Food and Chemical Toxicology 141 (2020) 111337

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, cinnamyl alcohol, CAS Registry Number 104-54-1

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A B S T R C T

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

Cinnamyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that cinnamyl alcohol 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 and local respiratory toxicity endpoints. The developmental and reproductive toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cinnamyl alcohol is below the TTC (0.03 mg/kg/day). Data provided a No Expected Sensitization Induction Level (NESIL) of 2900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cinnamyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cinnamyl alcohol 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.

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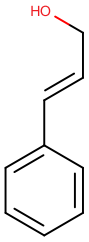
https://doi.org/10.1016/j.fct.2020.111337
Received 18 April 2019; Received in revised form 14 February 2020; Accepted 8 April 2020
Available online 24 April 2020

Version: 120619. This version replaces any previous versions.

Name: Cinnamyl alcohol
CAS Registry Number: 104-54-1



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., 2015a; 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
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
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.

Cinnamyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data show that cinnamyl alcohol 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 and local respiratory toxicity endpoints. The developmental and reproductive toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cinnamyl alcohol is below the TTC (0.03 mg/kg/day). Data provided a No Expected Sensitization Induction Level (NESIL) of 2900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; cinnamyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cinnamyl alcohol 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.	(Sekizawa and Shibamoto, 1982; Bickers et al., 2005; RIFM, 2013c)
Repeated Dose Toxicity: NOAEL = 22.62 mg/kg/day.	RIFM (2012)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 2900 μg/cm^2.	(Basketter et al., 2002; RIFM, 2001a; RIFM, 2001b; RIFM, 2002a; RIFM, 2002b; RIFM, 2004)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 55.5 mg/m^3	RIFM (2012)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 97.9% (OECD 301B) — RIFM (1993)
Bioaccumulation: Screening-level: 4.989 L/kg — (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h Fish LC50: 9.0 mg/L — (ECHA REACH Dossier: Cinnamyl alcohol; ECHA, 2012a)
Conclusion: Not PBT or vPvB as per IFRA Environmental standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 — (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 9.0 mg/L — (ECHA REACH Dossier: Cinnamyl alcohol; ECHA, 2012a)
RIFM PNEC is: 9.0 μg/L

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

1. Identification

1. **Chemical Name:** Cinnamyl alcohol
2. **CAS Registry Number:** 104-54-1
3. **Synonyms:** Cinnamic alcohol; 3-Phenyl-2-propen-1-ol; 2-Propen-1-ol, 3-phenyl-; Styryl carbinol; Zimtalcohol; Styryl alcohol; Styrone; 3-Phenylallyl alcohol; ｹｲ皮酸ｱﾙｺｰﾙ; 3-Phenylprop-2-en-1-ol; Cinnamic alcohol pure; ZIMTALKOHOL; Cinnamyl alcohol
4. **Molecular Formula:** $C_9H_{10}O$
5. **Molecular Weight:** 134.17
6. **RIFM Number:** 115

2. Physical data

1. **Boiling Point:** 258 °C (FMA), (calculated) 248.6 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA)
3. **Log K_{OW}:** 1.84 (EPI Suite)
4. **Melting Point**: 30 °C (FMA), (calculated) 15.84 °C (EPI Suite)
5. **Water Solubility:** 6188 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0570 torr (Vuilleumier et al., 1995), (calculated) 0.00141 mm Hg @ 20 °C (EPI Suite v4.0), (calculated) 0.001 mm Hg 20 °C (FMA), (calculated) 0.00268 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$).
9. **Appearance/Organoleptic:** White or opaque solid crystalline mass which has a warm-balsamic, floral, and sweet odor.

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.16% (RIFM, 2013e)
3. **Inhalation Exposure*:** 0.00043 mg/kg/day or 0.032 mg/day (RIFM, 2013e)
4. **Total Systemic Exposure** **: 0.0028 mg/kg/day (RIFM, 2013e)

*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:** 65.9%

Bickers et al., 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 et al., 1985**:** The absorption of radiolabeled cinnamyl alcohol in acetone through excised human abdominal skin was measured using an *in vitro* diffusion cell technique. Both occluded and non-occluded absorption were measured. Sections of skin c. 350 μm thick were removed from the surface of full-thickness skin. A flow-through cell was used; normal saline was pumped through the cells (skin surface area 0.64 cm^2) at a rate of c. 5 mL/h and collected in scintillation vials. The receptor fluid was saline. Cinnamyl alcohol in acetone was applied to the excised skin at a concentration of 4 $\mu g/cm^2$, and the surface of the skin was washed after 24 h. The study was continued until absorption was complete (48–72 h). The tops of the diffusion cells were sealed with parafilm for experiments measuring occluded absorption. Absorbed radioactivity was determined by liquid scintillation counting. The amount of cinnamyl alcohol absorbed through non-occluded skin was 33.9 ± 7.3% of the dose, and the amount absorbed through occluded skin was 65.9 ± 7.9%.

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:** None
   b. **Repeated Dose Toxicity:** Cinnamaldehyde (CAS # 104-55-2)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Cinnamaldehyde (CAS # 104-55-2)
   g. **Environmental Toxicity:** None
3. **Read-across Justification: See Appendix below**

6. Metabolism

Bickers et al., 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.

Nutley (1990): Groups of 4 male Fischer 344 rats received a single oral dose of 2.5 mmol 14C/d5 cinnamyl alcohol in trioctanoin. Urine was collected for 24 h. Metabolites were isolated and examined by GCMS. The following metabolites were identified as percent of the dose: hippuric acid (52.1%), benzoyl glucuronide (1.1%), 3-hydroxy-3-phenylpropionic acid (1.9%), benzoic acid (2.8%), acetophenone (0.3%), cinnamyl alcohol (0.4%), cinnamaldehyde (0.5%) and cinnamic acid (0.4%). Three unidentified metabolites were also excreted, unknown 1 (0.6%), unknown 2 (0.5%), unknown 3 (2.6%).

Nutley (1990): Groups of 4 male CD-1 mice received a single dose of 2.5 mmol 14C/d5 cinnamyl alcohol in trioctanoin by intraperitoneal injection. Urine was collected for 24 h. Metabolites were isolated and examined by GCMS. The following metabolites were identified as a percent of the dose: hippuric acid (32.1%), benzoyl glucuronide (3.8%), 3-hydroxy-3-phenylpropionic acid (2.4%), benzoic acid (1.4%), cinnamoyl glycine (2.0%), cinnamyl alcohol (1.2%) and cinnamic acid (0.3%). Four unidentified metabolites were also excreted, unknown 1 (4.2%), unknown 2 (1.2%), unknown 3 (2.7%) and unknown 4 (7.5%).

Moss et al., 2016: *In situ* metabolism/activation of cinnamyl alcohol was investigated using high-resolution magic angle spinning nuclear magnetic resonance on reconstructed human epidermis (RHE) models. Incubation of carbon-13 substituted cinnamyl derivatives with RHE did not result in the formation of cinnamaldehyde. The metabolites formed suggest the formation of an epoxy-alcohol and an allylic sulfate as potential electrophiles, which suggest that cinnamyl alcohol could induce skin sensitization through a route independent of the one involving cinnamaldehyde.

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

Cinnamyl alcohol is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Cherry.
Cinnamomum species.
Citrus fruits.
Fig (Ficus carica L.)
Guava and feyoa
Honey.
Melon.
Ocimum species.
Passion fruit (*Passiflora* species).
Raspberry, blackberry, and boysenberry.
Star anise.
Syzygium species.
Tapereba, caja fruit (*Spondias lutea* L.)
Vaccinium species.
Vanilla.

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

8. Reach dossier

Available; accessed on 03/15/19 (ECHA, 2012a)

9. Conclusion

The maximum acceptable concentrations[a] in finished products for cinnamyl alcohol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.22
2	Products applied to the axillae	0.067
3	Products applied to the face/body using fingertips	0.25
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	0.25
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.25
5D	Baby cream, oil, talc	0.085
6	Products with oral and lip exposure	0.13
7	Products applied to the hair with some hand contact	0.25
8	Products with significant ano-genital exposure (tampon)	0.085
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.76
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.76
10B	Aerosol air freshener	2.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.085
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	51

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 cinnamyl alcohol, the basis was the reference dose of 0.2262 mg/kg/day, a skin absorption value of 65.9%, and a skin sensitization NESIL of 2900 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 existing data and use levels, cinnamyl alcohol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of cinnamyl alcohol has been investigated in a mouse lymphoma assay. These results indicate that cinnamyl alcohol demonstrated reproducible dose-related increases in the incidence of reversions in L5178Y mouse lymphoma cells (Palmer, 1984). Little weight can be given to this study as the data are only given in an abstract and no other details were provided. In addition, no structural alerts were identified for cinnamyl alcohol by DEREK; this is supported by other available tests. Cinnamyl alcohol was not mutagenic in several Ames and modified Ames assays (Eder et al., 1980; Eder et al., 1982a; Eder et al., 1982b; Lutz et al., 1980). The negative result is most clearly supported in an Ames assay conducted in 5 strains of *S. typhimurium* and 1 *E. coli* strain. There was no increase in the number of revertant colonies in any strain when tested up to 3000 μg/plate, both with and without metabolic activation (Sekizawa and Shibamoto, 1982).

The clastogenic activity of cinnamyl alcohol was evaluated in an *in vitro* cytogenetic assay in Chinese hamster ovary cells. CHO-K1 cells were exposed to concentrations of cinnamyl alcohol up to 33.3 μM, and metaphase spreads were analyzed for sister chromatid exchanges (SECs). No effects were observed both with and without metabolic activation (Sasaki et al., 1989). Furthermore, the ECHA REACH Dossier for cinnamyl alcohol (ECHA, 2012a) provides an OECD Toolbox version 3.2 prediction for the chromosome aberration test on Chinese hamster

Lung (CHL) with S9 metabolic activation, and it was concluded that cinnamyl alcohol does not exhibit positive chromosomal effects (ECHA, 2012a). Furthermore, cinnamyl alcohol is rapidly converted to cinnamaldehyde, which in turn is converted to cinnamic acid. The intermediate metabolite, cinnamaldehyde, and the major metabolite, cinnamic acid, do not present a concern regarding genotoxicity (Bickers et al., 2005). Additionally, the Expert Panel for Fragrance Safety has concluded, based on a weight-of-evidence evaluation, that cinnamyl alcohol has no significant potential to produce genotoxic effects *in vivo* under the current conditions of use (Bickers et al., 2005).

The clastogenicity of the metabolite cinnamic acid (CAS # 621-82-9; See section V) was assessed in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes (HPBL) were treated with cinnamic acid at dose levels of 200–1480 μg/mL for 4 h with and without S9 metabolic activation and 50–800 μg/mL for 24 h without S9 metabolic activation. Under the conditions of this study, cinnamic acid did not cause a significant induction of micronuclei in either the non-activated or S9-activated treatment conditions (RIFM, 2013c). Based on this cinnamic acid is considered non-clastogenic in the *in vitro* mammalian cell micronucleus assay using HPBL.

Taken together, these data indicate that cinnamyl alcohol does not present a concern for genetic toxicity.

Additional References: Eder et al., 1980; Eder et al., 1982a; Eder et al., 1982b; Yoo (1986); Lutz et al., 1980; Palmer (1984); Yoo, 1986; Oda et al., 1978.

Literature Search and Risk Assessment Completed On: 05/26/16.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on cinnamyl alcohol are insufficient to determine a NOAEL for repeated dose toxicity. The metabolite cinnamaldehyde (CAS # 104-55-2; see Section V) has been extensively studied for repeated dose toxicity. In a gavage 90-day repeated dose study conducted in rats with a focus limited to kidney and serum effects, the NOAEL for cinnamaldehyde was determined to be 22.62 mg/kg/day (Gowder and Devaraj, 2008). A dermal absorption study was conducted on cinnamic alcohol *in vitro* with human skin (Bronaugh et al., 1985). Under the more severe condition of occlusion, 65.9% of cinnamic alcohol was absorbed. **Therefore, the cinnamyl alcohol 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 cinnamyl alcohol, 22.62/0.0028 or 8079.**

In addition, the total systemic exposure for cinnamyl alcohol (2.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

Section IX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.2262 mg/kg/day).

The RfD for cinnamyl alcohol was calculated by dividing the NOAEL of 22.62 mg/kg/day by the uncertainty factor, 100 = 0.2262 mg/kg/day.

Additional References: Zaitsev and Rakhmanina, 1974; Stoner et al., 1973; RIFM, 2012; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 06/08/16.

10.1.3. Developmental and Reproductive Toxicity

There are insufficient reproductive and developmental toxicity data on cinnamyl alcohol or any read-across materials. The exposure is below the TTC at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on cinnamyl alcohol or any of the read-across materials. A pilot gavage developmental toxicity study was conducted in rats, which showed no teratogenic effects and concluded a NOAEL of 53.5 mg/kg/day for developmental toxicity, the highest dosage tested (Zaitsev and Maganova, 1975). Since only 1 dose level was tested, a clear NOAEL could not be determined. A dermal absorption study was conducted on cinnamic alcohol *in vitro* with human skin (Bronaugh et al., 1985). Under the more severe condition of occlusion, 65.9% of cinnamic alcohol was absorbed. The total systemic exposure to cinnamyl alcohol (2.8 μg/kg bw/day) is below the TTC (30 μg/kg bw/day or 0.03 mg/kg bw/day; the RfD for a Cramer Class I material; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint at the current level of use.

There are no reproductive data on cinnamic alcohol or any read-across materials that can be used to support the reproductive toxicity endpoint. A dermal absorption study was conducted on cinnamic alcohol *in vitro* with human skin (Bronaugh et al., 1985). Under the more severe condition of occlusion, 65.9% of cinnamic alcohol was absorbed. The total systemic exposure to cinnamyl alcohol (2.8 μg/kg/day) is below the TTC (30 μg/kg bw/day or 0.03 mg/kg bw/day; the RfD for a Cramer Class I material; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint at the current level of use.

Additional References: Maganova and Saitsev, 1973; Forschmidt et al., 1979; Abramovici and Rachmuth-Roizman, 1983.

Literature Search and Risk Assessment Completed On: 06/08/16.

10.1.4. Skin sensitization

Based on the existing data, cinnamyl alcohol is considered to be a weak skin sensitizer with a defined NESIL of 2900 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, cinnamyl alcohol is considered to be a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins via Michael addition (Roberts et al., 2007; Toxtree 2.5.0) and can

Table 1
Cinnamyl alcohol – Data Summary.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm[b]	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]
5250 [1]	Weak	2953	2759	4724	2900

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.

undergo auto-oxidation resulting in degradation products that may be protein reactive (OASIS TIMES 2.27.18). Investigation of *in situ* metabolism of cinnamyl alcohol using high-resolution magic angle spinning nuclear magnetic resonance on RHE model suggests that cinnamyl alcohol could metabolize to epoxy-alcohol and/or an allylic sulfate as potential electrophiles and lead to skin sensitization through a route independent of the one involving cinnamaldehyde (Moss et al., 2016). Accordingly, cinnamyl alcohol was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, human cell line activation test (h-CLAT) and U937-CD86 test (Natsch et al., 2013; Emter et al., 2010; Bauch et al., 2012; Piroird et al., 2015). In a murine local lymph node assay (LLNA), cinnamyl alcohol was found to be sensitizing with an EC3 value of 21% or 5250 μg/cm^2 (Gerberick et al., 2005). Additionally, in a confirmatory human repeated insult patch test (HRIPT), 4% (4724 μg/cm^2) of cinnamyl alcohol in 3:1 DEP:EtOH caused sensitization reaction (RIFM, 2001a; RIFM, 2001b; RIFM, 2002b). However, no reactions indicative of sensitization were observed in an HRIPT conducted at 2.5% or 2953 μg/cm^2 cinnamyl alcohol in 1:3 ethanol:diethyl phthalate in 106 volunteers (RIFM, 2004). Similarly, no sensitization was observed in human maximization tests carried out with 2759 μg/cm^2 cinnamyl alcohol in petrolatum (RIFM, 1979). The available data demonstrate that cinnamyl alcohol is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 2900 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 of 0.2262 mg/kg/day).

Additional References: RIFM, 1982a; RIFM, 1977a; RIFM, 1979; RIFM, 1977b; RIFM, 1980; RIFM, 1981; RIFM, 1976a; RIFM, 1976b; RIFM, 1975a; Klecak et al., 1977; Jordan and King, 1977; RIFM, 1978; Greif (1967); Buehler and Ritz, 1985; RIFM, 1986a; Johnson and Goodwin, 1985; RIFM, 1975b; RIFM, 1986b; RIFM, 1985; Basketter (1992); Hausen et al., 1995; Basketter and Gerberick, 1996; Basketter et al., 2002; Elahi et al., 2002; Klecak (1985); RIFM, 1983; RIFM, 1982b; RIFM, 1982c; Modjtahedi et al., 2011; RIFM, 2002a.

Literature Search and Risk Assessment Completed On: 06/02/16.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no suitable phototoxicity studies available for cinnamyl alcohol 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, cinnamyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for cinnamyl alcohol indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 L mol^{-1} · cm^{-1}) considered to be of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/16.

10.1.6. Local Respiratory Toxicity

There are no inhalation data available on cinnamyl alcohol; however, in an acute 2-week inhalation study for the analog cinnamaldehyde (CAS # 104-55-2; see section V), a NOAEC of 55.5 mg/m^3 was reported in RIFM, 2012.

10.1.6.1. 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^3/1000L) = 0.0555 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0555 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 0.032 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015 and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.049 mg/kg lung weight/day resulting in an MOE of 43367 (i.e., [2125 mg/kg lung weight/day]/[0.049 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.032 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: The Union of German Candle Manufacturers, 1997; Kim et al., 2004; Johnson et al., 2005; RIVM et al., 2007; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 06/01/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of cinnamyl alcohol 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 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, cinnamyl alcohol 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, 2012b) identify cinnamyl alcohol as not persistent and not 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), cinnamyl alcohol presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 1993**:** A biodegradation test according to the OECD 301B method was conducted. After 28 days biodegradation of 97.9% was observed.

10.2.1.2.2. Ecotoxicity. RIFM, 2013b**:** A 96-h algae (*Pseudokirchneriella subcapitata*) acute test was conducted according to the OECD 201 method. Based on the day 0 measured test concentrations, the 72-h EbC50, ErC50, and NOEC were 26 mg/L, 28 mg/L, and 6.6 mg/L, respectively. The 96-h EbC50, ErC50, and NOEC were 28 mg/L, 29 mg/L, and 2.5 mg/L, respectively, RIFM, 2013d**:** A 48-h flow-through acute toxicity test with *Daphnia magna* was conducted according to the OECD 202 method. An EC50 of 77 mg/L was reported.

10.2.1.3. Other available data. Cinnamyl alcohol has been registered under REACH, and the following data is available:

A fish (*Danio rerio*) acute toxicity test was conducted according to the OECD 203 method under static conditions. The 96-h LC50 was reported to be 9 mg/L (ECHA, 2012a).

10.2.2. 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.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg /L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	249.3			1,000,000	0.2493	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.74	0.377	24.76	10,000	0.0377	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	153.4	85.8	60.16			Neutral Organics
Tier 3: Measured Data including REACH						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	9.0			1000	9.0	
Daphnia		77				
Algae		26				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.84	1.84
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 9 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 volume of use.

Literature Search and Risk Assessment Completed On: 02/28/19.

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 01/22/19.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111337.

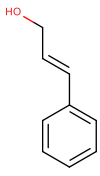
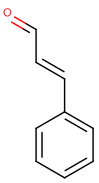
Appendix

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). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite (US EPA, 2012b).
- 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 and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2018).

	Target material	Read-across material
Principal Name	Cinnamyl alcohol	Cinnaldehyde
CAS No.	104-54-1	104-55-2
Structure		

Similarity (Tanimoto score)	1.0	0.92
Read-across endpoint		• Repeated dose toxicity • Local respiratory toxicity
Molecular Formula	$C_9H_{10}O$	C_9H_9O
Molecular Weight	134.17	132.16
Melting Point (°C, EPI Suite)	15.84	0.04
Boiling Point (°C, EPI Suite)	248.60	226.69
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.358	4.49
Log Kow (KOWWIN v1.68 in EPI Suite)	1.95	1.19
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	6188	1420
J_{max} (μg/cm^2/h, SAM)	186.1199	13.23
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.60e-002	3.59e-001
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Metabolism		
OECD QSAR Toolbox (3.1)	• See Supplemental Data 1	• See Supplemental Data 2
Rat liver S9 metabolism simulator	• 2 metabolites from rat S9 simulator. • An2, Michael addition, Schiff's base formation, Highly reactive, Aldehyde type compounds. • No metabolites observed in Rat or mammalian metabolism.	• 1 metabolite from rat S9 simulator. • AN2, Michael addition. • No metabolites observed in Rat or mammalian metabolism.

Metabolism

There are no metabolism data on cinnamyl alcohol (CAS # 104-54-1). Metabolism of the target material cinnamyl alcohol (CAS # 104-54-1) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (See table above). Cinnamyl alcohol is metabolized to cinnamaldehyde (CAS # 104-55-2) in the first step with 0.63 pre-calculated probability. Hence cinnamaldehyde can be used as read-across for cinnamyl alcohol. Cinnamaldehyde was out of domain for *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and justification is provided.

- Cinnamaldehyde (CAS # 104-55-2) is used as a read-across analog for cinnamyl alcohol (CAS # 104-54-1) for the repeated dose and respiratory toxicological endpoints.
  - o The target belongs to the class of α,β-unsaturated aryl alcohols while the analog is structurally similar and belongs to a class of α,β-unsaturated aryl aldehydes.
  - o The target and read-across analog have a Tanimoto score of 0.92 which is mainly driven by the aryl fragment. The differences in the structure that are responsible for Tanimoto score < 1 are not relevant from a toxicology endpoint perspective.
  - o The physical–chemical properties of the target and the read-across analog are very similar. Any differences in the physical–chemical properties are not relevant from a toxicological endpoint perspective.
  - o The structural alerts for the toxicological endpoints are consistent between the target as well as the read-across material.
  - 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 and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read-across metabolites show no structural alerts for reproductive and skin sensitization toxicity.
  - o The structural differences between target and the read-across analog appear to be toxicologically insignificant.

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