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RIFM fragrance ingredient safety assessment, phenethyl benzoate, CAS Registry Number 94-47-3

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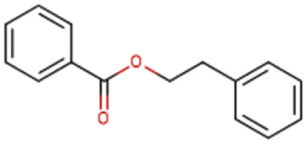

Name: Phenethyl benzoate CAS Registry Number: 94-47-3

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Abbreviation/Definition List:

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

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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)
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; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Phenethyl benzoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenethyl benzoate is not genotoxic. Data on read-across analogs phenethyl phenylacetate (CAS # 102-20-5) and benzyl benzoate (CAS # 120-51-4) provide a calculated MOE >100 for the repeated dose and developmental toxicity endpoints, respectively. The fertility endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). Data and read-across to benzyl benzoate (CAS # 120-51-4) provide phenethyl benzoate a NESIL of 59000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV/Vis spectra; phenethyl benzoate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analogs phenethyl alcohol (CAS # 60-12-8) and benzoic acid (CAS # 65-85-0). The environmental endpoints were evaluated; phenethyl benzoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2016a; RIFM, 2016b)
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: NESIL = 59000 μg/cm^2.	(RIFM, 2005; RIFM, 1970; Gerberick et al., 2005; RIFM, 2004)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1974b)
Local Respiratory Toxicity: NOAEC = 2.5 mg/m^3 (benzoic acid) and 5 mg/m^3 (phenethyl alcohol).	(ECHA REACH Dossier: Benzoic acid; ECHA, 2011; RIFM, 2013a)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 2.8 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 205 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 5.23 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5.23 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.005230.005554 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Phenethyl benzoate
2. **CAS Registry Number:** 94-47-3
3. **Synonyms:** Benzoic acid, 2-phenylethyl ester; Benzylcarbinyl benzoate; Phenylethyl benzoate; 2-Phenylethyl benzoate; 安息香酸フェニルアルキル(C = 2–3); Phenethyl benzoate
4. **Molecular Formula:** $C_{15}H_{14}O_2$
5. **Molecular Weight:** 226.27 g/mol
6. **RIFM Number:** 514
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 330.98 °C (EPI Suite)
2. **Flash Point:** >200 °F; CC (FMA)
3. **Log K_{OW}:** 4.03 (EPI Suite)
4. **Melting Point**: 80.21 °C (EPI Suite)
5. **Water Solubility:** 11.99 mg/L (EPI Suite)

6. **Specific Gravity**: 1.090 (FMA)
7. **Vapor Pressure:** 0.0000563 mm Hg at 20 °C (EPI Suite v4.0), 0.00011 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.18% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.00023 mg/kg/day or 0.018 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.0052 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (RIFM, 2015; 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

6.1. Cramer Classification

Class I, Low* (Expert Judgment)

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

*See the Appendix below for further details.

6.2. Analogs Selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** Phenethyl phenylacetate (CAS # 102-20-5)
c. **Reproductive Toxicity:** Benzyl benzoate (CAS # 120-51-4)
d. **Skin Sensitization:** Benzyl benzoate (CAS # 120-51-4)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and benzoic acid (CAS # 65-85-0)
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

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

Cinnamomum species	*Syzygium* species
Sea buckthorn (*Hippophaë rhamnoides L.*)	*Vaccinium* species

*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 11/12/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for phenethyl benzoate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.00011
2	Products applied to the axillae	1.4
3	Products applied to the face/body using fingertips	3.1
4	Products related to fine fragrances	25
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	6.4
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	1.7
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	3.5
5D	Baby cream, oil, talc	0.58
6	Products with oral and lip exposure	0.00011
7	Products applied to the hair with some hand contact	3.4
8	Products with significant ano-genital exposure (tampon)	0.58
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.2
10B	Aerosol air freshener	12
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.58
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For

phenethyl benzoate, the basis was the reference dose of 1.94 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 59000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human Health Endpoint Summaries

11.1.1. Genotoxicity

Based on the current existing data, phenethyl benzoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Phenethyl benzoate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic and clastogenic effects of the target material.

The mutagenic activity of phenethyl benzoate 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 methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with phenethyl benzoate 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, 2016a). Under the conditions of the study, phenethyl benzoate was not mutagenic in the Ames test.

The clastogenic activity of phenethyl benzoate 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 benzoate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of S9 for 4 and 24 h. Phenethyl benzoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016b). Under the conditions of the study, phenethyl benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/27/21.

11.2. Repeated dose toxicity

The MOE for phenethyl benzoate 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 benzoate. Read-across material phenethyl phenylacetate (CAS # 102-20-5; see Section VI), has a dietary 17-week chronic toxicity study in rats. 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. Body weight, food intake, and general condition were recorded weekly. Hematological examinations, including white cell counts, red cell counts, hemoglobin, and hematocrits, were conducted at the termination of the study. On completion of the study, all surviving animals were euthanized and examined macroscopically. Organ weights were recorded, and tissues were preserved for histopathologic examination. Detailed microscopic examinations were done on 6 or 8 animals evenly divided by sex in the control and high-dose groups. No test material-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 benzoate 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 benzoate, 500/0.0052, or 96153.**

In addition, the total systemic exposure to phenethyl benzoate (5.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity 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: 01/05/21.

11.1.3. Reproductive toxicity

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

There are no fertility data on phenethyl benzoate or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to phenethyl benzoate 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 benzoate. 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 test material-related maternal effects were reported. Fetal abnormalities reported included mandibular defects and the absence of a tongue or a cleft palate in one high-dose group fetus, but there was no significant difference in incidence when compared to controls. No effects were apparent in the low-dose group. The visceral observations revealed bilateral heterotaxia in one high-dose group fetus, but there was no significance when compared to controls. Other abnormalities reported included dilation of the renal pelvis (seen in one fetus in the low-dose group), dilation of the renal pelvis (2 fetuses), and bisection of the apex (one fetus) observed in the high-dose group. During the postpartum phase, pup bodyweight gains were decreased by day 14 and day 21; 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 benzoate 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 benzoate 194.3/0.0052, or 37365.**

In addition, the total systemic exposure to phenethyl benzoate (5.2 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 benzoate or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to phenethyl benzoate (5.2 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.

11.1.3.2. Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose (RfD) of 1.94 mg/kg/day

11.1.3.2.1. Derivation of RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for phenethyl benzoate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 194.3 mg/kg/day by the uncertainty factor, 100 = 1.94 mg/kg/day.

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 benzoate (CAS # 120-51-4), phenethyl benzoate is considered a weak sensitizer with a defined NESIL of 59000 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient data are available for phenethyl benzoate. Based on the existing data and read-across material benzyl benzoate (CAS # 120-51-4; see Section VI), phenethyl benzoate is a skin sensitizer. Phenethyl benzoate is not predicted to react directly with skin proteins, whereas the read-across benzyl benzoate is predicted to react with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). Benzyl benzoate was predicted to be a sensitizer in a KeratinoSens assay and a U-Sens assay, while it was not predicted to be a sensitizer in a direct peptide reactivity (DPRA) assay and human cell line activation test (h-CLAT) (Natsch et al., 2013; Piroird et al., 2015; Otsubo et al., 2017). In a murine local lymph node assay (LLNA), benzyl benzoate was found to be non-sensitizing up to 50% (12,500 μg/cm^2) in 1:3 ethanol:diethyl phthalate (EtOH:DEP) (RIFM, 2005). In another LLNA, benzyl benzoate was found to be sensitizing with an EC3 value of 17% (4250 μg/cm^2) in acetone:olive oil 1:4 (AOO) (Gerberick et al., 2005). In a Confirmation of No Induction in Human test (CNIH) with 59050 μg/cm^2 of benzyl benzoate in 1:3 EtOH:DEP, no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2004). Furthermore, in a confirmatory human maximization test, no skin sensitization reactions were observed with the target or read-across material (RIFM, 1974a; RIFM, 1970).

Based on weight of evidence (WoE) from structural analysis and animal and human studies of the read-across benzyl benzoate, phenethyl benzoate is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 59000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a reference dose of 1.94 mg/kg/day.

Additional References: RIFM, 1979; Hausen et al., 1992; Hausen et al., 1995; Klecak (1985); Ishihara et al., 1986; Gerberick et al., 2004; Natsch and Gfeller, 2008; Natsch et al., 2007.

Literature Search and Risk Assessment Completed On: 02/03/21.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. 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). In the available *in vivo* phototoxicity study, hairless mice and miniature swine did not demonstrate reactions to topical application of undiluted phenethyl benzoate; the material was not considered phototoxic (RIFM, 1974b). Based on the *in vivo* study data and the lack of absorbance in the critical range, phenethyl benzoate 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

There are no inhalation data available on phenethyl benzoate; however, the target material can undergo ester hydrolysis to form benzoic acid and phenethyl alcohol (CAS # 65-85-0 and CAS # 60-12-8; see Section VI). A NOAEC of 2.5 mg/m^3 was identified for benzoic acid (ECHA, 2011) and a NOAEC of 5 mg/m^3 was identified for phenethyl alcohol (RIFM, 2013a) based on the inhalation exposures in rats.

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 acute inhalation study conducted in rats, a NOAEC of 5.0 mg/m^3 was reported for phenethyl alcohol (RIFM, 2013a). Histopathology revealed effects limited to mucous secretions in the nasal cavity. Nasal levels II through VI in the 50 mg/m3 group males, level VI in the 0.5 mg/m3 group males, levels IV and V in all test material-exposed female groups, and level VI in the 5 and 50 mg/m3 group females exhibited luminal secretions consistent with mucous. The changes were more commonly observed in the caudal nasal sections (V and VI) of the nasal cavity. They were also observed in the control groups. Mild histiocytic (mononuclear) infiltrates in the lungs

Table 1
Data Summary for Benzyl Benzoate as read-across for phenethyl benzoate.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] μg/cm^2
>12,500 [1]; 4250 [1]	Weak	59050	20,690	NA	59000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

were noted in the 50 mg/m3 group females, but not in the control animals. As such, the NOAEC for local respiratory effects was observed at 5 mg/m^3.

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

- (5 mg/m^3) × (1 m^3/1000 L) = 0.0050 mg/L
- Minute ventilation (MV) 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
- (0.0050 mg/L) × (61.2 L/d) = 0.306 mg/day
- (0.306 mg/day)/(0.0016 kg lung weight of rat*) = 191.3 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.018 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 2015 and Safford et al., 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 et al., 2009) to give 0.028 mg/kg lung weight/day resulting in a MOE of 683 (i.e., [191.3 mg/kg lung weight/day]/[0.028 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 0.018 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

In a 28-day OECD 412, GLP-compliant study, Sprague Dawley CD rats (10/sex/dose) were exposed to benzoic acid at concentrations of 0, 25, 250, or 1200 mg/m^3 for 6 h/day, 5 days/week, through whole-body inhalation exposure for 4 weeks (ECHA, 2011). Standard endpoints evaluated included clinical signs, body weight, serum biochemistry, hematology, organ weight, necropsy (heart, kidney, lungs/trachea, brain, liver, and spleen), and histopathological examination. Treatment-related but not dose-dependent microscopic lesions were reported in the lungs of animals from the low-, mid-, and high-dose groups, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the 250 mg/m^3 dose, upper respiratory tract irritation was observed, which was confirmed by inflammatory exudate around the nares. Additionally, at the 250 mg/m^3 dose, decreased relative weight of trachea with lungs (females) were reported. The effects observed in the mid-dose of 250 mg/m^3 were confined to local effects observed in the respiratory tract. Based on the observations in the lungs, the local effects LOAEC was identified at 25 mg/m^3. Using a safety factor of 10, the estimated NOAEC is 2.5 mg/m^3.

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

- (2.5 mg/m^3) × (1 m^3/1000 L) = 0.0025 mg/L
- MV 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
- (0.0025 mg/L) × (61.2 L/d) = 0.153 mg/day
- (0.153 mg/day)/(0.0016 kg lung weight of rat*) = 95.63 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.018 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (RIFM, 2015 and Safford et al., 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 et al., 2009) to give 0.028 mg/kg lung weight/day resulting in a MOE of 3415.4 (i.e., [95.63 mg/kg lung weight of rat/-day]/[0.028 mg/kg lung weight of human/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 0.018 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: None.

Literature Search and Risk Assessment Completed On: 02/08/21.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenethyl benzoate 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 benzoate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify phenethyl benzoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

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

11.2.2.1. Key studies. **Biodegradation:**

No data available.

Ecotoxicity:

No data available.

Other available data:

Phenethyl benzoate has been registered for REACH with the

following additional data available at this time (ECHA, 2017a):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 47.36% was observed after 35 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 test concentration was reported to be 6.25 mg/L.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.03	4.03
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.005230.005554 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 01/12/21.

*11.3. 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 11/12/21.

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112924.

Appendix

Read-across Justification

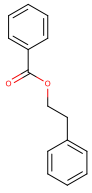
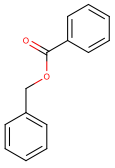
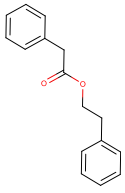
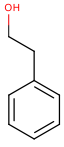
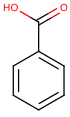
Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.23			1000000	0.00523	

Chemical Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Phenethyl benzoate	Benzyl benzoate	Phenethyl phenylacetate	Phenethyl alcohol	Benzoic acid
CAS No.	94-47-3	120-51-4	102-20-5	60-12-8	65-85-0
Structure					
Similarity (Tanimoto Score)		0.60	0.63	0.41	0.48
Endpoint		• Skin sensitization • Developmental toxicity	• Repeated dose toxicity	• Local Respiratory toxicity	• Local Respiratory toxicity
Molecular Formula	$C_{15}H_{14}O_2$	$C_{14}H_{12}O_2$	$C_{16}H_{16}O_2$	$C_8H_{10}O$	$C_7H_6O_2$
Molecular Weight (g/mol)	226.275	212.248	240.302	122.167	122.123
Melting Point (°C, EPI Suite)	80.21	21.00	26.50	−27.00	122.40
Boiling Point (°C, EPI Suite)	330.98	323.50	343.16	218.20	249.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.47E-02	2.99E-02	2.48E-02	1.16E+01	9.33E-02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.20E+01	1.54E+01	5.92E+00	2.22E+04	3.40E+03
Log KOW	4.01	3.97	4.28	1.36	1.87
J_{max} (μg/cm^2/h, SAM)	0.78	1.22	0.40	355.17	120.94
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.77E-01	2.84E-01	1.54E-01	2.59E-02	3.86E-03
Repeated Dose Toxicity					
Repeated Dose (HESS)	2-Amino-4,5-diphenyl thiazole (Renal toxicity) Alert|Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert|Anthraquinone (Renal toxicity) Alert|Carbamazepine (Hepatotoxicity) Alert|Carbamazepine (Renal Toxicity) Alert|Phenytoin (Hepatotoxicity) Alert|Propanolol (Renal toxicity) Alert|Tamoxifen (Hepatotoxicity) Alert		Anthraquinone (Renal toxicity) Alert|Carbamazepine (Hepatotoxicity) Alert|Carbamazepine (Renal Toxicity) Alert|Diclofenac (Hepatotoxicity) Alert|Phenytoin (Hepatotoxicity) Alert|Tamoxifen (Hepatotoxicity) Alert		
Developmental 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 (moderate reliability)	Toxicant (low reliability)			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
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	N/A	N/A

Summary

There are insufficient toxicity data on the target material phenethyl benzoate (CAS 94-47-3). 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, benzyl benzoate (CAS # 120-51-4), phenethyl phenylacetate (CAS # 102-20-5), phenethyl alcohol (CAS # 60-12-8), and benzoic acid (CAS # 65-85-0) were identified as read-across materials with data for their respective toxicity endpoints.

Metabolism

Metabolism of the target material was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to phenethyl alcohol (CAS # 60-12-8) and benzoic acid (CAS # 65-85-0) in the first step with a 0.95% probability. Hence, phenethyl alcohol (CAS # 60-12-8) and benzoic acid (CAS # 65-85-0) can be used as read-across analogs for the target material. Phenethyl alcohol (CAS # 60-12-8) and benzoic acid (CAS # 65-85-0) were out of domain for the *in vivo* rat and *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification was provided.

Conclusion

- Benzyl benzoate (CAS # 120-51-4) was used as a read-across analog for the target material phenethyl benzoate (CAS # 94-47-3) for the skin sensitization and developmental toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of phenyl esters.
  - The key difference between the target material and the read-across analog is that the target material is an ester of phenethyl alcohol, whereas 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 an equal or greater potential for toxicity as compared to the target material.
  - 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 read-across analog and the target material have an alert for an SN2 reaction. This alert is due to the fact that the materials possess a carbonyl group. The data on the read-across analog confirm that the material does not pose a concern for skin sensitization endpoint. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the *in silico* alerts are superseded by the data.
  - The read-across analog has an alert of toxicant by the CAESAR model. The data on the read-across analog confirms that the MOE for phenethyl benzoate is adequate for the developmental toxicity endpoint at the current level of use. Therefore, *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.
- Phenethyl phenylacetate (CAS # 102-20-5) was used as a read-across analog for the target material phenethyl benzoate (CAS # 94-47-3) for the repeated dose toxicity endpoint.
  - The target material and the read-across analog belong to a class of phenyl esters.

- The key difference between the target material and the read-across analog is that the target material is a benzoate ester whereas the read-across analog is a phenylacetate ester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
- 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 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.

- Read-across alcohol phenethyl alcohol (CAS # 60-12-8) and read-across acid benzoic acid (CAS # 65-85-0) were used as read-across analogs for the target ester phenethyl benzoate (CAS 94-47-3) for the local respiratory toxicity endpoint.
  - The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

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

Q1. A normal constituent of the body? **No**
Q2. Contains functional groups associated with enhanced toxicity? **No**
Q3. Contains elements other than C, H, O, N, and divalent S? **No**
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? **No**
Q6. Benzene derivative with certain substituents? **No**
Q7. Heterocyclic? **No**
Q17. Readily hydrolyzed to a common terpene? **No**
Q19. Open-chain? **No**
Q23. Aromatic? **Yes**
Q27. Rings with substituents? **Yes**
Q28. More than one aromatic ring? **Yes**
Q29. Readily hydrolyzed? **Yes**
Q30. Aromatic ring with complex substituents? **No**
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **No Class Low (Class I)**

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

Draize, J.H., Alvarez, E., Whitesell, M.F., Woodard, G., Hagan, E.C., Nelson, A.A., 1948. Toxicological investigations of compounds proposed for use as insect repellents. J. Pharmacol. Exp. Therapeut. 93 (1), 26–39.

ECHA, 2011. Benzoic Acid Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/13124/1/2.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017a. Phenethyl Benzoate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/19730.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Gerberick, G.F., Ryan, C.A., Kern, P.S., Schlatter, H., Dearman, R.J., Kimber, I., Patlewicz, G.Y., Basketter, D.A., 2005. Compilation of historical local lymph node data for evaluation of skin sensitization alternative methods. Dermatitis 16 (4), 157–202.

Gerberick, G.F., Vassallo, J.D., Bailey, R.E., Chaney, J.G., Morrall, S.W., Lepoittevin, J.-P., 2004. Development of a peptide reactivity assay for screening contact allergens. Toxicol. Sci. 81 (2), 332–343.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.

Hausen, B.M., Evers, P., Stuwe, H.-T., Konig, W.A., Wollenweber, E., 1992. Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. Contact Dermatitis 26 (1), 34–44.
Hausen, B.M., Simatupang, T., Bruhn, G., Evers, P., Koening, W.A., 1995. Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in Balsam of Peru. Am. J. Contact Dermatitis 6 (4), 199–208.
Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.
IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Res. 28 (Suppl. 2), 230–240.
Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. In: Curr. Probl. Dermatol., 14, pp. 152–171.
Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.
Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.
Lehman, A.J., 1955. Insect repellents. Assoc. Food Drug Off. United States 19 (2), 87–99.
Migally, N., 1979. Effect of castor oil and benzyl benzoate used as a vehicle for antiandrogens on the adrenal cortex. Arch. Androl. 2 (4), 365–369.
Morita, S., Yamada, A., Ohgaki, S., Noda, T., Taniguchi, S., 1980. Safety evaluation of chemicals for use in household products. I. Teratological studies on benzyl benzoate and 2-(morpholinothio) benzothiazole in rats. In: Annual Report Osaka City Inst. Public Health Environment Sci., 43, pp. 90–97.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.
Natsch, A., Gfeller, H., 2008. LC-MS-Based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitization potential. Toxicol. Sci. 106 (2), 464–478.
Natsch, A., Gfeller, H., Rothaupt, M., Ellis, G., 2007. Utility and limitations of a peptide reactivity assay to predict fragrance allergens in vitro. Toxicol. Vitro 21 (7), 1220–1226.
Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J. Appl. Toxicol. 33 (11), 1337–1352.
OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Ornellas, M.R., 1965. Chemotherapeutic activitty of benzyl benzoate. Bull. Cancer 52 (4), 371–378.
Otsubo, Y., Nishijo, T., Miyazawa, M., Saito, K., Mizumachi, H., Sakaguchi, H., 2017. Binary test battery with KeratinoSens™ and h-CLAT as part of a bottom-up approach for skin sensitization hazard prediction. Regul. Toxicol. Pharmacol. 88, 118–124.
Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. Vitro 29 (5), 901–916.
RIFM (Research Institute for Fragrance Materials, Inc), 1970. The Contact Sensitizing Potential of Fragrance Materials in Humans. Report to RIFM. RIFM Report Number 1760. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1974a. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1974b. Phototoxicity and Irritation Test of Fragrance Materials in the Mouse and Miniature Swine. Report to RIFM. RIFM Report Number 2037. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1979. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1697. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 1980. 30-Day Dermal Toxicity Study of Benzyl Benzoate in Rats. Report to RIFM. RIFM Report Number 4000. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2004. Repeated Insult Patch Test with Benzyl Benzoate. RIFM Report Number 47159. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2005. Benzyl Benzoate Diluted with Vehicle 1:3 ETOH:DEP: Local Lymph Node Assay. RIFM Report Number 47377. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013a. A Two-Week Inhalation Toxicity Study of Aerosolized Phenyl Ethyl Alcohol in the Sprague Dawley Rat. RIFM Report Number 65461. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Report on the Testing of Phenethyl Benzoate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66185. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2015. Novel Database for Exposure to Fragrance Ingredients in Cosmetics and Personal Care Products. RIFM Report Number 68681. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016a. Phenethyl Benzoate: Reverse Mutation Assay 'Ames Test' Using Salmonella typhimurium and Escherichia coli. RIFM Report Number 71131. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2016b. Phenethyl Benzoate: Micronucleus Test in Human Lymphocytes in Vitro. RIFM Report Number 71132. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey 23, January 2019.
RIFM (Research Institute for Fragrance Materials, Inc), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc), 2020b. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM Report Number 76775. RIFM, Woodcliff Lake, NJ, USA.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.