Food and Chemical Toxicology xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, longifolene, CAS Registry Number 475-20-7

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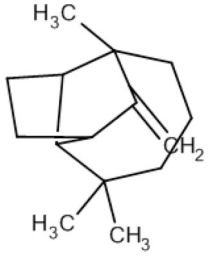
Version: 061019. This version replaces any previous versions.
Name: Longifolene CAS Registry Number: 475-20-7



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
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold

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https://doi.org/10.1016/j.fct.2019.110823
Received 9 July 2019; Accepted 16 September 2019
0278-6915/

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

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Longifolene was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that this material is not genotoxic. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to longifolene is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data provided longifolene a NESIL of 3500 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; longifolene is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; longifolene 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2001a; RIFM, 2015b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 3500 μg/cm^2. RIFM (2015a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: Not Persistent: 61% (after 65 days) RIFM (2009)
Bioaccumulation: Screening-level: 1916 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 7-day *Daphnia magna*: NOEC (reproduction): 0.02 mg/L RIFM (2005)
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: 7-day *Daphnia magna* NOEC (reproduction): 0.02 mg/L RIFM (2005)
RIFM PNEC is: 0.4 μg/L

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

1. Identification

1. Chemical Name: Longifolene
2. CAS Registry Number: 475-20-7
3. Synonyms: 1,4-Methanoazulene, decahydro-4,8,8-trimethyl-9-methylene-, [1S-(1α,3aβ,4α,8aβ; 4,8,8-Trimethyl-9-methylenedecahydro-1,4-methanoazulene; Longifolene
4. Molecular Formula: $C_{15}H_{24}$
5. Molecular Weight: 204.35
6. RIFM Number: 24

2. Physical data

1. **Boiling Point:** 254 °C @ 706 mm Hg (FMA Database), (calculated); 239.79 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** Log Pow greater than 6.0 (RIFM, 2007b), 5.48 (EPI Suite)
4. **Melting Point**: 46.04 °C (EPI Suite)
5. **Water Solubility:** 0.2525 mg/L (EPI Suite)
6. **Specific Gravity:** 0.9295 @ 25/25 °C (RIFM Database), 0.928 (FMA Database)
7. **Vapor Pressure:** 0.0108 mm Hg @ 20 °C (EPI Suite v4.0), 0.01 mm Hg 20 °C (FMA Database), 0.0187 mm Hg @ 25 °C (EPI Suite)
8. **UV spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Viscous oil with a medium, sweet, woody, rose, medical, and fir needle like odor*

*http://www.thegoodscentscompany.com/data/rw1020031.html (retrieved 11/18/13).

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.060% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00020 mg/kg/day or 0.014 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0050 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs selected:
   a. Genotoxicity: None
   b. Repeated Dose Toxicity: None
   c. Developmental and Reproductive Toxicity: None
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: None

7. Metabolism

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

7.1. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Longifolene is reported to occur in the following foods by the VCF*:

Artichoke
Carrot seed
Cinnamomum species
Citrus fruits
Fish
Guava and Feyoa
Hop (*Humulus lupulus*)
Mangifera species
Star anise
Vaccinium species

*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.

8. REACH dossier

Available; accessed 06/06/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for longifolene are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.27
2	Products applied to the axillae	0.080
3	Products applied to the face/body using fingertips	1.6
4	Products related to fine fragrances	1.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.38
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.38

5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.38
5D	Baby cream, oil, talc	0.38
6	Products with oral and lip exposure	0.88
7	Products applied to the hair with some hand contact	3.1
8	Products with significant ano-genital exposure (tampon)	0.16
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	11
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	5.8
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 longifolene, the basis was a predicted skin absorption value of 40% and a skin sensitization NESIL of 3500 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment

Longifolene was assessed in the BlueScreen assay and found negative for genotoxicity with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). The mutagenic potential of longifolene was assessed in a GLP study in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with longifolene in ethanol at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation (S9 mix). No substantial increase in revertant colony numbers of any of the 5 tester strains was observed following treatment with the test material at any dose level in the presence or absence of S9 mix (RIFM, 2001a). Under the conditions of the study, longifolene was determined not to cause a concern for mutagenic potential.

The clastogenic activity of longifolene was assessed in an *in vitro* micronucleus test conducted in accordance with OECD TG 487 and according to GLP regulations. Human peripheral lymphocytes were treated with longifolene in acetone at concentrations up to 80 μg/mL in the absence of metabolic activation and 120 μg/mL in the presence of metabolic activation. No significant increase in the number of micronuclei was observed at any of the concentrations tested when compared to the vehicle control (RIFM, 2015b). Under the conditions of the study, longifolene is considered not clastogenic in mammalian cells.

Based on the available data, longifolene does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/01/13.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment.

There are no repeated dose toxicity data on longifolene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to longifolene (5.0 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Ishida (1982); Asakawa (1986); Ishida (1980).

Literature Search and Risk Assessment Completed On: 06/15/16.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on longifolene or on any read-across materials. The total systemic exposure to longifolene is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment.

There are no developmental or reproductive toxicity data on longifolene or on any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to longifolene (5.0 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints for a Cramer Class I material at the current levels of use.

Additional References: Ishida (1982); Asakawa (1986); Ishida (1980).

Literature Search and Risk Assessment Completed On: 06/15/16.

10.1.4. Skin sensitization

Based on the available data, longifolene is considered to be a moderate skin sensitizer with a defined NESIL of 3500 μg/cm^2.

10.1.4.1. Risk assessment.

Based on the available data, longifolene is considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts, 2007; Toxtree 2.5.0; OECD Toolbox v3.1). Longifolene was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), but positive in KeratinoSens (RIFM, 2016). However, in the local lymph node assay (LLNA), positive results have been reported with EC3 values ranging from 1.75% to 31.4% (RIFM, 2001b; RIFM, 2012a). The wide range of EC3 values (therefore the sensitization potential) could be attributed to different levels of peroxide in the sample tested. The higher EC3 value of 31.4% was obtained in the sample with 0.03 mmol/kg of peroxide (RIFM, 2012a), while for the sample with 1 mmol/L of peroxide, a lower EC3 of 9.4% was observed (RIFM, 2012b). In a human maximization test, no reactions were observed at 10% (6900 μg/cm^2) (RIFM, 1977). In a human repeated insult patch test conducted according to the protocol provided by Politano and Api (Politano, 2008), longifolene did not induce sensitization reactions at 3% or 3543 μg/cm^2 in 105 subjects (RIFM, 2015a).

Based on weight of evidence from structural analysis and animal and human studies, longifolene is a sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 3500 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, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/

Table 1
Data summary for longifolene.

LLNA Weighted Mean EC3 Value μg/cm[b] (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm[b]	NOEL-HMT (Induction) μg/cm[b]	LOEL[b] (Induction) μg/cm[b]	WoE NESIL[c] μg/cm[b]
437–7850 [3]	Moderate	3543	6900	NA	3500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; 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 HRIPT or HMT.

[c] WoE NESIL limited to 3 significant figures.

qra2-dossier-final–september-2016.pdf).

Additional References: RIFM, 1974.bib_RIFM_1974

Literature Search and Risk Assessment Completed On: 10/19/15.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, longifolene would not be expected to present a concern for phototoxicity or photoallergenicity.

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

10.1.5.2. 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, $1000\,L\,mol^{-1}\cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/20/16.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There is limited inhalation data available on longifolene. Based on the Creme RIFM Model, the inhalation exposure is 0.014 mg/day. This exposure is 100 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: UGCM, 1997

Literature Search and Risk Assessment Completed On: 03/28/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of longifolene 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, longifolene 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 longifolene as being possibly persistent and 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.

10.2.1.1. Risk assessment. Based on the current VoU (2015), longifolene presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2009: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the test conditions, 100 mg of longifolene underwent 50% biodegradation after 28 days (61% after 60 days, 62% after 65 days).

RIFM, 2007a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Under the test conditions, biodegradation of 49% was observed after 28 days.

10.2.1.2.2. Ecotoxicity. Sweet (1997): Acute toxicity studies according to US EPA Guidelines were conducted on *Daphnia magna*,

Ceriodaphnia dubia, and *Pimephales promelas*. The mean E(L)C50 values were 0.44 mg/L, 0.41 mg/L, and 10.2 mg/L, respectively. In addition, 7-day chronic studies were conducted with *Ceriodaphnia dubia* and *Pimephales promelas*. The NOEC for survival and reproduction of *C. dubia* was 0.45 mg/L and 0.27 mg/L, respectively. For *P. promelas*, the NOEC for survival and growth was of 0.9 mg/L and 0.45 mg/L, respectively.

Passino-Reader (1997): A 48-hour *Daphnia magna* acute immobilization test was conducted according to the ASTM 1980 method. The EC50 for longifolene was reported to be 0.08 mg/L.

RIFM, 2005: Short-term chronic static renewal effluent toxicity tests with immature fathead minnows, *Pimephales promelas*, were conducted to estimate the NOEC of longifolene according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. At least 10 minnows per 250 mL container (in quadruplicate) were subjected to test or control solutions for at least 7 days. The NOEC for survival or growth was reported to be 0.76 mg/L.

RIFM, 2005: Short-term chronic static renewal effluent toxicity tests with *Ceriodaphnia dubia* were conducted to estimate the NOEC according to the EPA/600/4–90/027 and ASTM E729, 1997 methods. The NOEC for reproduction and survival was reported to be 0.02 mg/L and 0.1 mg/L, respectively.

10.2.1.2.3. Other available data. Longifolene has been registered for REACH with the following additional data:

The ready biodegradability of longifolene was evaluated in a closed bottle test according to the OECD 301D method. Biodegradation of 68% was observed after 28 days (ECHA, 2017).

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-hour EC50 was reported to be 0.119 mg/L (ECHA, 2017).

10.2.1.3. 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, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.0	6.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on the available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.4 µg/L. The revised PEC/PNECs for EU and North America 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: 04/02/19.

11. 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
- **TOXNET:** 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)		EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.091				1000000	9.13E-05	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	0.126	0.099		0.277	10000	0.0099	Neutral Organics
Tier 3: Measured Data							
	LC50	EC50		NOEC	AF	PNEC	Comments
Fish	10.2			0.45			
Daphnia		0.044		0.02	50	0.4	
Algae							

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 06/06/19.

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.

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