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# RIFM fragrance ingredient safety assessment, α-methylcinnamic alcohol, CAS Registry Number 1504-55-8

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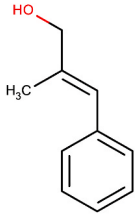


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**Abbreviation/Definition List:**

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

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**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; 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 Observed Effect Level
**MOE** - Margin of Exposure
**MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
**NA** - North America
**NESIL** - No Expected Sensitization Induction Level
**NOAEC** - No Observed Adverse Effect Concentration
**NOAEL** - No Observed Adverse Effect Level
**NOEC** - No Observed Effect Concentration
**NOEL** - No Observed Effect Level
**OECD** - Organisation for Economic Co-operation and Development
**OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
**PBT** - Persistent, Bioaccumulative, and Toxic
**PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RfD** - Reference Dose
**RIFM** - Research Institute for Fragrance Materials
**RQ** - Risk Quotient
**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**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-Methylcinnamic alcohol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs α-amylcinnamyl alcohol (CAS # 101-85-9), cinnamaldehyde (CAS # 104-55-2), and cinnamyl alcohol (CAS # 104-54-1) show that α-methylcinnamic alcohol is not expected to be genotoxic. The repeated dose and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to α-methylcinnamic alcohol is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data on read-across analog cinnamyl alcohol (CAS # 104-54-1) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data show that there are no safety concerns for α-methylcinnamic alcohol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible spectra; α-methylcinnamic alcohol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; α-methylcinnamic alcohol 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 genotoxic. | (RIFM, 1997a; RIFM, 1998; Wild et al., 1983) |
| **Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC. | |
| **Reproductive Toxicity:** Developmental NOAEL = 350 mg/kg/day. Fertility NOAEL = 350 mg/kg/day. | (ECHA Reach Dossier: Cinnamyl alcohol; ECHA, 2012b) |
| **Skin Sensitization:** Not sensitizing. | (RIFM, 1997b; RIFM, 1974) |
| **Phototoxicity/Photoallergenicity:** Not expected to be phototoxic/photoallergenic. | (UV/Vis Spectra; RIFM Database) |
| **Local Respiratory Toxicity:** NOAEC = 55.5 mg/m$^3$. | RIFM (2012) |
| **Environmental Safety Assessment** | |
| **Hazard Assessment:** | |
| **Persistence:** | |
| Screening-level: 3.05 (BIOWIN 3) | (EPI Suite v4.11; US EPA, 2012a) |
| **Bioaccumulation:** | |
| Screening-level: 9.73 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** | |
| Screening-level: Fish LC50: 544.3 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: 544.3 mg/L | (RIFM Framework; Salvito et al., 2002) |
| **RIFM PNEC is:** 0.5443 μg/L | |
| • **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level | |

## 1. Identification

1. **Chemical Name:** α-Methylcinnamic alcohol
2. **CAS Registry Number:** 1504-55-8
3. **Synonyms:** Cinnamyl alcohol, α-methyl-; Methylcinnamic alcohol; α-Methylcinnamyl alcohol; 3-Phenyl-2-methyl-2-propen-1-ol; 3-Phenylbut-2-en-1-ol; Cinarol; α-Methylcinnamic alcohol
4. **Molecular Formula:** $C_{10}H_{12}O$
5. **Molecular Weight:** 148.2
6. **RIFM Number:** 553
7. **Stereochemistry:** Isomer not specified. One geometric center present, and a total of 2 isomers possible.

## 2. Physical data

1. **Boiling Point:** 94.0 °C (367.2 K) at 0.27 kPa (RIFM, 2014a), 261.14 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log $K_{ow}$:** 1.5 (RIFM, 2014b), 2.39 (EPI Suite)
4. **Melting Point**: 24 °C (297 K) at 101.0 kPa (RIFM, 2013), 18.16 °C (EPI Suite)
5. **Water Solubility:** 2274 mg/L (EPI Suite)
6. **Specific Gravity:** 1.026–1.032 (FMA), 1.024–1.030 (FMA)
7. **Vapor Pressure:** 0.00089 mm Hg at 20 °C (EPI Suite v4.0), 0.00158 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless slightly viscous liquid. Sweet, balsamic floral, tenacious odor of oriental type. It is less "cinnamon-like" and more "styrax-like" (Arctander, 1969)

## 3. Volume of use (worldwide band)

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

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.3% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00071 mg/kg/day or 0.043 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0026 mg/kg/day (RIFM, 2020b)

*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**: 65.9%

**Bronaugh et al., 1985**: The absorption of radio-labelled read-across material cinnamyl alcohol (CAS # 104-54-1) in acetone through excised human abdominal skin was measured using an *in vitro* diffusion cell technique. Both occluded and non-occluded absorption was measured. The amount of cinnamyl alcohol absorbed through non-occluded skin was 33.9% ± 7.3% of the dose and the amount absorbed through occluded skin was 65.9% ± 7.9%.

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

## 6. Computational toxicology evaluation

### 6.1. Cramer Classification

Class I, Low

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| I | I | I |

### 6.2. Analogs Selected

a. **Genotoxicity:** α-Amylcinnamyl alcohol (CAS # 101-85-9); cinnamaldehyde (CAS # 104-55-2); cinnamyl alcohol (CAS # 104-54-1)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** Cinnamyl alcohol (CAS # 104-54-1)
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

### 6.3. Read-across Justification

See Appendix below

## 7. Metabolism

No relevant data available for inclusion in this safety assessment.

### 7.1. Additional references

None.

## 8. Natural occurrence

α-Methylcinnamic alcohol is not reported to occur in foods by the VCF*.

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

## 9. REACH dossier

α-Methylcinnamic alcohol has been pre-registered for 2010; no dossier available as of 09/27/21.

## 10. Conclusion

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

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

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

*11.1.1.1. Risk assessment.* The mutagenic potential of α-methylcinnamic alcohol was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA98, and TA100 were treated with α-methylcinnamic alcohol in dimethyl sulfoxide (DMSO) at concentrations ranging between 15 and 5000 μg/plate. Small but statistically significant, dose-dependent increases in the frequency of revertant colonies were observed in strains TA100, TA1535, TA98, and TA1537 in the absence of metabolic activation (RIFM, 1997a). These results were repeated in the confirmatory assay, and the authors concluded that α-methylcinnamic alcohol was weakly positive in the Ames test. The increases in the *Salmonella typhimurium* mutant strains, although statistically significant, are less than 2-fold for TA98 and TA100 in the first assay and less than 3-fold in TA1535 and TA1537 in 2 assays when compared with the vehicle control. In the repeat assay, TA98 did not show any positive response. A dose response was not observed in the first experiment, but the test compound did show a dose response in the second experiment; hence, the biological significance along with reproducibility of the results is also weak. According to current criteria for the Ames assay, the generated data would not be accepted as a

positive response, as the threshold for fold increases was not obtained. Due to inconsistencies in 2 assays, according to OECD guidelines, a decider third assay should be conducted in order to reach a final conclusion (Mahon et al., 1989; OECD 471). Further weight of evidence (WoE) can be made using the read-across material, α-amylcinnamyl alcohol (CAS # 101-85-9; see Section VI), which was assessed in an Ames assay conducted equivalent to OECD TG 471. At concentrations up to 3.6 mg/plate, no increases in the number of revertant colonies were observed (Wild et al., 1983). Under the conditions of the study, α-amylcinnamyl alcohol was considered negative in the Ames test. Another read-across material, unsubstituted cinnamyl alcohol (CAS # 104-54-1), was also found to be negative when tested up to 3000 μg/plate, both with and without metabolic activation (Sekizawa, 1982). Based on WoE, α-methylcinnamic alcohol does not present a concern for mutagenic potential in bacterial cells.

Additionally, α-methylcinnamic alcohol was tested for mutagenic activity in an *in vitro* mammalian cell gene mutation test conducted in accordance with OECD TG 476. L5178Y Mouse lymphoma cells were treated with α-methylcinnamic alcohol in DMSO at concentrations up to 600 μg/mL in the presence and absence of metabolic activation for 0, 24, and 48 h. The test material did not induce toxicologically significant increases in mutant frequency at any dose level, with or without metabolic activation, in either of the 2 experiments (RIFM, 1998). The test material was shown to be non-mutagenic to L5178Y cells under the conditions of the test.

*In silico* predictions using OASIS Times determined that α-methylcinnamic alcohol would be negative in the Ames assay. These results, taken together with a negative *in vitro* mammalian cell gene mutation test (MLA) and a negative Ames assay for a read-across material, conclude that α-methylcinnamic alcohol does not present a concern for mutagenicity.

There are no data assessing the clastogenicity of α-methylcinnamic alcohol. Read-across material α-amylcinnamyl alcohol (CAS # 101-85-9; See Section VI) was assessed in an *in vivo* micronucleus test conducted similarly to OECD TG 474. Groups of male and female NMRI mice were treated with α-amylcinnamyl alcohol in olive oil via a single intraperitoneal injection at concentrations of 204, 357, and 510 mg/kg. After 30 h, the bone marrow of each animal was removed, and samples were prepared. Compared to vehicle controls, no significant increase in the number of micronucleated polychromatic erythrocytes was observed (Wild et al., 1983). Under the conditions of the study, α-amylcinnamyl alcohol was considered not clastogenic in the *in vivo* micronucleus test, and this can be extended to α-methylcinnamic alcohol. Considering that the primary alcohol will be oxidized to an α,ß unsaturated aldehyde, mutagenicity and clastogenicity data on cinnamaldehyde is also considered. As described (Bickers et al., 2003), a full genotoxicity battery is available for cinnamaldehyde (CAS # 104-55-2). Cinnamaldehyde (*trans*- and unspecified stereochemistry) did not induce mutagenic responses in *S. typhimurium* strains TA98, TA102, TA104, TA1535, or TA1537. The assays were performed at concentrations ranging up to the level of cytotoxicity, both in the absence and presence of metabolic activation (S9 fraction; RIFM, 2005). While some weakly positive to positive results were reported in *S. typhimurium* strain TA100 using the preincubation method, the majority of similar studies in strain TA100 did not find any evidence of mutagenicity at doses up to 10000 μg/plate. Furthermore, tests for the induction of sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells produced negative results at low concentrations and weakly positive results at concentrations approaching cytotoxic levels, suggesting only weak SCE activity. Although cinnamaldehyde was reported to induce chromosome aberrations at low concentrations (i.e., <15 μg/mL) in Chinese hamster fibroblasts and B241 cells tested with and without metabolic activation, higher concentrations (i.e., up to 100 μg/mL) were negative in CHO cells, as well as in human diploid HAIN-55 fibroblast cells, both with and without metabolic activation. In a mouse blood micronucleus test, mice were fed diets containing 4100, 8200, 16500, or 33000 ppm microencapsulated *trans*-cinnamaldehyde; no increase in the frequency of micronucleated erythrocytes was observed in the peripheral blood of male or female mice after 3 months of exposure (NTP, 2004).

Based on WoE, it is concluded that α-methylcinnamic alcohol does not present a concern for genotoxic potential.

**Additional references**: Azizan and Blevins, 1995; Ishidate et al., 1984; Dillon et al., 1992; Dillon et al., 1998; Eder et al., 1982; Eder et al., 1991; Florin et al., 1980; Ishidate et al., 1984; Kasamaki et al., 1982; Kato et al., 1989; Lijinsky and Andrews, 1980; Lutz et al., 1982; Marnett et al., 1985; Neudecker et al., 1983; Prival et al., 1982; Sasaki and Endo, 1978, Sekizawa and Shibamoto, 1982; Galloway et al., 1987; Kasamaki et al., 1987; Kasamaki and Urasawa, 1983, Kasamaki and Urasawa, 1985

**Literature search and risk assessment completed on**: 01/12/21.

### *11.1.2. Repeated dose toxicity*

There are insufficient repeated dose toxicity data on α-methylcinnamic alcohol or any read-across materials. The total systemic exposure to α-methylcinnamic alcohol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on α-methylcinnamic alcohol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to α-methylcinnamic alcohol (2.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional references**: None.

**Literature search and risk assessment completed on**: 11/09/20.

### *11.1.3. Reproductive toxicity*

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

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on α-methylcinnamic alcohol. Read-across material cinnamyl alcohol (CAS # 104-54-1; see Section VI) has sufficient reproductive toxicity data. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered cinnamyl alcohol via oral gavage at doses of 0, 87.5, 175, or 350 mg/kg/day in the diet. Males were dosed for 35 days (2 weeks prior to mating and continued through the mating period until and up to termination), while females were dosed for 49–67 days (2 weeks prior to mating, during mating, post-coitum, and up to lactation day 13). No treatment-related mortality was observed in any dose groups. In addition, no changes were observed in mean body weight and organ weights (both relative and absolute). Further, no treatment-related effects were seen with respect to any fertility parameters for males and females. Similarly, pups did not show any clinical signs or external anomalies throughout the lactation period. No treatment-related changes in pup weights or ano-genital distance ratio were observed in any groups. Thus, the NOAEL for developmental toxicity and fertility was considered to be 350 mg/kg/day, the highest dose tested (ECHA, 2012b).

In addition, cinnamyl alcohol has a gavage developmental toxicity study conducted in rats, which showed no teratogenic effects and determined the NOAEL to be 53.5 mg/kg/day for developmental toxicity, the highest dosage tested (Zaitsev and Maganova, 1975).

A more robust OECD 421 study on cinnamyl alcohol was considered for this safety assessment**. Therefore, the α-methylcinnamic alcohol MOE for the reproductive toxicity endpoint can be calculated by dividing the cinnamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to α-methylcinnamic alcohol, 350/0.0026, or 134615.**

In addition, the total systemic exposure for α-methylcinnamic alcohol (2.6 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint

at the current level of use.

**Additional references**: None.

**Literature search and risk assessment completed on**: 12/11/20.

*11.1.4. Skin sensitization*

Based on the existing data, α-methylcinnamic alcohol does not present a concern for skin sensitization under the current, declared levels of use.

*11.1.4.1. Risk assessment.* Based on the available data; α-methylcinnamic alcohol does not present a concern for skin sensitization. The chemical structure indicates that this material would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). However, in a guinea pig maximization test, this material was reported to be a non-sensitizer (RIFM, 1997b). In a human maximization test conducted on 25 subjects, no reactions indicative of sensitization were observed with 2% α-methylcinnamic alcohol (1380 μg/cm$^2$) (RIFM, 1975).

Based on WoE from structural analysis and animal and human studies, α-methylcinnamic alcohol does not present a concern for skin sensitization under the current, declared levels of use.

**Additional references**: RIFM, 2014b.

**Literature search and risk assessment completed on**: 12/10/20.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, α-methylcinnamic alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no phototoxicity studies available for α-methylcinnamic alcohol in experimental models. UV/Vis absorption spectra indicate no significant absorption 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 absorbance, α-methylcinnamic alcohol does not present a concern for phototoxicity or photoallergenicity.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant 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**: 12/04/20.

*11.1.6. Local respiratory toxicity*

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

*11.1.6.1. Risk assessment.* There are no inhalation data available on α-methylcinnamic alcohol. Based on the Creme RIFM Model, the inhalation exposure is 0.043 mg/day. This exposure is 32.6 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional references**: None.

**Literature search and risk assessment completed on:** 11/18/20.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of α-methylcinnamic alcohol 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-methylcinnamic alcohol 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 is $< 1$).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify α-methylcinnamic alcohol 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, 2012a). 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 $\geq$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 the current Volume of Use (2015), α-methylcinnamic alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies.* **Biodegradation**: No data available.

**Ecotoxicity**: No data available.

**Other available data**: α-Methylcinnamic alcohol 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 Framework: Salvito et al., 2002).

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 1.53 | 1.53 |
| 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 RQ for this material is $< 1$. No additional assessment is necessary.

The RIFM PNEC is 0.5443 μg/L. The revised PEC/PNECs for EU and

| | LC50 (Fish) (mg/L) | EC50 (*Daphnia*) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (μg/L) | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 544.3 | | | 1000000 | 0.5443 | |

NA are not applicable; cleared at the screening-level, 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**: 12/01/20.

## 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 09/27/21.

## 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. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112684.

## Appendix

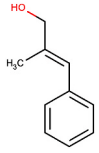
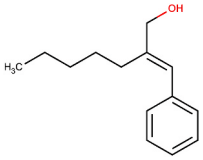
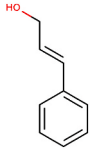
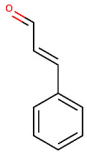
*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).

- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target Material | Read-across Material | Read-across Material | Read-across Material |
|---|---|---|---|---|
| Principal Name | α-Methylcinnamic alcohol | α-Amylcinnamyl alcohol | Cinnamyl alcohol | Cinnamaldehyde |
| CAS No. | 1504-55-8 | 101-85-9 | 104-54-1 | 104-55-2 |
| Structure |  |  |  |  |
| Similarity (Tanimoto Score) | | 0.24 | 0.09 | 0.07 |
| SMILES | CC(CO) = Cc1ccccc1 | CCCCCC(CO) = Cc1ccccc1 | OCC=Cc1ccccc1 | O=CC=Cc1ccccc1 |
| Endpoint | | • Genotoxicity | • Genotoxicity<br>• Reproductive toxicity | • Genotoxicity |
| Molecular Formula | $C_{10}H_{12}O$ | $C_{14}H_{20}O$ | $C_9H_{10}O$ | $C_9H_8O$ |
| Molecular Weight | 148.205 | 204.313 | 134.178 | 132.162 |
| Melting Point (°C, EPI Suite) | 18.16 | 50.46 | 33.00 | −7.50 |
| Boiling Point (°C, EPI Suite) | 261.14 | 321.54 | 250.00 | 246.00 |
| Vapor Pressure (Pa @ 25 °C, EPI Suite) | 2.11E-01 | 2.61E-03 | 3.20E+00 | 3.85E+00 |
| Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite) | 2.27E+03 | 2.57E+01 | 6.19E+03 | 1.42E+03 |
| Log $K_{ow}$ | 2.39 | 4.35 | 1.95 | 1.9 |
| $J_{max}$ (μg/cm$^2$/h, SAM) | 93.90 | 3.06 | 186.13 | 41.56 |
| Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite) | 2.51E-02 | 7.81E-02 | 1.60E-02 | 3.59E-01 |
| DNA Binding (OASIS v1.4, QSAR Toolbox v4.2) | No alert found | No alert found | No alert found | AN2\|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds\|AN2 ≫ Nucleophilic addition to α,β-unsaturated carbonyl compounds ≫ α,β-Unsaturated Aldehydes\|AN2 ≫ Schiff base formation\|AN2 ≫ Schiff base formation ≫ α,β-Unsaturated Aldehydes |
| DNA Binding (OECD QSAR Toolbox v4.2) | No alert found | No alert found | No alert found | No alert found |
| Carcinogenicity (ISS) | No alert found | No alert found | No alert found | No alert found |
| DNA Binding (Ames, MN, CA, OASIS v1.1) | No alert found | No alert found | No alert found | No alert found |
| *In Vitro* Mutagenicity (Ames, ISS) | No alert found | No alert found | No alert found | No alert found |
| *In Vivo* Mutagenicity (Micronucleus, ISS) | No alert found | No alert found | No alert found | No alert found |
| Oncologic Classification | Not classified | Not classified | Not classified | Aldehyde Type Compounds |
| Repeated Dose (HESS) | Menadione (Hepatotoxicity) Alert\|Styrene (Renal Toxicity) Alert\|Toluene (Renal toxicity) Alert | | | |
| ER Binding (OECD QSAR Toolbox v4.2) | Non-binder, without OH or NH2 group | | Non-binder, without OH or NH2 group | |
| Developmental Toxicity (CAESAR v2.1.6) | Toxicant (good reliability) | | Toxicant (good reliability) | |
| Protein Binding (OASIS v1.1) | No alert found | | | |
| Protein Binding (OECD) | No alert found | | | |
| Protein Binding Potency | Not possible to classify according to these rules (GSH) | | | |
| Protein Binding Alerts for Skin Sensitization (OASIS v1.1) | No alert found | | | |
| Skin Sensitization Reactivity Domains (Toxtree v2.6.13) | Alert for Michael Acceptor identified | | | |
| Respiratory Sensitization (OECD QSAR Toolbox v4.2) | No alert found | | | No alert found |
| 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 | See Supplemental Data 4 |

*Summary*

There are insufficient toxicity data on α-methylcinnamic alcohol (CAS # 1504-55-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism predictions, physical–chemical properties, and expert judgment, read-across analogs α-amylcinnamyl alcohol (CAS # 101-85-9), cinnamyl alcohol (CAS # 104-54-1), and cinnamaldehyde (CAS # 104-55-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

*Metabolism*

The metabolism of the target material α-methylcinnamic alcohol (CAS # 1504-55-8) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to α-methyl cinnamaldehyde (CAS # 15174-47-7) in the first step with a 0.95% probability. Cinnamaldehyde (CAS # 104-55-2) is a structurally similar analog to α-methyl cinnamaldehyde. Hence, cinnamaldehyde (CAS # 104-55-2) can be used as a read-across analog for the target material. Read-across analog cinnamaldehyde (CAS # 104-55-2) was in domain for the *in vivo* rat and in domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19).

*Conclusions*

- α-Amylcinnamyl alcohol (CAS # 101-85-9) was used as a read-across analog for the target material α-methylcinnamic alcohol (CAS # 1504-55-8) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of 2,3 unsaturated alkyl aromatic primary alcohols.
  - The target material and the read-across analog share a cinnamic alcohol substructure.
  - The key difference between the target material and the read-across analog is that the target material has methyl substitution on the 2 position while the read-across analog has pentyl substitution on the 2 position. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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 *in silico* alerts for the target material or the read-across analog for the genotoxicity endpoint. *In silico* alerts are consistent with data.
  - 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.
- Cinnamyl alcohol (CAS # 104-54-1) was used as a read-across analog for the target material α-methylcinnamic alcohol (CAS # 1504-55-8) for the genotoxicity and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of 2,3 unsaturated alkyl aromatic primary alcohols.
  - The target material and the read-across analog share a cinnamic alcohol substructure.
  - The key difference between the target material and the read-across analog is that the target material has a methyl substitution on the 2 position while the read-across analog does not have any substitution. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - 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 *in silico* alerts for the target material or the read-across analog for genotoxicity endpoint. *In silico* alerts are consistent with data.
  - The target material and the read-across analog are predicted to be toxicants by the CAESAR model. The data on the read-across analog confirms that the MOE for the read-across analog is adequate at the current level of use. Therefore, based on the structural similarity between the target material and the read-across analog and the data for the read-across analog, the *in silico* alert is superseded by the data.
  - 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.
- Cinnamaldehyde (CAS # 104-55-2) was used as a read-across analog for the target material α-methylcinnamic alcohol (CAS # 1504-55-8) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of chemicals with cinnamic alcohol or cinnamic aldehyde core.
  - The key difference between the target material and the read-across analog is that the read-across analog is a structurally similar chemical to the direct metabolite of the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target.
  - 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 *in silico* alerts for the target material or the read-across analog for the local respiratory toxicity endpoint. *In silico* alerts are consistent with data.
  - The read-across analog is predicted to be reactive via nucleophilic addition and Schiff base formation reactions. The data on the read-across analog confirms that the material does not pose a concern for genetic toxicity under the current declared level of use. Therefore, based on

the structural similarity between the read-across analog and the target material and the data on the read-across analog, the *in silico* alert is superseded.

- 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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