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Short Review

Update to RIFM fragrance ingredient safety assessment, α-amylcinnamaldehyde, CAS Registry Number 122-40-7

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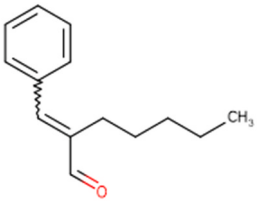
Version: 121923. This safety assessment is an updated version and replaces the previous version at https://doi.org/10.1016/j.fct.2015.01.008 (RIFM, 2015). All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: **fragrancematerialsafetyresource.elsevier.com**.



Name: α-Amylcinnamaldehyde
CAS Registry Number: 122-40-7
Additional CAS Numbers*:
78605-96-6 α-Amyl *trans*-cinnamaldehyde
(No Reported Use)
*This material was included in this safety assessment because they are isomers.

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2017; Comiskey et al., 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
ISS - Instituto Superiore di Sanita (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach

(*continued on next column*)

(*continued*)

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-Amylcinnamaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog α-hexylcinnamaldehyde (CAS # 101-86-0) show that α-amylcinnamaldehyde is not expected to be genotoxic. Data on read-across analog α-hexylcinnamaldehyde (CAS # 101-86-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints. Data provided α-amylcinnamaldehyde a No Expected Sensitization Induction Level (NESIL) of 23000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; α-amylcinnamaldehyde is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; α-amylcinnamaldehyde 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 (VoU) 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.	(ECHA, 2017a; Di Sotto et al., 2014)
Repeated Dose Toxicity: NOAEL = 12 mg/kg/day.	RIFM (1980a)
Reproductive Toxicity: NOAEL = 100 mg/kg/day.	RIFM (2010)
Skin Sensitization: NESIL = 23000 μg/cm^2.	RIFM (2005)
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1988a; RIFM, 1988b)
Local Respiratory Toxicity: NOAEC = 500 mg/m^3.	RIFM (2012)

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 90% (OECD 301F)	RIFM (1992a)
Bioaccumulation:	
Screening-level: 334 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.041 mg/L	ECHA (2017a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.041 mg/L	ECHA (2017a)

RIFM PNEC is: 0.82 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1

1. Identification

Chemical Name: α-Amylcinnamaldehyde	Chemical Name: a-Amyl *trans*-Cinnamaldehyde
CAS Registry Number: 122-40-7	**CAS Registry Number:** 78605-96-6
Synonyms: 'A.C.A.'; Amyl cinnamal; Amyl cinnamic aldehyde; α-Amyl β-phenylacrolein; Heptanal, 2-(phenylmethylene)-; α-Pentylcinnamaldehyde; α-Pentyl-β-phenylacrolein; α-Amyl cinnamic aldehyde; Heptanal, 2-(phenylmethylene); 2-(Phenylmethylene) heptanal; Flomine; AAC; 2-Benzylidene-heptanal; α-Amylcinnamaldehyde	**Synonyms:** a-Amyl *trans*-Cinnamaldehyde; *trans*-3-Phenyl-2-pentylacrolein; Heptanal, 2-(phenylmethylene)-, (2E)-
Molecular Formula: $C_{14}H_{18}O$	**Molecular Formula:** $C_{14}H_{18}O$
Molecular Weight: 202.29 g/mol	**Molecular Weight:** 202.29 g/mol
RIFM Number: 101	**RIFM Number:** N/A
Stereochemistry: No isomer specified. One geometric center and 2 total isomers are possible.	**Stereochemistry:** *Trans* isomer specified.

2. Physical data

CAS Registry Number: 122-40-7	CAS Registry Number: 78605-96-6
Boiling Point: 284 °C (Fragrance Materials Association [FMA]), 304.8 °C (EPI Suite v4.11)	**Boiling Point:** 304.8 °C (EPI Suite v4.11)
Flash Point: >93 °C (Globally Harmonized System [GHS]), >200 °F; closed cup (FMA)	**Flash Point:** 140 °C (GHS)
Log K_{OW}: 4.7 (RIFM, 1994b), 4.33 (EPI Suite v4.11)	**Log K_{OW}:** 4.33 (EPI Suite v4.11)
Melting Point: 33.9 °C (EPI Suite v4.11)	**Melting Point**: 33.9 °C (EPI Suite v4.11)
Water Solubility: 8.545 mg/L (EPI Suite v4.11)	**Water Solubility:** 8.545 mg/L (EPI Suite v4.11)
Specific Gravity: 0.965 (FMA)	**Specific Gravity:** Not available
Vapor Pressure: 0.000238 mm Hg at 20 °C (EPI Suite v4.0), 0.000452 mm Hg (0.0603 Pa) at 25 °C (EPI Suite v4.11)	**Vapor Pressure:** 0.000452 mm Hg (0.0603 Pa) at 25 °C (EPI Suite v4.11)
UV Spectra: Minor absorbance between 290 and 700 nm; molar absorption coefficients (188, 181, and 462 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** Not available
Appearance/Organoleptic: Pale yellowish to yellow liquid with a strong floral odor suggestive of jasmine on dilution	**Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient* (Creme RIFM Aggregate exposure model v3.2.10)

1. **95**th **Percentile Concentration in shower gel:** 0.20% (RIFM, 2022)

   (No Reported use in Fine Fragrance).

2. **Inhalation Exposure**:** 0.0013 mg/kg/day or 0.095 mg/day (RIFM, 2022)
3. **Total Systemic Exposure***:** 0.0021 mg/kg/day (RIFM, 2022)

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

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

5. Derivation of systemic absorption

1. **Dermal:** 9.54%

RIFM, 2013: An *in vitro* human skin absorption study was conducted with read-across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section VI). Permeation of α-hexylcinnamaldehyde was monitored (via HPLC-UV) by analyzing the receptor phase for α-hexylcinnamaldehyde and potential metabolites α-hexyl cinnamic alcohol and acid. Measurements were made at 12 time points over 24 h. At 24 h, the epidermal membranes were wiped and tape-stripped 10 times. The target material and potential metabolite content of the wipes, strips, and remaining epidermis were determined. The filter paper skin supports were extracted, and the diffusion cell donor chambers were washed and wiped. Analysis of these samples allowed the mass balance to be performed. As per SCCNFP guidelines, the levels of material in the epidermis (plus any remaining stratum corneum after tape stripping), filter paper membrane support, and receptor fluid were combined to produce a total absorbed dose value. Following 24 h of exposure under unoccluded conditions, 4.51% ± 0.80% (2.75% aldehyde, 0.0% alcohol, 1.765% acid) of the applied dose had permeated. The mass balance demonstrated that 92.3% of the applied dose was recovered. Following 24 h of exposure under occluded conditions, 9.54% ± 1.50% (5.75% aldehyde, 0.32% alcohol, 3.49% acid) of the applied dose had permeated. The mass balance demonstrated that 86.3% of the applied dose was recovered.

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** α-Hexylcinnamaldehyde (CAS # 101-86-0); Weight of Evidence (WoE) – cinnamaldehyde (CAS # 104-55-2)
   b. **Repeated Dose Toxicity:** α-Hexylcinnamaldehyde (CAS # 101-86-0)
   c. **Reproductive Toxicity:** α-Hexylcinnamaldehyde (CAS # 101-86-0)
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** α-Hexylcinnamaldehyde (CAS # 101-86-0)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

α-Amylcinnamaldehyde is reported to occur in the following foods by the VCF*:

Soybean (*Glycine max.* L. merr.)

Tea

α-Amyl *trans*-cinnamaldehyde 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 for α-amylcinnamaldehyde (ECHA, 2017a) and α-amyl *trans*-cinnamaldehyde (ECHA, 2013); accessed on 01/05/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for α-amylcinnamaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.073
2	Products applied to the axillae	0.51
3	Products applied to the face/body using fingertips	0.22
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.80
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.15
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.15
5D	Baby cream, oil, talc	0.049
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	0.15
8	Products with significant ano-genital exposure (tampon)	0.049
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.51
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.15
10B	Aerosol air freshener	0.80
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.049
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	33

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-amylcinnamaldehyde, the basis was the subchronic RfD of 0.12 mg/kg/day, a skin absorption value of 9.54%, and a skin sensitization NESIL of 23000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.3.

11. Summary

11.1. 1.Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, α-amylcinnamaldehyde does not present a concern for genotoxicity.

11.2. Risk assessment

The mutagenic activity of α-amylcinnamaldehyde has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with α-amylcinnamaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 750 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2017a). Under the conditions of the study, α-amylcinnamaldehyde was not mutagenic in the Ames test.

The mutagenic activity of α-amylcinnamaldehyde has been evaluated in an additional bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA97 and TA102 were treated with α-amylcinnamaldehyde (solvent not specified) at concentrations up to 1000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2017a). Under the conditions of the study, α-amylcinnamaldehyde was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of α-amylcinnamaldehyde; however, read-across can be made to α-hexylcinnamaldehyde (CAS # 101-86-0; see Section VI).

The clastogenic activity of α-hexylcinnamaldehyde was evaluated in an *in vitro* micronucleus test conducted in an equivalent manner to OECD TG 487. Human peripheral blood lymphocytes were treated with α-hexylcinnamaldehyde in ethanol at concentrations up to 500 μM (108.16 μg/mL) in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 50 μM (10.816 μg/mL) for 24 h in the absence of metabolic activation. α-Hexylcinnamaldehyde did not induce binucleated cells with micronuclei in the absence of an S9 activation system (Di Sotto et al., 2014). Under the conditions of the study, α-hexylcinnamaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to α-amylcinnamaldehyde.

As additional weight of evidence (WoE), due to the *in vitro* micronucleus test for α-hexylcinnamaldehyde only being conducted in the absence of metabolic information, the clastogenic activity of cinnamaldehyde (CAS # 104-55-2) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474 NTP, 2004). Under the conditions of the study, cinnamaldehyde was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to α-amylcinnamaldehyde.

Based on the data available, α-hexylcinnamaldehyde does not present a concern for genotoxic potential, and this can be extended to α-amylcinnamaldehyde.

Additional References: Fujita and Sasaki, 1987; Eder et al., 1993.

Literature Search and Risk Assessment Completed On: 03/10/23.

11.2.1. Repeated dose toxicity

The MOE for α-amylcinnamaldehyde is adequate for the repeated

dose toxicity endpoint at the current level of use.

11.2.1.1. Risk assessment. There are limited repeated dose toxicity data on α-amylcinnamaldehyde. In a subchronic toxicity study, groups of 15 CFE strain rats/sex/dose were administered α-amylcinnamaldehyde via diet at concentrations of 0, 80, 400, or 4000 ppm (corresponding to doses of 0, 6.1, 29.9, and 287.3 mg/kg for the males; and doses of 0, 6.7, 34.9, and 320.3 mg/kg for the females, according to the study report) for 14 weeks. Additional groups of 5 rats/sex/dose were given 400 or 4000 ppm for 2 or 6 weeks. No differences from controls were seen in the rate of bodyweight gain, the consumption of food and water, hematological measurements, serum analyses, urinary cell excretion, or renal concentration tests. There were increases in the relative liver and kidney weights of rats fed the highest dietary level, but these were not associated with any histopathological changes. One female rat at each of the 2 lower dietary levels developed small mammary adenomas, which are known to occur spontaneously in older female rats. Other histopathological changes in the kidney and lung were due to the presence of a mild infection rather than treatment with α-amylcinnamaldehyde. Due to the non-treatment-related infections, a reliable NOAEL could not be derived from this study (Carpanini et al., 1973).

Read-across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a subchronic toxicity study, groups of 15 Sprague Dawley rats/sex/dose were treated with α-hexylcinnamaldehyde dermally (via daily open applications on the clipped backs) at doses of 125, 250, 500, or 1000 mg/kg/day. A control group of 30 rats/sex was untreated and monitored throughout the study period. Observations included mortality, clinical signs, body weight, feed consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross necropsy, organ weights, and histopathology. Five male and 3 female rats died before 90 days of treatment at 1000 mg/kg/day. Body weights were significantly decreased in both sexes during treatment at 500 and 1000 mg/kg/day. Food consumption was increased in females at 250, 500, and 1000 mg/kg/day but was unaffected in males. Gross examination at necropsy revealed that administration of α-hexylcinnamaldehyde for 90 days produced dose-related irritation of the gastrointestinal tract mucosa and skin. The liver and kidney weights of treated females were significantly increased at 250, 500, and 1000 mg/kg/day, but male organ weights showed no significant changes. Histological examination of the treated animals revealed morphological alterations in the liver, spleen, stomach, and skin of rats treated with 1000 mg/kg/day. Bone marrow examination revealed increases in the myeloid-erythroid and decreased cell-fat ratios in the high-dose group. The NOAEL for systemic toxicity was determined to be 125 mg/kg/day (RIFM, 1980a).

To account for bioavailability following dermal application, data from an *in vitro* human skin absorption study (RIFM, 2013; see Section V) were used to revise the NOAEL of 125 mg/kg/day to reflect the systemic dose. At a dermal penetration of 9.54% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 12 mg/kg/day.

Therefore, the α-amylcinnamaldehyde MOE is equal to the α-hexylcinnamaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to α-amylcinnamaldehyde, 12/0.0021, or 5714.

With a MOE significantly greater than 100, any potential loss of material due to volatility in the dermal administration toxicity study can be disregarded.

In addition, the total systemic to α-amylcinnamaldehyde (2.1 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Derivation of Subchronic Reference Dose (RfD):

Section X 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. (2020) and a subchronic RfD of 0.12 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10) based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for α-amylcinnamaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 12 mg/kg/day by the uncertainty factor, 100 = 0.12 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/06/23.

11.2.2. Reproductive toxicity

The MOE for α-amylcinnamaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

11.3. Risk assessment

There are no reproductive toxicity data on α-amylcinnamaldehyde. Read-across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

In a DRF reproductive toxicity study, groups of 8 Crl:CD(SD) rats/sex/dose were administered α-hexylcinnamaldehyde via gavage (vehicle: corn oil) at doses of 0, 12.5, 25, 50, or 100 mg/kg/day. Males were treated once daily, beginning 14 days before cohabitation, through cohabitation, and continuing through the day before euthanasia (day 47 of the study). Females were treated once daily, beginning 2 weeks before cohabitation, through cohabitation, and continuing through the day before euthanasia. Females and their litters were euthanized on postnatal day 5. No treatment-related adverse effects on fertility parameters or developmental toxicity parameters were observed throughout the study, including mating, fertility, reproductive organ weights, reproductive organ microscopic examination, delivery parameters, pup body weights, and pup clinical and necropsy observations. Based on no adverse effects seen up to the highest dose tested, the developmental toxicity and fertility NOAEL for this study was considered to be 100 mg/kg/day (RIFM, 2010). The Expert Panel for Fragrance Safety and the Adjunct Reproduction Advisory Group* agree that there are enough data from the reproduction DRF study to show that there are no concerns for fertility or developmental effects of α-hexylcinnamaldehyde at dosages up to 100 mg/kg/day.

Therefore, the MOE for reproductive toxicity is equal to the α-hexylcinnamaldehyde NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.0021 or 47619.

In addition, the total systemic exposure to *p*-methyl-α-amyl cinnamic aldehyde (2.1 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint for a Cramer Class II material at the current level of use.

*The Expert Panel and Adjunct Reproduction Advisory Group are composed of scientific and technical experts in their respective fields. These groups provide advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/06/23.

11.3.1. Skin sensitization

Based on the existing data, α-amylcinnamaldehyde is considered a skin sensitizer with a defined NESIL of 23000 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section X.

11.3.1.1. Risk assessment. Based on the existing data, α-amylcinnamaldehyde is considered a skin sensitizer (Table 1). This material is predicted *in silico* to be reactive with skin proteins directly (Roberts

et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). α-Amylcinnamaldehyde was found to be negative in a direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the U-SENS test (Natsch et al., 2013; Piroird et al., 2015). Based on the 2 out of 3 Defined Approach from OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a), α-amylcinnamaldehyde is predicted *in vitro* to be a non-sensitizer. In a murine local lymph node assay (LLNA), α-amylcinnamaldehyde was found to be sensitizing with an EC3 value of 7.6% (1900 μg/cm^2) (RIFM, 2006). In 2 more LLNAs, α-amylcinnamaldehyde was found to be sensitizing with EC3 values of 10.6% (2650 μg/cm^2) (Elahi et al., 2004; Gerberick et al., 2005) and 11% (2750 μg/cm^2), respectively (Aptula et al., 2007; Roberts et al., 2007). In another LLNA, isomer α-amyl (*trans*- and *cis*-)cinnamaldehyde was found to be sensitizing with an EC3 value of 7.6% (1900 μg/cm^2) (ECHA, 2013). In guinea pig maximization tests, α-amylcinnamaldehyde led to skin sensitization reactions (RIFM, 1977e; Senma et al., 1978; RIFM, 1977b; RIFM, 1978). In human maximization tests, no skin sensitization reactions were observed with α-amylcinnamaldehyde when tested at 5520 μg/cm^2 and 4140 μg/cm^2, respectively (RIFM, 1973a; RIFM, 1977a; Greif, 1967; RIFM, 1973a). In 3 separate CNIHs with α-amylcinnamaldehyde at 9690 μg/cm^2 in alcohol SDA39C, 4845 μg/cm^2 in petrolatum, and 4845 μg/cm^2 (no vehicle reported), no reactions indicative of sensitization were observed in any of the 41, 45, or 39 volunteers, respectively (RIFM, 1977c; RIFM, 1977d; RIFM, 1964). Additionally, in 2 separate CNIHs with 23622 μg/cm^2 of α-amylcinnamaldehyde in 1:3 ethanol:diethyl phthalate and diethyl phthalate, respectively, no reactions indicative of sensitization were observed in any of the 108 or 95 volunteers (RIFM, 2005; RIFM, 1994a; Letizia and Api, 2002).

Based on WoE from structural analysis, *in vitro* studies, animal studies, and human studies, α-amylcinnamaldehyde is a sensitizer with a WoE NESIL of 23000 μg/cm^2 (Table 1). Section X provides the maximum

Table 1
Summary of existing data on α-amylcinnamaldehyde.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL (induction) μg/cm²	WoE NESIL[2] μg/cm²	LLNA[3] Weighted Mean EC3 Value μg/cm²	GPMT[4]	Buehler
Very weak	23622	4140	N/A	23000	1900 (7.6%) [2], 2650 (10.6%), 2750 (11%)	Positive	N/A
	In vitro Data[5]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	Positive		Schiff base formation; Michael addition	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
WoE NESIL limited to 2 significant figures.
Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
Studies conducted according to the OECD TG 406 are included in the table.
Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.12 mg/kg/day.

Additional References: Gerberick et al., 2004; RIFM, 1973b; RIFM, 1979; Maisey and Miller, 1986; Klecak (1979); Basketter and Gerberick, 1996; RIFM, 1988b; Klecak (1985); RIFM, 1977e; Klecak et al., 1977; RIFM, 1979.

Literature Search and Risk Assessment Completed On: 03/13/23.

11.3.2. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and existing data, α-amylcinnamaldehyde would not be expected to present a concern for photoirritation or photoallergenicity.

11.3.2.1. Risk assessment. UV/Vis absorption spectra for α-amylcinnamaldehyde indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). *In vivo* photoirritation (RIFM, 1988a) and photoallergenicity (RIFM, 1988b) studies in guinea pigs demonstrated α-amylcinnamaldehyde was not photoirritating (3%–30% α-amylcinnamaldehyde) or photoallergenic (10% α-amylcinnamaldehyde). Based on the lack of significant absorbance in the critical range and existing *in vivo* data, α-amylcinnamaldehyde does not present a concern for photoirritation or photoallergenicity.

11.3.2.2. UV spectra analysis. The available UV absorption spectrum for α-amylcinnamaldehyde demonstrates minor absorption between 290 and 700 nm. The corresponding molar absorption coefficients (188, 181, and 462 L mol^{-1} • cm^{-1}, for neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: Addo et al., 1982; RIFM, 1980b; Placzek et al., 2007.

Literature Search and Risk Assessment Completed On: 02/22/23.

11.3.3. Local respiratory toxicity

There are insufficient inhalation data available on α-amylcinnamaldehyde; however, in a 2-week inhalation study for read-across analog α-hexylcinnamaldehyde (CAS # 101-86-0; see Section VI), a NOAEC of 500 mg/m^3 was reported (RIFM, 2012).

11.3.3.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. A NOAEC of 56.5 ppm (500 mg/m^3; the highest dose tested) was reported for the read-across material α-hexylcinnamaldehyde (RIFM, 2012). This material was tolerated at all exposure levels. No significant change in bronchoalveolar lavage cell types, protein levels, or inflammatory cytokines was measured, and no change in body weight or organ weight and no histological changes indicative of inflammation were observed in the lung or nose.

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

- (500 mg/m^3) × (1 m^3/1000 L) = 0.500 mg/L
- Minute ventilation of 0.17 L/min* for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.500 mg/L) × (61.2 L/d) = 30.6 mg/d
- (30.6 mg/d)/(0.0016 kg lung weight of rat**) = 19125 mg/kg lw/day

The 95th percentile calculated exposure was reported to be 0.095 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.15 mg/kg lung weight/day resulting in a MOE of 127500 (i.e., [19125 mg/kg lung weight/-day]/[0.15 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.095 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

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

Additional References: Fukayama et al., 1999.

Literature Search and Risk Assessment Completed On: 03/06/23.

11.4. Environmental endpoint summary

11.4.1. Screening-level assessment

A screening-level risk assessment of α-amylcinnamaldehyde 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 of 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 VoU 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-amylcinnamaldehyde 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 α-amylcinnamaldehyde as possibly being 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, 2017b). 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.

11.4.1.1. Risk assessment. Based on the current VoU (2019), α-amylcinnamaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

11.4.2. Key studies

11.4.2.1. Biodegradation. **RIFM, 1992a:** A biodegradation study was conducted using activated sludge in a manometric respirometry test according to the OECD 301F method. The test material (100 mg/L) was incubated with activated sludge (30 mg/L) for 28 days. α-Amylcinnamaldehyde underwent 90% biodegradation in 28 days.

RIFM, 1992c: A biodegradation study according to the Commission Directive 79/831/EWG annex V part C method was conducted with α-amylcinnamaldehyde. The test material underwent 41% biodegradation in 28 days.

RIFM, 1996: A biodegradation study was conducted using activated sludge using the sealed vessel test according to the OECD 301B method. α-Amylcinnamaldehyde underwent 70.5% biodegradation in 28 days.

11.4.2.2. Ecotoxicity. **RIFM, 1992b**: A 48-h acute *Daphnia magna* test was conducted with α-amylcinnamaldehyde. The geometric mean of EC0/EC100 was 1.1 mg/L.

RIFM, 1993: A 96-h acute fish (*Brachydanio rerio*) study was conducted according to the OECD 203 C.1 method under semi-static conditions. Under the conditions of the study, the geometric mean of LC0/LC100 was 3.0 mg/L.

RIFM, 2003: An algae inhibition test (*Selenastrum capricornutum)* under static conditions in sealed containers was conducted according to the OECD 201 method. The 72-h NOEC was calculated using the number of cells/mL, the average specific growth rate, and the area under the growth curve was 0.154 mg/L. The 72-h EC50s were 1.18, 1.24, and 1.88 mg/L for the number of cells, the area under the growth curve, and the average specific growth rate, respectively.

11.4.2.3. Other available data. α-Amylcinnamaldehyde has been registered under REACH, and the following additional data are available (ECHA, 2017a):

An acute fish toxicity study was conducted according to the OECD 203 method under static conditions. The 96-h LC50 was reported to be 0.91 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 0.28 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 method under semi-static conditions. The 21-day NOEC was reported to be 0.041 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 was reported to be > 1.5 mg/L for growth rate and 2.3 mg/L for the area under growth. The NOEC was reported to be 0.66 mg/L and 0.21 mg/L for the area under the growth and growth rate, respectively.

11.4.3. 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.221			1000000	0.00122	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.162	0.729	1.007	10000	0.0162	Vinyl/Allyl Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	0.625	0.455	0.951			Neutral organics
Tier 3: Measured Data, including REACH data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	0.91					
Daphnia		0.28	0.041	50	0.82	
Algae		1.18	0.154			

Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.7	4.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.82 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: 03/02/23.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 12/19/23.

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.2024.114447.

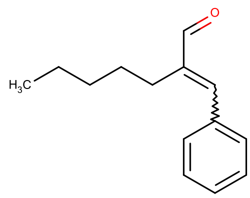
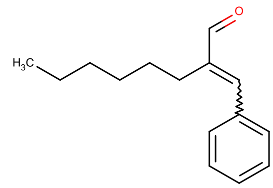
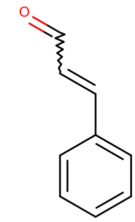
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals Agency read-across assessment framework (ECHA, 2017c).

- 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 (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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	WoE Material
Principal Name	α-Amylcinnamaldehyde	α-Hexylcinnamaldehyde	Cinnamaldehyde
CAS No.	122-40-7	101-86-0	104-55-2
Structure			
Similarity (Tanimoto Score)		0.98	0.54
SMILES	CCCCCC(C=O) = Cc1ccccc1	CCCCCCC(C=O) = Cc1ccccc1	O=CC=Cc1ccccc1
Endpoint		Genotoxicity Repeated dose toxicity Reproductive toxicity Local respiratory toxicity	Genotoxicity
Molecular Formula	$C_{14}H_{18}O$	$C_{15}H_{20}O$	C_9H_8O
Molecular Weight	202.297	216.324	132.162
Melting Point (°C, EPI Suite)	33.90	39.20	−7.50
Boiling Point (°C, EPI Suite)	285.00	318.74	246.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.79E-01	7.12E-02	3.85E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.13E+00	2.75E+00	1.42E+03
Log KOW	4.7	4.82	1.9
J_{max} (μg/cm^2/h, SAM)	0.59	0.37	41.56
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.90E-01	1.05E+00	3.59E-01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ Alpha, Beta-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Alpha, Beta-Unsaturated Aldehydes	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ Alpha, Beta-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Alpha, Beta-Unsaturated Aldehydes	AN2|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ Alpha, Beta-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ Alpha, Beta-Unsaturated Aldehydes
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	Aldehyde-type Compounds
Repeated Dose Toxicity			
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert	Styrene (Renal Toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group	
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on α-amylcinnamaldehyde (CAS # 122-40-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, α-hexylcinnamaldehyde (CAS # 101-86-0) was identified as a read-across analog and cinnamaldehyde (CAS # 104-55-2) was identified as a WoE analog with sufficient data for toxicological evaluation.

Conclusions

- α-Hexylcinnamaldehyde (CAS # 101-86-0) was used as a read-across analog for the target material, α-amylcinnamaldehyde (CAS # 122-40-7), for the genotoxicity, repeated dose toxicity, reproductive toxicity, and local respiratory toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the cinnamaldehyde group.
  - o The key difference between the target material and the read-across analog is that the target material has a 5-carbon side chain while the read-across analog has a 6-carbon side chain. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and the read-across analog have a nucleophilic addition to α, β-unsaturated carbonyl compounds and a Schiff base formation alert for DNA binding for genotoxicity, which is due to the conjugated aldehyde. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity. 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* alerts and predictions are superseded by the data.
  - o Neither the target material nor the read-across analog has alerts for developmental toxicity, fertility, or local respiratory toxicity. The data on the read-across analog confirms that the material does not pose a concern for developmental toxicity, fertility, or local respiratory toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts and predictions is consistent with the data.
  - o Both the target material and read-across analog have renal toxicity alerts for repeated dose toxicity. The data on the read-across analog confirms that the material does not pose a concern for repeated dose toxicity. 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* alerts and predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Cinnamaldehyde (CAS # 104-55-2) was used as a WoE analog for the target material on α-amylcinnamaldehyde (CAS # 122-40-7) for the genotoxicity endpoint.
  - o The target material and the WoE analog are structurally similar and belong to the cinnamaldehyde group.
  - o The key difference between the target material and the WoE analog is the target material has a 5-carbon saturated side chain at the α position while the WoE material does not. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the WoE analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$40%, and J_{max} for the WoE analog corresponds to skin absorption $\leq$80%. While the percentage of skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the WoE analog.
  - o Both the target material and the WoE analog have alerts for nucleophilic addition to α,β-unsaturated carbonyl compounds and Schiff base formation for DNA binding. Both the target material and the WoE analog are aldehyde-type compounds by oncologic classification. The data on the WoE analog confirms that the material does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the WoE analog, the *in silico* alert and predictions are superseded by the data.
  - o The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.

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