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RIFM fragrance ingredient safety assessment, α-amylcinnamaldehyde dimethyl acetal, CAS Registry Number 91-87-2

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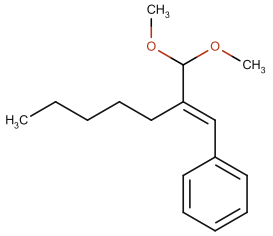

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Name: α-Amylcinnamaldehyde dimethyl acetal CAS Registry Number: 91-87-2

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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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., 2015; Safford 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
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
α-Amylcinnamaldehyde dimethyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) show that α-amylcinnamaldehyde dimethyl 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-amylcinnamaldehyde dimethyl 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 analogs α-amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) and cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) provided α-amyl cinnamaldehyde dimethyl 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 cinnamaldehyde dimethyl acetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; α-amyl cinnamaldehyde dimethyl 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. (RIFM, 2014a; RIFM, 2014b)
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: Screening-level: 2.95 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 602 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1.44 mg/L (RIFM 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) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1.44 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00144 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; Cleared at screening-level

1. Identification

1. **Chemical Name:** α-Amylcinnamaldehyde dimethyl acetal
2. **CAS Registry Number:** 91-87-2
3. **Synonyms:** α-Amylcinnamic aldehyde dimethyl acetal; α-Amyl-β-phenylacrolein dimethyl acetal; Benzene, [2-(dimethoxymethyl)-1-heptenyl]-; 1,1-Dimethoxy-2-amyl-3-phenyl-2-propene; 1,1-Dimethoxy-2-benzylideneheptane; α-Pentylcinnamaldehyde dimethyl acetal; [2-(Dimethoxymethyl)hept-1-en-1-yl]benzene; Amyl cinnamic aldehyde dimethyl acetal; α-Amylcinnamaldehyde dimethyl acetal
4. **Molecular Formula:** $C_{16}H_{24}O_2$
5. **Molecular Weight:** 248.36
6. **RIFM Number:** 524
7. **Stereochemistry:** Isomer not specified. One stereocenter present and 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 317.92 °C (EPI Suite)
2. **Flash Point:** 198 °F; CC (FMA)
3. **Log K_{OW}:** 4.72 (EPI Suite)
4. **Melting Point**: 43.31 °C (EPI Suite)
5. **Water Solubility:** 2.257 mg/L (EPI Suite)
6. **Specific Gravity:** 0.957 (FMA)
7. **Vapor Pressure:** 0.00027 mm Hg at 20 °C (EPI Suite v4.0), 0.000511 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 slightly oily liquid, with a peculiar animal-green odor, mild and reminiscent of parts of the Jasmin complex

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Deodorant Roll-on***: 0.048% (RIFM, 2016)
   (No reported use in Fine Fragrance)
2. **Inhalation Exposure****: 0.000036 mg/kg/day or 0.0026 mg/day (RIFM, 2016)
3. **Total Systemic Exposure*****: 0.0079 mg/kg/day (RIFM, 2016)

* 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 et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 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 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 II, Intermediate (Expert Judgment)

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

*See the Appendix below for further details.

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:** α-Amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) and 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-Amylcinnamaldehyde dimethyl 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

Pre-registered for 2010; no dossier available as of 03/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for α-amylcinnamaldehyde dimethyl 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-amylcinnamaldehyde dimethyl acetal, the basis was the predicted skin absorption value of 40% and 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).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, α-amylcinnamaldehyde dimethyl acetal does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. α-Amylcinnamaldehyde dimethyl 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.

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

The mutagenic activity of cinnamic aldehyde dimethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in 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 cinnamic aldehyde dimethyl 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 (RIFM, 2014a). Under the conditions of the study, cinnamic aldehyde dimethyl acetal was not mutagenic in the Ames test, and this can be extended to α-amylcinnamaldehyde dimethyl acetal.

The clastogenic activity of cinnamic aldehyde dimethyl acetal 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 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 in 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, 2014b). 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-amylcinnamaldehyde dimethyl acetal.

Based on the available data, read-across cinnamic aldehyde dimethyl acetal does not present a concern for genotoxic potential, and this can be extended to α-amylcinnamaldehyde dimethyl acetal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/17/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on α-amylcinnamaldehyde dimethyl acetal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to α-amylcinnamaldehyde dimethyl acetal (7.9 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on α-amylcinnamaldehyde dimethyl acetal or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to α-amylcinnamaldehyde dimethyl acetal (7.9 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 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: 12/15/20.

11.1.4. Skin sensitization

Based on the existing data for the read-across materials α-amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) and cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1), α-amyl cinnamaldehyde dimethyl acetal is considered to be a skin sensitizer with a defined NESIL of 820 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for α-amyl cinnamaldehyde dimethyl acetal. Based on the existing data and read-across materials α-amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9; see Section VI) and cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1; see Section VI), α-amyl cinnamaldehyde diethyl acetal is considered a skin sensitizer. The chemical structure of the target material and the read-across material α-amyl cinnamic aldehyde diethyl acetal indicate that they would not be expected to react directly with skin proteins, while the chemical structure of the read-across material cinnamic aldehyde dimethyl acetal indicates that it would be reactive (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed with the target material (RIFM, 1974). In a murine local lymph node assay (LLNA), the read-across material α-amyl cinnamic aldehyde diethyl acetal was found to be sensitizing with an EC3 value of 8.6% (2150 μg/cm^2) (ECHA, 2017). In 2 other human maximization tests with the read-across material cinnamic aldehyde dimethyl acetal, skin sensitization reactions were observed (RIFM, 1972; RIFM, 1974). Multiple Confirmation of No Induction in Humans tests (CNIH) have been conducted with the read-across material cinnamic aldehyde dimethyl acetal. In a CNIH with 826 μg/cm^2 of the read-across material cinnamic aldehyde dimethyl acetal, no reactions indicative of sensitization was observed in any of the 92 volunteers (RIFM, 2008). In 2 other CNIHs with 484 μg/cm^2 and 747 μg/cm^2 of cinnamic aldehyde dimethyl acetal in ethanol (EtOH), 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 cinnamic aldehyde dimethyl acetal in alcohol SDA39C, no reactions indicative of skin sensitization were observed in any of the 41 volunteers (RIFM, 1973). On the other hand, when cinnamic aldehyde dimethyl acetal was tested at 1938 μg/cm^2 and 4845 μg/cm^2 in EtOH, 6/30 and 2/6 volunteers exhibited reactions indicative of skin sensitization, respectively.

Based on the available data on the target material and the read-across materials α-amyl cinnamic aldehyde diethyl acetal and cinnamic aldehyde dimethyl acetal, summarized in Table 1, α-amylcinnamaldehyde dimethyl 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 (1985).

Literature Search and Risk Assessment Completed On: 12/18/20.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis absorption spectra, α-amylcinnamaldehyde dimethyl acetal does not present a concern for phototoxicity or photoallergenicity.

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

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for α-amylcinnamaldehyde dimethyl acetal were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/11/20.

11.1.6. Local respiratory toxicity

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

11.1.6.1. Risk assessment. There are insufficient inhalation data available on α-amylcinnamaldehyde dimethyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.0026 mg/day. This exposure is 180.8 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: RIFM, 1980; UGCM, 1997; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola et al., 2004; Rogers et al., 2005; Vethanayagam et al., 2013.

Literature Search and Risk Assessment Completed On: 12/16/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of α-amylcinnamaldehyde dimethyl acetal 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 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-amylcinnamaldehyde dimethyl acetal 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 α-amylcinnamaldehyde dimethyl acetal as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.2. Risk assessment

Based on current VoU (2015), α-amylcinnamaldehyde dimethyl acetal does not present a risk to the aquatic compartment in the

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

screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. α-Amylcinnamaldehyde dimethyl acetal has been pre-registered for REACH with no additional data at this time.

11.2.3. 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.72	4.72
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	<1

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

The RIFM PNEC is 0.00144 μg/L. The revised PEC/PNECs for EU 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: 12/16/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **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 03/10/21.

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 related to this article can be found at https://doi.org/10.1016/j.fct.2021.112493.

Appendix

Read-across Justification

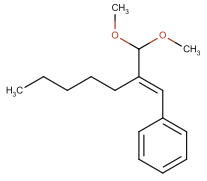
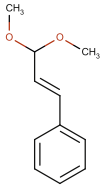
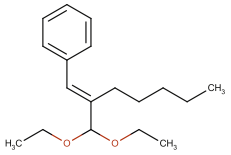
Methods

The read-across analogs were 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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.44			1000000	0.00144	

(OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- 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	Read-across Material
Principal Name	α-Amylcinnamaldehyde dimethyl acetal	Cinnamic aldehyde dimethyl acetal	α-Amyl cinnamic aldehyde diethyl acetal
CAS No.	91-87-2	4364-06-1	60763-41-9
Structure			
Similarity (Tanimoto Score)		0.58	0.89
Read-across Endpoint		• Genotoxicity • Skin sensitization	• Skin sensitization
Molecular Formula	$C_{16}H_{24}O_2$	$C_{11}H_{14}O_2$	$C_{18}H_{28}O_2$
Molecular Weight	248.366	178.231	276.420
Melting Point (°C, EPI Suite)	43.31	10.04	63.91
Boiling Point (°C, EPI Suite)	317.92	243.83	343.19
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.07	5.04	0.011
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.72	2.21	5.70
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.26E+00	7.33E+02	2.28E-01
J_{max} (μg/cm^2/h, SAM)	5.689	75.145	1.211
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.47E+00	3.01E-01	2.58E+00
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	• No alert found
Protein Binding (OECD)	• No alert found	• 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)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• 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	• No skin sensitization reactivity domain alerts 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	• See Supplemental Data 3

Summary

There are insufficient toxicity data on α-amylcinnamaldehyde dimethyl acetal (CAS # 91-87-2). 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, cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) was identified as a read-across analog with sufficient data for toxicological evaluation. α-Amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) has been used as an additional WoE for the skin sensitization endpoint.

Conclusions

- Cinnamic aldehyde dimethyl acetal (CAS # 4364-06-1) was used as a read-across analog for the target material α-amylcinnamaldehyde dimethyl acetal (CAS # 91-87-2) for the skin sensitization and genotoxicity endpoints.
  - 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 methanol 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 a comparison of their toxicological properties.
  - 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.
- α-Amyl cinnamic aldehyde diethyl acetal (CAS # 60763-41-9) was used as a WoE analog for the target material α-amylcinnamaldehyde dimethyl acetal (CAS # 91-87-2) for the skin sensitization endpoint.
  - 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 2 methanol branches, whereas the read-across analog has 2 ethanol branches. 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 a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - 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.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No;
Q2. Contains functional groups associated with enhanced toxicity? No;
Q3. Contains elements other than C, H, O, N, divalent S? No;
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No;
Q6. Benzene derivative with certain substituents? No;
Q7. Heterocyclic? No;
Q16. Common terpene? No;
Q17. Readily hydrolyzed to a common terpene? No;
Q19. Open chain? No;
Q23. Aromatic? Yes;
Q27. Rings with substituents? Yes;
Q28. More than one aromatic ring? No;
Q30. Aromatic Ring with complex substituents? Yes;
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No;
Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below? Yes, Class Intermediate (Class II)

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