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Short Review

RIFM fragrance ingredient safety assessment, benzyl benzoate, CAS Registry Number 120-51-4

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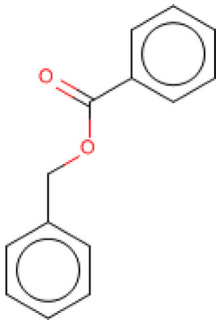
Version: 120619. This version replaces any previous versions.
Name: Benzyl benzoate
CAS Registry Number: 120-51-4



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 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
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 Observable 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

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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
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.

Benzyl benzoate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data from read-across analog phenethyl benzoate (CAS # 94-47-3) show that benzyl benzoate is not expected to be genotoxic. Data on analog phenethyl phenylacetate (CAS # 102-20-5) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on benzyl benzoate provide a calculated MOE > 100 for the reproductive toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 59000 μg/cm^2 for the skin sensitization endpoint. The developmental toxicity and local respiratory toxicity endpoints were completed using the threshold of toxicological concern (TTC) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively); exposure is below the TTC. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; benzyl benzoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; benzyl 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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (Florin et al., 1980; RIFM, 2016a; RIFM, 2016b)

Repeated Dose Toxicity: NOAEL = 500 mg/kg/day. (Hagan et al., 1967)

Developmental and Reproductive Toxicity:

Developmental toxicity NOAEL = 194.3 mg/kg/day. No NOAEL available for reproductive toxicity; exposure is below the TTC. (Morita et al., 1980)

Skin Sensitization: NESIL = 59000 μg/cm^2. (RIFM, 2005; RIFM, 1970; RIFM, 2004)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM Database; RIFM, 1981)

Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 93% (OECD 301B) (RIFM, 1994)

Bioaccumulation: Screening-level: 193.4 L/kg (EPI Suite v4.11; US ECHA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 72-h Algae NOEC (growth rate): 0.247 mg/L (RIFM, 2003b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 72-hr Algae NOEC (growth rate): 0.247 mg/L (RIFM, 2003b)

RIFM PNEC is: 4.94 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** Benzyl benzoate
2. **CAS Registry Number**: 120-51-4
3. **Synonyms**: Benzoic acid, phenylmethyl ester; Benzyl phenylformate; Benylate; Benzoic acid, benzyl ester; Phenylmethyl benzoate; 安息香酸ベンジル; Benzyl benzoate
4. **Molecular Formula:** $C_{14}H_{12}O_2$
5. **Molecular Weight**: 212.25
6. **RIFM Number**: 108

2. Physical data

1. **Boiling Point:** 323 °C (FMA Database), (calculated) 317.89 °C (US EPA, 2012)
2. **Flash Point:** > 212 °F; CC (FMA Database)
3. **Log K_{OW}:** 3.54 (US EPA, 2012)
4. **Melting Point**: 70.75 °C (US EPA, 2012)
5. **Water Solubility:** 15.3 mg/L at 20 ± 0.5 °C (RIFM, 1992b), (calculated) 15.39 mg/L (US EPA, 2012)
6. **Specific Gravity:** 1.118–1.122 (FMA Database), 1.116–1.120 (FMA Database)
7. **Vapor Pressure:** < 0.001 mm Hg 20 °C (FMA Database), (calculated) 0.000328 mm Hg @ 20 °C (US EPA, 2012), (calculated) 0.000555 mm Hg @ 25 °C (US EPA, 2012)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to very pale yellow liquid having a slight aromatic odor

3. Exposure

1. **Volume of Use (worldwide band):** > 1000 metric tons per year	IFRA (2015)
2. **95th Percentile Concentration in Fine Fragrances**: 0.62%	RIFM (2019)
3. **Inhalation Exposure*:** 0.012 mg/kg/day or 0.88 mg/day	RIFM (2019)
4. **Total Systemic Exposure**:** 0.022 mg/kg/day	RIFM (2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

4. Derivation of systemic absorption

1. **Dermal:** 71.2%

Bronaugh (1990): The skin absorption of [7–^{14}C] benzyl benzoate was measured in 4 female rhesus monkeys. The test material in acetone was applied at a concentration of 4 μg/cm^2 to a 1-cm^2 area of abdominal skin for 24 h. Urine was collected for an additional 4 days. The extent of dermal absorption was estimated from the amount of ^{14}C-equivalents excreted in the urine over the 5-day collection period. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl benzoate was 71.2% ± 4.4% and 64.7% ± 10.2%, respectively. When the site was not occluded, the absorption was 57.0% ± 10.4%. The most conservative dermal absorption of 71.2% was considered for the safety assessment of benzyl benzoate.

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (see Table 1)
2. **Analogs Selected**:
   a. **Genotoxicity:** Phenethyl benzoate (CAS # 94-47-3)
   b. **Repeated Dose Toxicity:** Phenethyl phenylacetate (CAS # 102-20-5)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Benzyl benzoate is reported to occur in the following foods by the VCF* and in some natural complex substances:

Babaco fruit (*Carica pentagona* Heilborn)Buckwheat Chamomile Celery (*Apium graveolens* L.) *Cinnamomum* species Cloudberry (*Rubus chamaemorus* L.) Cloves (*Eugenia caryophyllata* Thunberg) Endive (*Cichorium endivia* L.) Guava and feyoa Guava wine Hog plum (*Spondias mombins* L.) Maize (*Zea mays* L.) Mastic (*Pistacia lentiscus*) Milk and milk products Papaya (*Carica papaya* L.) Parsley (*Petroselium* species) Passion fruit (*Passiflora* species) Sea buckthorn (*Hippophae rhamnoides* L.) Tapereba, caja fruit (*Spondias lutea* L.) Tea Turpentine oil (*Pistacia terebinthus*) *Vaccinium* species Vanilla.

*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.

Table 1
Cramer classification.

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

8. REACH dossier

Available; accessed 08/27/13 (ECHA, 2013).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for benzyl benzoate are detailed below (Table 2).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, benzyl benzoate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of benzyl benzoate was assessed in an Ames study conducted using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with benzyl benzoate in ethanol at the concentration of 3 μmol/plate in the presence and absence of metabolic activation (S9). No significant increases in the numbers of revertant colonies were observed (Florin, 1980). Under the conditions of the study, benzyl benzoate was considered not mutagenic in the Ames test. Additional weight of evidence was used since this study does not strictly follow the current OECD 471 test guidelines. The read-across material phenethyl benzoate (CAS # 94-47-3) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (OECD, 1997) 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 significant 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.

There are no studies assessing the clastogenic activity of benzyl benzoate. However, read-across can be made to phenethyl benzoate (CAS # 94-47-3; see Section V). 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 (OECD, 2010). Human peripheral blood lymphocytes were treated with phenethyl benzoate in DMSO at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Phenethyl benzoate did not induce binucleated cells with micronuclei when tested up to the maximum allowed concentration by cytotoxicity or precipitation of the test material 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 available data, benzyl benzoate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/14/17.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on benzyl benzoate. Read-across material, phenethyl phenylacetate (CAS # 102-20-5; see Section V) has a dietary 17-week chronic toxicity study in rats. Groups of 10 rats/sex/dose were administered 0, 1000, 2500, or

Table 2
Maximum acceptable concentrations in finished products.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	1.7
2	Products applied to the axillae	1.4
3	Products applied to the face/body using fingertips	0.41
4	Products related to fine fragrances	4.8
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	4.3
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.21
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.83
5D	Baby cream, oil, talc	0.070
6	Products with oral and lip exposure	0.41
7	Products applied to the hair with some hand contact	0.41
8	Products with significant ano-genital exposure (tampon)	0.070
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.9
10B	Aerosol air freshener	12
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.070
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 benzyl benzoate, the basis was the reference dose of 1.943 mg/kg/day, a skin absorption value of 71.2%, and a skin sensitization NESIL of 59000 μg/cm^2.
[b] For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10000 ppm phenethyl phenylacetate (equivalent to 0, 50, 125, or 500 mg/kg/day) in the diet for 17 weeks. No treatment-related alterations were observed among the treated animals. 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, 1967). Therefore, the benzyl 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 benzyl benzoate, 500/0.022 or 22727.

When correcting for skin absorption (see Section IV), the total systemic exposure to benzyl benzoate (22 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: 03/16/20.

10.1.3. Developmental and Reproductive Toxicity

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

There are no reproductive toxicity data on benzyl benzoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to benzyl benzoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on benzyl benzoate for the developmental toxicity endpoint. Groups of 21 pregnant Wistar rats were administered diets supplemented with 0.04% and 1% benzyl benzoate. Of the 21 females per group, 14 animals were terminated at days 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 include mandibular defects and the absence of a tongue or a cleft palate in 1 high-dose group fetus, but there was no significant difference in incidence when compared to controls. No effects were apparent in the low-dose treatment group. There was a statistically significantly decreased number of fetuses with incomplete sternebrae in the high-dose group, which was considered a non-adverse effect. The visceral observations revealed bilateral heterotaxia in 1 high-dose group fetus, but there was no significance when compared to controls. Other abnormalities reported include dilation of the renal pelvis (seen in 1 fetus in the low-dose group), dilation of the renal pelvis (2 fetuses) and bisection of the apex (1 fetus) observed in the high-dose group. During the postpartum phase, the pup bodyweight gains were decreased by day 14 and 21 in all treatment groups. 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, 1980). Therefore, the benzyl 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 benzyl benzoate, 194.3/0.022 or 8832.

When correcting for skin absorption (see Section IV), the total systemic exposure to benzyl benzoate (22 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint for a Cramer Class I material at the current level of use.

There are insufficient reproductive toxicity data on benzyl benzoate or on any read-across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section IV), the total systemic exposure to benzyl benzoate (22 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Section IX 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 1.943 mg/kg/day.

The RfD for benzyl benzoate was calculated by dividing the NOAEL for developmental toxicity of 194.3 mg/kg/day by the uncertainty factor, 100 = 1.943 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/16/20.

10.1.4. Skin sensitization

Based on the existing data, benzyl benzoate is considered to be an extremely weak skin sensitizer with a defined NESIL of 59000 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, benzyl benzoate does not present a concern for skin sensitization. The chemical structure of this material indicates that it could possibly react with proteins, although little or no reaction would likely occur under physiological conditions (Roberts, 2007; Toxtree 2.6.13; OECD Toolbox v3.4). Benzyl benzoate was found to be negative in the DPRA, h-CLAT, and U-Sens tests while positive in KeratinoSens (Urbisch, 2015; Piroird, 2015). In a murine local lymph node assay (LLNA), benzyl benzoate was found to be non-sensitizing up to 50% (12500 μg/cm^2) (RIFM, 2005). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 59050 μg/cm^2 of benzyl benzoate in 1:3 ethanol:diethyl phthalate, 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 (RIFM, 1970). This material is considered a fragrance allergen and is required to be labeled as one of the 26 fragrance allergens in Europe (SCCS, 2012). Based on the available data, benzyl benzoate is considered an extremely weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 59000 μg/cm^2 (Table 3). Section IX 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 1.943 mg/kg/day.

Additional References: Hausen (1992); Hausen (1995); Klecak (1985); RIFM, 1981; Ishihara (1986); Gerberick (2005).bib_Gerberick_et_al_2005

Literature Search and Risk Assessment Completed On: 05/12/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing *in vivo* study data, benzyl benzoate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Benzyl benzoate at concentrations up to 50% in acetone was not observed to result in phototoxic responses in guinea pigs (RIFM, 1981). Based on the lack of absorbance and *in vivo* study data, Benzyl benzoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101; OECD, 1981) were obtained. The spectra indicate no significant 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/17.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for benzyl benzoate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on benzyl benzoate. Based on the Creme RIFM Model, the inhalation exposure is 0.88 mg/day. This exposure is 1.59 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/16/20.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of benzyl 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

Table 3
Data Summary for Benzyl benzoate.

LLNA Weighted Mean EC3 Value μg/Cm[b] [No. Studies]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm[b]	NOEL-HMT (induction) μg/cm[b]	LOEL[b] (induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
> 12500 [1]	Extremely weak	59050	20690	NA	59000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

Table 4
Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L) Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	13.09			1,000,000	0.0130	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.597	6.3438	2.117	10,000	0.2117	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	7.277	4.762	6.376			Neutral Organic
Tier 3: Measured Data Including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	2.32					
Daphnia		3.09	0.258			
Algae		0.311	0.247	50	4.94	

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, benzyl benzoate 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 did not identify benzyl 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value $<$ 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value $<$ 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current VoU (2015), benzyl benzoate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. RIFM, 1994: Biodegradability was determined using a CO_2 production test based on OECD Guideline 301B. An aliquot of 10 mg/L of benzyl benzoate was added to the vessels, and the incubation was conducted for 28 days. The biodegradation rate was 64.9% and 93% by days 10 and 28, respectively.

RIFM, 1992a: Biodegradability was determined by the manometric respirometry test according to the OECD 301F method. Mineral medium inoculated with fresh activated sludge and 100 mg/L of benzyl benzoate was incubated for 28 days. The biodegradation rate was 94%, and benzyl benzoate was classified as readily biodegradable.

10.2.4. Ecotoxicity

RIFM, 2003a: A 48-h *Daphnia magna* acute test was conducted with the test material according to the OECD 202 method. The EC50 for benzyl benzoate in *Daphnia magna* was 3.09 mg/L.

RIFM, 1993: A 96-h acute toxicity study was conducted with Zebrafish. The Geometric mean of LC0/LC100 was 2.32 mg/L.

RIFM, 2003b: An algae growth inhibition study was conducted according to the OECD 201 method under static conditions in sealed

Table 5
Exposure information and PEC calculation (following RIFM Framework: Salvito, 2002).

Exposure	Europe	North America
Log K_{ow} used	3.54	3.54
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	> 1000
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 4.94 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 volumes of use.

containers. Exposure of algae to benzyl benzoate for 72 h resulted in EC50s of 0.475 mg/L when calculated using the average specific growth rate, 0.363 mg/L when calculated using the number of cells/mL, and 0.311 mg/L when calculated using the area under the growth curve. The 72-h No Observed Effect Concentration (NOEC) was 0.247 mg/L benzyl benzoate when determined using the number of cells/mL or the average specific growth rate and 0.0647 mg/L when determined using the area under the growth.

10.2.5. Other available data

Benzyl benzoate has been registered under REACH, and the following additional data is available:

A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC was reported to be 0.258 mg/L (ECHA, 2013).

10.2.6. Risk assessment refinement

Literature Search and Risk Assessment Completed On: 02/21/19.

11. 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
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/05/19.

12. Conflicts of interest

The authors declare that they have no conflicts of interest.

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.2020.111500.

Appendix

Read-across Justification

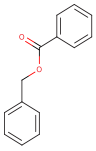
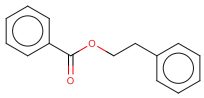
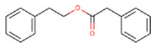
Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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 substance 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, and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- The major metabolites for the target material and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD,

2018).

Table 6
Target material and read-across analogs

	Target material	Read-across material	Read-across material
Principal Name	Benzyl benzoate	Phenethyl benzoate	Phenethyl phenylacetate
CAS No.	120-51-4	94-47-3	102-20-5
Structure			
Similarity (Tanimoto score)		0.64	0.87
Read-across endpoint		• Genotoxicity	• Repeated dose
Molecular Formula	$C_{14}H_{12}O_2$	$C_9H_{10}O_2$	$C_{16}H_{16}O_2$
Molecular Weight	212.25	150.18	240.30
Melting Point (°C, EPI Suite)	70.75	−0.50	89.40
Boiling Point (°C, EPI Suite)	317.89	215.57	343.16
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.0741	25	0.0248
Log Kow (KOWWIN v1.68 in EPI Suite)	3.97	1.96	3.8[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	15.39	3100	22
J_{max} (μg/cm^2/h, SAM)	13.221	64.032	0.838
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.84E-01	3.77E-01	1.54E-01
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-Carcinogen (good reliability)	• Non-Carcinogen (experimental value)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found	
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Repeated dose toxicity			
Repeated Dose (HESS)	• Tamoxifen (Hepatotoxicity alert)		• Not categorized
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplementary Data 1	See Supplementary Data 2	See Supplementary Data 3

Summary

There are insufficient toxicity data on the benzyl benzoate (CAS # 120-51-4). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs phenethyl benzoate (CAS # 94-47-3) and phenethyl phenylacetate (CAS # 102-20-5) were identified as read-across materials with sufficient toxicological data.

Conclusions

- Phenethyl benzoate (CAS # 94-47-3) was used as a read-across analog for the target material benzyl benzoate (CAS # 120-51-4) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of esters.
  - o The target substance and the read-across analog share a benzyl fragment on the alcohol portion of the ester.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has a 1-carbon longer alkyl chain on the alcohol portion (phenethyl alcohol) compared to the target substance (benzyl alcohol). This structural difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the ester functional group and benzyl fragment of the alcohol portion. Differences between the structures that affect the Tanimoto score do not affect consideration for the toxicity endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the genotoxicity endpoint.

- Phenethyl phenylacetate (CAS # 102-20-5) was used as a read-across analog for the target material benzyl benzoate (CAS # 120-51-4) for the repeated dose toxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of esters.
  - o The target substance and the read-across analog share an aromatic ester fragment.
  - o The key difference between the target substance and the read-across analog is that the target has benzyl substitutions on the acid and alcohol portions of the ester while the read-across analog has phenyl substitutions on the acid and alcohol portions of the ester. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aromatic ester fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq 80\%$ skin absorption for the target substance and $\leq 40\%$ absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Therefore, the J_{max} of the target substance and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the repeated dose toxicity endpoint are consistent between the target substance and the read-across analog.
  - o The target is categorized as Tamoxifen (Hepatotoxicity alert) while the read-across is not categorized by the HESS categorization scheme. The data described in the repeated dose section above shows that the margin of exposure of the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for repeated dose toxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the repeated dose toxicity endpoint.

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