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Short Review

RIFM fragrance ingredient safety assessment, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one, CAS Registry Number: 51519-65-4

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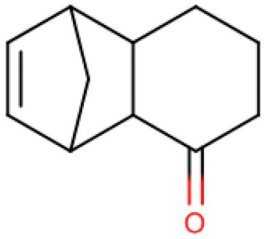
Name: 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one
CAS Registry Number: 51519-65-4



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., 2015b, 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

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

Summary: The use of this material under current conditions is supported by existing information.

4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one is not genotoxic. The skin sensitization endpoint was completed by utilizing the non-reactive DST. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.0015, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one. The environmental endpoints were evaluated; 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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, 2016b; RIFM, 2016a)

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

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

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1984)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 7.3 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 319.3 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

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

Critical Ecotoxicity Endpoint: Fish LC50: 319.3 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.3139 μg/L

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

1. Identification

1. **Chemical Name:** 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one
2. **CAS Registry Number:** 51519-65-4
3. **Synonyms:** 1,4-Methanonaphthalen-5(1H)-one, 4,4a,6,7,8,8a-hexahydro-; Tricyclo-[6,2,1,02,7]-undec-9-en-3-one; Tamisone; 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one
4. **Molecular Formula:** $C_{11}H_{14}O$
5. **Molecular Weight:** 162.23
6. **RIFM Number:** 6419
7. **Stereochemistry:** Isomer not specified. Four stereocenters and 16 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 249.49 °C (EPI Suite)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{ow}:** 1.82 (EPI Suite)
4. **Melting Point**: 42.05 °C (EPI Suite)
5. **Water Solubility:** 1861 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.0181 mm Hg @ 20 °C (EPI Suite 4.0), 0.031 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} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.012% (RIFM, 2016c)
3. **Inhalation Exposure*:** 0.000053 mg/kg/day or 0.0041 mg/day (RIFM, 2016c)
4. **Total Systemic Exposure**:** 0.00027 mg/kg/day (RIFM, 2016c)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015b; 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., 2015b; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	III	II

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   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: None

6. Metabolism

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

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

4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one is not reported to occur in food 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 that contains 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 available as of 2/22/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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 and pre-incubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. A small, statistically significant increase in revertant colonies was observed in TA100 in the absence of S9 at concentrations of 1.5, 5, and 1500 μg/plate using the pre-incubation method. These increases were within laboratory historical controls and were below the threshold of a 2-fold increase in revertant colonies. Additionally, there was no evidence of a dose response or reproducibility. No other increases in revertant colonies were observed in any other tester strain in the presence or absence of S9 when using the plate incorporation or pre-incubation methods (RIFM, 2016a). Under the conditions of the study, 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one was not mutagenic in the Ames test.

The clastogenic activity of 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one in DMSO at concentrations up to 1622.3 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 4,4a, 6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in the 4-h exposure group in the absence of S9. A small but statistically significant increase was observed in the 4-h group in the presence of S9. However, this increase was observed at a middle concentration and was within the historical control range and was considered to be biologically not relevant. All concentrations in the 24-h test group in the absence of S9 demonstrated small but statistically significant increases in micronuclei. The vehicle control value of this treatment group was abnormally low, and the increases were within or marginally above the historical control range for the vehicle. Additionally, a dose-related response was not observed, and these results were not considered as

biologically relevant (RIFM, 2016b). Under the conditions of the study, 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 8/28/2017.

10.1.2. Repeated Dose Toxicity

There are insufficient repeated dose toxicity data on 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one or any read-across materials. The total systemic exposure to 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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 no repeated dose toxicity data on 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (0.27 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/08/17.

10.1.3. Reproductive Toxicity

There are insufficient reproductive toxicity data on 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one or any read-across materials. The total systemic exposure to 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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 no reproductive toxicity data on 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (0.27 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: None.

Literature Search and Risk Assessment Completed On: 09/08/17.

10.1.4. Skin Sensitization

Based on the existing data and the application of DST, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one does not present a safety 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 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one. In a human repeat insult patch test, no reactions were observed (RIFM, 1984). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford et al., 2015a). 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 acceptable concentration for 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/12/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra and human study data, 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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 et al., 2009). In a photo-HRIPT, application of 4% 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one did not result in phototoxicity or photoallergenicity (RIFM, 1984). Based on lack of absorbance and human study data, 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one. Based on the Creme RIFM model, the inhalation exposure is 0.0041 mg/day. This exposure is 115 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: 08/31/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers 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 1
Acceptable concentration limits for 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.01%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No data
9	Products with body and hand exposure, primarily rinse off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.01%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.1%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).

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, 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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) did not identify 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one as possibly being either 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 ≥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.

10.2.2. Risk assessment

Based on current VoU (2015), 4,4a, 6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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:. RIFM, 2000: A Daphnia magna immobilization test was conducted according to OECD Guideline 202 Part I under static conditions. The 48-h EC50 was reported to be 9.5 mg/L.

10.2.2.3. Other available data. 4,4a,6,7,8,8a-Hexahydro-1,4-methanonaphthalen-5(1H)-one has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Since 4,4a,6,7,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	319.3			1,000,000	0.3139	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.8	1.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.3139 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/17/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix

Explanation of Cramer Classification:

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 detailed 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)? No.

Q26. Monocycloalkanone or a bicyclo compound? No.

Q22. Common component of food? No.

Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No, Class III (High Class).

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