CAS # 102-16-9), phenethyl phenylacetate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient data are available for phenethyl phenylacetate. Based on the existing data and to benzyl phenylacetate (CAS # 102-16-9; see Section VI), phenethyl phenylacetate is not considered a skin sensitizer. *In silico*, phenethyl phenylacetate is not predicted to be reactive to skin proteins, whereas the read-across material benzyl phenylacetate is predicted to react with skin proteins (OECD Toolbox v4.2; Toxtree v3.1.0), but this prediction was not supported by the *in vitro* and *in vivo* data. The read-across material benzyl phenylacetate was not predicted to be a sensitizer in a direct peptide reactivity assay (DPRA) (ECHA, 2013) and a U-Sens assay (ECHA, 2013), whereas it was predicted to be a sensitizer in a KeratinoSens assay (ECHA, 2013). In an open epicutaneous test, both the target material and the read-across material did not show any skin sensitization reactions in guinea pigs (Klecak, 1985). In a separate confirmatory human maximization test, the target material phenethyl phenylacetate did not induce skin sensitization in 25 subjects (RIFM, 1971a). In a separate human maximization test conducted similarly, the read-across material did not induce skin sensitization in 25 subjects (RIFM, 1971a). Moreover, no sensitization reactions were observed in Confirmation of No Induction in Humans (CNIH) tests with phenethyl phenylacetate when tested at 2%, using petrolatum as the vehicle (RIFM, 1971c; RIFM, 1971b).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/02/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, phenethyl phenylacetate 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 phenylacetate 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 phenylacetate 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: 02/09/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenethyl phenylacetate 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 phenethyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.033 mg/day. This exposure is 42.4 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: The Union of German Candle Manufacturers, 1997

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenethyl phenylacetate 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 phenylacetate was identified as a fragrance material with the 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 phenethyl phenylacetate as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), phenethyl phenylacetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1994: The ready biodegradability of the test material was evaluated in a sealed vessel test according to the OECD 301B method. Biodegradation of 79% was observed after 28 days.

RIFM, 1999a: The ready biodegradability of the test material was determined by the manometric respirometry test following the OECD 301F method. Under the condition of the study, biodegradation of 104% was observed after 28 days.

11.2.1.3. Ecotoxicity. RIFM, 2001a: A *Daphnia magna* immobilization test was conducted according to the OECD 202I method under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 9.1 mg/L.

RIFM, 2016b: An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 values based on nominal test concentration for growth rate and yield were reported to be 2.43 mg/L and 1.27 mg/L, respectively.

RIFM, 2017: An acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value based on geometric mean measured concentration was reported to be 3.65 mg/L.

11.2.1.4. Other available data. Phenethyl phenylacetate has been registered under REACH, with the following additional data available at this time (ECHA, 2013):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 32% was observed after 28 days.

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under static conditions. The 96-h LC50 value based on nominal concentration was reported to be ≥ 7.4–≤15.55 mg/L.

Algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 72-h EC50 value based on nominal test concentration for growth rate was reported to be 13.9 mg/L.

11.2.1.5. 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.8	3.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 1.27 µg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.805			1000000	0.008805	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.493	2.439	0.723	10000	0.0723	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.770	1.240	2.206			Neutral Organics
Tier 3: Measured Data including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	3.65					
Daphnia		9.1				
Algae		1.27		1000	1.27	

Literature Search and Risk Assessment Completed On: 01/13/21.

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 09/31/21.

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 related to this article can be found at https://doi.org/10.1016/j.fct.2021.112711.

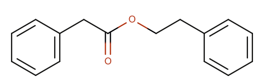
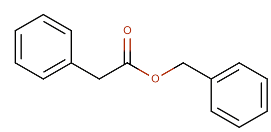
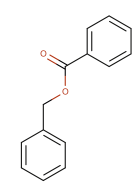
Appendix

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
Principal Name	Phenethyl phenylacetate	Benzyl phenylacetate	Benzyl benzoate
CAS No.	102-20-5	102-16-9	120-51-4
Structure			
Similarity (Tanimoto Score)		0.66	0.41
Endpoint		Skin sensitization	Reproductive toxicity
Molecular Formula	$C_{16}H_{16}O_2$	$C_{15}H_{14}O_2$	$C_{14}H_{12}O_2$
Molecular Weight	240.30	226.28	212.25
Melting Point (°C, EPI Suite)	26.50	80.21	21.00
Boiling Point (°C, EPI Suite)	343.16	330.98	323.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.02	0.01	0.03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5.92	18.53	15.39
Log K_{OW}	4.28	3.79	3.97
J_{max} (μg/cm^2/h, SAM)	0.40	0.93	1.22
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.15	0.12	0.28
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group		Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Toxicant (low reliability)
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 domains 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

Summary

There are insufficient toxicity data on phenethyl phenylacetate (CAS # 102-20-5). Hence *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, benzyl benzoate (CAS # 120-51-4) and benzyl phenylacetate (CAS # 102-16-9) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusion

- Benzyl benzoate (CAS # 120-51-4) was used as a read-across analog for phenethyl phenylacetate (CAS # 102-20-5) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog belong to the structural class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the target material and the read-across analog share an aliphatic chain of different lengths on the acid and alcohol portion. This structural difference between the target material and the read-across analog does not affect consideration of the toxic endpoint.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the toxicity endpoints are consistent between the target material and the read-across analog.
  - o The CAESAR model for developmental toxicity predicts that the read-across analog benzyl benzoate to be toxicant with low reliability, whereas it predicts that target material to be non-toxicant. This suggests that the read-across analog is predicted to have a higher reactivity or toxicity compared to the target material. The ER binding alert is negative for the target material and the read-across analog. The data described in the reproductive toxicity section above shows that the MOE for the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- Benzyl phenylacetate (CAS # 102-16-9) was used as a read-across analog for phenethyl phenylacetate (CAS # 102-20-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the structural class of aromatic esters.
  - o The key difference between the target material and the read-across analog is that the target material and the read-across analog share an aliphatic chain of different lengths on the alcohol portion. This structural difference between the target material and the read-across analog does not affect consideration of the toxic endpoint.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the toxicity endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog benzyl phenylacetate shows several protein binding alerts for the skin sensitization endpoint, which are due to the S_N2 mechanism occurring at the activated carbon. The CAESAR model for skin sensitization predicted the target material to be a sensitizer due to the S_N2 mechanism, whereas it gives an experimental value for the read-across analog showing it to be a sensitizer. The data described in the skin sensitization section shows that the read-across analog poses no concern for the skin sensitization endpoint. Therefore, the alerts will be superseded by the availability of data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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