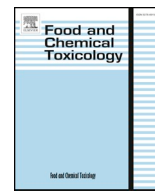




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## RIFM fragrance ingredient safety assessment, 5,7-dihydro-2-methylthieno(3,4-d)pyrimidine, CAS Registry Number 36267-71-7

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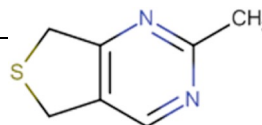
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Version: 011119. This version replaces any previous versions.

Name: 5,7-Dihydro-2-methylthieno(3,4-d)pyrimidine

CAS Registry Number: 36267-71-7



#### 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., 2015a, 2017) compared to a deterministic aggregate approach

**DEREK** - Derek Nexus is an *in silico* tool used to identify structural alerts

**DST** - Dermal Sensitization Threshold

**ECHA** - European Chemicals Agency

**EU** - Europe/European Union

**GLP** - Good Laboratory Practice

**IFRA** - The International Fragrance Association

**LOEL** - Lowest Observable Effect Level

**MOE** - Margin of Exposure

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**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  
**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

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

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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.**

5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class III material, and the exposure to 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 µg/cm<sup>2</sup>); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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, 2016a; RIFM, 2016b)

**Repeated Dose Toxicity:** No NOAEL available. Exposure is below the TTC

**Reproductive Toxicity:** No NOAEL available. Exposure is below the TTC.

**Skin Sensitization:** Not a sensitization concern; exposure is below the DST.

**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:** Screening-level: 2.7 (BIOWIN 3)

(EPI Suite v4.11; US EPA, 2012a)

**Bioaccumulation:** Screening-level: 2.3 L/kg

(EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:** Screening-level: Fish LC50: 1322 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: 1322 mg/L

(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1.322 µg/L

● **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe; not applicable; cleared at screening-level

## 1. Identification

- Chemical Name:** 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine
- CAS Registry Number:** 36267-71-7
- Synonyms:** Thieno [3,4d]pyrimidine, 5,7-dihydro-2-methyl-; 2-Methyl-5,7-dihydrothieno [3,4-d]pyrimidine; 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine
- Molecular Formula:** C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>S
- Molecular Weight:** 152.22
- RIFM Number:** 6755
- Stereochemistry:** No stereocenter and no stereoisomers exist.

## 2. Physical data

- Boiling Point:** 250.37 °C (EPI Suite)
- Flash Point:** > 200 °F; CC (FMA Database)
- Log K<sub>ow</sub>:** 1.07 (EPI Suite)
- Melting Point:** 64 °C (FMA Database), 71.81 °C (EPI Suite)
- Water Solubility:** 9134 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.0053 mm Hg @ 20 °C (EPI Suite v4.0), 0.02 mm Hg @ 25 °C (FMA Database), 0.00944 mm Hg @ 25 °C (EPI Suite)
- UV Spectra:** Minor absorbance between 290 and 700 nm; molar

absorption coefficient is below the benchmark ( $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ )

- Appearance/Organoleptic:** Strong, popcorn-like odor that also includes sweet roasted almond notes (Perfumer & Flavorist, 36 [6], June 2011)

### 3. Exposure

- Volume of Use (worldwide band):** < 0.1 metric ton per year (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcoholics:** 0.00029% (RIFM, 2018)
- Inhalation Exposure\*:** 0.000021 mg/kg/day or 0.0016 mg/day (RIFM, 2018)
- Total Systemic Exposure\*\*:** 0.000024 mg/kg/day (RIFM, 2018)

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

### 4. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

### 5. Computational toxicology evaluation

- Cramer Classification:** Class III, High

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
III	III	III

#### 2. Analogs Selected:

- Genotoxicity:** None
  - Repeated Dose Toxicity:** None
  - Reproductive Toxicity:** None
  - Skin Sensitization:** None
  - Phototoxicity/Photoallergenicity:** None
  - Local Respiratory Toxicity:** None
  - Environmental Toxicity:** None
- Read-across Justification:** None

### 6. Metabolism

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

### 7. Natural occurrence (Discrete chemical) or composition (NCS)

5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine 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.

### 8. IFRA standard

None.

### 9. REACH dossier

Pre-registered for 2010; no dossier as of 01/11/19.

### 10. Summary

#### 10.1. Human health endpoint summaries

##### 10.1.1. Genotoxicity

Based on the current existing data, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine does not present a concern for genotoxicity.

**10.1.1.1. Risk assessment.** 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine in water 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, 2016a). Under the conditions of the study, 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine was not mutagenic in the Ames test.

The clastogenic activity of 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine in water at concentrations up to 1520 µg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/06/18.

##### 10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine or any read-across materials. The total systemic exposure to 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

**10.1.2.1. Risk assessment.** There are insufficient repeated dose toxicity

data on 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine (0.024 µg/kg/day) is below the TTC (1.5 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

**Additional References:** RIFM, 1970.

**Literature Search and Risk Assessment Completed On:** 01/04/19.

### 10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine or on any read-across materials. The total systemic exposure to 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

**10.1.3.1. Risk assessment.** There are insufficient reproductive toxicity data on 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine (0.024 µg/kg/day) is below the TTC (1.5 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

**Additional References:** RIFM, 1970.

**Literature Search and Risk Assessment Completed On:** 12/11/18.

### 10.1.4. Skin sensitization

Based on the existing data and the application of DST, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine does not present a concern for skin sensitization under the current, declared levels of use.

**10.1.4.1. Risk assessment.** The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine. Acting conservatively, due to the absence of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm<sup>2</sup> (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile

concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 12/06/18.

### 10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine does not present a concern for phototoxicity or photoallergenicity.

**10.1.5.2. UV spectra analysis.** UV/Vis absorption spectra (OECD TG 101) for 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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<sup>-1</sup> · cm<sup>-1</sup> (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/20/18.

### 10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The exposure level for 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine is below the Cramer Class III TTC value for inhalation exposure local effects.

**10.1.6.1. Risk assessment.** There are no inhalation data available on 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine. Based on the Creme

**Table 1**

Maximum acceptable concentrations 5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category <sup>a</sup>	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU <sup>b</sup>
2	Products applied to the axillae	0.021%	2.6 × 10 <sup>-7</sup> %
3	Products applied to the face using fingertips	0.41%	1.2 × 10 <sup>-6</sup> %
4	Fine fragrance products	0.39%	3.0 × 10 <sup>-4</sup> %
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	6.7 × 10 <sup>-5</sup> %
6	Products with oral and lip exposure	0.23%	6.0 × 10 <sup>-6</sup> %
7	Products applied to the hair with some hand contact	0.79%	NRU <sup>b</sup>
8	Products with significant ano-genital exposure	0.041%	No Data <sup>c</sup>
9	Products with body and hand exposure, primarily rinse-off	0.75%	3.5 × 10 <sup>-4</sup> %
10	Household care products with mostly hand contact	2.7%	0.080%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data <sup>c</sup>
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.0090%

Note.

<sup>a</sup> For a description of the categories, refer to the IFRA/RIFM Information Booklet.

<sup>b</sup> No reported use.

<sup>c</sup> Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

RIFM Model, the inhalation exposure is 0.0016 mg/day. This exposure is 293.8 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

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

## 10.2. Environmental endpoint summary

### 10.2.1. Screening-level assessment

A screening-level risk assessment of 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine 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

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).

### 10.2.2. Risk assessment

Based on the current Volume of Use (2015), 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine does not present a risk to the aquatic compartment in the screening-level assessment.

#### 10.2.2.1. Biodegradation

No data available.

#### 10.2.2.2. Ecotoxicity

No data available.

#### 10.2.2.3. Other available data

5,7-Dihydro-2-methylthieno (3,4-d)pyrimidine has been pre-registered for REACH with no additional data at this time.

### 10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in  $\mu\text{g/L}$ ).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 ( <i>Daphnia</i> ) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ( $\mu\text{g/L}$ )	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1322</u>			1000000	<u>1.322</u>	

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, 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 5,7-dihydro-2-methylthieno (3,4-d)pyrimidine as not possibly persistent or bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF  $\geq 2000$  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

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

Exposure	Europe (EU)	North America (NA)
Log $K_{ow}$ Used	1.0	1.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	< 1	< 1
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt; 1</b>	<b>&lt; 1</b>

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

The RIFM PNEC is 1.322  $\mu\text{g/L}$ . The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 12/10/18.

## 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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** [https://ofmpub.epa.gov/opthpv/public\\_search\\_publicdetails?submission\\_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User\\_title=DetailQuery%20Results&EndPointRpt=Y#submission](https://ofmpub.epa.gov/opthpv/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](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](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 05/31/19.

#### 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. 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.

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