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RIFM fragrance ingredient safety assessment, isobutyl cinnamate, CAS Registry Number 122-67-8

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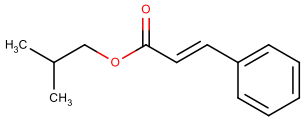

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 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, 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.

Isobutyl cinnamate (CAS # 122-67-8) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl cinnamate (CAS # 103-36-6) show that isobutyl cinnamate is not expected to be genotoxic. Data on read-across analog methyl cinnamate (CAS # 103-26-4) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints. Data on isobutyl cinnamate and from read-across analog methyl cinnamate (CAS # 103-26-4) provided a defined NESIL of 2900 μg/cm^2. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; isobutyl cinnamate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to isobutyl cinnamate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; isobutyl cinnamate 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 expected to be genotoxic.	(Ishidate, 1984; RIFM, 2015b; RIFM, 2015c)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	RIFM (2013b)
Reproductive Toxicity: NOAEL = 300 mg/kg/day.	RIFM (2013b)
Skin Sensitization: NESIL = 2900 μg/cm^2.	RIFM (2015a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Screening-level: 2.91 (BIOWIN 3)	((EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 140 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 8.109 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: LC50: 8.109 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.008109 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Isobutyl cinnamate
2. **CAS Registry Number:** 122-67-8
3. **Synonyms:** Isobutyl 3-phenylpropenoate; Isobutyl β-phenylacrylate; Labdanol; 2-Methylpropyl cinnamate; 2-Methylpropyl 3-phenyl-propenoate; 2-Methylpropyl β-phenylacrylate; 2-Propenoic acid, 3-phenyl-, 2-methylpropyl ester; Isobutyl 3-phenylacrylate; Isobutyl cinnamate
4. **Molecular Formula:** $C_{13}H_{16}O_2$
5. **Molecular Weight:** 204.26
6. **RIFM Number:** 679V
7. **Stereochemistry:** Isomer not specified. One stereocenter and a total of 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 280.47 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 3.76 (EPI Suite)
4. **Melting Point**: 21.36 °C (EPI Suite)
5. **Water Solubility:** 25.75 mg/L (EPI Suite)
6. **Specific Gravity:** 1.004 (FMA Database), 1.001–1.004 (RIFM Database)
7. **Vapor Pressure:** 0.00339 mm Hg (0.452 Pa) at 20 °C (EPI Suite v4.0), 0.002 mm Hg (0.267 Pa) at 20 °C (FMA Database), 0.00547 mm Hg (0.729 Pa) at 25 °C (EPI Suite)

8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a sweet fruity balsamic odor

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.069% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000051 mg/kg/day or 0.0037 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0038 mg/kg/day (RIFM, 2017)

*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 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 (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
a. **Genotoxicity:** Ethyl cinnamate (CAS # 103-36-6)
b. **Repeated Dose Toxicity:** Methyl cinnamate (CAS # 103-26-4)
c. **Reproductive Toxicity:** Methyl cinnamate (CAS # 103-26-4)
d. **Skin Sensitization:** Methyl cinnamate (CAS # 103-26-4)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

Isobutyl cinnamate is reported to occur in the following foods by the VCF*:

Citrus fruits

*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

Isobutyl cinnamate has been pre-registered for 2010; no dossier available as of 10/08/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for isobutyl cinnamate 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)	0.22
2	Products applied to the axillae	0.066
3	Products applied to the face/body using fingertips	1.3
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.32
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.32
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.32
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.73
7	Products applied to the hair with some hand contact	2.5
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.55
10B	Aerosol air freshener	0.55
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 isobutyl cinnamate, the basis was the reference dose of 1.0 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2900 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, isobutyl cinnamate

does not present a concern for genetic toxicity.

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

There are no data assessing the mutagenic activity of isobutyl cinnamate; however, read-across can be made to ethyl cinnamate (CAS # 103-36-6; see Section VI). The mutagenic activity of ethyl cinnamate has been evaluated in a bacterial reverse mutation assay using guidelines similar to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA92, and TA94 were treated with ethyl cinnamate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Ishidate, 1984). Under the conditions of the study, ethyl cinnamate was not mutagenic in the Ames test. The study was well documented and well performed. However, no OECD guideline was followed, and the study was non-GLP. Therefore, a weight of evidence (WoE) approach was made by considering a mammalian cell gene mutation assay (HPRT) conducted according to OECD TG 476 and GLP guidelines. Chinese hamster V79 lung cells were treated with ethyl cinnamate in DMSO at concentrations up to 1760 μg/mL (equivalent to approximately 10 mM) for 4 h with metabolic activation and 24 h without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2015b). Under the conditions of the study, ethyl cinnamate was not mutagenic to mammalian cells in vitro. Overall, ethyl cinnamate was not considered to be mutagenic, and this can be extended to isobutyl cinnamate.

There are no data assessing the clastogenic activity of isobutyl cinnamate; however, read-across can be made to ethyl cinnamate (CAS # 103-36-6; see Section VI). The clastogenic activity of ethyl cinnamate 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 ethyl cinnamate in DMSO at concentrations up to 1760 μg/mL (equivalent to approximately 10 mM) in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 20 h. Ethyl cinnamate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2015c). Under the conditions of the study, ethyl cinnamate was considered to be non-clastogenic in the in vitro micronucleus test, and this can be extended to isobutyl cinnamate.

Based on the available data, ethyl cinnamate does not present a concern for genotoxic potential, and this can be extended to isobutyl cinnamate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for isobutyl cinnamate 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 isobutyl cinnamate. Read-across material methyl cinnamate (CAS # 103-26-4; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD/GLP 422 oral gavage combined repeated dose toxicity study with a developmental and reproductive toxicity screening test was conducted in Han Wistar rats. Groups of 12 rats/sex/dose were gavaged daily with methyl cinnamate at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. The highest-dose group was administered 1000 mg/kg/day for the first week and then decreased to 600 mg/kg/day for the remainder of the study due to reversible clinical signs. Male rats were dosed for 14 days prior to mating and through mating, for a total of at least 28 days. Female rats were dosed for 14 days prior to mating, and through the mating and gestation periods, until day 4 postpartum. There were statistically significant decreases in body weights (did not fully recover) and food consumption (days 1–8 only, recovered thereafter) among high-dose males. Dose-dependent effects on white blood cell populations (decreased white blood cell count, absolute monocytes, large unstained cells, and/or lymphocytes) were observed in females at 100 mg/kg/day and in both sexes at 300 and 600 mg/kg/day. However, associated histopathological alterations (atrophy of lymphatic tissues) of low severity grades were only observed in females of the 600 mg/kg/day dose group. The relative liver weights were increased among high-dose group animals (statistically significant for males only). In the absence of histopathological evidence of liver cell damage and clinical chemistry alterations, the liver weight increases were considered to be adaptive (Hall, 2012). At 600 mg/kg/day, atrophy of lymphoid tissues (spleen, thymus, and lymph nodes) was observed in females, and tubular basophilia in the kidneys was observed in males. These findings were low in severity grades, and therefore, not considered to be adverse. Furthermore, the atrophy corresponded to the hematological changes and was considered to be most likely due to stress. Thus, the NOAEL for systemic toxicity was considered to be 300 mg/kg/day, based on decreases in body weights and white blood cell populations among high-dose group animals (RIFM, 2013b).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 = 100 mg/kg/day.

Therefore, the isobutyl cinnamate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl cinnamate NOAEL in mg/kg/day by the total systemic exposure to isobutyl cinnamate, 100/0.0038, or 26316.

In addition, the total systemic exposure to isobutyl cinnamate (3.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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 1.0 mg/kg/day.

Derivation of reference dose (RfD)

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for isobutyl cinnamate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 100 mg/kg/day by the uncertainty factor, 100 = 1.0 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: 11/03/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on isobutyl cinnamate. Read-across material methyl cinnamate (CAS # 103-26-4; see Section VI) has sufficient developmental and reproductive toxicity data to support the developmental and reproductive toxicity endpoints. An OECD/GLP 422 oral gavage combined repeated dose toxicity study with a developmental and reproductive toxicity screening test was conducted in Han Wistar rats. Groups of 12 rats/sex/dose were gavaged daily with methyl cinnamate at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. The highest-dose group was administered 1000 mg/kg/day for the first week and then decreased to 600 mg/kg/day for the remainder of the study due to reversible clinical signs. Male rats were dosed for 14 days prior to mating and through mating, for a total of at least 28 days. Female rats were dosed for 14 days prior to mating, and through the mating and gestation periods, until day 4 postpartum. At 300 and 600 mg/kg/day, the post-implantation loss was increased (not statistically significant at 12.6 and 12.8%, respectively), which was reflected in a decreased live-birth index (87.4 and 87.2%, respectively as compared to 91.9% in controls). This effect was not dose-dependent or statistically significant and was within the range of the historical control data. At 600 mg/kg/day, the gestation index was slightly reduced. The decrease in the gestation index of high-dose dams (83.3%) when compared to controls (100%) was considered to be due to treatment-related findings of toxicological relevance in hematology, clinical chemistry, and histopathology in the highest-dose group. There were no other reproductive effects reported. In the presence of maternal toxicity, the NOAEL for developmental and reproductive toxicity was considered to be 300 mg/kg/day, based on a decrease in gestation index among high-dose dams (RIFM, 2013b). Therefore, the isobutyl cinnamate MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the methyl cinnamate NOAEL in mg/kg/day by the total systemic exposure to isobutyl cinnamate, 300/0.0038, or 78947.

In addition, the total systemic exposure to isobutyl cinnamate (3.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.4. Skin sensitization

Based on the existing data and read-across to methyl cinnamate (CAS # 103-26-4), isobutyl cinnamate is considered a weak sensitizer with a defined NESIL of 2900 μg/cm^2.

11.1.4.1. Risk assessment. Limited data for skin sensitization are available for isobutyl cinnamate. Based on available data on read-across analog methyl cinnamate (CAS # 103-26-4; see Section VI), isobutyl cinnamate is considered a weak skin sensitizer with a defined NESIL of 2900 μg/cm^2. The chemical structures of these materials indicate that they are expected to react directly with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, open epicutaneous test, Freund's Complete Adjuvant test, and Draize test, reactions indicative of sensitization with read-across analog methyl cinnamate were observed (RIFM, 1976). In human maximization tests, no skin sensitization reactions were observed with isobutyl cinnamate or with read-across analog methyl cinnamate (RIFM, 1975a; RIFM, 1970; RIFM, 1975b). Additionally, in a confirmatory Confirmation of No Induction in Humans test (CNIH) with 2953 μg/cm2, read-across analog methyl cinnamate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2015a).

Based on the weight of evidence (WoE) from structural analysis and read-across analog methyl cinnamate, isobutyl cinnamate is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 2900 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, 2020a) and a reference dose of 1.0 mg/kg/day.

Additional References: Klecak (1977); Klecak (1985); RIFM, 1971.

Literature Search and Risk Assessment Completed On: 10/28/20.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for isobutyl cinnamate. 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, 2009). Based on the lack of absorbance, isobutyl cinnamate 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 minor 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: 11/03/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on isobutyl cinnamate. Based on the Creme RIFM Model, the inhalation exposure is 0.0037 mg/day. This exposure is 378 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/05/20.

Table 1
Data summary for methyl cinnamate as read-across for isobutyl cinnamate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
NA	Weak	2953	6900	NA	2900

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.

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isobutyl cinnamate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, isobutyl cinnamate 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 isobutyl cinnamate 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).

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Isobutyl cinnamate has been pre-registered for REACH with no additional data at this time.

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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.76	3.76
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 0.008109 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 11/06/20.

12. Literature Search*

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

Search keywords: CAS number and/or material names.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.109			1,000,000	0.008109	

*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 11/13/20.

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.2021.112456.

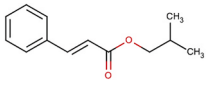
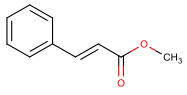
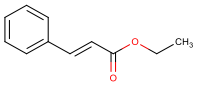
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material	
Principal Name	Isobutyl cinnamate	Methyl cinnamate	Ethyl cinnamate
CAS No.	122-67-8	103-26-4	103-36-6
Structure			
Similarity (Tanimoto Score)		0.63	0.74
Read-across Endpoint		• Reproductive toxicity • Repeated dose toxicity • Skin sensitization	• Genotoxicity
Molecular Formula	$C_{13}H_{16}O_2$	$C_{10}H_{10}O_2$	$C_{11}H_{12}O_2$
Molecular Weight	204.26	162.18	176.21
Melting Point (°C, EPI Suite)	21.36	9.69	20.45
Boiling Point (°C, EPI Suite)	280.47	239.90	257.46
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.729	1.65	1.17
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	3.76	2.62	2.99
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	25.75	387.1	178
J_{max} (μg/cm^2/h, SAM)	13.300	74.786	9.008
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.82E-001	4.20E-001	5.57E-001
Genotoxicity			
	• No alert found		• No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)			
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found		• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)		• Non-carcinogen (moderate reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found		• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found		• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found		• No alert found
Oncologic Classification	• Acrylate reactive functional groups		• Acrylate reactive functional groups
Repeated Dose toxicity			
Repeated Dose (HESS)	Coumarin (Hepatotoxicity) Alert|Propanolol (Renal toxicity) Alert|Styrene (Renal Toxicity) Alert	Carbamazepine (Hepatotoxicity) Alert|Carbamazepine (Renal Toxicity) Alert|Coumarin (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Toxicant (good reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• Michael addition	• Michael addition	
Protein Binding (OECD)	• Michael addition	• Michael addition	
Protein Binding Potency	• Moderately reactive (GSH)	• Moderately reactive (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Michael addition	• Michael addition	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• Michael acceptor	• Michael acceptor	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on isobutyl cinnamate (CAS # 122-67-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, methyl cinnamate (CAS # 103-26-4) and ethyl cinnamate (CAS # 103-36-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Methyl cinnamate (CAS # 103-26-4) was used as a read-across analog for the target material isobutyl cinnamate (CAS # 122-67-8) for the reproductive toxicity, repeated dose toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of cinnamyl esters.
  - o The target material and the read-across analog share a cinnamyl fragment.
  - o The key difference between the target material and the read-across analog is that the target material is an isobutyl ester, and the read-across analog is a methyl ester. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cinnamyl fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity. According to this alert, the read-across analog is more reactive than the target material. As described in the developmental and reproductive toxicity section above, the MOE for the read-across analog is adequate for this endpoint at the current level of use. Therefore, this alert can be ignored. Data supersedes predictions in this case.
  - o The target material and the read-across analog have several protein binding alerts. According to the data described in the skin sensitization section above, the read-across analog is considered a weak sensitizer. Data are consistent with *in silico* alerts.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Ethyl cinnamate (CAS # 103-36-6) was used as a read-across analog for the target material isobutyl cinnamate (CAS # 122-67-8) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of cinnamyl esters.
  - o The target material and the read-across analog share a cinnamyl fragment.

- The key difference between the target material and the read-across analog is that the target material has an isobutyl ester, and the read-across analog has an ethyl ester. This structural difference is toxicologically insignificant.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cinnamyl fragment. 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.
- Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} for the target material corresponds to skin absorption $\leq$80%, and the J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While percentage skin absorption estimated from the J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- 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 read-across analog have an acrylate reactive functional group alert for oncologic classification. According to this alert, the target material and the read-across analog have comparable reactivity. As described in the genotoxicity section above, the read-across analog does not pose a concern for genotoxic potential, and this can be applied to the target material. Therefore, this alert can be ignored. Data supersedes predictions in this case.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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