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Short Review

RIFM fragrance ingredient safety assessment, pyridine, 5-hexyl-2-methyl-, CAS Registry Number 710-40-7

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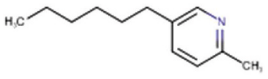
Name: Pyridine, 5-hexyl-2-methyl-CAS Registry Number: 710-40-7



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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
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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., 2015; Safford et al., 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
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
ISS - Instituto Superiore di Sanita (Italian National Institute of Health)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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.

Pyridine, 5-hexyl-2-methyl- was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. The genotoxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC), and the exposure to pyridine, 5-hexyl-2-methyl- is below the TTC (0.0025 μg/kg/day). Data on read-across analog 5-ethyl-2-methylpyridine (CAS # 104-90-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra for read-across analog 2,6-dimethylpyridine (CAS # 108-48-5); pyridine, 5-hexyl-2-methyl- is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class II material, and the exposure to pyridine, 5-hexyl-2-methyl- is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; pyridine, 5-hexyl-2-methyl- 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 (VoU) 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: No data; exposure is below the TTC.	
Repeated Dose Toxicity: NOAEL = 31.7 mg/kg/day.	ECHA (2013)
Reproductive Toxicity: NOAEL = 95 mg/kg/day.	ECHA (2013)
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.	
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 2.74 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 346.9 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 2.155 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: 2.155 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.002155 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Pyridine, 5-hexyl-2-methyl-
2. **CAS Registry Number:** 710-40-7
3. **Synonyms:** 2-Picoline, 5-hexyl-; 5-Hexyl-2-methylpyridine; 5-Hexyl-2-methyl pyridine; Pyridine orange; Pyridine, 5-hexyl-2-methyl-
4. **Molecular Formula:** $C_{12}H_{19}N$
5. **Molecular Weight:** 177.29 g/mol
6. **RIFM Number:** 9408
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 255.82 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.35 (EPI Suite v4.11)
4. **Melting Point**: 49.02 °C (EPI Suite v4.11)
5. **Water Solubility:** 2.16E+02 at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.59E+00 at 25 °C (EPI Suite v4.11)

8. **UV Spectra:** Not available
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 v3.2.10)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0 0000057 % (RIFM, 2022)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000006 mg/day (RIFM, 2022)
3. **Total Systemic Exposure**:** 0.0000001 mg/kg/day (RIFM, 2022)

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
II	III	III

*See the Appendix below for details.

2. **Analogs Selected**:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** 5-Ethyl-2-methylpyridine (CAS # 104-90-5)
   c. **Reproductive Toxicity:** 5-Ethyl-2-methylpyridine (CAS # 104-90-5)
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** 2,6-Dimethylpyridine (CAS # 108-48-5)
   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.
Additional References:
None.

8. Natural occurrence

Pyridine, 5-hexyl-2-methyl- is reported to occur in the following foods by the VCF*:

Citrus fruits.

*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

Available (ECHA, 2012a); accessed on 03/09/23.

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, pyridine, 5-hexyl-2-methyl- does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenicity or clastogenicity of pyridine, 5-hexyl-2-methyl- or any read-across materials that can be used to support the genotoxicity endpoint. Hence, according to the RIFM Criteria Document (Api et al., 2015), the TTC value of 0.0025 μg/kg/day should be used as a threshold to support safety for the genotoxicity endpoint. The total systemic exposure for pyridine, 5-hexyl-2-methyl- (0.0001 μg/kg/day) is below the TTC for genotoxicity (0.0025 μg/kg/day; Kroes et al., 2004) at the current level of use, and, therefore, it does not present a risk for toxicological concern.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/05/23.

11.1.2. Repeated dose toxicity

The MOE for pyridine, 5-hexyl-2-methyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on pyridine, 5-hexyl-2-methyl-. Read-across material 5-ethyl-2-methylpyridine (CAS # 104-90-5; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a GLP- and OECD 407-compliant study, groups of 6 Sprague Dawley rats/sex/dose were administered 5-ethyl-2-methylpyridine via gavage at doses of 0, 30, 95, and 300 mg/kg/day for 28 days. No mortality occurred throughout the study period. No treatment-related adverse effects were observed in clinical signs. Bodyweight gains and food consumption were significantly reduced in males at the high dose. Erythrocyte and hematocrit levels were significantly reduced in females at the high dose. Mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration levels were significantly increased in females at the high dose. Mottled kidneys were observed in high-dose males. Significant reduction in kidney weights were seen in high-dose group males. Nephropathy was seen in mid- and high-dose group males. The lesions were similar to the protein nephropathy induced by xenobiotics in the male rat. It is reported that several chemicals specifically increased α2u-globulin accumulation in the proximal convoluted tubular epithelium of the male rat as a primary acute toxicological effect (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990; Hard et al., 1993). Based on reduced

bodyweight gains and food consumption in males at 300 mg/kg/day and reduced erythrocyte and hematocrit levels in females at 300 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 95 mg/kg/day (ECHA, 2013).

In a GLP- and OECD 421-compliant study, groups of 10 Sprague Dawley rats/sex/dose were administered 5-ethyl-2-methylpyridine via gavage at doses of 0, 30, 95, and 300 mg/kg/day. Females were treated for 15 days pre-mating, throughout the mating period until Day 4 postpartum, and males were treated for 15 days pre-mating until successful littering of the females. Two high-dose males were euthanized in extremis during the study period; these males exhibited ataxia, abnormal respiration, reduced body temperature, prostrate posture, underactivity, reduced/dehydrated gastrointestinal contents, accentuated lobular liver patterns, reduced testes, epididymides, prostate glands and seminal vesicles, and a small mass on 1 epididymis in each male. Microscopic examination of both masses revealed the presence of spermatozoal granuloma. Both deaths were considered to be related to treatment. Other than in the 2 deceased males, no adverse effects were observed in clinical signs, gross pathology, or histopathology. Bodyweight gains were significantly reduced in males at the high dose. Liver weights were significantly increased in both sexes, and kidney weights were significantly increased in males at the high dose. Based on mortality and reduced bodyweight gains in males at 300 mg/kg/day, the repeated dose toxicity NOAEL for this study was considered to be 95 mg/kg/day (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012b). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 95/3 or 31.7 mg/kg/day.

Therefore, the pyridine, 5-hexyl-2-methyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the 5-ethyl-2-methylpyridine NOAEL in mg/kg/day by the total systemic exposure to pyridine, 5-hexyl-2-methyl-, 31.7/0.0000001 or 317000000.

In addition, the total systemic exposure to pyridine, 5-hexyl-2-methyl- (0.0001 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/26/23.

11.1.3. Reproductive toxicity

The MOE for pyridine, 5-hexyl-2-methyl- is adequate for the reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on pyridine, 5-hexyl-2-methyl-. Read-across material 5-ethyl-2-methylpyridine (CAS # 104-90-5; see Section VI) has sufficient data to support the reproductive toxicity endpoints.

In a GLP- and OECD 421-compliant study, groups of 10 Sprague Dawley rats/sex/dose were administered 5-ethyl-2-methylpyridine via gavage at doses of 0, 30, 95, and 300 mg/kg/day. Females were treated for 15 days pre-mating, throughout the mating period until Day 4 postpartum, and males were treated for 15 days pre-mating until successful littering of the females. Two high-dose males were euthanized in extremis during the study period; these males exhibited ataxia, abnormal respiration, reduced body temperature, prostrate posture, underactivity, reduced/dehydrated gastrointestinal contents, accentuated lobular liver patterns, reduced testes, epididymides, prostate glands and seminal vesicles, and a small mass on 1 epididymis in each male. Microscopic examination of both masses revealed the presence of spermatozoal granuloma. Both deaths were considered to be related to treatment. Bodyweight gains were significantly reduced in males at the high dose. Epididymides and seminal vesicles were significantly reduced in high-dose males, which was considered to be secondary to reduced bodyweight gains. No treatment-related adverse effects were observed on the estrous cycle or reproductive performance. Pup body weights and bodyweight gains were reduced at the high dose. Pups were less viable and in poorer condition at the high dose. Based on reduced testes, epididymides, prostate glands, and seminal vesicles in the 2 decreased males at 300 mg/kg/day, the fertility NOAEL for this study was considered to be 95 mg/kg/day. Based on the poor condition and reduced viability and body weights in pups at 300 mg/kg/day, the developmental toxicity NOAEL for this study was considered to be 95 mg/kg/day (ECHA, 2013).

Therefore, the pyridine, 5-hexyl-2-methyl- MOE for the reproductive toxicity endpoints can be calculated by dividing the 5-ethyl-2-methylpyridine NOAEL in mg/kg/day by the total systemic exposure to pyridine, 5-hexyl-2-methyl-, 95/0.0000001, or 950000000.

In addition, the total systemic exposure to pyridine, 5-hexyl-2-methyl- (0.0001 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/26/23.

11.1.4. Skin sensitization

Based on existing data and the application of DST, pyridine, 5-hexyl-2-methyl- is a sensitizer but 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 pyridine, 5-hexyl-2-methyl- (Table 1). Pyridine, 5-hexyl-2-methyl- is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a guinea pig maximization test, pyridine, 5-hexyl-2-methyl- did lead to skin sensitization reactions (RIFM, 1994). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 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 reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for pyridine, 5-hexyl-2-methyl- 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: 05/07/23.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra for the structurally related analog 2,6-dimethylpyridine (CAS # 108-48-5), pyridine, 5-hexyl-2-methyl- would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photosafety studies or UV absorption spectra available for pyridine, 5-hexyl-2-methyl- in experimental models. UV/Vis absorption spectra on the structurally related material 2,6-dimethylpyridine (CAS # 108-48-5) indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance for the structurally related analog 2,6-dimethylpyridine (CAS # 108-48-5), pyridine, 5-hexyl-2-methyl- does not present a concern for

Table 1
Summary of existing data on pyridine, 5-hexyl-2-methyl-.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA Weighted Mean EC3 Value µg/cm²	GPMT[2]	Buehler
Sensitizer; Human potency category unknown; Current exposure level below the DST for non-reactive materials.	N/A	N/A	N/A	N/A	N/A	Positive	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; GMPT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.
[1]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).
[2]Studies conducted according to the OECD TG 406 are included in the table.

photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were not available for the target material pyridine, 5-hexyl-2-methyl-. UV/Vis absorbance spectra on the structurally related material 2,6-dimethylpyridine (CAS # 108-48-5) indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (0, 27, and 0 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/02/23.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for pyridine, 5-hexyl-2-methyl- 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 pyridine, 5-hexyl-2-methyl-. Based on the Creme RIFM Model, the inhalation exposure is 0.0000006 mg/day. This exposure is 783333 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/01/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of pyridine, 5-hexyl-2-methyl- 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 of 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, pyridine, 5-hexyl-2-methyl- 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 pyridine, 5-hexyl-2-methyl- as possibly being

Table 2
Supported concentrations for pyridine, 5-hexyl-2-methyl- 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 Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049	NRU[d]
2	Products applied to the axillae	0.0015	7.5×10^{-7}
3	Products applied to the face using fingertips	0.029	1.7×10^{-7}
4	Fine fragrance products	0.027	5.7×10^{-6}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070	8.6×10^{-7}
6	Products with oral and lip exposure	0.016	NRU[d]
7	Products applied to the hair with some hand contact	0.056	7.5×10^{-8}
8	Products with significant ano-genital exposure	0.0029	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054	6.3×10^{-7}
10	Household care products with mostly hand contact	0.19	8.3×10^{-7}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	4.2×10^{-5}

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent maximum acceptable concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.
[d] No reported use.

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, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental 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), pyridine, 5-hexyl-2-methyl- presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. Pyridine, 5-hexyl-2-methyl- has been pre-registered for REACH with no additional data at this time.

11.2.2. 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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe	North America
Log K_{ow} Used	4.3	4.3
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined regional values.

Based on available data, the RQ for this material is < 1. No further assessment is necessary.
The RIFM PNEC is 0.002155 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: 04/25/23.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 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://pubchem.ncbi.nlm.nih.gov/source/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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.155			1000000	0.002155	

links listed above were active as of 11/15/23.Structured

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114412.

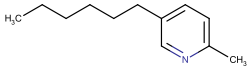
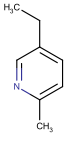
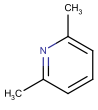
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals Agency read-across assessment framework (ECHA, 2017b).

- 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 (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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Pyridine, 5-hexyl-2-methyl-	5-Ethyl-2-methylpyridine	2,6-Dimethylpyridine
CAS No.	710-40-7	104-90-5	108-48-5
Structure			
Similarity (Tanimoto Score)		0.78	0.38
SMILES	CCCCCCc1ccc(C)nc1	CCc1ccc(C)nc1	Cc1cccc(C)n1

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Endpoint		Repeated dose toxicity Reproductive toxicity	Photoirritation Photoallergenicity
Molecular Formula	$C_{12}H_{19}N$	$C_8H_{11}N$	C_7H_9N
Molecular Weight (g/mol)	177.291	121.183	107.156
Melting Point (°C, EPI Suite)	49.02	−70.90	−6.10
Boiling Point (°C, EPI Suite)	255.82	178.30	144.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.59E+00	1.91E+02	7.53E+02
UV Spectra	Not available	Not available	Minor absorbance between 290 and 700 nm; molar absorption coefficients (0, 27, 0) are below the benchmark (1000 L mol^{-1} • cm^{-1})
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.16E+02	1.20E+04	3.00E+05
Log K_{OW}	4.35	2.39	1.68
J_{max} (μg/cm^2/h, SAM)	33.18	881.80	11481.63
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.59E+00	1.93E+00	1.05E+00
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)	Non-toxicant (good reliability)	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on pyridine, 5-hexyl-2-methyl- (CAS # 710-40-7). 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, 5-ethyl-2-methylpyridine (CAS # 104-90-5) and 2,6-dimethylpyridine (CAS # 108-48-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 5-Ethyl-2-methylpyridine (CAS # 104-90-5) was used as a read-across analog for the target material, pyridine, 5-hexyl-2-methyl- (CAS # 710-40-7), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are pyridines with alkyl substitutuents in the *ortho* and *meta* positions.
  - o The key difference between the target material and the read-across analog is that the target material has a longer alkyl chain attached to pyridine. This structural difference is toxicologically insignificant.
  - 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog have non-binder and non-toxicant alerts. The data described in the repeated dose toxicity and developmental and reproductive toxicity sections confirm that the MOE for the target material is adequate under the current usage. *In silico* alerts are consistent with data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2,6-Dimethylpyridine (CAS # 108-48-5) was used as a read-across analog for the target material, pyridine, 5-hexyl-2-methyl- (CAS # 710-40-7), for the photoirritation and photoallergenicity endpoint.
  - o The target material and the read-across analog are pyridines with alkyl substitutuents.
  - o The key difference between the target material and the read-across analog is that the read-across analog has alkylation in both *ortho* positions, while the target material has alkylation at the *ortho* and *meta* positions. This structural difference is toxicologically insignificant.
  - 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 v4.5, 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, and 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 photoirritation endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with 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 (Cramer et al., 1978).

Q1	A 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? Yes.
Q8	Lactone or cyclic diester? No.
Q10	3-membered heterocycles? No.
Q11	Has a heterocyclic ring with complex substituents? No.
Q12	Heteroaromatic? Yes.
Q13	Does the ring bear any substituents? Yes.
Q14	More than one aromatic ring? No.
Q22	A common component of food? No.
Q30	Aromatic ring with complex substituents? Yes.
Q31	Is the substance an acyclic acetal or ester of substances defined in Q30? No.
Q32	Does it contain only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms, or c) a polyoxyethylene ($n \geq 4$) on the aromatic or aliphatic side chain? Yes.
Class Intermediate (Class II).	

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