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RIFM fragrance ingredient safety assessment, caryophyllene acetylated, CAS Registry Number 75975-83-6

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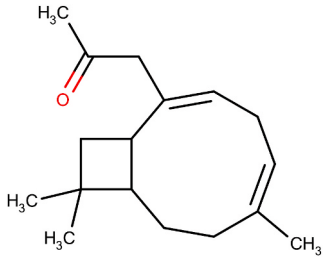
Name: Caryophyllene acetylated CAS Registry Number: 75975-83-6



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)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
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, 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

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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.

Caryophyllene acetylated was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6 show that caryophyllene acetylated is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to caryophyllene acetylated is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day and 0.47 mg/day, respectively). Data provided caryophyllene acetylated a No Expected Sensitization Induction Level (NESIL) of 3100 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and UV spectra; caryophyllene acetylated is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; caryophyllene acetylated was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the Persistent, Bioaccumulative, and Toxic (PBT) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2017a; RIFM, 2017b)

Repeated Dose Toxicity: No NOAEL was determined. Material is below the TTC.

Reproductive Toxicity: No NOAEL was determined. Material is below the TTC.

Skin Sensitization: NESIL = 3100 μg/cm^2. RIFM (2018)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra; RIFM Database; RIFM, 1999)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 39% (OECD 302C) RIFM (2016)

Bioaccumulation:
Screening-level: 1171 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: 48-h *Daphnia magna* EC50: 0.225 mg/L (ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.225 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0225 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Caryophyllene acetylated
2. **CAS Registry Number:** 75975-83-6
3. **Synonyms:** Acetic acid, anhydride, reaction products with (1R,4E,9S)-4,11,11-trimethyl-8-methylenebicyclo[7.2.0]undec-4-ene; Vetyvenal; Caryophyllene, acetylated terpenes; Caryophyllene, Reaction product with Acetic anhydride and acetic acid; Vetynal extra; Caryophyllene acetylated
4. **Molecular Formula:** $C_{15}H_{24}.C_4H_6O_3$
5. **Molecular Weight:** 246.39
6. **RIFM Number:** 7086
7. **Stereochemistry:** No isomer specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 321.45 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.16 (EPI Suite)
4. **Melting Point**: 90.23 °C (EPI Suite)
5. **Water Solubility:** 0.98 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000283 mm Hg @ 25 °C (EPI Suite), 0.000148 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics***:** 0.53% (RIFM, 2017e)
2. **Inhalation Exposure*:** 0.00027 mg/kg/day or 0.019 mg/day (RIFM, 2017e)
3. **Total Systemic Exposure**:** 0.007 mg/kg/day (RIFM, 2017e)

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

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

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

5. Derivation of systemic absorption

1. **Dermal:** 40% SAM model
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

When correcting for skin absorption, the total systemic exposure (see Section IV) to caryophyllene acetylated (7 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Name	Caryophyllene acetylated
J_{max} (mg/cm^2/h)	0.12[1]
Skin Absorption Class	40%

[1] J_{max} was calculated based on estimated log K_{OW} = 5.16 (consensus model) and Solubility = 0.98 mg/L (consensus model).

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	III	I

*Due to potential discrepancies with 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). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

Caryophyllene acetylated 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

Not pre-registered; no dossier available as of 05/18/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for caryophyllene acetylated 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)	0.24
2	Products applied to the axillae	0.071
3	Products applied to the face/body using fingertips	1.4
4	Products related to fine fragrances	1.3
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.34
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.34
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.34
5D	Baby cream, oil, talc	0.34
6	Products with oral and lip exposure	0.78
7	Products applied to the hair with some hand contact	2.7
8	Products with significant ano-genital exposure (tampon)	0.14
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.6
10A		9.3

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
	Household care products with mostly hand contact (hand dishwashing detergent)	
10B	Aerosol air freshener	9.3
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	5.2
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted

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 caryophyllene acetylated, the basis was a skin sensitization NESIL of 3100 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, caryophyllene acetylated does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of caryophyllene acetylated; however, read-across can be made to ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6; see Section VI). The mutagenic activity of ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo [7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] in dimethylformamide 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, 2017a). Under the conditions of the study, ethanone, 1-(4,11,11, -trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] was not mutagenic in the Ames test, and this can be extended to caryophyllene acetylated.

There are no studies assessing the clastogenic activity of caryophyllene acetylated; however, read-across can be made to ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6; see Section VI). The clastogenic activity of ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] 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 ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] in dimethyl sulfoxide (DMSO) at concentrations up to 2000 μg/mL in the DRF study; micronuclei analysis was conducted at concentrations up to 174 μg/mL in the presence and absence of metabolic activation. Ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo [7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] did not induce binucleated cells with micronuclei when tested up to cytotoxic levels concentration in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, ethanone, 1-(4,11,11, -trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to caryophyllene acetylated.

Based on the data available, ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b]does not present a concern for genotoxic potential, and this can be extended to caryophyllene acetylated.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/28/21.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on caryophyllene acetylated or any read-across materials. The total systemic exposure to caryophyllene acetylated 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 caryophyllene acetylated or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (7.0 μg/kg/day) is below the TTC for caryophyllene acetylated (9 μg/kg/day; Kroes, 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on caryophyllene acetylated or any read-across materials. The total systemic exposure to caryophyllene acetylated 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 caryophyllene acetylated or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (7.0 μg/kg/day) is below the TTC for caryophyllene acetylated (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/21.

11.1.4. Skin sensitization

Based on the existing data, caryophyllene acetylated is considered a skin sensitizer with a defined NESIL of 3100 μg/cm^2.

11.1.4.1. Risk assessment. Existing data demonstrates that caryophyllene acetylated is considered a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; OECD Toolbox v4.3). In a murine local lymph node assay (LLNA), caryophyllene acetylated was found to be sensitizing with an EC3 value of 12.9% (3225 μg/cm^2) (RIFM, 2002). In a confirmatory Confirmation of No Induction in Humans (CNIH) with 2.7% or 3188 μg/cm^2 of caryophyllene acetylated in 1:3 ethanol:diethyl phthalate (EtOH:DEP) no reactions indicative of sensitization were observed in any of the 98 volunteers (RIFM, 2018).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, caryophyllene acetylated is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 3188 μg/cm^2 (Table 1). 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: None.

Literature Search and Risk Assessment Completed On: 05/10/21.

Table 1
Data Summary for caryophyllene acetylated.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
3225 [1]	Weak	3188	NA	NA	3100

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5. Phototoxicity/photoallergenicity

Based on the UV/Vis absorption spectra and available *in vivo* study data, caryophyllene acetylated would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). In an *in vivo* photoallergenicity study, the authors concluded caryophyllene acetylated was not photoallergenic, though the severe reactions observed during induction to undiluted caryophyllene acetylated make it difficult to interpret the results with confidence (RIFM, 1999). Based on the lack of absorbance and the available *in vivo* study data, caryophyllene acetylated 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 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for caryophyllene acetylated is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on caryophyllene acetylated. Based on the Creme RIFM Model, the inhalation exposure is 0.019 mg/day. This exposure is 24.7 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of caryophyllene acetylated was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, caryophyllene acetylated was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified caryophyllene acetylated as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), caryophyllene acetylated presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 2016: The inherent biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 302C guideline. Biodegradation of 39% was observed after 28 days (56% after 67 days).

RIFM, 2015: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 12% was observed after 28 days (41% after 62 days).

RIFM, 2010: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 16% was observed after 28 days (25% after 60 days).

11.2.2.1.2. Ecotoxicity. RIFM, 2017c: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions in a closed system without headspace. Due to the low water solubility of the test material, the test concentrations were individually prepared as Water Accommodated Fraction/Water Soluble Fraction (WAF) with the loading rates of 1.0, 3.2, 10, 32, and 100 mg/L.

Under the conditions of the study and based on the loading rate of the test material, the 48-h EL50 was 6.1 mg/L (95% CI: 4.4–8.6 mg/L).

RIFM, 2017d: An algae acute growth inhibition test was conducted according to the OECD 201 method under static conditions. Due to the low water solubility of the test material, the test concentrations were prepared as Water Accommodated Fraction/Water Soluble Fraction (WAF) with the loading rates of 1.0, 3.2, 10, 32, and 100 mg/L. Based on loading rates of the test material, the 72-h EL50 values for growth rate and yield were reported to be > 100 mg/L and 28 mg/L (95% CI: 24–31 mg/L), respectively.

11.2.2.1.3. Other available data. Caryophyllene acetylated has not been registered for REACH for this time.

11.2.3. Risk assessment refinement

Since caryophyllene acetylated has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	6.2	6.2
Biodegradation Factor Used	0.1	0.1
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 further assessment is necessary.

The RIFM PNEC is 0.0225 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

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

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**
- **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 05/18/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.07			1000000	0.00007	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.981	0.244	0.270			Vinyl/Allyl Ketones

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112488.

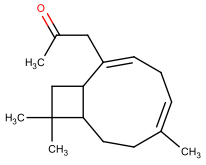
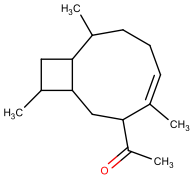
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- 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 analog 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 analog were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Caryophyllene acetylated	Ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b]
CAS No.	75975-83-6	70801-04-6
Structure		
Similarity (Tanimoto Score)		0.77
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{17}H_{26}O$	$C_{16}H_{26}O$
Molecular Weight	246.39	234.38
Melting Point (°C, EPI Suite)	90.23	65.44
Boiling Point (°C, EPI Suite)	321.45	306.31
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.77E-002	1.45E-001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.16	4.71
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.979	2.716
J_{max} (μg/cm^2/h, SAM)	3.430	5.415
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.55E+001	4.03E+001
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
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• No metabolites	• See Supplemental Data 1

Summary

There are insufficient toxicity data on caryophyllene acetylated (CAS # 75975-83-6). 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, ethanone, 1-(4,11,11,-

trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Ethanone, 1-(4,11,11,-trimethyl-8-methylenebicyclo[7.2.0]undec-4-enyl)-[1R-(1a,4E,9b] (CAS # 70801-04-6) was used as a read-across analog for the target material caryophyllene acetylated (CAS # 75975-83-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of macrocyclic unsaturated ketones.
  - o The target material and the read-across analog share a ketone branch attached to a fused ring macrocycle.
  - o The key difference between the target material and the read-across analog is that the target material has 1 additional double bond compared to the read-across analog as well as the disposition of the methyl groups. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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.

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, and 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 (see Cramer et al., 1978 for detaile?d explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? Yes, Intermediate (Class II).

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