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Short Review

RIFM fragrance ingredient safety assessment, amyl cinnamate, CAS Registry Number 3487-99-8

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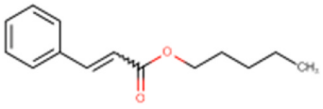

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Name: Amyl cinnamate
CAS Registry Number: 3487-99-8

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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations

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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., 2024; 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
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (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
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.

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

Amyl cinnamate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl cinnamate (CAS # 103-36-6) show that amyl cinnamate is not expected to be genotoxic. Data on read-across analog methyl cinnamate (CAS # 103-26-4) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog methyl cinnamate (CAS # 103-26-4) provide amyl cinnamate a No Expected Sensitization Induction Level (NESIL) of 2900 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; amyl cinnamate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to amyl cinnamate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; amyl cinnamate 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.	(Ishidate Jr et al., 1984; RIFM, 2015b; RIFM, 2015c)
Repeated Dose Toxicity: NOAEL = 100 mg/kg/day.	RIFM (2013)
Reproductive Toxicity: NOAEL = 300 mg/kg/day.	RIFM (2013)
Skin Sensitization: NESIL = 2900 μg/cm^2.	RIFM (2015a)
Photoirritation/ Photoallergenicity: Not expected to be photoirritating/ photoallergenic.	(UV/Vis spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.17 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 329 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: LC50: 2.82 mg/L	(RIFM Environmental Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe)	(RIFM Environmental Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 2.83 mg/L	(RIFM Environmental Framework; Salvito et al., 2002)
RIFM PNEC is: 0.002823 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe (not reported): Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Amyl cinnamate
2. **CAS Registry Number:** 3487-99-8
3. **Synonyms:** Pentyl cinnamate; Pentyl 3-phenyl-2-propenoate; 2-Propenoic acid, 3-phenyl-,pentyl ester; Pentyl 3-phenylacrylate; Cinnamic acid, pentyl ester; Amyl cinnamate
4. **Molecular Formula:** $C_{14}H_{18}O_2$
5. **Molecular Weight:** 218.29 g/mol
6. **RIFM Number:** 6202
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 304.7 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available

3. **Log K_{OW}:** 4.32 (EPI Suite v4.11)
4. **Melting Point**: 51.15 °C (EPI Suite v4.11)
5. **Water Solubility:** 7.167 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000874 mm Hg (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless, somewhat viscous liquid with a faintly balsamic, mild Ambre-like, cocoa bean-like odor; has a sweet and heavy flavor

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in AirFresh Aerosol:** 0.036% (RIFM, 2017)

(No reported use in Fine Fragrance)

2. **Inhalation Exposure*:** 0.00010 mg/kg/day or 0.0070 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0094 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 5. 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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl cinnamate (CAS # 103-36-6)
   b. **Repeated Dose Toxicity:** Methyl cinnamate (CAS # 103-26-4)
   c. **Reproductive Toxicity:** Methyl cinnamate (CAS # 103-26-4)
   d. **Skin Sensitization:** Methyl cinnamate (CAS # 103-26-4)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   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

Amyl cinnamate 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

Amyl cinnamate has been pre-registered for 2010; no dossier available as of 04/09/24.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for amyl cinnamate 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)	0.22
2	Products applied to the axillae	0.066
3	Products applied to the face/body using fingertips	1.3
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.32
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.32
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.32
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.73
7	Products applied to the hair with some hand contact	2.5
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	8.7
10B	Aerosol air freshener	8.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 amyl cinnamate, the basis was the subchronic reference dose of 1 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2900 μg/cm^2.
As a conservative approach, we assumed that 100% of the material exposed via the skin is bioavailable (see Section 5), thereby deriving the most stringent MOE. Since the MOE is > 100 (see the repeated dose and reproductive toxicity sections), we then refined the exposure to 40% using an *in silico* Skin Absorption

Model (SAM) to determine the Maximum Allowable Concentrations for each category listed in Section 10.

[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 v3.2.11.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, amyl cinnamate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Amyl cinnamate was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity without metabolic activation and negative for both cytotoxicity and genotoxicity with metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). While the BlueScreen assay on the target material showed positive results, data from additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of amyl cinnamate; however, read-across can be made to ethyl cinnamate (CAS # 103-36-6; see Section 6).

The mutagenic activity of ethyl cinnamate has been evaluated in a bacterial reverse mutation assay using guidelines similar to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA92, and TA94 were treated with ethyl cinnamate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Ishidate Jr et al., 1984). Under the conditions of the study, ethyl cinnamate was not mutagenic in the Ames test, and this can be extended to amyl cinnamate.

A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster V79 lung cells were treated with ethyl cinnamate in DMSO at concentrations up to 1760 μg/mL for 4 h with metabolic activation and 24 h without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (RIFM, 2015b). Under the conditions of the study, ethyl cinnamate was not mutagenic to mammalian cells *in vitro*, and this can be extended to amyl cinnamate.

The clastogenic activity of ethyl cinnamate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl cinnamate in DMSO at concentrations up to 1760 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 20 h. Ethyl cinnamate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2015c). Under the conditions of the study, ethyl cinnamate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to amyl cinnamate.

Based on the available data, ethyl cinnamate does not present a concern for genotoxic potential, and this can be applied to amyl cinnamate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on amyl cinnamate. Read-across material methyl cinnamate (CAS # 103-26-4; see Section 6) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 422- and GLP-compliant oral gavage combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Han Wistar rats. Groups of 12 rats/sex/dose were gavaged daily with methyl cinnamate at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. The highest dose group was administered 1000 mg/kg/day for the first week and then decreased to 600 mg/kg/day for the remainder of the study due to reversible clinical signs. Male rats were dosed for 14 days prior to mating, through mating, for a total of at least 28 days. Female rats were dosed for 14 days prior to mating, through mating and gestation periods, until day 4 postpartum. There were statistically significant decreases in body weights (did not fully recover) and food consumption (days 1–8 only, recovered thereafter) among high-dose males. Dose-dependent effects on white blood cell populations (decreased white blood cell count, absolute monocytes, large unstained cells, and/or lymphocytes) were observed in females at 100 mg/kg/day and both sexes at 300 and 600 mg/kg/day. However, associated histopathological alterations (atrophy of lymphatic tissues) of low severity grades were only observed in the 600 mg/kg/day female dose group. The relative liver weights were increased among high-dose group animals (statistically significant for males only). In the absence of histopathological evidence of liver cell damage and clinical chemistry alterations, liver weight increases were considered to be adaptive (Hall et al., 2012). At 600 mg/kg/day, atrophy of lymphoid tissues (spleen, thymus, and lymph nodes) was observed in females, and tubular basophilia in the kidneys was observed in males. These findings were low in severity grades and, therefore, not considered to be adverse. Furthermore, the atrophy corresponded to hematological changes and was considered to be most likely due to stress. Thus, the NOAEL for systemic toxicity was considered to be 300 mg/kg/day, based on decreases in body weights and white blood cell populations among the high-dose group animals (RIFM, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day.

Therefore, the amyl cinnamate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl cinnamate NOAEL in mg/kg/day by the total systemic exposure to amyl cinnamate, 100/0.0094, or 10638.

In addition, the total systemic exposure to amyl cinnamate (9.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section 10 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 reference dose (RfD) of 1 mg/kg/day.

11.1.2.1.1. Derivation of subchronic RfD. 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 amyl cinnamate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 100 mg/kg/day by the uncertainty factor, 100 = 1 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice

and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/24.

11.1.3. Reproductive toxicity

The MOE for amyl cinnamate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on amyl cinnamate. Read-across material methyl cinnamate (CAS # 103-26-4; see Section 6) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. An OECD 422- and GLP-compliant oral gavage combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Han Wistar rats. Groups of 12 rats/sex/dose were gavaged daily with test material methyl cinnamate at doses of 0, 100, 300, or 1000 mg/kg/day in corn oil. The highest dose group was administered 1000 mg/kg/day for the first week and then decreased to 600 mg/kg/day for the remainder of the study due to reversible clinical signs. Male rats were dosed for 14 days prior to mating, through mating, for a total of at least 28 days. Female rats were dosed for 14 days prior to mating, through mating and gestation periods, until day 4 postpartum. At 300 and 600 mg/kg/day, the post-implantation loss was increased (not statistically significant at 12.6% and 12.8%, respectively), which was reflected in a decreased live birth index (87.4% and 87.2%, respectively, as compared to 91.9% in controls). This effect was not dose-dependent, was not statistically significant, and was within the range of the historical control data. At 600 mg/kg/day, the gestation index was slightly reduced. The decrease in the gestation index of high-dose dams (83.3%) when compared to controls (100%) was considered to be due to treatment-related findings of toxicological relevance in hematology, clinical chemistry, and histopathology in the highest dose group. There were no other reproductive effects reported. In the presence of maternal toxicity, the NOAEL for developmental toxicity and fertility was considered to be 300 mg/kg/day, based on a decrease in the gestation index among high-dose dams (RIFM, 2013). **Therefore, the amyl cinnamate MOE for the developmental toxicity and fertility endpoint can be calculated by dividing the methyl cinnamate NOAEL in mg/kg/day by the total systemic exposure to amyl cinnamate, 300/0.0094 or 31915.**

In addition, the total systemic exposure to amyl cinnamate (9.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Table 1
Summary of existing data on methyl cinnamate as a read-across for amyl cinnamate.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[2] (induction) μg/cm²	WoE NESIL[3] μg/cm²	LLNA Weighted Mean EC3 Value μg/cm²	GPMT[4]	Buehler[4]
Weak	2953	6900	NA	2900	NA	Positive	NA
	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
	NA	NA	NA		Michael addition	Michael addition	Michael addition

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; NA = Not Available.
1WoE 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).
2Data derived from CNIH or HMT.
3WoE NESIL limited to 2 significant figures.
4Studies conducted according to the OECD TG 406 are included in the table.
5Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/24.

11.1.4. Skin sensitization

Based on read-across to methyl cinnamate (CAS # 103-26-4), amyl cinnamate was assigned a NESIL of 2900 μg/cm^2, and the maximum acceptable concentrations in finished products are provided in Section 10.

11.1.4.1. Risk assessment. Limited data are available on the skin sensitization potential of amyl cinnamate. Therefore, a structurally related material, methyl cinnamate (CAS # 103-26-4; see Section 6), was used for the risk assessment of amyl cinnamate. The data on the read-across material are summarized in Table 1. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a guinea pig maximization test, open epicutaneous test, Freund's Complete Adjuvant test, and Draize test, reactions indicative of sensitization with read-across analog methyl cinnamate were observed (RIFM, 1976). In human maximization tests, no skin sensitization reactions were observed with read-across analog methyl cinnamate (RIFM, 1970; RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 2953 μg/cm^2 read-across analog methyl cinnamate in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 105 volunteers (RIFM, 2015a).

Based on the weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies on the read-across material and the target material, amyl cinnamate was assigned a WoE NESIL of 2900 μg/cm^2 (Table 1). Section 10 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 1 mg/kg/day.

Additional References: Klecak et al., 1977; Klecak (1979); Klecak (1985); RIFM, 1971.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, amyl cinnamate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for amyl cinnamate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. Based on the lack of absorbance, amyl cinnamate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. Thus, it is not a concern for photoirritating or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/24.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on amyl cinnamate. Based on the Creme RIFM Model, the inhalation exposure is 0.0070 mg/day. This exposure is 200 times lower than the Cramer Class I TTC value of 1.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of amyl cinnamate 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. (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, amyl cinnamate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify amyl cinnamate 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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current VoU (2019), amyl cinnamate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Amyl cinnamate has been pre-registered for REACH with no additional data at this time.

11.2.1.3. 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)**	2.823			1000000	0.002823	

Environmental Framework: Salvito et al., 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.32	4.32
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	N/A	<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 0.002823 μg/L. The revised PEC/PNECs for EU (not reported) and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/01/24.

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 04/09/24.

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.2024.114702.

Appendix

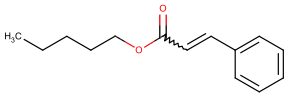
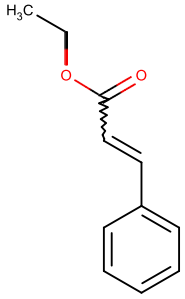
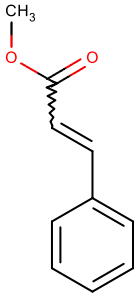
Read-across Justification

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, 2017b).

- 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, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- 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	Read-across Material
Principal Name	Amyl cinnamate	Ethyl cinnamate	Methyl cinnamate
CAS No.	3487-99-8	103-36-6	103-26-4
Structure			
Similarity (Tanimoto Score)		0.80	0.73
SMILES	CCCCCOC(=O)C=Cc1ccccc1	CCOC(=O)C=Cc1ccccc1	COC(=O)C=Cc1ccccc1
Endpoint		Genotoxicity	Repeated dose toxicity Reproductive toxicity Skin sensitization
Molecular Formula	$C_{14}H_{18}O_2$	$C_{11}H_{12}O_2$	$C_{10}H_{10}O_2$
Molecular Weight	218.296	176.215	162.188
Melting Point (°C, EPI Suite)	51.15	7.00	36.00
Boiling Point (°C, EPI Suite)	304.70	271.00	260.40
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.17E-01	4.36E-01	4.60E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.17E+00	1.78E+02	3.87E+02
Log KOW	4.32	2.99	2.62
J_{max} (μg/cm^2/h, SAM)	0.70	9.01	16.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.31E+00	4.32E-01	4.19E-01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found	
Carcinogenicity (ISS)	No alert found	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Acrylate Reactive Functional Groups	Acrylate Reactive Functional Groups	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Coumarin (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert		Carbamazepine (Hepatotoxicity) Alert| Carbamazepine (Renal Toxicity) Alert| Coumarin (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (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 (good reliability)		Toxicant (good reliability)
Skin Sensitization			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Protein Binding (OASIS v1.1)	Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds		Michael addition|Michael addition ≫ Michael addition on conjugated systems with electron withdrawing group|Michael addition ≫ Michael addition on conjugated systems with electron withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds
Protein Binding (OECD)	Michael addition|Michael addition ≫ Polarized Alkenes| Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters		Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters
Protein Binding Potency	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)		Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkyl 2-alkenoates (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds		Michael Addition|Michael Addition ≫ Michael addition on conjugated systems with electron withdrawing group|Michael Addition ≫ Michael addition on conjugated systems with electron withdrawing group ≫ α,β-Carbonyl compounds with polarized double bonds
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified		Alert for Michael Acceptor identified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on amyl cinnamate (CAS # 3487-99-8). 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, ethyl cinnamate (CAS # 103-36-6) and methyl cinnamate (CAS # 103-26-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl cinnamate (CAS # 103-36-6) was used as a read-across analog for the target material, amyl cinnamate (CAS # 3487-99-8), for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the cinnamate group.
  - o The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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.
    - oThe 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 The target material and the read-across analog do not have alerts for genotoxicity. 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 lack of *in silico* alerts is consistent with 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.
- Methyl cinnamate (CAS # 103-26-4) was used as a read-across analog for the target material amyl cinnamate (CAS # 3487-99-8) for the repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the cinnamate group.
  - o The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 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 read-across 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 read-across analog.
  - o The target material and the read-across material have alerts for hepatotoxicity and renal toxicity 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 do not have alerts for reproductive toxicity. The data on the read-across analog confirms that the material does not pose a concern for reproductive 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 is consistent with the data.
- o The target material and the read-across analog have Michael addition alerts for skin sensitization. The data on the read-across analog confirms that the material is a weak sensitizer. 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 are consistent with 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.

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