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Short Review

RIFM fragrance ingredient safety assessment, α-amylcinnamaldehyde, CAS registry number 122-40-7

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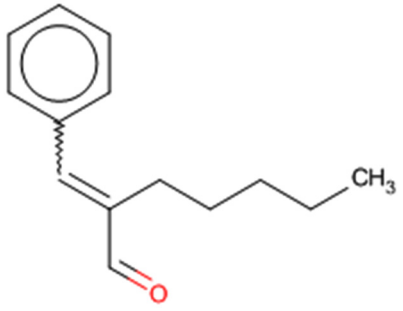

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Abbreviation/Definition list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
DEREK – Derek nexus is an *in silico* tool used to identify structural alerts
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
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
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
REACH – Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
* RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 29.9 mg/kg/day, based on a dietary 14-week subchronic toxicity study conducted in rats, that resulted in an MOE of 1300, considering 9.54% absorption from skin contact and 100% from inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not Genotoxic (Wild et al., 1983)
Repeated Dose Toxicity: NOAEL = 29.9 mg/kg/day (Carpanini et al., 1973)
Developmental and Reproductive Toxicity: NOAEL = 100 mg/kg/day (RIFM (Research Institute for Fragrance Materials, Inc.), 2010)
Skin Sensitization: NESIL = 23,600 μg/cm^2 RIFM (Research Institute for Fragrance Materials, Inc.), 2005)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM (Research Institute for Fragrance Materials, Inc.), 1988; RIFM (Research Institute for Fragrance Materials, Inc.), 1988a)
Local Respiratory Toxicity: NOAEC = 56.5 ppm or 500 mg/m^3 (0.5 mg/L) (RIFM (Research Institute for Fragrance Materials, Inc.), 2012)

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 41–90% (RIFM (Research Institute for Fragrance Materials, Inc.), 1992; RIFM (Research Institute for Fragrance Materials, Inc.), 1996; RIFM (Research Institute for Fragrance Materials, Inc.), 1992b)
Bioaccumulation: Screening Level: 334 L/kg (EPISUITE ver. 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 72 hrs Algae EC50: 1.18 mg/L (RIFM (Research Institute for Fragrance Materials, Inc.), 2003)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) > 1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 72 hrs Algae EC50: 1.18 mg/L (RIFM (Research Institute for Fragrance Materials, Inc.), 2003)
RIFM PNEC is: 1.18 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe <1

1. Identification

1. **Chemical Name:** α-Amylcinnamaldehyde
2. **CAS Registry Number:** 122-40-7
3. **Synonyms:** 'A.C.A.', Amyl cinnamal, Amyl cinnamic aldehyde, α-Amylcinnamaldehyde, α-Amyl β-phenylacrolein, Heptanal, 2-(phenylmethylene)-, α-Pentylcinnamaldehyde, α-Pentyl-β-phenylacrolein, α-Amyl cinnamic aldehyde,

Heptanal, 2-(phenylmethylene), 2-(Phenylmethylene)heptanal, Flomine, AAC, ２－アルキル（Ｃ＝４～６）ケイ皮アルデヒド, 2-Benzylideneheptanal

4. **Molecular Formula:** $C_{14}H_{18}O$
5. **Molecular Weight:** 202.3
6. **RIFM Number:** 101

2. Physical data

1. **Boiling Point:** 284 °C [IFRA], (calculated) 304.8 °C [EPI Suite]
2. **Flash Point:** >200 °F; CC [IFRA]
3. **Log K_{ow}:** Log P_{ow} = 4.7 (at 24 °C) (RIFM (Research Institute for Fragrance Materials, Inc.), 1994c), 4.33 [EPI Suite]
4. **Melting Point**: (calculated) 33.9 °C [EPI Suite]
5. **Water Solubility:** (calculated) 8.545 mg/L [EPI Suite]
6. **Specific Gravity:** 0.965 [IFRA]
7. **Vapor Pressure:** <0.001 mm Hg 20 °C [IFRA], (calculated) 0.000238 mm Hg @ 20 °C [EPI Suite 4.0], (calculated) 0.000452 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Absorbs in the region of 290–700 nm
9. **Appearance/Organoleptic:** Pale yellowish to yellow liquid with strong floral odor suggestive of jasmine on dilution

3. Exposure

1. **Volume of Use (worldwide band):** <1000 metric tons per year (IFRA (International Fragrance Association), 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 0.93% [IFRA, 2011]
3. **97.5th Percentile**: 5.48% (IFRA (International Fragrance Association), 2002)
4. **Dermal Exposure***: 0.1396 mg/kg/day (IFRA (International Fragrance Association), 2002)
5. **Oral Exposure**: Not available
6. **Inhalation Exposures****: 0.0085 mg/kg/day (IFRA (International Fragrance Association), 2002)
7. **Total Systemic Exposure (Dermal + Inhalation)**: (0.1396 mg/kg/day × 9.54% absorption) + 0.0085 mg/kg/day = 0.022 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. Dermal: 9.54%

RIFM (Research Institute for Fragrance Materials, Inc.), 2014: An *in vitro* human skin absorption study was conducted with read across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section 5). Permeation of α-hexylcinnamaldehyde was monitored (via HPLC-UV) by analyzing the receptor phase for α-hexylcinnamaldehyde and potential metabolites α-hexyl cinnamic alcohol and acid. Measurements were made at twelve time-points over 24 hours. At 24 hours, the epidermal membranes were wiped, tape stripped 10 times and the target material and potential metabolite content of the wipes, strips and remaining epidermis determined. The filter paper skin supports were extracted and the diffusion cell donor chambers washed and wiped. Analysis of these samples allowed mass balance to be performed. As per SCCNFP guideline, the levels of material in the epidermis (plus any remaining stratum corneum after tape stripping), filter paper membrane support and receptor fluid were combined to produce a total absorbed dose value. Following 24 hours exposure, under un-occluded conditions, 4.51 ± 0.80% (2.75% Ald, 0.0% alc, 1.765% acid) of the applied dose had permeated. The mass balance demonstrated that 92.3% of the applied does was recovered. Following 24 hours exposure, under occluded conditions, 9.54 ± 1.50% (5.75% Ald, 0.32% alc, 3.49% acid) of the applied dose had permeated. The mass balance demonstrated that 86.3% of the applied dose was recovered. For conservative purposes, 9.54% absorption is considered.

2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Dermal (9.54%) + Inhalation (assume 100%) absorbed = (0.1396 mg/kg/day × 9.54%) + 0.01 mg/kg/day = 0.023 mg/kg/day

5. 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 Appendix below for explanation.

2. **Analogues Selected:**
   - **a.** Genotoxicity: None
   - **b.** Repeated Dose Toxicity: α-Hexylcinnamaldehyde (CAS # 101-86-0)
   - **c.** Developmental and Reproductive Toxicity: α-Hexylcinnamaldehyde (CAS # 101-86-0)
   - **d.** Skin Sensitization: None
   - **e.** Phototoxicity/Photoallergenicity: None
   - **f.** Local Respiratory Toxicity: α-Hexylcinnamaldehyde (CAS # 101-86-0)
   - **g.** Environmental Toxicity: None
3. **Read-across Justification: See Appendix below**

6. Metabolism

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

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

Fragrance Ingredient is a component of the following naturals:
α-Amylcinnamaldehyde is reported to occur in food*:
Black tea
Soybean
Soybean (glycine max. L. Merr.)
Tea

* 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

IFRA Standard Restricted – The use of the material should be limited quantitatively. See Skin Sensitization Section (IFRA (International Fragrance Association), 2013).

9. Reach DOSSIER

Pre-Registered for 2010; No dossier available as of 05/08/13.

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

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

10.1.1. Risk assessment

The genotoxic potential of α-amylcinnamaldehyde (CAS # 122-40-7) has been evaluated for mutagenicity in bacteria, and *Drosophila*, and for clastogenicity *in vivo*. No mutagenicity was observed in an Ames study conducted in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, at doses up to 3.6 mg/plate with and without S9 metabolic activation (Wild et al., 1983). Additionally, a second Ames study conducted in *S. typhimurium* strains TA97 and TA102 using the preincubation method was negative at doses up to 1 mg/plate both with and without metabolic activation (Fujita and Sasaki, 1987). Further support for a lack of mutagenicity was demonstrated by a lack of significant increases in sex-linked recessive lethal (SRL) mutations in a Basc test using Berlin K (wild type) and Basc strains of *Drosophila melanogaster* when 10 mM of α-amylcinnamaldehyde in 5% saccharose was added to the diet. With regard to the clastogenicity endpoint, no effects were observed in an *in vivo* mouse micronucleus test in which groups of male and female NMRI mice were dosed up to 1213 mg/kg via intraperitoneal injection (Wild et al., 1983). Taken together, these data indicate that α-amylcinnamaldehyde does not have the potential to be genotoxic.

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

Literature Search and Risk Assessment Completed on: 05/03/13

10.2. Repeated dose toxicity

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

10.2.1. Risk assessment

The repeated dose toxicity data on α-amylcinnamaldehyde are sufficient for the repeated dose toxicity endpoint. A dietary 14-week subchronic toxicity study conducted in rats determined a NOAEL of 400 ppm (29.9 and 34.9 mg/kg/day in males and females, respectively), based on liver and kidney weights (Carpanini et al., 1973). For conservative purposes the lower male NOAEL is considered. Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 29.9/0.023 or 1300.

Additional References: Oser et al., 1965; Bar et al., 1967; Jimbo, 1983; RIFM (Research Institute for Fragrance Materials, Inc.), 1980a; RIFM (Research Institute for Fragrance Materials, Inc.), 1981; RIFM (Research Institute for Fragrance Materials, Inc.), 2012; RIFM (Research Institute for Fragrance Materials, Inc.), 1980b; RIFM (Research Institute for Fragrance Materials, Inc.), 1996a.

Literature Search and Risk Assessment Completed on: 05/03/13.

10.3. Developmental and reproductive toxicity

The margin of exposure for α-amylcinnamaldehyde is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.3.1. Risk assessment

There are no developmental or reproductive toxicity data on α-amylcinnamaldehyde. Read across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section 5) has a gavage reproduction dose-range finder study in rats that is sufficient for both the developmental and reproductive endpoints. The NOAEL for both toxicity endpoints was determined to be 100 mg/kg/day, the highest dosage tested (RIFM (Research Institute for Fragrance Materials, Inc.), 2010). Therefore, the MOE for developmental and reproductive toxicity is equal to the α-hexylcinnamaldehyde NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.023 or 4347.

RIFM's Expert Panel and the Adjunct Reproduction Advisory Group* agree that there are enough data from the reproduction dose-range finder to show that there are no concerns for reproductive or developmental effects of α-hexylcinnamaldehyde at dosages up to 100 mg/kg/day (RIFM (Research Institute for Fragrance Materials, Inc.), 2010). No effects were observed on mating, fertility, reproductive organ weights, reproductive organ microscopic examination, delivery parameters, pup body weights, and pup clinical and necropsy observations. There were non-significant decreases in maternal body weight gain and feed consumption during lactation. In a subsequent 14-day repeat dose study, it was shown that α-hexylcinnamaldehyde is lethal, irritating and systemically toxic at 1000 mg/kg/day (RIFM (Research Institute for Fragrance Materials, Inc.), 2010). In the 14-day study, the NOAEL for stomach and kidney lesions was 500 mg/kg/day. It was noted that 500 mg/kg/day, with only mild and transient effects, may be too low to produce the required 'slight parental toxicity' in a 1-generation reproduction study. However, there were concerns about possible animal distress if tested at a higher dosage for longer than 14 days. In a dermal 90-day repeat dose study for α-hexylcinnamaldehyde, liver and kidney weights were significantly increased in females at 250 mg/kg/day and higher. This provides a more than adequate margin of exposure for the use of this material as a fragrance ingredient. There are scientific data to show that a NOAEL from a 90-day study would also be sufficiently conservative for a reproductive NOAEL (Dent, 2007; Janer et al., 2007). Janer et al. (2007) demonstrated that well designed 90-day studies, including assessment of reproductive parameters could result in the absence of reproductive effects. In a review by Dent (2007), also comparing reproductive effects of 90-day studies with two-generation reproductive toxicity, similar results were seen compared to Janer et al. (2007).

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

Additional References: Oser et al., 1965; Bar et al., 1967; Jimbo, 1983; RIFM (Research Institute for Fragrance Materials, Inc.), 1980a; RIFM (Research Institute for Fragrance Materials, Inc.), 1981; RIFM (Research Institute for Fragrance Materials, Inc.), 2012; RIFM (Research Institute for Fragrance Materials, Inc.), 1980b; RIFM (Research Institute for Fragrance Materials, Inc.), 1996a.

Literature Search and Risk Assessment Completed on: 05/03/13.

10.4. Skin sensitization

Based on the existing data, summarized in the IFRA Standard, α-amylcinnamaldehyde is considered to be an extremely weak skin sensitizer with a defined NESIL of 23,600 μg/cm^2.

Table 1
α-Amylcinnamaldehyde – data summary.

LLNA weighted mean EC3 value μg/cm² [No. Studies]	Potency classification based on animal data[a]	Human data			
		NOEL-HRIPT (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[b] (induction) μg/cm²	WoE NESIL[c] μg/cm²
2942 [3]	Extremely Weak	23,622	NA	NA	23,600

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from HRIPT or HMT.
[c] WoE NESIL limited to three significant figures.
NOEL = no observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = not available.

10.4.1. Risk assessment

The available data demonstrate that α-amylcinnamaldehyde is an extremely weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 23,600 μg/cm² (Table 1). Using this NESIL, the application of the Quantitative Risk Assessment (QRA), as described by Api et al. (2008), resulted in the acceptable exposure limits summarized in Table 2.

The chemical structure and properties of α-amylcinnamaldehyde indicates that it would have the potential to act as a skin sensitizer. α-Amylcinnamaldehyde is predicted to react with skin proteins via Michael addition or Schiff base formation; however within reactivity assays minimal depletion has been reported toward cysteine and lysine based peptides (Gerberick et al., 2004; OECD, 2012 Toolbox V3.1; Roberts et al., 2007; Toxtree 2.5.0; Natsch et al., 2013).

α-Amylcinnamaldehyde was evaluated in numerous guinea pig sensitization studies (Basketter and Gerberick, 1996; RIFM (Research Institute for Fragrance Materials, Inc.), 1973a; RIFM (Research Institute for Fragrance Materials, Inc.), 1977a; RIFM (Research Institute for Fragrance Materials, Inc.), 1988a; Klecak et al., 1977; Klecak, 1979; Klecak, 1985; RIFM (Research Institute for Fragrance Materials, Inc.), 1977d; RIFM (Research Institute for Fragrance Materials, Inc.), 1978; Senma et al., 1978; RIFM (Research Institute for Fragrance Materials, Inc.), 1979) and the murine local lymph node assay (LLNA). The weight of evidence from these predictive assays shows that α-amylcinnamaldehyde is an extremely weak sensitizer. In the LLNA, a vehicle weighted EC3 value of 11.7% (2942 ug/cm²) was reported (Aptula et al., 2007; Elahi et al., 2004; RIFM (Research Institute for Fragrance Materials, Inc.), 2006; Roberts et al., 2007).

The dermal sensitization potential of α-amylcinnamaldehyde has been evaluated in the Human Repeated Insult Patch Test (HRIPT) and the human maximization test. The weight of evidence from these studies shows that a No Observed Effect Level (NOEL) of 23,622 μg/cm² exists in the HRIPT (RIFM (Research Institute for Fragrance Materials, Inc.), 1977; Greif, 1967; RIFM (Research Institute for Fragrance Materials, Inc.), 1994b; RIFM (Research Institute for Fragrance Materials, Inc.), 1994; RIFM (Research Institute for Fragrance Materials, Inc.), 1994a; RIFM (Research Institute for Fragrance Materials, Inc.), 2005; RIFM (Research Institute for Fragrance Materials, Inc.), 1964; RIFM (Research Institute for Fragrance Materials, Inc.), 1977b; RIFM (Research Institute for Fragrance Materials, Inc.), 1977c; RIFM (Research Institute for Fragrance Materials, Inc.), 1973; Letizia and Api, 2002; RIFM (Research Institute for Fragrance Materials, Inc.), 1979).

Additional References: Maisey et al., 1986.

Literature Search and Risk Assessment Completed on: 11/27/13.

Table 2
α-Amylcinnamaldehyde – acceptable exposure limits.

IFRA category[a]	Examples of product type	QRA-calculated
1	Lip products	0.7%
2	Deodorant/antiperspirant	0.9%
3	Hydroalc., shaved skin	3.6%
4	Hydroalc., unshaved skin	10.7%
5	Women facial cream	5.6%
6	Mouthwash	17.1%
7	Intimate wipes	1.8%
8	Hair styling aids non-spray	2.0%
9	Conditioners, rinse-off	5.0%
10	Hard surface cleaners	2.5%
11	Candle (non-skin/incidental skin)	Not restricted

Note: [a]For a description of the categories, refer to the QRA Informational Booklet. (http://www.rifm.org/doc/QRAInfoJuly201.pdf).

10.5. Phototoxicity/photoallergenicity

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

10.5.1. Risk assessment

Based on the current existing data, α-amylcinnamaldehyde does not present a phototoxic concern. While the UV absorption spectrum for α-amylcinnamaldehyde demonstrates that it absorbs UV light in the 290–700 nm region (spectra are not suitable for calculating a molar absorption coefficient), no photoallergic or phototoxic effects were observed in guinea pig assays (RIFM (Research Institute for Fragrance Materials, Inc.), 1988; RIFM (Research Institute for Fragrance Materials, Inc.), 1988a).

Additional References: Addo et al., 1982; RIFM (Research Institute for Fragrance Materials, Inc.), 1980; Placzek et al., 2007.

Literature Search and Risk Assessment Completed on: 11/27/13.

10.6. Local respiratory toxicity

The margin of exposure for α-amylcinnamaldehyde is adequate for the respiratory endpoint at the current level of use.

10.6.1. Risk assessment

The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. α-Amylcinnamaldehyde was tested as part of a mixture at the exposure concentration of 5.3 μg/m³ for 6 weeks. No effects were observed and there was no NOAEC determined in this study (Fukayama et al., 1999).

A NOAEC of 56.5 ppm (500 mg/m³; the highest dose tested) was reported for the read across material α-hexylcinnamaldehyde (CAS # 101-86-0; see Section 5) by RIFM (Research Institute for Fragrance Materials, Inc.) (2012). At this dose, the material was tolerated and showed no significant change in bronchoalveolar lavage cell types, protein levels or measured inflammatory cytokines. Furthermore, no histological changes indicative of inflammation were observed in the lung or nose. This NOAEC expressed in mg/kg lung weight/day is:

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

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 5.48%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.51 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD *in silico* models. To compare this estimated exposure with the read across material NOAEC expressed in mg/kg lung weight/day this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.784 mg/kg lung weight/day resulting in an MOE of 24,394 (i.e., [19,125 mg/kg lw/day]/[0.784 mg/kg lung weight/day]).

Since the MOE is significantly greater than 100, without the adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure, by inhalation, at 5.48% in a combination of the products noted above, is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/27/13.

2. Environmental Endpoint Summary:

10.7. Screening-Level Assessment

A screening level risk assessment of α-amylcinnamaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, α-amylcinnamaldehyde was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify α-amylcinnamaldehyde as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver. 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.8. Risk assessment

Based on current VoU (2011), α-amylcinnamaldehyde presents a risk to the aquatic compartment in the screening level assessment.

10.8.1. Biodegradation

A biodegradation study was conducted using activated sludge in a Manometric Respirometry Test per OECD guideline 301F. Test material (100 mg/L) was incubated with activated sludge (30 mg/L) for 28 days. α-Amylcinnamaldehyde underwent 90% biodegradation in 28 days and was considered readily biodegradable (RIFM (Research Institute for Fragrance Materials, Inc.), 1992).

A biodegradation study according to the Commission Directive 79/831/EWG annex V part C method was conducted with α-amylcinnamaldehyde. The test material underwent 41% biodegradation in 28 days (RIFM (Research Institute for Fragrance Materials, Inc.), 1992b).

A biodegradation study was conducted using activated sludge using the sealed vessel test according to the OECD 301B method. α-Amylcinnamaldehyde underwent 70.5% biodegradation in 28 days (RIFM (Research Institute for Fragrance Materials, Inc.), 1996).

10.8.2. Ecotoxicity

A 48 hours acute Daphnia magna test was conducted with α-amylcinnamaldehyde. The geometric mean of EC0/EC100 was 1.1 mg/L (RIFM (Research Institute for Fragrance Materials, Inc.), 1992a).

A 96 hours acute fish (*Brachydanio rerio*) study according to the OECD 203 C.1 method was conducted. Under the conditions of the study the geometric mean of LC0/LC100 was 3.0 mg/L (RIFM (Research Institute for Fragrance Materials, Inc.), 1993).

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

10.9. Other available data

α-Amylcinnamaldehyde has been pre-registered for REACH 2013. No additional data available at this time.

10.10. 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.

Note: The lowest EC50 of 1.1 mg/L was reported in Daphnia magna study. However, since it was not a GLP study and the geometric ratio of EC0/EC100 was reported, an algae EC50 of 1.18 mg/L was selected for calculations of PNEC.

	LC50 (fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (algae) (mg/L)	AF	PNEC (µg/L)	Chemical class
RIFM Framework Screening Level **(Tier 1)**	1.22 mg/L			1,000,000	0.0012 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.16	0.729	1.007	10,000	0.016 µg/L	Vinyl/allyl aldehydes
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.625	0.455	0.951			Neutral organics
Tier 3: Measured data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	3.0 mg/L (EC0/100)					
Daphnia		1.1 mg/L (EC0/100)				
Algae		1.18 mg/L	0.154 mg/L	1000	1.18 µg/L	

The RIFM PNEC is 1.18 µg/L. The revised PEC/PNECs for EU and NA is <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use**.**

Literature Search and Risk Assessment Completed on: 05/03/13.

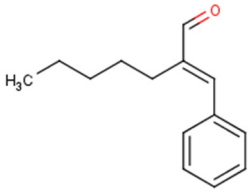
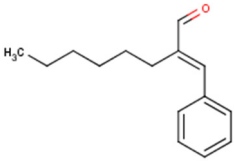
11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

* Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

Appendix

	Target material	Read across material
Principal name	α-Amylcinnamaldehyde	α-Hexylcinnamaldehyde
CAS No.	122-40-7	101-86-0
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/122-40-7.html	http://www.thegoodscentscompany.com/opl/101-86-0.html
Read-across endpoint		• Skin Absorption • Repeated Dose • Devel/Repro • Respiratory
Molecular formula	C14H18O	C15H20O
Molecular weight	202.3	216.33
Melting point (°C, EPISUITE)	33.90	44.38
Boiling point (°C, EPISUITE)	304.80	318.74
Vapor pressure (Pa @ 25 °C, EPISUITE)	0.06026	0.07119
Log Kow (KOWWIN v1.68 in EPISUITE)	4.33	4.82
Water solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	8.545	2.75
J_{max} (mg/cm^2/h, SAM)	6.948593284	3.195124367
Henry's law (Pa·m^3/mol, Bond method, EPISUITE)	0.790031	1.048714
Similarity (Tanimoto score)[1]		100%
Skin absorption		
Skin Absorption percentage (SAM)	40%	40%
Repeated dose toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and reproductive toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (low reliability)	Toxicant (low reliability)
Metabolism		
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on α-Amylcinnamaldehyde (CAS # 122-40-7). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA.
- The J_{max} was calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model.
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1).
- Developmental toxicity was estimated using CAESAR (v.2.1.6).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1).

Conclusion/Rationale

- α-Hexylcinnamaldehyde (analog) was used as a read-across for α-amylcinnamaldehyde (target) based on:
  - The target and analog both belong to the generic class of aromatic aldehydes. They are α, β unsaturated aldehyde.
  - They have common structural fragments of cinnamaldehyde.
  - The only difference is that the analog has a longer branch chain with an extra carbon. The difference between structures does not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog are predicted to have the same level of skin absorption.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog are expected to metabolize via similar pathway. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer class

The Cramer class of the target material was determined 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 30? **No**
Q32. Contains only the functional groups listed in Q30 or Q31 and those listed below. **Yes** Class Intermediate (Class II)

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.008.

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