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Short Review

RIFM fragrance ingredient safety assessment, benzyl cinnamate, CAS Registry Number 103-41-3

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Name: Benzyl cinnamate
CAS Registry Number: 103-41-3

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.847			1,000,000	0.005874	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.983	3.305	1.014	10,000	0.1014	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.737	1.881	3.081			Neutral Organic SAR (Baseline toxicity)

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, 2017; Safford et al., 2015; Safford 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
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 cinnamate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, and environmental safety. Data on read-across material phenethyl cinnamate (CAS # 103-53-7) show that benzyl cinnamate is not expected to be genotoxic. The repeated dose toxicity and developmental and reproductive toxicity endpoints were completed using data on the target material, which provided a margin of exposure (MOE) > 100. The local respiratory toxicity endpoint was completed using the threshold of toxicological concern (TTC) for a Cramer Class I material (1.4 mg/day); exposure is below the TTC. Data provided a No Expected Sensitization Induction Level (NESIL) of 4700 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoint was evaluated based on ultraviolet (UV) spectra; the material is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, and the material was not found to be persistent, bioaccumulative, and toxic (PBT) as per International Fragrance Association (IFRA) environmental standards; its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]) are < 1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 2015a; RIFM, 2015b)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2016a)
Developmental and Reproductive Toxicity: NOAEL = 200 and 600 mg/kg/day, respectively.	RIFM (2016a)
Skin Sensitization: NESIL = 4700 μg/cm^2.	(RIFM, 2005b; RIFM, 2005a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 94% (OECD 301F)	(ECHA REACH Dossier: Benzyl cinnamate; ECHA, 2016a)
Bioaccumulation: Screening-level: 223 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 1.014 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Environmental Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 1.014 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1014 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1	

1. Identification

1. **Chemical Name:** Benzyl cinnamate
2. **CAS Registry Number:** 103-41-3
3. **Synonyms:** Benzyl 3-phenylpropenoate; Cinnamein; 2-Propenoic acid, 3-phenyl-, phenylmethyl ester; Phenylmethyl 3-phenyl-2-propenoate; Cinnamic acid, benzyl ester; Benzyl γ-phenylacrylate; ｹｲ皮酸ﾌｪﾆﾙｱﾙｷﾙ(C = 1～3); Benzyl 3-phenylacrylate; Benzylcinnamat; Benzyl cinnamate
4. **Molecular Formula:** $C_{16}H_{14}O_2$
5. **Molecular Weight:** 238.29
6. **RIFM Number:** 284

2. Physical data

1. **Boiling Point:** 350 °C (FMA Database), 346.81 °C (US EPA, 2012a)
2. **Flash Point:** > 100 °C (GHS), > 212 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.06 (US EPA, 2012a)
4. **Melting Point**: 87.93 °C (US EPA, 2012a,b)
5. **Water Solubility:** 9.269 mg/L (US EPA, 2012a,b)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000505 mm Hg @ 20 °C (US EPA, 2012a,b v4.0), 9.86e-005 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A white to pale yellow fused solid or crystal melting at very warm room temperature to a yellow liquid. It has a sweet balsamic odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.019% (RIFM, 2016b)
3. **Inhalation Exposure*:** 0.000060 mg/kg/day or 0.0044 mg/day (RIFM, 2016b)
4. **Total Systemic Exposure**:** 0.00092 mg/kg/day (RIFM, 2016b)

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** Phenethyl cinnamate (CAS # 103-53-7)
   b. **Repeated Dose Toxicity:** None
   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

Not considered for this risk assessment.

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

Benzyl cinnamate is not reported to occur in food by the VCF* but is found in some natural complex substances.

*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.

8. REACH dossier

Available; accessed 03/05/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for benzyl cinnamate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.36
2	Products applied to the axillae	0.11
3	Products applied to the face/body using fingertips	1.2
4	Products related to fine fragrances	2.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.51
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.51
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.51
5D	Baby cream, oil, talc	0.17
6	Products with oral and lip exposure	1.2
7	Products applied to the hair with some hand contact	2.4
8	Products with significant ano-genital exposure (tampon)	0.17
9	Products with body and hand exposure, primarily rinse-off (bar soap)	3.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.9
10B	Aerosol air freshener	14
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.17
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 cinnamate, the basis was the reference dose of 2.0 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 4700 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, benzyl cinnamate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of benzyl cinnamate was assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and *Escherichia coli* strain WP2uvrA were treated with benzyl cinnamate in dimethyl sulfoxide (DMSO) at concentrations ranging between 3 and 5000 μg/plate in the presence and absence of metabolic activation (S9). No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015a). Under the conditions of the study, benzyl cinnamate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of benzyl cinnamate. The clastogenicity of read-across material phenethyl cinnamate (CAS # 103-53-7) 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 cinnamate in DMSO at concentrations up to 2523 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Phenethyl cinnamate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2015b). Under the conditions of the study, phenethyl cinnamate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to benzyl cinnamate.

Based on the available data, benzyl cinnamate does not present a concern for genotoxic potential.

Additional References: Florin et al., 1980.

Literature Search and Risk Assessment Completed On: 4/19/16.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on benzyl cinnamate for the repeated dose toxicity endpoint. A 19-week oral dietary toxicity study was conducted in Osborne-Mendel rats with benzyl cinnamate. Groups of 5 weanling rats/sex/dose were given benzyl cinnamate by dietary admixture at concentrations of 0, 1000, or 10000 ppm (equivalent to 0, 50, or 500 mg/kg/day) for 19 weeks. There were no mortalities or adverse clinical signs. No effects on growth, hematological evaluations, and macroscopic or microscopic changes in the tissues were observed. The NOAEL was considered to be

500 mg/kg/day, the highest dose tested (Hagan et al., 1967). An OECD 422 gavage study followed by a 14-day recovery period was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered test material via gavage at doses of 0, 65, 200, or 600 mg/kg/day in corn oil. Additional groups of 5 rats/sex/dose were added to the control and high-dose group to serve as the 14-day treatment-free recovery groups. The animals were dosed once daily prior to mating as well as during mating and post mating periods (for males), during pregnancy, and up to lactation day 4 (for females). The males were treated for a period of approximately 42 days and the females were treated for a period of approximately 52 days. There were no treatment-related adverse effects in body weights, organ weights, hematology, clinical chemistry, or in any of the systemic parameters evaluated. The NOAEL for repeated dose toxicity in parental rats was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2016a). The NOAEL of 600 mg/kg/day from the more robust OECD 422 study was used for this safety assessment.

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012a). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 600/3 or 200 mg/kg/day.

Therefore, the benzyl cinnamate MOE for the repeated dose toxicity endpoint is equal to the benzyl cinnamate NOAEL in mg/kg/day divided by the total systemic exposure to benzyl cinnamate, 200/0.00092 or 217391.

In addition, the total systemic exposure to benzyl cinnamate (0.92 μg/kg/day) is below the TTC (30 μg/kg/day) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. These factors can be refined based on availability of data. Due to insufficient intraspecies susceptibility data for benzyl cinnamate, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences, respectively (Renwick, 1993).

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 2.0 mg/kg/day.

The RfD for benzyl cinnamate was calculated by dividing the NOAEL of 200 mg/kg/day by the uncertainty factor, 100 = 2.0 mg/kg/day.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/17.

10.1.3. Developmental and reproductive toxicity

The MOE for benzyl cinnamate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on benzyl cinnamate for the developmental toxicity endpoint. An OECD 422 gavage study followed by a 14-day recovery period was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered test material via gavage at doses of 0, 65, 200, or 600 mg/kg/day in corn oil. Additional groups of 5 rats/sex/dose were added to the control and high-dose groups to serve as the 14-day treatment-free recovery groups. The animals were dosed once daily prior to mating, during mating and post mating periods (for males), and during pregnancy and up to lactation day 4 (for females). The males were treated for a period of approximately 42 days, and the females were treated for a period of approximately 52 days. In addition to systemic toxicity parameters, precoital time, gestation length, mating, and fertility parameters were also evaluated. There were no treatment-related effects on the mean litter size in all the doses tested. Day 4 survival index was significantly lower among the 600 mg/kg/day dose group, due to the total death/cannibalism of pups observed in 2 dams. This was considered to be incidental since no other reproductive parameters were affected. The mean body weight of male pups on day 1 as well as female and combined sex of pups on days 1 and 4 were significantly lower when compared to the controls at the high dose. Gross examination of pups on lactation day 4 did not reveal any abnormalities. The study report did not derive a NOAEL for the developmental toxicity. Since no treatment-related adverse effects were observed in pup body weight, litter size, and survival index, a NOAEL for developmental toxicity was considered to be 200 mg/kg/day, based on decrease in mean pup weights among high-dose group litters (RIFM, 2016a). **Therefore, the benzyl cinnamate MOE for the developmental toxicity endpoint is equal to the benzyl cinnamate NOAEL in mg/kg/day divided by the total systemic exposure to benzyl cinnamate, 200/0.00092 or 217391.**

There are sufficient reproductive toxicity data on benzyl cinnamate for the reproductive toxicity endpoint. An OECD 422 gavage study followed by a 14-day recovery period was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered test material via gavage at doses of 0, 65, 200, or 600 mg/kg/day in corn oil. Additional groups of 5 rats/sex/dose were added to the control and high-dose group to serve as the 14-day treatment-free recovery groups. The animals were dosed once daily prior to mating, during mating and post mating periods (for males), and during pregnancy and up to lactation day 4 (for females). The males were treated for a period of approximately 42 days, and the females were treated for a period of approximately 52 days. In addition to systemic toxicity parameters, pre-coital time, gestation length, mating, and fertility parameters were also evaluated. Histopathological examination of testes in the high-dose group included a qualitative assessment of stages of spermatogenesis. There were 6 male (2 control, 1 low-dose, 3 mid-dose) and 6 female rats (2 control, 1 low-dose, 1 mid-dose, 2 high-dose) that failed to mate. Histopathological examination of reproductive (including qualitative assessment of stages of spermatogenesis) organs revealed no significant alterations in the animals that failed to mate. There were no adverse effects in any of the systemic or reproductive parameters evaluated. The NOAEL for reproductive toxicity was considered to be 600 mg/kg/day, the highest dose tested (RIFM, 2016a). **Therefore, the benzyl cinnamate MOE for the reproductive toxicity endpoint is equal to the benzyl cinnamate NOAEL in mg/kg/day divided by the total systemic exposure to benzyl cinnamate, 600/0.00092 or 652174.**

In addition, the total systemic exposure to benzyl cinnamate (0.92 μg/kg/day) is below the TTC (30 μg/kg/day) for the developmental and reproductive toxicity endpoints for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/17.

10.1.4. Skin sensitization

Based on the existing data, benzyl cinnamate is considered a weak sensitizer with a defined NESIL of 4700 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, benzyl cinnamate is considered a weak sensitizer. The chemical structure of this material

Table 1
Data Summary for Benzyl cinnamate.

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]
4600 [1]	Weak	4720	5520	NA	4700

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.

indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). Benzyl cinnamate was found to be negative in DPRA and h-CLAT tests while positive in *in vitro* KeratinoSens and U937-CD86 tests (RIFM, 2015c; RIFM, 2015d; Piroird et al., 2015). However, in a murine local lymph node assay (LLNA), benzyl cinnamate was found to be sensitizing with an EC3 value of 18.4% (4600 μg/cm^2) (RIFM, 2005a). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1972; RIFM, 1975). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 4700 μg/cm^2 of benzyl cinnamate in 1:3 ethanol:diethyl phthalate no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2005b). Based on available data, benzyl cinnamate is considered a weak sensitizer with the Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 4700 μg/cm^2 (Table 1). 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 2.0 mg/kg/day.

Additional References: Emter et al., 2010; Hausen et al., 1995; Klecak (1985); Hausen and Wollenweber, 1988; Klecak et al., 1977.

Literature Search and Risk Assessment Completed On: 05/15/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, benzyl cinnamate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for benzyl cinnamate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, benzyl cinnamate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for benzyl cinnamate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol^{-1} · cm^{-1}, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

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

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for benzyl cinnamate 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 cinnamate. Based on the Creme RIFM Model, the inhalation exposure is 0.0044 mg/day. This exposure is 318.2 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/16/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of benzyl cinnamate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, benzyl cinnamate 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 v4.1 (US EPA, 2012a) did not identify benzyl cinnamate as possibly persistent nor 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, 2012b). 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

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

10.2.2. Key studies

10.2.2.1. Biodegradation. RIFM, 1999a**:** The ready biodegradability of the test material was evaluated according to the 92/69/EWG Method C.4-E guideline. After 28 days, biodegradation of 50% was observed.

10.2.2.2. Ecotoxicity. RIFM, 1999b**:** A *Daphnia magna* acute toxicity study was conducted according to the 92/69/EEC Method C.2 guideline. The 48-h EC0/EC100 was reported to be 2.8 mg/L.

RIFM, 2017a**:** An algae growth inhibition test was conducted according to the OECD 201 method. The 0–72 h EC50 (based on time weighted average test concentration) was reported to be 0.386 mg/L for growth rate and 0.158 mg/L for yield.

RIFM, 2017b**:** The acute toxicity of the test material to Zebra fish was evaluated in a semi-static limit test at a nominal concentration of 0.8 mg/L following the OECD 203 guidelines. Based on geometric mean measured test concentrations, the LC100 and LC0 at 96 h was 0.643 mg/L.

10.2.3. Other available data

Benzyl cinnamate has been registered under REACH with the following additional data available:

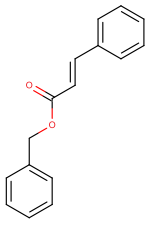
The ready biodegradability of the test material was evaluated according to the OECD 301F method. After 28 days, biodegradation of 94% was observed (ECHA, 2016a).

10.2.4. Risk assessment refinement

Since benzyl cinnamate has passed the screening criteria, measured data is included in the document for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.



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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.1014 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.

Literature Search and Risk Assessment Completed On: 03/05/19.

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 05/13/19.

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.2020.111381.

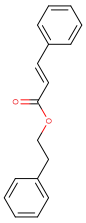
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by the OECD on the reporting of the defined approached used within the Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemical Agency (ECHA) read-across assessment framework or RAAF (ECHA, 2016b).

- Materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster were examined. Finally, appropriate read-across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a,b).
- 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).

	Target material	Read-across Material
Principal Name	Benzyl cinnamate	Phenethyl cinnamate
CAS No.	103-41-3	103-53-7
Structure		

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5.847			1,000,000	0.005874	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.983	3.305	1.014	10,000	0.1014	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.737	1.881	3.081			Neutral Organic SAR (Baseline toxicity)

Similarity (Tanimoto score)		0.94
Read-across endpoint		• Genotoxicity
Molecular Formula	$C_{16}H_{16}O_2$	$C_{17}H_{16}O_2$
Molecular Weight	238.29	252.32
Melting Point (°C, EPI Suite)	89.40	96.95
Boiling Point (°C, EPI Suite)	343.16	358.42
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.0248	0.0022
Log Kow (KOWWIN v1.68 in EPI Suite)	4.18	4.56
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.60	1
J_{max} (μg/cm^2/h, SAM)	2.924	2.190
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.38E-002	4.50E-002
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 (moderate reliability)	• Non-Carcinogen (moderate reliability)
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	• Acrylate reactive functional group	• Acrylate reactive functional group
Metabolism		
OECD QSAR Toolbox (3.4) **Rat liver S9 metabolism simulator and structural alerts for metabolites**	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on the benzyl cinnamate (CAS # 103-41-3). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenethyl cinnamate (CAS # 103-53-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Phenethyl cinnamate (CAS # 103-53-7) was used as a read-across analog for the target material benzyl cinnamate (CAS # 103-41-3) 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 cinnamyl fragment on the acid portion of the ester.
  - o The key difference between the target substance and the read-across analog is that the target has a benzyl fragment on the alcohol portion of the ester while the read-across has a phenylethyl fragment on the alcohol portion. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o 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 cinnamyl fragment on the acid portion of the ester. 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.
  - 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 read-across analog and target material have genotoxicity alerts by OECD and OASIS models. The read-across analog and target are predicted to cause Michael addition and have an acrylate reactive functional group. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. 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 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.

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