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RIFM fragrance ingredient safety assessment, cinnamyl acetate, CAS Registry Number 103-54-8

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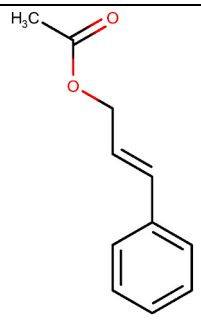

Abbreviation/Definition List:

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

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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.

Cinnamyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cinnamyl acetate is not genotoxic. Data on cinnamyl acetate provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for cinnamyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cinnamyl acetate 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 acetate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; cinnamyl acetate 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.	(RIFM, 2003; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day.	RIFM, (2016)
Reproductive Toxicity: Developmental toxicity NOAEL = 600 mg/kg/day; Fertility NOAEL = 200 mg/kg/day.	RIFM, (2016)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	RIFM, (2018a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 104% (OECD 301F)	RIFM, (1999a)
Bioaccumulation:	
Screening-level: 35.17 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Fish LC50: 0.932 mg/L	(EPI Suite v4.11; US EPA, 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, 2002)
Critical Ecotoxicity Endpoint: 96-h Fish LC50: 0.932 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0932 μg/L

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

1. Identification

1. **Chemical Name:** Cinnamyl acetate
2. **CAS Registry Number:** 103-54-8
3. **Synonyms:** 3-Phenylallyl acetate; 3-Phenyl-2-propen-1-yl acetate; 2-Propen-1-ol, 3-phenyl-, acetate; Acetic acid, cinnamyl ester; 3-Phenyl-2-propen-1-ol acetate; ｱﾙｶﾝ酸(C = 1–6)ｼﾝﾅﾐﾙ; 3-Phenyl-prop-2-en-1-yl acetate; Cinnamylacetat; Cinnamyl acetate
4. **Molecular Formula:** $C_{11}H_{12}O_2$
5. **Molecular Weight:** 176.21
6. **RIFM Number:** 329

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

2. Physical data

1. **Boiling Point:** 113 °C at 3 mm Hg (Fragrance Materials Association [FMA]), 257.46 °C (EPI Suite), 269.0 °C (corrected to normal atmospheric pressure of 1013 hPa) (RIFM, 2017c)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA), 130 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2015c)
3. **Log K_{OW}:** 2.7 at 35 °C (RIFM, 1999b), 2.85 (EPI Suite)
4. **Melting Point**: 20.45 °C (EPI Suite), −3.7 °C at 1005 hPa (RIFM, 2015b)
5. **Water Solubility:** 212.3 mg/L (EPI Suite)
6. **Specific Gravity:** 1.05 (FMA)
7. **Vapor Pressure:** 0.00751 mm Hg at 20 °C (EPI Suite v4.0), 0.008 mm Hg at 20 °C (FMA), 0.0121 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} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless to slightly yellow, oily liquid with a sweet, balsamic, floral odor

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.017% (RIFM, 2018b)
2. **Inhalation Exposure*:** 0.00036 mg/kg/day or 0.027 mg/day (RIFM, 2018b)
3. **Total Systemic Exposure**:** 0.0011 mg/kg/day (RIFM, 2018b)

*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

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:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

Bickers (2005)**:** Cinnamyl acetate is expected to be metabolized to cinnamyl alcohol and acetic acid (phase I metabolites).

Cinnamyl alcohol, cinnamaldehyde, and cinnamic acid are 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 (Fig. 1). 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

Cinnamyl acetate is reported by the VCF* to occur in the following foods:

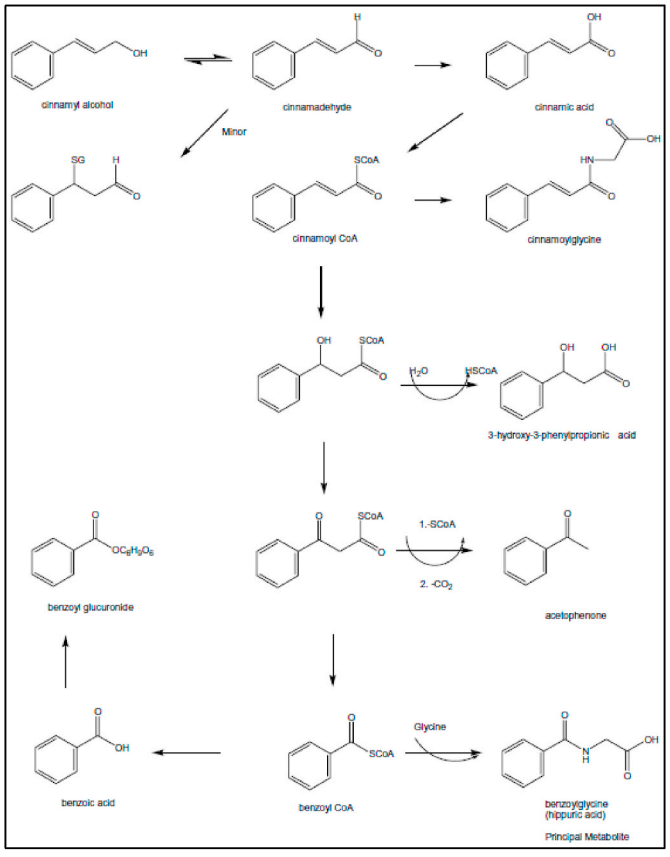

Fig. 1. Metabolism of cinnamyl alcohol, cinnamaldehyde, and cinnamic acid (adopted from Bickers, 2005).

Cinnamomum species
Guava and feyoa
Laurel (*Laurus nobilis* L.)
Litchi (*Litchi chinensis* Sonn.)
Melon
Ocimum species
Star anise
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Syzygium species
Tapereba, caja fruit (*Spondias lutea* L.)
Tarragon (*Artemisia dracunculus* L.)

*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 04/08/21 (ECHA, 2016).

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 acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of cinnamyl acetate was assessed in an Ames study conducted in compliance with GLP requirements and in accordance with OECD TG 471 using both the standard plate incorporation 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 considered negative in the Ames test.

The clastogenic activity of cinnamyl acetate 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 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, 2015a). Under the conditions of the study, cinnamyl acetate was not considered clastogenic in the *in vitro* MNT assay. Chinese hamster ovary (CHO) cells were treated with cinnamyl acetate alone at doses of 1.0–100 μM; cells pretreated with mitomycin C at 0.15 μM for 21 h were also treated with the test material. No increases in SCE frequency was observed in any of the test conditions at any concentration (Sasaki, 1989).

Based on the available data, cinnamyl acetate does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. The repeated dose toxicity data on cinnamyl acetate are sufficient for the repeated dose toxicity endpoint. An OECD 422 and GLP-compliant, 28-day gavage combined repeated dose with a reproductive and developmental toxicity screening study was conducted with the test material. 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 was 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, 2016).

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 acetate 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 acetate, 200/0.0011, or 181818.

In addition, the total systemic exposure to cinnamyl acetate (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: None.

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

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. The reproductive toxicity data on cinnamyl acetate are sufficient for the developmental toxicity and fertility endpoints. An OECD 422 and GLP-compliant, 28-day gavage combined repeated dose with a reproductive and developmental toxicity screening study was conducted with the 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. 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 200 mg/kg/day, since male and female mating and fertility indices were significantly lower at the highest dose (RIFM, 2016).

Therefore, the cinnamyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl acetate, 600/0.0011, or 545455. The cinnamyl acetate MOE for the fertility endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl acetate, 200/0.0011, or 181818.

In addition, the total systemic exposure to cinnamyl acetate (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: None.

Literature Search and Risk Assessment Completed On: 08/12/20.

11.1.4. Skin sensitization

Based on the existing data, cinnamyl acetate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on existing data, cinnamyl acetate is not considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 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 a human maximization test, no skin sensitization reactions were observed with 5% (3450 μg/cm^2) cinnamyl acetate (RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 3424 μg/cm^2 of cinnamyl acetate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2018a).

Based on weight of evidence (WoE) from structural analysis and human studies, cinnamyl acetate 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 acetate 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 acetate 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, 2009). Based on the lack of absorbance, cinnamyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (0, 0, and 43 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are 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 for cinnamyl acetate could not be calculated due to a lack of appropriate data. The exposure level for cinnamyl acetate 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 acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.027 mg/day. This exposure is 51.9 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, 2013; Carpenter (1949); DeCeaurriz (1981); Brondeau (1990); Carlson (1946); Linyucheva (1971); Zissu (1995); Amdur (1961); Silver (1992); Zuskin (1997); Khare (1998); Helmig (1999a); Helmig (1999b); Montero (2001); Suzuki (2001); Morris (2002); Gagnaire (2002); NIOSH, 2006; Cain (2010); Willis (2011).

Literature Search and Risk Assessment Completed On: 08/19/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cinnamyl acetate 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 acetate 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 v4.11 (US EPA, 2012a) did not identify cinnamyl acetate 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1999a: The ready biodegradability of the test material was determined by the manometric respirometry test according to OECD 301F guidelines. Biodegradation of 104% was observed after 28 days.

RIFM, 1999b: The degradation of the test material was evaluated using a closed bottle method according to OECD 301D guidelines. After 28 days, biodegradation of 75% was observed.

11.2.2.1.2. Ecotoxicity. RIFM, 1999c: A 48-h acute *Daphnia magna* study was conducted under static conditions. The EC50 was reported to be 29.4 mg/L.

11.2.2.1.3. Other available data. Cinnamyl acetate has been registered under REACH with the following additional data available at this time (ECHA, 2016):

The acute fish (*Danio rerio*) toxicity test was conducted according to the EU method C.1 under static conditions. The 96-h LC50 value based on mean measured concentrations was reported to be 2.76 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on the time-weighted concentration was reported to be 12.3 mg/L (95% CI: 12–12.5 mg/L).

11.2.3. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.7	2.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0932 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 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
- **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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>58.48</u>			1000000	0.05848	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	7.531	14.29	5.32			Esters

- **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 10/06/21.

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.

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