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Short Review

RIFM fragrance ingredient safety assessment, 2-nonyn-1-al dimethylacetal, CAS Registry Number 13257-44-8

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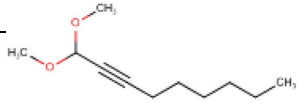
CAS Registry Number: 13257-44-8



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

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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
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
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 as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
2-Nonyn-1-al dimethylacetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-nonyn-1-al dimethylacetal 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 2-nonyn-1-al dimethylacetal is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data from 2-nonyn-1-al dimethylacetal provided a NESIL of 23000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-nonyn-1-al dimethylacetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-nonyn-1-al dimethylacetal 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, 2017b; RIFM, 2017c)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 23000 μg/cm^2. RIFM (2011)
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: 41% (OECD 302C) RIFM (2013b)
Bioaccumulation:
Screening-level: 40.7 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 10.08 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: 10.08 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.01008 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

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1. Identification

1. **Chemical Name:** 2-Nonyn-1-al dimethylacetal
2. **CAS Registry Number:** 13257-44-8
3. **Synonyms:** 1,1-Dimethoxynon-2-yne; 2-Nonyne, 1,1-dimethoxy-; Parmavert; 2-Nonoyn-1-al-Dimeth-Acetyl; 2-Nonyn-1-al dimethylacetal
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.27
6. **RIFM Number:** 728
7. **Stereochemistry:** isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 104 °C @ 7 mm Hg (FMA Database), 228.62 °C (EPI Suite)
2. **Flash Point:** 91 °C (GHS), 196 °F; CC (FMA Database)
3. **Log K_{OW}:** 3.6 (RIFM, 2013a), 2.94 (EPI Suite)
4. **Melting Point**: 38.6 °C (EPI Suite)
5. **Water Solubility:** 160.3 mg/L (EPI Suite)
6. **Specific Gravity:** 0.89 (FMA Database)
7. **Vapor Pressure:** 0.0551 mm Hg @ 20 °C (EPI Suite v4.0), 0.03 mm Hg 20 °C (FMA Database), 0.0918 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:** Arctander Volume II 1969: Colorless oily liquid. Powerful Floral Green sweet and violet leaf-like odor of moderate to poor tenacity.

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)

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

1. **95th Percentile Concentration in Hydroalcoholics:** 0.01% (RIFM, 2015)
2. **Inhalation Exposure*:** 0.000021 mg/kg/day or 0.0016 mg/day (RIFM, 2015)
3. **Total Systemic Exposure**:** 0.00016 mg/kg/day (RIFM, 2015)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

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

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

7. Metabolism

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

8. Natural occurrence (discrete chemical) or Composition (NCS)

2-Nonyn-1-al dimethylacetal 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

Pre-registered; no dossier available as of 02/18/19.

10. Conclusion

The maximum acceptable concentrations[a] in the finished products for 2-nonyn-1-al dimethyl acetal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	1.8
2	Products applied to the axillae	0.53
3	Products applied to the face/body using fingertips	11
4	Products related to fine fragrances	9.8
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	2.5
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	2.5
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	2.5
5D	Baby cream, oil, talc	2.5
6	Products with oral and lip exposure	5.8

7	Products applied to the hair with some hand contact	20
8	Products with significant ano-genital exposure (tampon)	1.0
9	Products with body and hand exposure, primarily rinse-off (bar soap)	19
10A	Household care products with mostly hand contact (hand dishwashing detergent)	69
10B	Aerosol air freshener	69
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	38
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 2-nonyn-1-al dimethylacetal, the basis was a skin sensitization NESIL of 23000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-nonyn-1-al dimethylacetal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-nonyn-1-al dimethylacetal 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 2-nonyn-1-al dimethylacetal in dimethyl sulfoxide (DMSO) 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, 2017c). Under the conditions of the study, 2-nonyn-1-al dimethylacetal was not mutagenic in the Ames test.

The clastogenic activity of 2-nonyn-1-al dimethylacetal 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 2-nonyn-1-al dimethylacetal in DMSO up to 1840 μg/mL in the dose range finding (DRF) study. Micronuclei analysis in the main study was conducted up to 120 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 2-Nonyn-1-al dimethylacetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 2-nonyn-1-al dimethylacetal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-nonyn-1-al dimethylacetal does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 2-nonyn-1-al dimethylacetal or on any read-across materials. The total systemic exposure to 2-nonyn-1-al dimethylacetal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Table 1
Data Summary for 2-nonyn-1-al dimethyl acetal.

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]
> 5000 [1]	Weak	23622	2760	NA	23000

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 2 significant figures.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-nonyn-1-al dimethylacetal or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-nonyn-1-al dimethylacetal (0.16 μg/kg/day) is below the TTC (1.5 μg/kg/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: 12/17/18.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 2-nonyn-1-al dimethylacetal or on any read-across materials. The total systemic exposure to 2-nonyn-1-al dimethylacetal is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-nonyn-1-al dimethylacetal or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-nonyn-1-al dimethylacetal (0.16 μg/kg/day) is below the TTC (1.5 μg/kg/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: 11/05/18.

11.1.4. Skin sensitization

Based on the available data, 2-nonyn-1-al dimethylacetal is considered a weak skin sensitizer with a defined NESIL of 23600 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 2-nonyn-1-al dimethylacetal is considered a weak sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.1; Toxtree 2.6.13). 2-Nonyn-1-al dimethylacetal exhibited minimal reactivity in the *in chemico* Direct Peptide Reactivity Assay (DPRA) and was found to be positive in the KeratinoSens and human Cell Line Activation Test (h-CLAT) (RIFM, 2016a; RIFM, 2016b; RIFM, 2016c). However, in a murine local lymph node assay (LLNA), 2-nonyn-1-al

dimethylacetal did not induce contact sensitization up to 20% (5000 μg/cm^2) (RIFM, 2010). In a guinea pig maximization test, 2-nonyn-1-al dimethylacetal showed reactions indicative of sensitization (RIFM, 1978). In a human maximization test, no skin sensitization reactions were observed when conducted in 25 subjects at concentration of 4% (2760 μg/cm^2) in petrolatum (RIFM, 1975). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 23622 μg/cm^2 of 2-nonyn-1-al dimethylacetal in 3:1 diethyl phthalate:ethanol, no reactions indicative of sensitization were observed in any of the 108 volunteers (RIFM, 2011).

Based on weight of evidence from structural analysis and animal and human studies, 2-nonyn-1-al dimethylacetal is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 23600 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/qra2-dossier-final–september-2016.pdf).

Additional References: RIFM, 2017a.

Literature Search and Risk Assessment Completed On: 02/25/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-nonyn-1-al dimethylacetal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-nonyn-1-al dimethylacetal 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 et al., 2009). Based on the lack of absorbance, 2-nonyn-1-al dimethylacetal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/22/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to lack of appropriate data. The material, 2-nonyn-1-al dimethylacetal, the exposure level 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 2-nonyn-1-al dimethylacetal. Based on the Creme 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: 10/23/18.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-nonyn-1-al dimethylacetal was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-nonyn-1-al dimethylacetal 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 2-nonyn-1-al dimethylacetal as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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.

11.2.1.1. Risk assessment. Based on the current VoU (2015), 2-nonyn-1-al dimethylacetal presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 2013b**:** An inherent biodegradability of the test material was evaluated according to the OECD 302C method. Biodegradation of 41% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.3. Other available data. 2-Nonyn-1-al dimethylacetal has been pre-registered for REACH with no additional data at this time.

11.2.1.4. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	10.08			1000000	0.01008	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.6	3.6
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 class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.01008 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level 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: 11/06/18.

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
- **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.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 05/20/19.

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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