Food and Chemical Toxicology 167 (2022) 113232

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

# RIFM fragrance ingredient safety assessment, cinnamic acid, CAS Registry Number 621-82-9

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ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

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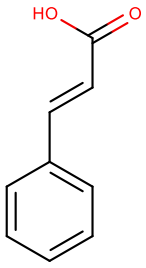
https://doi.org/10.1016/j.fct.2022.113232
Received 14 January 2022; Accepted 10 June 2022
Available online 16 June 2022

Version: 011422. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrance materialsafetyresource.elsevier.com

Name: Cinnamic acid
CAS Registry Number: 621-82-9
Additional CAS Number*:
140-10-3 *trans*-Cinnamic acid
*Included because the materials are isomers




**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**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

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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.**

Cinnamic acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cinnamic acid is not genotoxic. Data on read-across analog cinnamaldehyde (CAS # 104-55-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and local respiratory toxicity endpoints. Data on cinnamic acid provided a calculated MOE >100 for the developmental toxicity endpoint. The fertility endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to cinnamic acid is below the TTC (0.03 mg/kg/day). Data show that there are no safety concerns for cinnamic acid for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on data; cinnamic acid is not phototoxic/photoallergenic. The environmental endpoints were evaluated; cinnamic acid was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

| Human Health Safety Assessment | |
|---|---|
| **Genotoxicity:** Not genotoxic. | (ECHA REACH Dossier: *trans*-Cinnamic acid; ECHA, 2018; RIFM, 2013b) |
| **Repeated Dose Toxicity:** NOAEL = 7.5 mg/kg/day. | RIFM (2012) |
| **Reproductive Toxicity:** Developmental toxicity: NOAEL = 50 mg/kg/day. Fertility: Exposure is below the TTC. | Zaitsev (1975) |
| **Skin Sensitization:** No concern for skin sensitization under the current, declared levels of use. | (Bickers, 2005; ECHA REACH Dossier: *trans*-Cinnamic acid; ECHA, 2018) |
| **Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic. | (Pathak, 1959a; Pathak, 1959b; RIFM, 2003; RIFM, 2015) |
| **Local Respiratory Toxicity:** NOAEC = 55.5 mg/m$^3$. | RIFM (2012) |

| Environmental Safety Assessment | |
|---|---|
| **Hazard Assessment:** | |
| **Persistence:** | |
| Screening-level: 3.25 (BIOWIN 3) | (EPI Suite v4.11; US EPA, 2012a) |
| **Bioaccumulation:** | |
| Screening-level: 3.162 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Critical Ecotoxicity Endpoint: Fish LC50: 173.7 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:** Fish LC50: 173.7 mg/L | (RIFM Framework; Salvito, 2002) |
| **RIFM PNEC is:** 0.1737 µg/L | |
| • **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level | |

## 1. Identification

| | |
|---|---|
| Chemical Name: Cinnamic acid | Chemical Name: *trans*-Cinnamic acid |
| **CAS Registry Number:** 621-82-9 | **CAS Registry Number:** 140-10-3 |
| **Synonyms:** Benzylideneacetic acid; Cinnamylic acid; 3-Phenylacrylic acid; 3-Phenylpropenoic acid; 2-Propenoic acid, 3-phenyl-; 皮酸; Cinnamic acid | **Synonyms:** 3-Phenylacrylic acid; *trans*-3-Phenylacrylic acid; (E)-3-Phenyl-2-propenoic acid; 2-Propenoic acid, 3-phenyl-, (E)- |
| **Molecular Formula:** $C_9H_8O_2$ | **Molecular Formula:** $C_9H_8O_2$ |

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(*continued*)

| | |
|---|---|
| **Molecular Weight:** 148.16 g/mol<br>**RIFM Number:** 783<br>**Stereochemistry:** Stereoisomer not specified. One geometric center present, and a total of 2 stereoisomers possible | **Molecular Weight:** 148.16 g/mol<br>**RIFM Number:** 5166<br>**Stereochemistry:** *trans* stereoisomer specified |

## 2. Physical data*

1. **Boiling Point:** 147 °C at 3 mm Hg (Fragrance Materials Association [FMA]), 287.54 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log $K_{OW}$:** 2.07 (EPI Suite)
4. **Melting Point**: 134 °C (FMA), 69.48 °C (EPI Suite)
5. **Water Solubility:** 2911 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000823 mm Hg at 20 °C (EPI Suite v4.0), 0.000161 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, peaking at 270 nm and returning to baseline by 350 nm. Molar absorption coefficients (15608, 5298, 15323 L $mol^{-1}$ • $cm^{-1}$ under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** White colorless crystalline powder with honey, floral odor

*Physical data are identical for both materials in the assessment.

## 3. Volume of use (Worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM Aggregate exposure model v3.1.3)*

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.043% (RIFM, 2020b)
2. **Inhalation Exposure**:** 0.000036 mg/kg/day or 0.0026 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure***:** 0.00097 mg/kg/day (RIFM, 2020b)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrances, inhalation exposure, and total exposure.

**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:** 83.9%

**Bickers (2005):** The available information on percutaneous absorption suggests that there is significant absorption of cinnamyl alcohol, cinnamaldehyde, and cinnamic acid through the skin. For humans, only data from in vitro studies are available. Based on these data, the conservative estimate is that greater than 50% of the applied doses of these 3 materials are absorbed through the skin under occluded conditions.

**Bronaugh (1985):** Radiolabeled cinnamic acid ([$^{14}$C]cinnamic acid) was applied on the skin of female rhesus monkeys. The test material was dissolved in an acetone vehicle and applied at a concentration of 4 μg/$cm^2$ on a lightly clipped area of abdominal skin. After application, the animals were kept in metabolic cages for urine collection for a 4-day period. The amount absorbed in the urine was determined by liquid scintillation counting. The test was conducted under occluded and non-occluded conditions. The amounts absorbed under occluded and non-occluded conditions were 83.9% ± 2.7 (n = 4) and 38.6% ± 8.3 (n = 4), respectively.

Concurrently, absorption of the test material was also evaluated through human abdominal excised skin. Sections of 350 μm were removed, and permeation of the skin was tested using tritiated water. The skin surface area being used was 1.13 $cm^2$. The test material was applied to the excised skin in a normal saline vehicle at a concentration of 4 μg/$cm^2$, and the surface of the skin was washed after 24 h. The studies were continued until absorption was complete (48–72 h). A diffusion cell was used; normal saline was pumped through the cells (skin surface area 0.64 $cm^2$) at a rate of 5 mL/h and collected in scintillation vials. The receptor fluid was saline. The absorbed radioactivity was measured using a liquid scintillation counter. Occlusion was accomplished by sealing the tops of the diffusion cells with parafilm. The amounts absorbed under non-occluded and occluded conditions were 17.8% ± 4.9 (n = 6) and 60.8% ± 10.2 (n = 7), respectively.

The most conservative skin absorption value of 83.9% obtained under occlusion in rhesus monkeys was selected for cinnamic acid.

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

## 6. Computational toxicology evaluation

### 6.1. Cramer classification

Class I, Low.

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

### 6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** Cinnamaldehyde (CAS # 104-55-2)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Cinnamaldehyde (CAS # 104-55-2)
g. **Environmental Toxicity:** None

### 6.3. Read-across justification

See Appendix below.

## 7. Metabolism

**Bickers (2005):** Cinnamyl alcohol, cinnamaldehyde, and cinnamic acid are rapidly absorbed, metabolized, and excreted in the urine. They all follow the same metabolic pathway in that the alcohol is transformed into the aldehyde, which is metabolized to the acid. The final metabolite is hippuric acid, which is the principal metabolite being excreted in the urine. The qualitative pattern of metabolism of cinnamaldehyde and

cinnamic acid in humans is similar to that seen in laboratory species, and it is anticipated that this would also be broadly true for the metabolic fate of cinnamyl alcohol.

**Additional References:** None.

## 8. Natural occurrence

Cinnamic acid is reported to occur in the following foods by the VCF*:

| | |
|---|---|
| Beer | Litchi (*Litchi chinensis* Sonn.) |
| Cherry (*Prunus avium* [sweet], *Pr. Cerasus* [sour]) | Loquat (*Eriobotrya japonica* Lindl.) |
| | Rambutan (*Nephelium lappaceum* L.) |
| Grape brandy | Starfruit (*Averrhoa carambola* L.) |
| Honey | Strawberry (*Fragaria* species) |
| *trans*-Cinnamic acid is reported to occur in the following foods by the VCF*: | |
| Beer | Cloudberry (*Rubus chamaemorus* L.) |
| Black chokeberry juice (*Aronia melanocarpa* Ell.) | Grape (*Vitis* species) |
| Capers (*Capparis spinoza*) | Guava and feyoa |
| | Honey |
| *Cinnamomum* species | Malt |
| | Strawberry (*Fragaria* species) |

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

## 9. REACH dossier

No dossier available for cinnamic acid as of 06/08/21. Dossier available for *trans*-cinnamic acid (ECHA, 2018).

## 10. Conclusion

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

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data and use levels, cinnamic acid does not present a concern for genotoxic potential.

*11.1.1.1. Risk assessment.* The mutagenic activity of isomer and additional material trans-cinnamic acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with trans-cinnamic acid in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small increases in the mean number of revertant colonies were observed in strain TA1537 at 5000 μg/plate in the presence of S9 and in strain WP2uvrA at 150 μg/plate in the absence of S9 (ECHA, 2018). However, these increases were within the historical control range and therefore considered not to be biologically relevant. Under the conditions of the study, trans-cinnamic acid was not mutagenic in the Ames test.

The clastogenic activity of cinnamic acid 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 cinnamic acid in DMSO at concentrations up to 1480 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1480 μg/mL in the presence and absence of metabolic activation. Cinnamic acid did not induce binucleated cells with micronuclei when tested up to the cytotoxic or maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2013b). Under the conditions of the study, cinnamic acid was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, cinnamic acid does not present a concern for genotoxic potential.

**Additional References:** Yoo (1986); Eder (1991); Kakinuma (1984); Palmer (1984); Mulky (1987); Oda (1978).

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

#### 11.1.2. Repeated dose toxicity

The MOE for cinnamic acid is adequate for the repeated dose toxicity data at the current level of use.

*11.1.2.1. Risk assessment.* The repeated dose toxicity data on cinnamic acid are insufficient to determine a NOAEL for repeated dose toxicity. Cinnamic acid is a metabolite of read-across analog cinnamaldehyde (CAS # 104-55-2), which has sufficient repeated dose toxicity data (Peters, 1994). Groups of 10 Sprague Dawley (SD) rats/sex/dose were administered aerosolized cinnamal (cinnamaldehyde synonym) by nose-only inhalation at target concentrations of 0, 1, 10, and 100 ppm (overall mean exposure concentrations were 0, 5.4, 54.1, and 541 mg/m3) for 2 weeks (6 h/day, 5 days/week). The study was conducted according to OECD 412/GLP guidelines. The NOAEL was determined to be 54.1 mg/m3 (equivalent to 14 mg/kg/day based on minute volume and bodyweight parameters for SD rats) based on clinical signs, body weight, food consumption, local lung effects, and hepatotoxicity (RIFM, 2012; RIFM, 2013a). A dermal absorption study was conducted on cinnamic acid in vitro with human skin and *in vivo* with rhesus monkeys. The most conservative skin absorption value of 83.9% obtained under occlusion in rhesus monkeys was selected for cinnamic acid (Bronaugh, 1985). Another gavage repeated dose study was conducted in male rats treated with 0, 2.14, 6.96, 22.62, and 73.5 mg/kg body weight/day of cinnamaldehyde for 10, 30, and 90 days, with a focus limited to the kidney and serum effects. The NOAEL was determined to be 22.62 mg/kg/day based on alteration in the blood chemistry and terminal body weight among the animals of the high-dose group (Gowder, 2008).

A default safety factor of 3 was used when deriving a NOAEL from the 30-day studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 22.62/3 or 7.5 mg/kg/day.

The most conservative NOAEL of 7.5 mg/kg/day was selected for the repeated dose toxicity endpoint.

Therefore, the cinnamic acid MOE for the repeated dose toxicity endpoint can be calculated by dividing the cinnamaldehyde NOAEL in mg/kg/day by the total systemic exposure for cinnamic acid, 7.5/0.00097, or 7732.

In addition, the total systemic exposure for cinnamic acid (0.97 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint at the current level of use.

*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:** Marrs (1989).

**Literature Search and Risk Assessment Completed On:** 05/31/21.

#### 11.1.3. Reproductive toxicity

The MOE for cinnamic acid is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on cinnamic acid or any read-across materials. The exposure is below the TTC at the current

level of use.

*11.1.3.1. Risk assessment.* There are sufficient developmental toxicity data on cinnamic acid. A gavage developmental toxicity study was conducted in rats. Cinnamic acid showed no teratogenic effects, and a NOAEL of 50 mg/kg/day was concluded for developmental toxicity, the highest dosage tested (Zaitsev, 1975). A dermal absorption study was conducted on cinnamic acid in vitro with human skin and *in vivo* with rhesus monkeys. The most conservative skin absorption value of 83.9% obtained under occlusion in rhesus monkeys was selected for cinnamic acid (Bronaugh, 1985).

Therefore, the cinnamic acid MOE for the developmental toxicity endpoint can be calculated by dividing the cinnamic acid NOAEL in mg/kg/day by the total systemic exposure for cinnamic acid, 50/0.00097, or 51564.

In addition, the total systemic exposure for cinnamic acid (0.97 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint at the current level of use.

There are no fertility data on cinnamic acid or any read-across materials that can be used to support the fertility endpoint. In a dermal absorption study conducted on cinnamic acid in vitro with human skin and *in vivo* with rhesus monkeys, the most conservative skin absorption value of 83.9% obtained under occlusion in rhesus monkeys was selected for cinnamic acid (Bronaugh, 1985). The total systemic exposure for cinnamic acid (0.97 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the fertility endpoint at the current level of use.

**Additional References:** Rice (1994).

**Literature Search and Risk Assessment Completed On:** 05/31/21.

*11.1.4. Skin sensitization*

Based on the existing data, cinnamic acid does not present a concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* Based on the existing data, cinnamic acid is not considered a skin sensitizer. The chemical structure of this material indicates that it is expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0). However, trans-cinnamic acid was found to be negative in an in vitro direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the human cell line activation test (h-CLAT) (ECHA, 2018). Additionally, the weight of evidence from several guinea pig tests indicates that cinnamic acid does not exhibit the potential to induce skin sensitization (Weibel, 1989; Buehler, 1985; Basketter, 1996; Ishihara, 1986; RIFM, 2003). In a human maximization test, no reactions indicative of sensitization were observed at 4% (2760 μg/cm2) (RIFM, 1976). Additionally, the Expert Panel for Fragrance Safety* reviewed the available data on cinnamic acid and concluded that it does not present a concern for skin sensitization in humans (Bickers, 2005).

Based on the weight of evidence (WoE) from structural analysis, in vitro experiments, and animal and human studies, cinnamic acid does not present a concern for skin sensitization under the current, declared levels of use.

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

**Additional References:** Lahti (1985); Lahti (1984).

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

*11.1.5. Phototoxicity/photoallergenicity*

Although cinnamic acid absorbs in the UV/Vis range, based on the available *in vivo* data, the material does not present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* UV/Vis spectra indicate significant absorbance in the critical range of 290–700 nm. The molar absorption coefficients are above the benchmark of concern for phototoxicity/photoallergenicity (Henry, 2009). In an in vitro 3T3-Neutral Red Uptake phototoxicity assay (OECD 432), cinnamic acid was not predicted to have phototoxic potential (RIFM, 2015). Additionally, in multiple *in vivo* guinea pig phototoxicity and photoallergenicity studies, reactions indicative of phototoxicity/photoallergenicity were not observed (RIFM, 2003; Pathak, 1959b; Pathak, 1959a). Based on the in vitro and *in vivo* study data, cinnamic acid is not expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.2. UV spectra analysis.* The UV/Vis spectra (OECD TG 101) for cinnamic acid indicate absorption in the region of 290–700 nm, peaking at 270 nm and returning to baseline by 350 nm. Molar absorption coefficients (15608, 5298, 15323 L $mol^{-1}$ • $cm^{-1}$ under neutral, acidic, and basic conditions, respectively) are above 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:** 06/01/21.

*11.1.6. Local respiratory toxicity*

There are no inhalation data available on cinnamic acid; however, in a 2-week acute inhalation study for the read-across analog, cinnamaldehyde (CAS # 104-55-2; see Section VI), a NOAEC of 55.5 mg/$m^3$ was reported (RIFM, 2012).

*11.1.6.1. Risk assessment.* The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week acute inhalation study conducted in rats, a NOAEC of 55.5 mg/$m^3$ was reported for cinnamaldehyde (RIFM, 2012). Exposures were terminated for the 526 mg/$m^3$ treated group following the fifth exposure, and the animals were euthanized on study day 7 due to adverse clinical observations, substantial bodyweight loss, and decreased food consumption. Histologic alterations associated with the highest concentration exposure were limited to the nasal cavity, larynx, and liver. Responses consistent with chemical irritation were seen only at the highest administered concentration (526 mg/$m^3$). Exposures at 5.8 and 55.5 mg/$m^3$ did not result in any adverse findings. The NOAEC was determined to be 55.5 mg/$m^3$.

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

- (55.5 mg/$m^3$) × (1 $m^3$/1000 L) = 0.0555 mg/L
- MV of 0.17 L/min for an SD rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0555 mg/L) × (61.2 L/day) = 3.40 mg/day
- (3.40 mg/day)/(0.0016 kg lung weight of rat*) = 2125 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0026 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; Safford, 2015). To

compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.004 mg/kg lung weight/day, resulting in an MOE of 531250 (i.e., [2125 mg/kg lung weight/day]/[0.004 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0026 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

**Additional References:** Marrs (1989); Rice (1994); RIVM, 2007; RIFM, 2013a.

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

### 11.2. Environmental endpoint summary

#### 11.2.1. Screening-level assessment

A screening-level risk assessment of cinnamic acid 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, Cinnamic acid 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 cinnamic acid 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).

*11.2.1.1. Risk assessment.* Based on the current Volume of Use (2015), cinnamic acid presents no risk to the aquatic compartment in the screening-level assessment.

#### 11.2.2. Key studies

*11.2.2.1. Biodegradation.* Not available.

*11.2.2.2. Ecotoxicity.* Not available.

*11.2.2.3. Other available data.* *trans*-Cinnamic acid (CAS # 140-10-3) has been registered for REACH with the following additional information available at this time (ECHA, 2018):

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under semi-static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 32 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values based on mean measured concentrations for growth rate and yield were reported to be 19 mg/L and 14 mg/L, respectively.

*11.2.2.4. Risk assessment refinement.* Since cinnamic acid has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

The endpoint used to calculate PNEC is underlined.

Exposure information and PEC Calculation (following RIFM Framework; Salvito, 2002).

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 2.7 | 2.7 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band* | <1 | <1 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

*Combined regional Volumes of use for both CAS #s.

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

The RIFM PNEC is 0.1737 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 05/13/21.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr

| | LC50 (Fish) (mg/mL) | EC50 (*Daphnia*) (mg/mL) | EC50 (Algae) (mg/mL) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 173.7 | | | 1000000 | 0.1737 | |

- **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 01/14/22.

## 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 G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.113232.

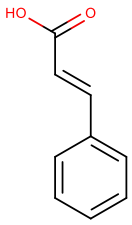
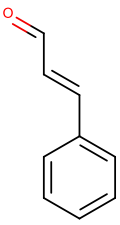
## Appendix

*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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | Cinnamic acid | Cinnamaldehyde |
| **CAS No.** | 621-82-9 | 104-55-2 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 0.75 |
| **SMILES** | OC(=O)C=Cc1ccccc1 | O=CC=Cc1ccccc1 |
| **Endpoint** | | Repeated dose toxicity<br>Local respiratory toxicity |
| **Molecular Formula** | $C_9H_8O_2$ | $C_9H_8O$ |
| **Molecular Weight (g/mol)** | 148.161 | 132.162 |
| **Melting Point (°C, EPI Suite)** | 133.00 | −7.50 |
| **Boiling Point (°C, EPI Suite)** | 300.00 | 246.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 6.67E-03 | 3.85E+00 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 5.70E+02 | 1.42E+03 |
| **Log KOW** | 2.13 | 1.9 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 16.09 | 41.56 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.73E-03 | 3.59E-01 |
| ***Repeated Dose Toxicity*** | | |
| **Repeated Dose (HESS)** | Carbamazepine (Hepatotoxicity) Alert\|Carbamazepine (Renal Toxicity) Alert\|Coumarin (Hepatotoxicity) Alert\|Styrene (Renal Toxicity) Alert\|Toluene (Renal toxicity) Alert | Styrene (Renal Toxicity) Alert\|Toluene (Renal toxicity) Alert |
| ***Metabolism*** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on cinnamic acid (CAS # 621-82-9). 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, cinnamaldehyde (CAS # 104-55-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

*Metabolism*

Metabolism of the read-across material cinnamaldehyde (CAS # 104-55-2) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2) (See table above). Cinnamaldehyde is metabolized to cinnamic acid in the first step with a 0.63 pre-calculated probability. Hence, cinnamaldehyde can be used as a read-across for cinnamic acid. Cinnamaldehyde was out of domain for the *in vivo* and in vitro rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and justification was provided.

*Conclusions*

- Cinnamaldehyde (CAS # 104-55-2) is used as a structurally similar read-across analog for cinnamic acid (CAS # 104-54-1) for repeated dose toxicity and local respiratory toxicity endpoints.
  - o The target belongs to a class of α,β-unsaturated carboxylic aromatic acids while the analog is structurally similar and belongs to a class of α,β-unsaturated aryl aldehydes.
  - o The target material and read-across analog have a Tanimoto score of 0.92, which is mainly driven by the aryl fragment. The differences in the structure responsible for the Tanimoto score <1 are not relevant from a toxicology endpoint perspective.
  - o The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o Any differences in the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant.
  - o The structural alerts for the toxicological endpoints are consistent between the target as well as the read-across material. Any differences in the alerts can be overridden by data for each toxicological endpoint.
  - o The structural alerts show that the predicted metabolites of the read-across material are similarly reactive as compared to the target material or its predicted metabolites.
  - o The target material and read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target and the read-across analog appear to be toxicologically insignificant.

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