Food and Chemical Toxicology 161 (2022) 112875

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, phenethyl acetate, CAS Registry Number 103-45-7

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]

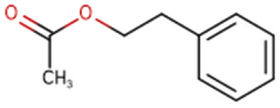
[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA*
[c] *Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 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*

ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 101221. 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 acetate
CAS Registry Number: 103-45-7



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

https://doi.org/10.1016/j.fct.2022.112875
Received 12 October 2021; Received in revised form 21 December 2021; Accepted 15 February 2022
Available online 18 February 2022

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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., 2017; Safford et al., 2015a, 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
p 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.
Phenethyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from phenethyl acetate and read-across analog phenethyl formate (CAS # 104-62-1) show that phenethyl acetate is not expected to be genotoxic. Data on read-across analog benzyl acetate (CAS # 140-11-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for phenethyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; phenethyl acetate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl acetate 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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2002; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 260 mg/kg/day.	NTP (1993)
Reproductive Toxicity: Developmental NOAEL = 100 mg/kg/day. Fertility NOAEL = 460 mg/kg/day.	(Ishiguro, 1993; NTP, 1986)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1985b; RIFM, 1986; RIFM, 1987; RIFM, 1988a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3.	RIFM (2013)

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 89.7% (OECD 301B)	RIFM (1994)
Bioaccumulation:	
Screening-level: 15.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 7.732 mg/L	(ECOSAR; US EPA, 2012b)
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)

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Critical Ecotoxicity Endpoint: 96-h Algae EC50: 7.732 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.7732 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1	

1. Identification

1. **Chemical Name:** Phenethyl acetate
2. **CAS Registry Number:** 103-45-7
3. **Synonyms:** Acetic acid, 2-phenylethyl ester; Benzylcarbinyl acetate; Phenylethyl acetate; 2-Phenylethyl acetate; Methylbenzylacetate; Phenylethyl ethanoate; β-Phenylethyl acetate; ｱﾙｶﾝ酸(C = 1～9)ﾌｪﾆﾙｴﾁﾙ; Phenethyl acetate
4. **Molecular Formula:** $C_{10}H_{12}O_2$
5. **Molecular Weight:** 164.2 g/mol
6. **RIFM Number:** 144
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 232 °C (Fragrance Materials Association [FMA]), 234.31 °C (EPI Suite)
2. **Flash Point:** 101 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 2.4 at 25 °C (RIFM, 1995b), 2.57 (EPI Suite)
4. **Melting Point**: 10.6 °C (EPI Suite)
5. **Water Solubility:** 710.8 mg/L (EPI Suite)
6. **Specific Gravity:** 1.030–1.034 (FMA), 1.05 g/mL (RIFM, 1994), 1.032–1.036 (FMA)
7. **Vapor Pressure:** 0.0442 mm Hg at 20 °C (EPI Suite v4.0), 0.04 mm Hg 20 °C (FMA), 0.0683 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid, powerfully fruity, and an intensely sweet odor of moderate to poor tenacity. Fruity notes resemble cherry, milder, and sweeter, less pungent than benzyl acetate. Sweet fruity taste reminiscent of banana and cherry (Arctander, Volume II, 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 v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.08% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00041 mg/kg/day or 0.030 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0033 mg/kg/day (RIFM, 2018)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer classification

Class I, Low

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

6.2. Analogs selected

a. **Genotoxicity:** Phenethyl formate (CAS # 104-62-1)
b. **Repeated Dose Toxicity:** Benzyl acetate (CAS # 140-11-4)
c. **Reproductive Toxicity:** Benzyl acetate (CAS # 140-11-4)
d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
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

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

Apple brandy (Calvados)	Cocoa category
Blue cheeses	Mentha oils
Cider (apple wine)	Mulberry spirit (Mouro)
Cinnamomum species	Whisky
Cloves (*Eugenia caryophyllata* Thunberg)	Wine

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Available; accessed 06/14/21 (ECHA, 2013).

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 acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 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.

There are no studies assessing the clastogenic activity of phenethyl acetate; however, read-across can be made to phenethyl formate (CAS # 104-62-1; see Section VI).

The clastogenic activity of phenethyl formate 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 formate in DMSO at concentrations up to 1500 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1500 μg/mL in the presence and absence of metabolic activation. Phenethyl formate 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, 2015b). Under the conditions of the study, phenethyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to phenethyl acetate.

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

Additional References: RIFM, 1980; RIFM, 2000b; NTP, 1993; Florin (1980); Mortelmans (1986); Schunk (1986); Tennant (1987); Rogan (1986); Mirsalis (1989); Steinmetz (1984); Mirsalis (1983); Fourman (1994); Matsuoka (1996); Yoshikawa (1996); Miyagawa (1995); Mitchell (1987); Zimmerman (1989); Honma (1999); Kevekordes (1999); Rossman (1991); Kevekordes (2001); Sekihashi (2002); Demir (2010); Scott (2007); Yasunaga (2004); Witt (2000); Sasaki (2000); Oda (1978); Elmore (1990); Longnecker (1990); Galloway (1987); Caspary (1988); Rudd (1983); McGregor (1988).

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenethyl acetate. Read-across material benzyl acetate (CAS # 140-11-4; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. Groups of 10 F344/N rats/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12500, 25000, or 50000 ppm (equivalent to 0, 230, 460, 900, 1750, or 3900 mg/kg/day for males and 0, 240, 480, 930, 1870, or 4500 mg/kg/day for females) for 13 weeks. Mortality was reported among high-dose group animals. Bodyweight gain and final body weights for the males of the 25000-ppm dose group were significantly lower than the control. There was a reduction in food consumption reported among 25000 ppm and 50000 ppm males and the 50000 ppm females; this was attributed to the palatability of the test material and not considered an adverse effect. Tremors and ataxia were reported among high-dose group animals. Test material-related lesions were reported in the brain, kidney, tongue, and skeletal muscles of the thigh. Necrosis of the brain involving the cerebellum and/or the hippocampus, degeneration and regeneration of the renal tubule epithelium, and degeneration and sarcolemma nuclear hyperplasia of the tongue and skeletal muscles were reported in most high-dose animals. There were no alterations reported among animals treated with 12500 ppm or lower dose groups; thus, the NOAEL was considered to be 12500 ppm or 900 mg/kg/day for males and 930 mg/kg/day for females (NTP, 1993). In another study, groups of 10 B6C3F1 mice/sex were fed diets containing benzyl acetate at doses of 0, 3,130, 6250, 12500, 25000, or 50000 ppm (equivalent to 0, 425, 1000, 2000, 3700, or 7900 mg/kg/day for males and 0, 650, 1280, 2980, 4300, or 9400 mg/kg/day for females) for 13 weeks. Mortality was reported among high-dose group animals. Bodyweight gains and final body weights (8%–31% lower among males and 12%–33% lower among females) among treated animals were significantly lower than the control. Feed consumption among males of the 3100-ppm group and all treated females was lower than the control. Alteration in organ weights was reported among treated animals; however, this was attributed to lower body weight in relation to lower food consumption; hence, it was difficult to make comparisons. Tremors were reported among females of the 12500 and higher dose groups. Necrosis of the brain involving the hippocampus was reported among animals of the high-dose groups. Hepatocellular necrosis was reported among one high-dose male, characterized by necrosis of the hepatocytes of moderate severity randomly distributed throughout the hepatic lobules. No other treatment-related alterations were reported among animals of the 6250 ppm or lower dose groups. Due to reduction in body weights and bodyweight gains among all treated animals in conjunction with reduced food consumption, a NOAEL could not be derived from the study conducted on mice (NTP, 1993). Later, a dietary 2-year chronic toxicity study was conducted in F344/N rats. Groups of 60 rats/sex/dose were fed diets containing 0, 3000, 6000, or 12000 ppm benzyl acetate (average daily consumption level of 0, 130, 260, or 510 mg/kg/day for males and 0, 145, 290, or 575 mg/kg/day for females) for 2 years. High-dose males and all exposed females had lower mean body weights than controls. Feed consumption was slightly reduced in high-dose males; there were no differences in feed consumption in females. Food consumption among the high-dose males was lower than in the control. There were no clinical findings reported among treated animals. Thus, the NOAEL for males and females was considered to be 6000 ppm based on lower body weight at higher doses (NTP, 1993). In another study, groups of 60 male and female B6C3F1 mice were fed benzyl acetate in the diet at concentrations of 0, 330, 1000, or 3000 ppm equivalent to 0, 35, 110, or 345 mg/kg/day for males and 0, 40, 130, or 375 for females. The high-dose female mice showed a statistically significant increase in survival. The mean body weights of treated mice were significantly lower (2%–14%) than the controls except for the 330 ppm groups. There was no significant difference in terms of food consumption among treated and control group mice. In the 2-year NTP study with mice, benzyl acetate administration in the food of female and male mice was associated with a dose-related increase in the incidence or severity of non-neoplastic nasal lesions (i.e., mucosal atrophy and degeneration, cystic hyperplasia of the submucosal gland, and luminal exudates and pigmentation of the mucosal epithelium). NTP stated that although the nose was not the deposition site for benzyl acetate, nasal tissue could have been exposed directly to high concentrations of the chemical or its degradation products (NTP, 1993). Thus, it was concluded that there was no evidence of carcinogenic activity among animals treated with benzyl acetate via diet. Overall, the most conservative NOAEL of 6000

ppm or 260 mg/kg/day was considered, derived from the 2-year chronic study conducted on rats.

Therefore, the phenethyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to phenethyl acetate, 260/0.0033 or 78787.

In addition, the total systemic exposure to phenethyl acetate (3.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.3. Reproductive toxicity

The MOE for phenethyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on phenethyl acetate. Read-across material benzyl acetate (CAS # 140-11-4; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

In a developmental toxicity study, groups of 20–22 pregnant rats were gavaged daily from gestation days 6–15 with 0, 10, 100, 500, or 1000 mg/kg/day benzyl acetate in olive oil. Body weights of the live 1000 mg/kg/day male and female fetuses were significantly reduced. The number of fetuses with internal variations (dilation of the renal pelvis and dilation of the lateral ventricle) was significantly increased in the 500 and 1000 mg/kg/day litters. The number of fetuses with skeletal variations (wavy ribs, dumbbell shape of thoracic vertebra body, absence of thoracic vertebra body, splitting of thoracic vertebra body, lumbar ribs, and reduced ossification of cervical vertebra body, caudal vertebra body, and sternebrae) was significantly increased in the 1000 mg/kg/day litters. Within this dose range, benzyl acetate produced a delayed development of the fetuses at 1000 mg/kg/day but did not produce teratogenic effects. Thus, the developmental toxicity NOAEL was considered to be 100 mg/kg/day (Ishiguro, 1993). **Therefore, the phenethyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to phenethyl acetate, 100/0.0033, or 30303.**

In another study, groups of 10 F344/N rats/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12500, 25000, or 50000 ppm (equivalent to 0, 230, 460, 900, 1750, or 3900 mg/kg/day for males and 0, 240, 480, 930, 1870, or 4500 mg/kg/day for females) for 13 weeks. Detailed histopathological evaluations were performed on all control, 25000, and 50000 ppm dose group rats, including the male (preputial, prostate, testis with epididymis and seminal vesicles) and female (ovary, preputial or clitoral glands, and uterus) reproductive organs. The testis and epididymis were evaluated for males of the 6250 and 12500 ppm dose groups as well. Sperm morphology and vaginal cytology were evaluated among all control and treated rats. Results showed mild to moderate aspermatogenesis among the high-dose males and atrophy of the seminiferous tubules among the 12500 and 25000 ppm dose group males. No other test material lesions were reported among the 6250 ppm or lower dose group animals. There were no treatment-related alterations in sperm morphology or estrous cycles reported among treated animals. Thus, the NOAEL for the reproductive toxicity was considered to be 6250 ppm, or 460 mg/kg/day and 480 mg/kg/day for males and females, respectively (NTP, 1993). Groups of 10 B6C3F1 mice/sex were fed diets containing benzyl acetate at doses of 0, 3130, 6250, 12500, 25000, or 50000 ppm (equivalent to 0, 425, 1000, 2000, 3700, or 7900 mg/kg/day for males and 0, 650, 1280, 2980, 4300, or 9400 mg/kg/day for females) for 13 weeks. Detailed histopathological evaluations were performed on all control mice, 25000 ppm females, and all 50000 ppm mice, including the male (preputial, prostate, testis with epididymis and seminal vesicles) and female (ovary, preputial or clitoral glands, and uterus) reproductive organs. Sperm morphology and vaginal cytology were evaluated among all control and treated mice. No treatment-related alterations were reported among the male and female reproductive organs of the treated animals. No chemical-related effects on sperm morphology were reported among treated animals. A significant dose-related decrease in body weight and significant lengthening of the estrous cycle was reported among female mice. The lengthening of the estrous cycle was reported to be related to a significant decrease in body weights (approximately 30%), and food consumption and, hence, was not considered to be an adverse effect. Thus, the NOAEL was considered to be 50000 ppm, or 7900 mg/kg/day and 9400 mg/kg/day for males and females, respectively (NTP, 1993). The most conservative NOAEL of 460 mg/kg/day was considered from the 13-week study conducted on rats for the reproductive toxicity endpoint. **Therefore, the phenethyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the benzyl acetate NOAEL in mg/kg/day by the total systemic exposure to phenethyl acetate, 460/0.0033, or 139393.**

In addition, the total systemic exposure to phenethyl acetate (3.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for phenethyl acetate. Based on the available material-specific data and read-across to benzyl acetate (CAS # 140-11-4; see Section VI), phenethyl acetate 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, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In several guinea pig test methods, no reactions indicative of sensitization were observed with read-across material benzyl acetate (RIFM, 1985a; RIFM, 1986; RIFM, 1985b; RIFM, 1985c. Phenethyl acetate did not result in reactions indicative of skin sensitization in guinea pig tests (Klecak, 1985). Additionally, in human maximization tests, no reactions indicative of sensitization were observed with phenethyl acetate and read-across material benzyl acetate (RIFM, 1970; Greif, 1967). In Confirmation of No Induction in Humans tests (CNIH) of up to 8% (9449 μg/cm^2) of read-across material, benzyl acetate, in 3:1 ethanol:diethylphthalate (EtOH:DEP), no reactions indicative of skin sensitization were observed (RIFM, 1987; RIFM, 1988a; RIFM, 1975a; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e).

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

Additional References: RIFM, 1964; RIFM, 2004d; RIFM, 1961.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra, phenethyl acetate 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 acetate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, phenethyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Local respiratory toxicity

There is insufficient inhalation data available on phenethyl acetate; however, in a 2-week inhalation study for the analog benzyl acetate (CAS # 140-11-4; see Section VI), a NOAEC of 61.4 mg/m^3 was reported (RIFM, 2013).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013). Test substance-related higher levels of lactate dehydrogenase were noted in the bronchoalveolar lavage fluid. Although the authors did not consider these effects as adverse, for the purpose of estimating local respiratory toxicity MOE, a NOAEC of 61.4 mg/m^3 (the mid-dose given) was considered.

This NOAEC expressed in mg/kg lung weight/day is:

- (61.4 mg/m^3)/(1 m^3/1000 L) = 0.0614 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0614 mg/L) × (61.2 L/day) = 3.76 mg/day
- (3.76 mg/day)/(0.0016 kg lung weight of rat*) = 2350 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.030 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 2015a; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.046 mg/kg lung weight/day resulting in a MOE of 51087 (i.e., [2350 mg/kg lung weight/day]/[0.046 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.03 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Rumyantsev (1987); Jager (1992); Buchbauer (1993); Troy (1977); UGCM (1997); Silver (1992); RIFM, 1997; RIFM, 2003a; RIFM, 2003b; Rogers (2003a); RIFM, 2003c; RIFM, 2003d; RIFM, 2004b; RIFM, 2004c; RIFM, 2004a; Isola (2004a); Rogers (2005); RIFM, 2014; Vethanayagam (2013).

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenethyl acetate 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, phenethyl acetate 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 acetate 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, 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.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1994:** The ready biodegradability of phenethyl acetate was determined using the sealed vessel test following the OECD 301B method. Medium inoculated with filtered secondary effluent and 10 mg/L of phenethyl acetate was incubated in sealed vessels for 28 days. The biodegradation rate at the end of 28 days was 89.7%.

RIFM, 1995a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. 100 mg/L of the test material was incubated for 28 days. Biodegradation of 72% was observed.

11.2.2.1.2. Ecotoxicity. **RIFM, 2000a:** An acute *Daphnia magna* toxicity test was conducted under static conditions following the OECD 202 method. The EC50 was calculated as a geometric mean of the

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	99.39			1000000	0.09939	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	10.17	19.89	7.732	10000	0.773	Esters
ECOSAR Acute Endpoints **(Tier 2)** v1.11	41.33	24.74	22.92			Neutral Organics SAR (baseline toxicity)

EC0/EC100 values and was reported to be 36.6 mg/L.

11.2.2.1.3. Other available data. Phenethyl acetate has been registered under REACH, and the following additional data is available (ECHA, 2013):

A 72-h algal growth inhibition test was carried out in accordance with OECD 201 under static conditions. Results were based on time-weighted average concentrations. The EC50s of 40 mg/L and 13 mg/L for growth rate and biomass, respectively, were reported.

11.2.3. Risk assessment refinement

Since phenethyl acetate has passed the screening criteria, the measured ecotoxicity data is included in this document for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.4	2.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	10–100
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 0.773 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.

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

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/12/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112875.

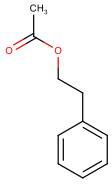
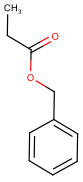
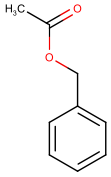
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 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, 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 acetate	Phenethyl formate	Benzyl acetate
CAS No.	103-45-7	104-62-1	140-11-4
Structure			
Similarity (Tanimoto Score)		0.68	0.41
Endpoint		• Genotoxicity	• Skin sensitization • Repeated dose toxicity • Reproductive toxicity • Local respiratory toxicity
Molecular Formula	$C_{10}H_{12}O_2$	$C_9H_{10}O_2$	$C_9H_{10}O_2$
Molecular Weight (g/mol)	164.204	150.177	150.177
Melting Point (°C, EPI Suite)	−31.10	8.20	−51.30
Boiling Point (°C, EPI Suite)	232.60	217.34	213.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.19E+00	2.00E+01	2.36E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.11E+02	1.41E+03	3.10E+03
Log KOW	2.3	2.02	1.96
J_{max} (μg/cm^2/h, SAM)	17.66	32.07	64.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.90E+00	2.60E+00	1.14E+00
Genotoxicity			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	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	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Aldehyde Type Compounds	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Pethidine (Hepatotoxicity) Alert|Toluene (Renal toxicity) Alert		Menadione (Hepatotoxicity) Alert| Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group		Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		Toxicant (moderate reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		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)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom| SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		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)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		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)	Alert for Acyl Transfer agent 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

Phenethyl acetate (CAS # 103-45-7) lacks toxicity data for the genotoxicity, repeated dose toxicity, reproductive toxicity, skin sensitization, and local respiratory toxicity endpoints. 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, phenethyl formate (CAS # 104-62-1) and benzyl acetate (CAS # 140-11-4) were identified as read-across analogs for their respective toxicity endpoints.

Conclusions

- Phenethyl formate (CAS # 104-62-1) was used as a read-across analog for the target material phenethyl acetate (CAS # 103-45-7) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of benzylic esters.
  - o The target material and the read-across analog have a phenethyl alochol fragment common among them.
  - o The key difference between the target material and the read-across analog is that the target material is an acetate of phenethyl alcohol while the read-across analog is a formate of phenethyl alcohol. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal potential for toxicity as compared to the target.
  - 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 and the read-across analog have an alert for Michael addition and quinone formation. This is due to the presence of a benzene ring in the structure, which can undergo epoxidation and quinone formation. The data for the read-across analog confirms that the analog does

not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the alerts are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the 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 phenethyl acetate (CAS # 103-45-7) for the skin sensitization, repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of benzylic esters.
  - The key difference between the target material and the read-across analog is that the target material is an ester of phenethyl alcohol while the read-across analog is an ester of benzyl alcohol. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 a 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.
  - The target material and the read-across analog have an alert SN2 reaction. This is due to the presence of a benzene ring in the structure, which can undergo epoxidation and quinone formation. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the alerts are superseded by the data.
  - The target material and the read-across analog have menadione hepatotoxicity and toluene renal toxicity alerts. They also have been predicted by the CAESAR model to be toxicants. These alerts are due to benzylic alcohol and the reactivity of the aromatic ring. The data on the read-across analog confirms that it does not pose a concern for any of these endpoints at the current levels of use. 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* alerts are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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