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Short Review

RIFM fragrance ingredient safety assessment, methoxyprazine, CAS registry number 3149-28-8



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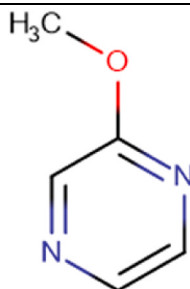
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Name: Methoxyppyrazine
CAS Registry Number: 3149-28-8



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH - Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

(continued)

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

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. This material has not been fully evaluated for photoallergenic potential.

Methoxyppyrazine was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that methoxyppyrazine is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to methoxyppyrazine is below the TTC (0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. Based on data, methoxyppyrazine is not expected to be photoirritating. Methoxyppyrazine was not evaluated for photoallergy. The environmental endpoints were evaluated; methoxyppyrazine was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

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

Repeated Dose Toxicity: NOAEL = 20 mg/kg/day. (RIFM (1981))

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

Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.

Photoirritation/Photoallergenicity: Not photoirritating/not evaluated for photoallergy. (RIFM (2016))

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.89 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 1292 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: 1292 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 1.292 $\mu\text{g}/\text{L}$

• Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1

1. Identification

1. Chemical Name: Methoxyppyrazine

(continued on next column)

Table 1

Summary of existing data on methoxypyrazine.

WoE Skin Sensitization Potency Category ^a	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm ²	NOEL-HMT (induction) µg/cm ²	LOEL ^b (induction) µg/cm ²	WoE NESIL ^c µg/cm ²	LLNA ^d Weighted Mean EC3 Value µg/cm ²	GPMT ^e	Buehler ^e
Human potency category unknown; current exposure level below the DST for non-reactive materials.	NA	NA	NA	NA	NA	NA	NA
	In vitro Data^f				In silico protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		No alert found	No alert found	Schiff base formation

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

^a WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

^b Data derived from CNIH or HMT.

^c WoE NESIL limited to 2 significant figures.

^d Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

^e Studies conducted according to the OECD TG 406 are included in the table.

^f Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

2. **CAS Registry Number:** 3149-28-8

3. **Synonyms:** 2-Methoxy-1,4-diazine; Pyrazine, methoxy-; 2-Methoxy-pyrazine; Methoxypyrazine

4. **Molecular Formula:** C₅H₆N₂O

5. **Molecular Weight:** 110.11 g/mol

6. **RIFM Number:** 6746

7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 169.48 °C (EPI Suite)

2. **Flash Point:** 123 °F; CC (Fragrance Materials Association [FMA])

3. **Log K_{OW}:** 0.92 (EPI Suite)

4. **Melting Point:** 24.99 °C (EPI Suite)

5. **Water Solubility:** 25870 mg/L (EPI Suite)

6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 1.13 mm Hg at 20 °C (EPI Suite v4.0), 2.6 mm Hg at 20 °C (FMA), 1.6 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm. Molar absorption coefficients (3363, 3608, and 4108 L mol⁻¹ • cm⁻¹ under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol⁻¹ • cm⁻¹)

9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95th Percentile Concentration in Fine Fragrance:** 0.0000014% (RIFM, 2020)

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2020)

3. **Total Systemic Exposure**:** <0.0001 mg/kg/day (RIFM, 2020)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015a; Safford, 2017; 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, 2015a; Safford, 2017; 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 v3.1	OECD QSAR Toolbox v4.2
III	III	III

2. Analogs Selected:

a. **Genotoxicity:** None

b. **Repeated Dose Toxicity:** None

c. **Reproductive Toxicity:** None

d. **Skin Sensitization:** None

e. **Photoirritation/Photoallergenicity:** None

f. **Local Respiratory Toxicity:** None

g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

8. Natural occurrence

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

Beef	Licorice (<i>Glycyrrhiza</i> species)
Cocoa	Malt
Krill	

*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

Table 2
Supported concentrations for methoxyppyrazine that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category ^a	Description of Product Type	Supported Concentrations ^b (%) 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 ^c
2	Products applied to the axillae	0.021	1.6 × 10 ⁻⁷
3	Products applied to the face using fingertips	0.41	NRU ^c
4	Fine fragrance products	0.39	1.4 × 10 ⁻⁶
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	NRU ^c
6	Products with oral and lip exposure	0.23	NRU ^c
7	Products applied to the hair with some hand contact	0.79	NRU ^c
8	Products with significant ano-genital exposure	0.041	No Data ^d
9	Products with body and hand exposure, primarily rinse-off	0.75	NRU ^c
10	Household care products with mostly hand contact	2.7	NRU ^c
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data ^d
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	NRU ^c

Note:

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.

^b These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.

^c No reported use.

^d Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

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

Methoxyppyrazine has been pre-registered for 2010; no dossier available as of 04/08/22.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methoxyppyrazine does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Methoxyppyrazine was assessed in the Blue-Screen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of methoxyppyrazine 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 methoxyppyrazine 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, 2017a). Under the conditions of the study, methoxyppyrazine was not mutagenic in the Ames test.

The clastogenic activity of methoxyppyrazine 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 methoxyppyrazine in DMSO at concentrations up to 1102 µg/mL in the dose range finding study; micronuclei analysis was conducted at concentrations up to 1102 µg/mL in the presence and absence of metabolic activation. Methoxyppyrazine 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, 2017b). Under the conditions of the study, methoxyppyrazine was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/22.

11.1.2. Repeated dose toxicity

The MOE for methoxyppyrazine is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methoxyppyrazine. In a non-guideline subchronic study, groups of CD-Crl(SD)BR were administered methoxyppyrazine via diet at doses of 0 (N = 24 rats/sex), 20 (N = 16 rats/sex), 63 (N = 12 rats/sex), and 200 (N = 10 rats/sex) mg/kg/day for 13 weeks. No mortality occurred throughout the study. No treatment-related adverse effects were observed in clinical signs, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. Food consumption and bodyweight gains were reduced in both sexes at the mid and high doses, but food efficiency was unaffected. Absolute and relative liver weights were slightly increased in both sexes at the high dose. Based on reduced food consumption and bodyweight gains at the mid and high doses, the repeated dose toxicity NOAEL for this study was considered to be 20 mg/kg/day (RIFM, 1981).

Therefore, the methoxyppyrazine MOE for the repeated dose toxicity endpoint can be calculated by dividing the methoxyppyrazine NOAEL in mg/kg/day by the total systemic exposure to methoxyppyrazine, 20/0.0001, or 200000.

Additionally, the total systemic exposure to methoxyppyrazine (0.1 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: 03/04/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on methoxyppyrazine or any read-across materials. The total systemic exposure to methoxyppyrazine 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 methoxyppyrazine or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.1 µg/kg/day) is below the TTC for methoxyppyrazine (1.5 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/22.

11.1.4. Skin sensitization

Based on existing data and the application of DST, methoxyppyrazine does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for methoxyppyrazine (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm² (Safford, 2008; Safford, 2011; Roberts et al., 2015; Safford, 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for methoxyppyrazine that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent supported 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: 03/15/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vitro* study data, methoxyppyrazine would not be expected to present a concern for photoirritation. Methoxyppyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of fragrance materials.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red uptake photoirritation assay (OECD 432), methoxyppyrazine was not predicted to have photoirritating effects (RIFM, 2016). Based on the available *in vitro* study data, methoxyppyrazine would not be expected to present a concern for photoirritation. Methoxyppyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of fragrance materials.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 330 nm. Molar absorption coefficients (3363, 3608, and 4108 L mol⁻¹ • cm⁻¹ under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating effects, 1000 L mol⁻¹ • cm⁻¹ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/31/

22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for methoxyppyrazine 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 methoxyppyrazine. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 4700 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: 03/28/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methoxyppyrazine 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, methoxyppyrazine 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 methoxyppyrazine 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, 2017). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), methoxyppyrazine does not present a risk to the aquatic compartment in the

screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. *Biodegradation*. No data available.

11.2.1.2.2. *Ecotoxicity*. No data available.

11.2.1.2.3. *Other available data*. Methoxyprazine has been pre-registered for REACH with no additional data at this time.

11.2.1.3. *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.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1292</u>			1000000	1.292	

Exposure information and PEC calculation (following RIFM Framework: [Salvito, 2002](#)).

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	0.92	0.92
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 1.292 µg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/31/22.

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:** <https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm>
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubChem:** <https://pubchem.ncbi.nlm.nih.gov/>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA ChemView:** <https://chemview.epa.gov/chemview/>

- **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 02/09/23.

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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