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RIFM fragrance ingredient safety assessment, piperidine, CAS Registry Number 110-89-4

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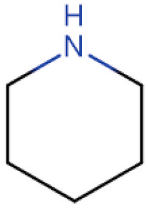
Name: Piperidine



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CAS Registry Number: 110-89-4

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
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)

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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

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

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

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

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

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

Piperidine was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that piperidine is not genotoxic. The repeated dose and reproductive toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to piperidine is below the TTC (0.009 mg/kg/day and 0.009 mg/kg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra for read-across analog diethylamine (CAS 109-89-7); piperidine is not expected to be phototoxic/photoallergenic. Data on piperidine provide a calculated margin of exposure (MOE) > 100 for the local respiratory endpoint. The environmental endpoints were evaluated; piperidine 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Piperidine; ECHA, 2013)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(Thomas and Brogat, 2017)
Local Respiratory Toxicity: NOEC = 70 mg/m^3.	(ECHA REACH Dossier: Piperidine; ECHA, 2013)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 100% (OECD 301 C)	ECHA REACH Dossier: Piperidine; ECHA, 2013
Bioaccumulation: Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 581.9 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 581.9 mg/L	(RIFMFramework; Salvito, 2002)
RIFM PNEC is: 0.5819 μg/L	

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

1. Identification

1. **Chemical Name:** Piperidine
2. **CAS Registry Number:** 110-89-4
3. **Synonyms:** Hexahydropyridine; Hexazane; Pentamethylenimine; Piperidine
4. **Molecular Formula:** $C_5H_{11}N$
5. **Molecular Weight:** 85.15 g/mol
6. **RIFM Number:** 6694
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 106 °C (Fragrance Materials Association [FMA]), 106.3 °C (Bazarova and Osipenko, 1967), 127.91 °C (EPI Suite)
2. **Flash Point:** 9 °C (Globally Harmonized System), 40 °F; CC (FMA)
3. **Log K_{OW}:** 1.19 (EPI Suite)
4. **Melting Point**: 9 °C (Bazarova and Osipenko, 1967), −24.69 °C (EPI Suite)
5. **Water Solubility:** 249400 mg/L (EPI Suite)
6. **Specific Gravity:** 0.86 (FMA), 0.860 (Bazarova and Osipenko, 1967)
7. **Vapor Pressure:** 22 mm Hg at 20 °C (EPI Suite v4.0), 23 mm Hg at 20 °C (FMA), 28.9 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide Band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000012% (RIFM, 2017)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000011 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0000002 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015; Safford et al., 2015a; 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 II, Intermediate (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	III	III

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** Diethylamine (CAS 109-89-7)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

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

Barley	Fish
Beef	Hop (*Humulus lupulus*)
Caviar	Malt
Cheese, Various Types	Pepper (*Piper nigrum* L.)
Coffee	Sherry

*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. This is a partial list.

9. REACH dossier

Dossier available; accessed on 08/05/21 (ECHA, 2013).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT assay) was conducted according to OECD TG 476 and GLP guidelines. Chinese hamster lung cells were treated with piperidine in deionized water at concentrations up to 860 μg/mL (as determined in a preliminary toxicity assay), for 4 and 24 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2013). Under the conditions of the study, piperidine was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of piperidine was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in water via oral gavage to groups of male and female NMRI mice. Doses of 40, 120, and 400 mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013). Under the conditions of the study, piperidine was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on piperidine or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.0002 μg/kg/day) is below the TTC for piperidine (9 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/18/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on piperidine or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.0002 μg/kg/day) is below the TTC for piperidine (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/18/21.

11.1.4. Skin sensitization

Based on existing data and the application of DST, piperidine 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 studies are available for piperidine. 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). A guinea pig Buehler test did not present reactions indicative of sensitization at 25% in water (ECHA, 2013). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (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 piperidine 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: 7/22/21.

11.1.5. Phototoxicity/photoallergenicity

Based on UV absorption spectra for the structurally related material diethylamine (CAS # 109-89-7), piperidine would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies in experimental models or UV absorption spectra available for piperidine. UV absorption spectra on the structurally related material diethylamine (CAS # 109-89-7) indicate no absorption between 290 and 450 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance for the structurally related analog, piperidine does not present a concern for phototoxicity or photoallergenicity.

UV Spectra Analysis: UV/Vis absorption spectra were not available for the target material piperidine. UV absorbance spectra on the structurally related material diethylamine (CAS # 109-89-7) indicate no absorbance in the range of 290–450 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: 07/30/21.

11.1.6. Local Respiratory Toxicity

The MOE for piperidine is adequate for the respiratory endpoint at the current level of use.

Table 1
Maximum acceptable concentrations for piperidine that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	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[b]
2	Products applied to the axillae	0.021%	3.0×10^{-6}%
3	Products applied to the face using fingertips	0.41%	4.7×10^{-8}%
4	Fine fragrance products	0.39%	1.2×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	1.0×10^{-6}%
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	2.2×10^{-7}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	2.0×10^{-6}%
10	Household care products with mostly hand contact	2.7%	1.2×10^{-6}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	3.0×10^{-5}%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 28-day inhalation exposure study, 10 Wistar rats/sex/group were exposed to piperidine at 0, 20, 70, and 350 mg/m^3 for 6 h/day and 5 days/week (ECHA, 2013). A complete respiratory tract microscopic analysis included nasal cavities, paranasal sinuses, trachea, and lungs. All animals survived the exposures. The only indication of respiratory irritation was reddish crusts or bloody nasal discharge in the animals from the highest exposure concentration group. Based on these observations, the local respiratory effects NOEC is identified at 70 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (70 mg/m^3) × (1 m^3/1000 L) = 0.07 mg/L
- Minute ventilation of 0.14 L/min for a Wistar rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 50.4 L/day

- (0.07 mg/L) × (50.4 L/d) = 3.528 mg/day
- (3.528 mg/day)/(0.0016 kg lung weight of rat*) = 2205 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0000011 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015 and Safford et al., 2015a). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.0000017 mg/kg lung weight/day resulting in a MOE of 1297058823 (i.e., [2205 mg/kg lung weight of rat/day]/[0.0000017 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0000011 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Smyth et al., 1962; Bazarova and Osipenko, 1967

Literature Search and Risk Assessment Completed On: 07/13/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of piperidine was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, piperidine 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 piperidine 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, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), piperidine presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation.

No data available.

11.2.4. Ecotoxicity

No data available.

11.2.5. Other available data

Piperidine has been registered for REACH, and the following additional information is available at this time (ECHA, 2013):

The ready biodegradability of the test material was evaluated using the modified MITI test according to the OECD 301C guidelines. Biodegradation of 100% (GC) was reported after 14 days.

The acute fish (*Leuciscus idus*) toxicity test was conducted according to the DIN 38 412 guidelines under static conditions. The 96-h LC50 based on nominal test concentration was reported to be 68.12 mg/L (not pH-adjusted). The LC50 value was calculated as geometric mean LC0 and LC100 values.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on geometric mean measured concentration was reported to be 19 mg/L (95% CI: 17.6–20.7 mg/L).

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on nominal test concentration was reported to be 3.8 mg/L.

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on nominal test concentration was reported to be 12.5 mg/L.

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on nominal test concentration was reported to be 2.2 mg/L.

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on nominal test concentration was reported to be 5 mg/L.

The algae growth inhibition test was conducted according to the EU C.3 method, under static conditions. The 72-h EC50 values based on time-weighted average concentration for growth rate and yield were reported to be 106 mg/L and 27.4 mg/L, respectively.

11.2.6. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.19	1.19
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 additional

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	581.9			1000000	0.5819	

assessment is necessary.

The RIFM PNEC is 0.5819 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 07/19/21.

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
- **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://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 03/15/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113085.

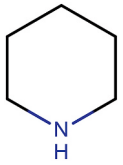
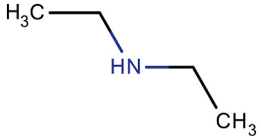
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Piperidine	Diethylamine
CAS No.	110-89-4	109-89-7
Structure		
Similarity (Tanimoto Score)		0.0
Endpoint		Phototoxicity/photoallergenicity
Molecular Formula	$C_5H_{11}N$	$C_4H_{11}N$
Molecular Weight (g/mol)	85.15	73.14
Melting Point (°C, EPI Suite)	−7.00	−50.00
Boiling Point (°C, EPI Suite)	106.00	55.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	4279.64	31597.31
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1000000.00	1000000.00
Log K_{OW}	0.84	0.58
J_{max} (μg/cm^2/h, SAM)	17724.47	15777.41
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.45	2.58
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	N/A*

*Not applicable for the endpoint under consideration.

Summary

There are insufficient toxicity data on piperidine (CAS # 110-89-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, diethylamine (CAS # 109-89-7) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Diethylamine (CAS # 109-89-7) was used as a read-across analog for the target material piperidine (CAS # 110-89-4) for the phototoxicity/photoallergenicity endpoint.
  - o The target material and the read-across analog belong to a structural class of secondary amines.
  - o The target material and the read-across analog share a secondary amine.
  - o The key difference between the target material and the read-across analog is that the target material is a cyclic secondary amine whereas the read-across analog is a straight chain secondary amine. This structural difference does not alter the chromophore and light-absorbing properties of the molecule.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the phototoxicity/photoallergenicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

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? Yes, Intermediate (Class II)

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