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Short Review

RIFM fragrance ingredient safety assessment, cinnamyl formate, CAS Registry Number 104-65-4

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [i], H. Moustakas [a], M. Na [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [k], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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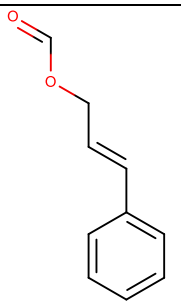

Abbreviation/Definition List:

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)
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

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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 formate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog cinnamyl acetate (CAS # 103-54-8) show that cinnamyl formate is not expected to be genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for cinnamyl formate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cinnamyl formate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cinnamyl formate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; cinnamyl formate 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 expected to be genotoxic.	(RIFM, 2003; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM (2016a)
Reproductive Toxicity: Developmental toxicity: NOAEL = 600 mg/kg/day. Fertility: NOAEL = 600 mg/kg/day.	RIFM (2016a)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	RIFM (2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.03 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 15.31 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: LC50: 119.9 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: 119.9 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.1199 μg/L

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

1. Identification

1. Chemical Name: Cinnamyl formate
2. CAS Registry Number: 104-65-4
3. Synonyms: 3-Phenylallyl formate; 3-Phenyl-2-propen-1-yl formate; 2-Propen-1-ol, 3-phenyl-, formate; 3-Phenylprop-2-en-1-yl formate; Cinnamyl formate
4. Molecular Formula: $C_{10}H_{10}O_2$
5. Molecular Weight: 162.18
6. RIFM Number: 382

7. Stereochemistry: Isomer not specified. One geometric center present and a total of 2 stereoisomers possible.

2. Physical data

1. Boiling Point: 241.56 °C (EPI Suite)
2. Flash Point: >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA]), 212 °F; CC (Givaudan Index, 1961)
3. Log K_{OW}: 2.3 (EPI Suite)
4. Melting Point: 18.36 °C (EPI Suite)
5. Water Solubility: 725.1 mg/L (EPI Suite)
6. Specific Gravity: 1.08 (FMA), 1.074–1.079 (Givaudan Index, 1961)
7. Vapor Pressure: 0.0154 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0245 mm Hg at 25 °C (EPI Suite)
8. UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. Appearance/Organoleptic: Colorless to slightly yellow liquid, possessing a balsamic odor with a cinnamon background (Givaudan Index, 1961)

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. 95th Percentile Concentration in Fine Fragrance: 0.0038% (RIFM, 2016b)
2. Inhalation Exposure*: 0.00035 mg/kg/day or 0.026 mg/day (RIFM, 2016b)
3. Total Systemic Exposure**: 0.0011 mg/kg/day (RIFM, 2016b)

*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: Cinnamyl acetate (CAS # 103-54-8)
b. Repeated Dose Toxicity: Cinnamyl acetate (CAS # 103-54-8)
c. Reproductive Toxicity: Cinnamyl acetate (CAS # 103-54-8)
d. Skin Sensitization: Cinnamyl acetate (CAS # 103-54-8)
e. Phototoxicity/Photoallergenicity: None
f. Local Respiratory Toxicity: None
g. Environmental T**oxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

There are no metabolism data on cinnamyl formate (CAS # 104-65-4). Metabolism of the target material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2) (see the Appendix). The target material is metabolized via ester hydrolysis to cinnamyl alcohol (CAS # 104-54-1) and formic acid (CAS # 64-18-6) in the first step with 0.511 pre-calculated and 0.95 intrinsic probability. Cinnamyl alcohol undergoes aliphatic oxidation to form cinnamaldehyde (CAS # 104-55-2) in the second step with 0.49 pre-calculated and 0.95 intrinsic probability.

Additional References: None.

8. Natural occurrence

Cinnamyl formate is not reported to occur in foods by the VCF*.

*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

Available; accessed 08/27/20.

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, cinnamyl formate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cinnamyl formate was tested using the BlueScreen assay and found to be genotoxic without S9 metabolic activation (RIFM, 2014). There are no studies evaluating the mutagenicity of cinnamyl formate. The mutagenic activity of read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) was assessed in an Ames assay conducted equivalent to OECD TG 471 using the standard plate incorporation method and modified preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with cinnamyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in any of the test strains at any concentration (RIFM, 2003). Under the conditions of the study, cinnamyl acetate was not considered mutagenic in the Ames test and this can be applied to cinnamyl formate.

There are no studies assessing the clastogenic activity of cinnamyl formate. The clastogenic activity of cinnamyl acetate (CAS # 103-54-8) was assessed 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 cinnamyl acetate in

DMSO at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation at the 3-h and 24-h time points. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at the lowest evaluated concentration in the approximate 24-h treatment without S9. However, the BNMN frequency (1.10%) observed at this concentration was within the historical control range for this test condition and did not show a dose response; therefore, this increase was not considered biologically relevant. Cinnamyl acetate did not induce BNMN when tested up to the maximum dose in the 3-h treatments with and without metabolic activation (RIFM, 2015). Based on the findings of the study, cinnamyl acetate was concluded to be negative for the induction of micronuclei in the *in vitro* mammalian cell micronucleus test using human peripheral blood lymphocytes.

Based on the available data, cinnamyl acetate does not present a concern for genotoxic potential and this can be extended to cinnamyl formate.

Additional References: RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

The MOE for cinnamyl formate 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 cinnamyl formate. Read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) has sufficient repeated dose toxicity data. An OECD 422 and GLP-compliant 28-day gavage combined repeated dose study with a developmental and reproductive toxicity screening study was conducted with test material cinnamyl acetate. Groups of 10 Wistar rats/sex/dose were administered the test material via gavage at dose levels of 0, 65, 200, and 600 mg/kg/day in corn oil. An additional 14-day recovery group of 5 rats/sex assigned to the control and high-dose groups were also included. There were no treatment-related adverse effects reported among the treated animals up to the highest dose tested. Thus, the NOAEL for the repeated dose toxicity endpoint was determined to be 600 mg/kg/day, the highest dose tested (RIFM, 2016a).

A default safety factor of 3 was used when deriving a NOAEL from the 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 600/3 or 200 mg/kg/day.

Therefore, the cinnamyl formate MOE for the repeated dose toxicity endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl formate, 200/0.0011, or 181,818.

In addition, the total systemic exposure to cinnamyl formate (1.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material 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: Zaitsev (1974).

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

The MOE for cinnamyl formate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cinnamyl formate. Read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) have sufficient developmental and reproductive toxicity data. An OECD 422 and GLP-compliant 28-day gavage combined repeated dose with a developmental and reproductive toxicity screening study was conducted with cinnamyl acetate. Groups of 10 Wistar rats/sex/dose were administered the test material via gavage at dose levels of 0, 65, 200, and 600 mg/kg/day in corn oil. An additional 14-day recovery group of 5 rats/sex assigned to the control and high-dose groups were also included. The male and female mating and fertility indices were significantly lower at the 65 and 600 mg/kg/day doses when compared to controls. The changes observed at the 65 mg/kg/day dose were considered incidental as the observed changes were within the historical control data. The lower male and female mating and fertility indices at 600 mg/kg/day were considered treatment-related as the changes were lower than the historical control data. However, there were no effects of treatment on the reproductive organs among the treated males and females. The pup survival index was also not altered by the treatment at all dose levels tested. No treatment-related developmental toxicity effects were reported among the treated animals up to the highest dose tested. Thus, the NOAEL for the developmental toxicity endpoint was determined to be 600 mg/kg/day, the highest dose tested. The NOAEL for the fertility endpoint was also determined to be 600 mg/kg/day since there were no effects observed on the reproductive organs among treatment group rats (RIFM, 2016a).

Therefore, the cinnamyl formate MOE for the reproductive toxicity endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl formate, 600/0.0011, or 545,455.

In addition, the total systemic exposure to cinnamyl formate (1.1 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Zaitsev (1974).

Literature Search and Risk Assessment Completed On: 08/16/20.

11.1.4. Skin sensitization

Based on existing data and read-across cinnamyl acetate (CAS # 103-54-8), cinnamyl formate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for cinnamyl formate. Based on the existing data and read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI), cinnamyl formate is not considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material cinnamyl acetate was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA) (RIFM, 2017a), and human cell line activation test (h-CLAT) (RIFM, 2017b). In human maximization tests, no skin sensitization reactions were observed with cinnamyl formate or read-across material cinnamyl acetate (RIFM, 1973; RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 3424 μg/cm^2 of read-across material cinnamyl acetate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2018).

Based on weight of evidence (WoE) from structural analysis, human studies, and read-across material cinnamyl acetate, cinnamyl formate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/05/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cinnamyl formate 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 cinnamyl formate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, cinnamyl formate 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 no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/10/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on cinnamyl formate. Based on the Creme RIFM Model, the inhalation exposure is 0.026 mg/day. This exposure is 53.8 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: Troy (1977); UGCM, 1997; Regnault-Roger (1995); Rice (1994); Kim (2004); Johnson (2005); Harth (2007); RIVM, 2007; RIFM, 2013a; Carlson (1946); Klimisch (1988); Silver (1992); Khare (1998); Montero (2001); Suzuki (2001); Larsen (2012).

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cinnamyl formate 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, cinnamyl formate 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 cinnamyl formate 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 ≥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) cinnamyl formate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. **Biodegradation:**

No data available.

Ecotoxicity:

No data available.

Other available data:

Cinnamyl formate has been 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, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.3	2.3
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 0.1199 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 VoU.

Literature Search and Risk Assessment Completed On: 08/20/20.

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

	(mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	119.9			1000000	0.1199	

- **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 04/13/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112366.

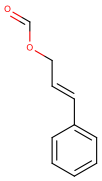
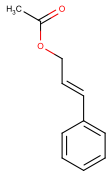
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). 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 the *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Cinnamyl formate	Cinnamyl acetate
CAS No.	104-65-4	103-54-8
Structure		
Similarity (Tanimoto Score)		0.85
Endpoint		• Genotoxicity • Skin sensitization • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{10}H_{10}O_2$	$C_{11}H_{12}O_2$
Molecular Weight	162.188	176.215
Melting Point (°C, EPI Suite)	18.36	20.45
Boiling Point (°C, EPI Suite)	252.00	265.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.27 E+00	1.61 E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.25 E+02	2.12 E+02
Log K_{OW}	2.3	2.85
J_{max} (μg/cm^2/h, SAM)	18.92	8.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.43 E+00	1.04 E+00
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
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	Aldehyde Type Compounds	Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert| Toluene (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)	Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Protein Binding (OECD)	No alert found	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified.	Alert for Michael Acceptor identified.
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 is insufficient toxicity data on cinnamyl formate (CAS # 104-65-4). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, cinnamyl acetate (CAS # 103-54-8) was identified as a read-across analog with sufficient data for the respective toxicity endpoints.

Conclusion/Rational

- Cinnamyl acetate (CAS # 103-54-8) was used as a structurally similar read-across analog for target material cinnamyl formate (CAS # 104-65-4) for the genotoxicity, skin sensitization, repeated dose toxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated aliphatic esters with an aryl moiety in extended conjugation.

- The target material and the read-across analog have a cinnamyl alcohol substructure common among them.
- The key difference between the target material and the read-across analog is that the target material is a formate ester, while the read-across analog is an acetate ester. The read-across analog contains the structural features of the target material that are relevant to the endpoints and is expected to have an equal or greater potential for toxicity as compared to the target material.
- The target material and the read-across analog have a Tanimoto score, as mentioned in the above table. The Tanimoto score is mainly driven by the cinnamyl formate fragment. The differences in the structure which are responsible for the Tanimoto score <1 are not relevant from a toxic endpoint perspective.
- The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant.
- The read-across analog has AN2, SN2, and SN1 reaction alerts for genotoxicity by OASIS under QSAR Toolbox. The alert is because the read-across analog is an acetate ester. The QSAR Toolbox confirms that the training set for this alert had esters of acetic acid with a diverse extended fragment attached. The role of acetic acid is not completely known, and necessary conditions for eliciting direct or indirect DNA interaction, described in this general mechanistic profile, are met. However, the specific structural boundaries providing sufficiency for interaction to DNA may not be identified. These specific structural boundaries are examined in the corresponding endpoint-specific profile. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, the alert is superseded by the data.
- The target material has an alert for aldehyde-type by oncologic classification scheme in OECD QSAR Toolbox. This alert is given because the target material is a formate ester, and the substructure matches with an aldehyde substructure. The formate ester would release formic acid as a metabolite. However, the reversible conversion of formic acid to formaldehyde is not accepted to be efficient and probabilistic. There are many esters of formic acid proven to be safe under current levels of exposure. Therefore, based on the structural similarity between the target material and the read-across analog and data for the read-across analog, the alert is superseded by the data.
- The target material has an alert for styrene and toluene renal toxicity. The read-across analog has coumarin hepatotoxicity, styrene, and toluene renal toxicity alerts. These alerts are given because of a structural similarity score of more than 0.5 with the expert judgment rules under HESS. The mechanistic domain is not met with the target material or the read-across analog. The data on the read-across analog confirms that the MOE is adequate under the current level of use. Therefore, the alert is superseded by the data.
- The read-across analog has an alert for SN2 reaction and Michael acceptor alert by several models for skin sensitization. This is because of the α-β-unsaturation of the carbonyl group in the read-across analog. The target material has the same substructural feature but does not have the alert. However, the data on the read-across analog confirms that the read-across analog presents no concern for skin sensitization under the current, declared levels of use. Therefore, based on the structural similarity between the target material and the read-across analog, and the data on the read-across analog, the *in silico* alert is superseded by the data.
- The target material and the read-across analog are expected to be similarly metabolized, as shown by a metabolism stimulator.
- The structural alerts for genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.

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