Food and Chemical Toxicology 159 (2022) 112716

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, α-amyl cinnamic aldehyde diethyl acetal, CAS Registry Number 60763-41-9

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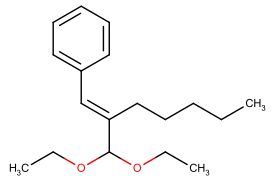
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

Version: 071921. Initial publication. 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**.



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Name: α-Amyl cinnamic aldehyde diethyl acetal
CAS Registry Number: 60763-41-9

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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https://doi.org/10.1016/j.fct.2021.112716
Received 19 July 2021; Received in revised form 1 November 2021; Accepted 24 November 2021
Available online 26 November 2021

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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., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 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-Amyl cinnamic aldehyde diethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from α-amyl cinnamic aldehyde diethyl acetal and read-across analog cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) show that α-amyl cinnamic aldehyde diethyl acetal is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class II material, and the exposure to α-amyl cinnamic aldehyde diethyl acetal is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data from read-across analog cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) provided α-amyl cinnamic aldehyde diethyl acetal a NESIL of 820 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; α-amyl cinnamic aldehyde diethyl acetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; α-amyl cinnamic aldehyde diethyl acetal was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: 2-Diethoxymethyl-1-phenylhept-1-ene; ECHA, 2017a; RIFM, 2014)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 820 μg/cm^2.	RIFM, (2008)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 77% (OECD 301D)	RIFM, (2016c)
Bioaccumulation: Screening-level: 2680 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia Magna* LC50: 0.04 mg/L	(ECOSAR; US EPA; 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.04 mg/L	(ECOSAR; US EPA; 2012b)
RIFM PNEC is: 0.004 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** α-Amyl cinnamic aldehyde diethyl acetal
2. **CAS Registry Number:** 60763-41-9
3. **Synonyms:** Benzene, [2-(diethoxymethyl)-1-heptenyl]-; 1,1-Diethoxy-2-amyl-3-phenylacrolein; 1,1-Diethoxy-2-amyl-3-phenyl-2-propene; 2-Diethoxymethyl-1-phenylhept-1-ene; α-ｱﾐﾙｹｲ皮ｱﾙﾃﾞﾋﾄﾞｼﾞｱﾙｷﾙ(C = 1,2)ｱｾﾀｰﾙ; [2-(Diethoxymethyl)hept-1-en-1-yl]benzene; Reaction mass of [(1E)-2-(diethoxymethyl)hept-1-en-1-yl]benzene and [(1Z)-2-(diethoxymethyl)hept-1-en-1-yl]benzene; α-Amyl cinnamic aldehyde diethyl acetal
4. **Molecular Formula:** $C_{18}H_{28}O_2$
5. **Molecular Weight:** 276.42
6. **RIFM Number:** 212
7. **Stereochemistry:** Isomer not specified. One stereocenter present and 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 343.19 °C (EPI Suite)
2. **Flash Point:** 163 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 5.7 (EPI Suite)
4. **Melting Point**: 63.91 °C (EPI Suite)
5. **Water Solubility:** 0.2275 mg/L (EPI Suite)
6. **Specific Gravity:** 0.936 (FMA)
7. **Vapor Pressure:** 0.000042 mm Hg at 20 °C (EPI Suite v4.0), 8.28e-005 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Almost colorless oily liquid with a leafy floral odor (Arctander, 1969)

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95th Percentile Concentration in Fine Fragrance*:** 0.38% (RIFM, 2016a)
2. **Inhalation Exposure**:** 0.000048 mg/kg/day or 0.0031 mg/day (RIFM, 2016a)
3. **Total Systemic Exposure***:** 0.0031 mg/kg/day (RIFM, 2016a)

*See IFRA Category 4 in Section X for maximum acceptable concentrations in finished products.

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

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** Cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

α-Amyl cinnamic aldehyde diethyl acetal is not reported to occur in food by the VCF*:

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 07/19/21 (ECHA, 2017a).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for α-amyl cinnamic aldehyde diethyl acetal 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)	0.063
2	Products applied to the axillae	0.019
3	Products applied to the face/body using fingertips	0.38
4	Products related to fine fragrances	0.35
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.089
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.089
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.089
5D	Baby cream, oil, talc	0.089
6	Products with oral and lip exposure	0.21
7	Products applied to the hair with some hand contact	0.72
8	Products with significant ano-genital exposure (tampon)	0.037
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.69
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.5
10B	Aerosol air freshener	2.5
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.4
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 α-amyl cinnamic aldehyde diethyl acetal, the basis a skin sensitization NESIL of 820 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).

Summary

Human health endpoint summaries

Genotoxicity

Based on the current existing data and use levels, α-amyl cinnamic aldehyde diethyl acetal does not present a concern for genetic toxicity.

Risk assessment. α-Amyl cinnamic aldehyde diethyl acetal was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013).

BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of α-amyl cinnamic aldehyde diethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-amyl cinnamic aldehyde diethyl acetal 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 (ECHA, 2017a). Under the conditions of the study, α-amyl cinnamic aldehyde diethyl acetal was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of α-amyl cinnamic aldehyde diethyl acetal; however, read-across can be made to cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1; see Section VI).

The clastogenic activity of cinnamic aldehyde dimethyl acetal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with cinnamic aldehyde dimethyl acetal in DMSO at concentrations up to 1783 μg/mL in the dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of S9 for 3 h and the absence of metabolic activation for 24 h. Cinnamic aldehyde dimethyl acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, cinnamic aldehyde dimethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to α-amyl cinnamic aldehyde diethyl acetal.

Based on the data available, α-amyl cinnamic aldehyde diethyl acetal and read-across cinnamic aldehyde dimethyl acetal do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

Repeated dose toxicity

There are no repeated dose toxicity data on α-amyl cinnamic aldehyde diethyl acetal or any read-across materials. The total systemic exposure to α-amyl cinnamic aldehyde diethyl acetal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Risk assessment. There are no repeated dose toxicity data on α-amyl cinnamic aldehyde diethyl acetal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to α-amyl cinnamic aldehyde diethyl acetal (3.1 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

Reproductive toxicity

There are no reproductive toxicity data on α-amyl cinnamic aldehyde diethyl acetal or any read-across materials. The total systemic exposure to α-amyl cinnamic aldehyde diethyl acetal is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Risk assessment. There are no reproductive toxicity data on α-amyl cinnamic aldehyde diethyl acetal or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to α-amyl cinnamic aldehyde diethyl acetal (3.1 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/21.

Skin sensitization

Based on the existing data for the read-across material, cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1), α-amyl cinnamic aldehyde diethyl acetal is considered to be a skin sensitizer with a defined NESIL of 820 μg/cm^2.

Risk assessment. Limited skin sensitization studies are available for α-amyl cinnamic aldehyde diethyl acetal. Based on the existing data and read-across material cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1; see Section VI), α-amyl cinnamic aldehyde diethyl acetal is considered a skin sensitizer. The chemical structure of the target material indicates that it would not be expected to react with skin proteins, while the chemical structure of the read-across material indicates that it would be reactive (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), α-amyl cinnamic aldehyde diethyl acetal was found to be sensitizing with an EC3 value of 8.6% (2150 μg/cm^2) (ECHA, 2017a). In a human maximization test, no skin sensitization reactions were observed with the target material (RIFM, 1971). In 2 other human maximization tests with the read-across material, skin sensitization reactions were observed (RIFM, 1972; RIFM, 1974). Multiple Confirmation of No Induction in Humans tests (CNIHs) have been conducted with the read-across material, cinnamic aldehyde dimethyl acetal. In a CNIH with 826 μg/cm^2 read-across material, no reactions indicative of sensitization were observed in any of the 92 volunteers (RIFM, 2008). In 2 other CNIHs with 484 μg/cm^2 and 747 μg/cm^2 of the read-across material in ethanol, no reactions indicative of skin sensitization were observed in any of the 30 and 12 volunteers, respectively (RIFM, 1964b; RIFM, 1964a). Similarly, in another CNIH with 775 μg/cm^2 of the read-across material in alcohol SDA39C, no reactions indicative of skin sensitization were observed in any of the 41 volunteers (RIFM, 1973). On the other hand, when the read-across material was tested at 1938 μg/cm^2 and 4845 μg/cm^2 in ethanol, 6/30 and 2/6 volunteers exhibited reactions indicative of skin sensitization.

Based on the available data on the target material and the read-across material cinnamic aldehyde dimethyl acetal, summarized in

Table 1
Cinnamic aldehyde dimethyl acetal – Data summary as read-across for α-amyl cinnamic aldehyde diethyl acetal.

LLNA weighted mean EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] μg/cm^2
2150 [1][4]	NA	826	NA	1938	820

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[2] Data derived from CNIH or HMT.

[3] WoE NESIL limited to 2 significant figures.

[4] The LLNA data is for the target material, α-amyl cinnamic aldehyde diethyl acetal.

Table 1, α-amyl cinnamic aldehyde diethyl acetal is considered to be a skin sensitizer with a defined NESIL of 820 μg/cm^2.

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. (RIFM, 2020).
Additional References: Klecak (1979).

Literature Search and Risk Assessment Completed On: 05/26/21.

Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, α-amyl cinnamic aldehyde diethyl acetal does not present a concern for phototoxicity or photoallergenicity.

Risk assessment. There are no phototoxicity studies available for α-amyl cinnamic aldehyde diethyl acetal in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, α-amyl cinnamic aldehyde diethyl acetal does not present a concern for phototoxicity or photoallergenicity.

UV spectra analysis

The available UV/Vis absorption spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern, 1000 L mol^{-1} • cm^{-1}, for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for α-amyl cinnamic aldehyde diethyl acetal is below the Cramer Class III* TTC value for inhalation exposure local effects.

Risk assessment. There are insufficient inhalation data available on α-amyl cinnamic aldehyde diethyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.0031 mg/day. This exposure is 151.6 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: RIFM, 1980; The Union of German Candle Manufacturers, 1997; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola (2004a); Rogers (2005); Vethanayagam (2013).

Literature Search and Risk Assessment Completed On: 05/28/21.

Environmental endpoint summary

Screening-level assessment

A screening-level risk assessment of α-amyl cinnamic aldehyde diethyl acetal was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, α-amyl cinnamic aldehyde diethyl acetal 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) identified α-amyl cinnamic aldehyde diethyl acetal as not possibly persistent but bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

Risk assessment. Based on the current VoU (2015), α-amyl cinnamic aldehyde diethyl acetal presents a risk to the aquatic compartment in the screening-level assessment.

Key studies

Biodegradation. RIFM, 2016c: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guidelines. Biodegradation of 77% was observed after 28 days.

Ecotoxicity. RIFM, 2016b: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under semi-static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 0.45 mg/L (95% CI: 0.21–>0.80 mg/L).

RIFM, 2017: The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 value based on the mean measured concentration for growth was reported to be > 0.42 mg/L.

Other available data. α-Amyl cinnamic aldehyde diethyl acetal has been registered for REACH with no additional data available at this time.

Risk assessment refinement. Since α-amyl cinnamic aldehyde diethyl acetal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.225			1000000	0.000225	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.254	0.040	0.070	10000	0.004	Vinyl/Allyl Ethers
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.108	0.086	0.264			Neutral Organics SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.7	5.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.004 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 volumes of use.

Literature Search and Risk Assessment Completed On: 05/25/21.

Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 07/19/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112716.

Appendix

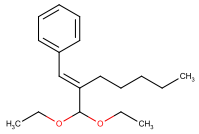
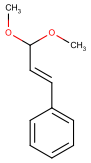
Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment

(OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	α-Amyl cinnamic aldehyde diethyl acetal	Cinnamic aldehyde dimethyl acetal
CAS No.	60763-41-9	4364-06-1
Structure		
Similarity (Tanimoto Score)		0.52
Read-across Endpoint		• Genotoxicity • Skin sensitization
Molecular Formula	$C_{18}H_{28}O_2$	$C_{11}H_{14}O_2$
Molecular Weight	276.42	178.231
Melting Point (°C, EPI Suite)	63.91	10.04
Boiling Point (°C, EPI Suite)	343.19	243.83
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.01	5.04
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.7	2.21
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.28E-01	7.33E+02
J_{max} (μg/cm^2/h, SAM)	1.211	75.145
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.58E+00	3.01E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No skin sensitization reactivity domain alerts identified	• Alert for Michael Acceptor identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on α-amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9). Hence, an *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) was used as a read-across analog for the target material α-amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) for the skin sensitization and genotoxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of cinnamic acetals.

- The target material and the read-across analog share a cinnamyl acetal group.
- The key difference between the target material and the read-across analog is that the target material has a C5 branch in the α position and 2 ethanol branches, whereas the read-across analog has 2 methanol branches and does not have any branch in the α position. This structural difference is toxicologically insignificant.
- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. 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 percentage 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.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The read-across analog has an alert for Michael Acceptor for the Skin Sensitization Reactivity Domains categorization scheme, which is not found in the target material. This alert is due to the presence of an unsubstituted vinylene group in the read-across analog. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
- There are no toxicological alerts for the target material as well as for the read-across analog for the genotoxicity endpoint. Data are consistent with *in silico* alerts.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- 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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