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Short review

RIFM fragrance ingredient safety assessment, α-amylcinnamyl alcohol, CAS Registry Number 101-85-9

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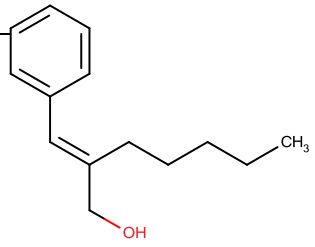
Version: 031419. This version replaces any previous versions.

Name: α-Amylcinnamyl alcohol
CAS Registry Number: 101-85-9



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., 2015; 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

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ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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
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 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.

α-Amylcinnamyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data on read-across analogs α-methylcinnamic alcohol (CAS # 1504-55-8) and cinnamyl alcohol (CAS # 104-54-1) show that α-amylcinnamyl alcohol is not expected to be genotoxic. Data on read-across analog α-amylcinnamaldehyde (CAS # 122-40-7) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on α-amylcinnamyl alcohol provided a NESIL of 3500 μg/cm^2 for the skin sensitization endpoint. The developmental and reproductive toxicity and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to α-amylcinnamyl alcohol is below the TTC (0.009 mg/kg/day and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; α-amylcinnamyl alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; α-amylcinnamyl alcohol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Wild et al, 1983; RIFM, 1997; RIFM, 1998)
Repeated Dose Toxicity: NOAEL = 29.9 mg/kg/day. Carpanini et al, (1973)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 3500 μg/cm^2. RIFM (2004b)
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: 3.22 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 192.5 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2.487 mg/L Salvito et al, (2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 Salvito et al, (2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.487 mg/L Salvito et al, (2002)
RIFM PNEC is: 0.002487 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** α-Amylcinnamyl alcohol
2. **CAS Registry Number:** 101-85-9
3. **Synonyms:** α-Amylcinnamic alcohol; 2-Amyl-3-phenyl-2-propen-1-ol; 2-Benzylideneheptanol; 1-Heptanol, 2-(phenylmethylene)-; α-Pentylcinnamyl alcohol; Amylcinnamyl alcohol; AACA; 2-ﾍﾟﾝﾁﾙ-3-ﾌｪﾆﾙ-2-ﾌﾟﾛﾍﾟﾝ-１-ｵｰﾙ; 2-Benzylideneheptan-1-ol; α-Amylcinnamyl alcohol
4. **Molecular Formula:** $C_{14}H_{20}O$
5. **Molecular Weight:** 204.31
6. **RIFM Number:** 375

2. Physical data

1. **Boiling Point:** > 200 °C (FMA Database), 321.54 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.35 (EPI Suite)
4. **Melting Point**: 50.46 °C (EPI Suite)
5. **Water Solubility:** 25.72 mg/L (EPI Suite)
6. **Specific Gravity:** 0.958 (FMA Database)
7. **Vapor Pressure:** 0.00000923 mm Hg @ 20 °C (EPI Suite v4.0), 1.96e-005 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark
9. **Appearance/Organoleptic:** Givaudan Index (1961) Colorless oily liquid, with a very weak odor

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0079% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.000018 mg/kg/day or 0.0013 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al, 2015, 2017, Comiskey et al, 2015; Safford, 2015, 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, 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** α-Methylcinnamic alcohol (CAS # 1504-55-8); cinnamyl alcohol (CAS # 104-54-1)
   b. **Repeated Dose Toxicity:** α-Amylcinnamaldehyde (CAS # 122-40-7)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

Metabolism was considered in this risk assessment (see applicable sections).

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

α-Amylcinnamyl alcohol is not reported to occur in food 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.

8. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 03/14/2019.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for α-amylcinnamyl 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)	0.27
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	0.14
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.28
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.28
5D	Baby cream, oil, talc	0.094
6	Products with oral and lip exposure	0.00020
7	Products applied to the hair with some hand contact	0.28
8	Products with significant ano-genital exposure (tampon)	0.094
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.99
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.99
10B	Aerosol air freshener	1.4
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.094

12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	43

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 α-amylcinnamyl alcohol, the basis was the reference dose of 0.299 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 3500 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 data, α-amylcinnamyl alcohol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of α-amylcinnamyl alcohol was assessed in an Ames assay conducted equivalent to OECD TG 471. *Salmonella* Typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with α-amylcinnamyl alcohol concentrations up to 3.6 mg/plate in the presence and absence of metabolic activation. No increases in the number of revertant colonies were observed (Wild et al., 1983). Under the conditions of the study, α-amylcinnamyl alcohol was considered negative in the Ames test. Due to the limited details provided in the study on the target material, additional weight of evidence was added by reading across to α-methylcinnamic alcohol (CAS # 1504-55-8). α-Methylcinnamic alcohol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with guidelines similar to OECD TG 471 using the standard plate incorporation method. *Salmonella* Typhimurium strains TA1535, TA1537, TA102, TA98, and TA100 were treated with α-methylcinnamic alcohol in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Small but statistically significant, dose-dependent increases in the frequency of revertant colonies were observed in strains TA100, TA1535, TA98, and TA1537 in the absence of metabolic activation (RIFM, 1997). These results were repeated in the confirmatory assay, and the authors concluded that α-methylcinnamic alcohol was considered weakly positive in the Ames test. The increases in the *Salmonella* Typhimurium mutant strains, although statistically significant, are less than 2-fold for TA98 and TA100 in the first assay and less than 3-fold in TA1535 and TA1537 in 2 assays when compared with the vehicle control. In the repeat assay, TA98 did not show any positive response. A dose response was not observed in the initial experiment, but the test compound did show a dose response in the repeat confirmatory experiment; hence, the biological significance along with reproducibility of the results is also weak. According to current criteria for the Ames assay, the generated data would not be accepted as a positive response, as the threshold for fold increases was not obtained. Due to inconsistencies in the 2 assays, according to OECD 471 guidelines, a decider third assay should be conducted in order to reach a final conclusion (Mahon et al., 1989). Additionally, α-methylcinnamic alcohol was tested for mutagenic activity in an *in vitro* mammalian cell gene mutation test conducted in accordance with OECD TG 476. L5178Y Mouse lymphoma cells were treated with α-methylcinnamic alcohol in DMSO at concentrations up to 600 μg/mL in the presence and absence of metabolic activation for 0, 24, and 48 h. The test substance did not induce toxicologically significant increases in mutant frequency at any dose level, with or without metabolic activation, in either of the 2 experiments (RIFM, 1998). The test material was shown to be non-mutagenic to L5178Y cells under the conditions of the test. Another read-across material, unsubstituted cinnamyl alcohol (CAS # 104-54-1) was also negative when tested up to 3000 μg/plate, both with and without metabolic activation (Sekizawa and Shibamoto, 1982). Based on the weight of evidence, α-methylcinnamic alcohol does not present a concern for mutagenic potential in bacterial cells, and this can be extended to α-amylcinnamyl alcohol. *In silico* predictions using OECD Toolbox version 3.2 determined that the target material, α-amylcinnamyl alcohol, and both read-across materials, α-methylcinnamic alcohol and cinnamyl alcohol, were predicted to be negative in the Ames assay. The battery of Ames assays on structurally related materials along with negative results in an *in vitro* mammalian cell gene mutation test (MLA) and negative *in silico* predictions conclude that α-methylcinnamic alcohol does not present a concern for mutagenicity.

The clastogenicity of α-amylcinnamyl alcohol was assessed in an *in vivo* micronucleus test conducted equivalent to OECD TG 474. Groups of male and female NMRI mice were treated with α-amylcinnamyl alcohol in olive oil via a single intraperitoneal injection at the concentrations of 204, 357, and 510 mg/kg. After 30 h, the bone marrow of each animal was removed, and samples were prepared. Compared to vehicle controls, no statistically significant increases in the number of micronucleated polychromatic erythrocytes were observed (Wild et al., 1983). Under the conditions of the study, α-amylcinnamyl alcohol was considered not clastogenic in the *in vivo* micronucleus test. Due to limited details provided in the study on the target material, additional weight of evidence was added by reading across to cinnamyl alcohol (CAS # 104-54-1). 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 with or without metabolic activation (Sasaki et al., 1989). Furthermore, the ECHA REACH Dossier for cinnamyl alcohol provided an OECD Toolbox v3.2 prediction for the chromosome aberration test on Chinese hamster Lung (CHL) with S9 metabolic activation; it was concluded that cinnamyl alcohol does not exhibit positive chromosomal effects (https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/12023, 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). Taken together, α-amylcinnamyl alcohol does not present a concern for clastogenic potential.

Based on the available data, α-amylcinnamyl alcohol does not present a concern for genotoxicity.

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: 05/07/17.

10.1.2. Repeated dose toxicity

The margin of exposure for α-amylcinnamyl alcohol is adequate for repeated dose toxicity at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on α-amylcinnamyl alcohol. α-Amylcinnamyl alcohol is expected to be metabolized via oxidation to α-amylcinnamaldehyde (CAS # 122-40-7; see Section V). The metabolite, α-amylcinnamaldehyde has a dietary 14-week subchronic toxicity study conducted in rats that determined the NOAEL to be 400 ppm, or 29.9 and 34.9 mg/kg/day in males and females, respectively, based on increased liver and kidney weights (Carpanini et al., 1973). **Therefore, the α-amylcinnamyl alcohol MOE is equal to the α-amylcinnamaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to α-amylcinnamyl alcohol,**

Table 1
Data Summary for α-Amylcinnamyl alcohol.

LLNA Weighted Mean EC3 μg/cm[b] [No. Studies]	Skin Sensitization 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]
6250 [1]	Weak	3543	5520	NA	3500

NOEL = No observed effect level; LOEL = lowest observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; 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.

29.9/0.00014 or 213571.

In addition, the total systemic exposure to α-amylcinnamyl alcohol (0.14 μg/kg/day) is below the TTC (9 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class II material 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 0.299 mg/kg/day.

The RfD for α-amylcinnamaldehyde was calculated by dividing the NOAEL of 29.9 mg/kg/day by the uncertainty factor, 100 = 0.299 mg/kg/day.

Additional References: RIFM, 2007a; Belsito et al., 2007; Jimbo (1983); RIFM, 2007b; Oser et al., 1965; Bar and Griepentrog, 1967.

Literature Search and Risk Assessment Completed On: 5/4/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on α-amylcinnamyl alcohol or on any read-across materials. The total systemic exposure to α-amylcinnamyl alcohol is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental and reproductive toxicity data on α-amylcinnamyl alcohol or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to α-amylcinnamyl alcohol (0.14 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/17.

10.1.4. Skin sensitization

Based on the existing data, α-amylcinnamyl alcohol is considered a weak skin sensitizer with a NESIL of 3500 μg/cm^2.

10.1.4.1. Risk assessment. Based on the available animal and human data, α-amylcinnamyl alcohol is considered a weak sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). α-Amylcinnamyl alcohol was found to be positive in *in vitro* Direct Peptide Reactivity Assay (DPRA) and U937-CD86 test but not in KeratinoSens (RIFM, 2015a; RIFM, 2015b; RIFM, 2015c; Piroird et al., 2015). In a murine local lymph node assay, α-amylcinnamyl alcohol was found to be negative up to the maximum tested concentration of 25%, which resulted in a Stimulation Index (SI) of 2.93 (RIFM, 2004a). In a human repeat insult patch test (HRIPT), α-amylcinnamyl alcohol did not induce sensitization reactions at 3% or 3543 μg/cm^2 (RIFM, 2004b). Based on the available animal and human data, α-amylcinnamyl alcohol is considered a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 3500 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 reference dose 0.299 mg/kg/day.

Additional References: RIFM, 2004c.

Literature Search and Risk Assessment Completed On: 03/31/16.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, α-amylcinnamyl alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for α-amylcinnamyl alcohol 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 et al., 2009). Based on lack of absorbance, α-amylcinnamyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. Key Studies. There are no studies available on α-amylcinnamyl alcohol in experimental models.

10.1.5.3. 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for α-amylcinnamyl alcohol is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on α-

amylcinnamyl alcohol. Based on the Creme RIFM Model, the inhalation exposure is 0.0013 mg/day. This exposure is 362 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/08/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of α-amylcinnamyl alcohol was performed following the RIFM Environmental Framework (Salvito et al., 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. (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, α-amylcinnamyl alcohol 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 v4.1 (US EPA, 2012a) did not identify α-amylcinnamyl alcohol 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 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).

10.2.2. Risk assessment

Based on the c urrent VoU (2015), α-amylcinnamyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. α-Amylcinnamyl alcohol has been pre-registered for REACH with no additional data at this time.

10.2.4. 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)**	<u>216.6</u>			1,000,000	0.2166	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.35	4.35
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 0.002487 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/05/19.

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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110712.

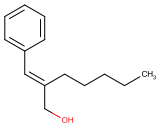
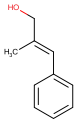
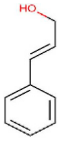
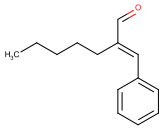
Appendix

Read-across Justification

Methods

The read-across analogs were 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 Chemicals 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 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted 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	α-Amylcinnamyl alcohol	α-Methylcinnamic alcohol	Cinnamyl alcohol	α-Amylcinnamaldehyde
CAS No.	101-85-9	1504-55-8	104-54-1	122-40-7
Structure				
Similarity (Tanimoto Score)		0.71	0.62	NA[a]
Read-across Endpoint		• Genotoxicity	• Genotoxicity	• Repeated dose
Molecular Formula	$C_{14}H_{20}O$	$C_{10}H_{12}O$	$C_9H_{10}O$	$C_{14}H_{18}O$
Molecular Weight	204.31	148.21	134.18	202.30
Melting Point (°C, EPI SUITE)	50.46	18.16	15.84	33.90
Boiling Point (°C, EPI SUITE)	321.54	261.14	248.60	304.80
Vapor Pressure (Pa @ 25°C, EPI SUITE)	0.00261	0.21	0.358	0.0603
Log Kow (KOWWIN v1.68 in EPI SUITE)	4.35	1.5	1.84	4.7
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI SUITE)	25.72	2018	6188	8.545
J_{max} (μg/cm²/h, SAM)	7.601	20.754	213.968	9.088
Henry's Law (Pa·m³/mol, Bond Method, EPI SUITE)	7.81E-002	2.52E-002	1.60E-002	7.90E-001
Genotoxicity				
DNA Binding (OASIS v 1.4 QSAR Toolbox v3.4)	• No alert found	• No alert found	• No alert found	

DNA Binding by OECD QSAR Toolbox (v3.4)	• No alert found	• No alert found	• No alert found	
Carcinogenicity (Genotox and Non-genotox) Alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)	
DNA Alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames test) Alerts by ISS**	• No alert found	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus) Alerts by ISS**	• No alert found	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	• Not classified	
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized			• Not categorized
Metabolism				
OECD QSAR Toolbox (3.4) Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

[a]Target is metabolite/analog of metabolite of read-across material.

Summary

There are insufficient toxicity data on the α-Amylcinnamyl alcohol (CAS 101-85-9). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties and expert judgment, analogs α-methylcinnamic alcohol (CAS 1504-55-8), cinnamyl alcohol (CAS 104-54-1) and α-amylcinnamaldehyde (CAS 122-40-7) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusions

- α-methylcinnamic alcohol (CAS 1504-55-8) was used as a read-across analog for the target material, α-amylcinnamyl alcohol (CAS 101-85-9), for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of alcohols.
  - The target substance and the read-across analog share a cinnamyl alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target has an amyl substitution at the alpha position, while the read-across analog has a methyl substitution at the alpha position. This structure difference between the target substance and the read-across analog is not toxicologically significant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the cinnamyl alcohol fragment. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq 40\%$ skin absorption for the target substance and $\leq 80\%$ absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they may not be toxicologically relevant. Therefore, the J_{max} of the target substance and the appropriate read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for genotoxicity are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are toxicologically insignificant.
- Cinnamyl alcohol (CAS 104-54-1) was used as a read-across analog for the target material, α-amylcinnamyl alcohol (CAS 101-85-9), for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the structural class of alcohols.
  - The target substance and the read-across analog share a cinnamyl alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target has an amyl substitution at the alpha position, while the read-across analog cinnamyl alcohol does not have any substitution. This structure difference between the target substance and the read-across analog is not toxicologically significant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the cinnamyl alcohol fragment. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to $\leq 40\%$ skin absorption for the target substance and $\leq 80\%$ absorption for the read-across analog. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they may not be toxicologically significant. Therefore, the J_{max} of the target substance and the read-across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for genotoxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - The structural differences between the target material and the read-across analog are not toxicologically significant.
- Metabolism

The metabolism of the read-across material α-amylcinnamaldehyde (CAS # 122-40-7) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). α-Amylcinnamyl alcohol (CAS # 101-85-9) is predicted to be metabolized to α-amylcinnamaldehyde (CAS # 122-40-7) in the first step with 0.95 pre-calculated probability. Hence, α-amylcinnamaldehyde (CAS # 122-40-7) can be used as read-across for α-amylcinnamyl alcohol (CAS # 101-85-9). α-Amylcinnamaldehyde (CAS 122-40-7) was out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

- α-Amylcinnamaldehyde (CAS 122-40-7) is used as read-across analog for α-amylcinnamyl alcohol (CAS 101-85-9) for repeated dose toxicity endpoint.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - The target substance is an alcohol formed from the read-across analog aldehyde.
  - Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analog. Therefore, the toxicity profile of the target is expected to be that of metabolites. Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is driven mainly by the cinnamyl fragment. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
  - The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analog are not toxicologically significant.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the repeated dose toxicity endpoint are consistent between the target substance and the read-across analog.
  - The structural alerts for the repeated dose toxicity endpoint are consistent between the metabolites of the read-across analog and the target substance.
  - The structural differences between the target material and the read-across analog are not toxicologically significant.

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