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Short Review

RIFM fragrance ingredient safety assessment, 2-ethyl-3-methylpyrazine, CAS Registry Number 15707-23-0



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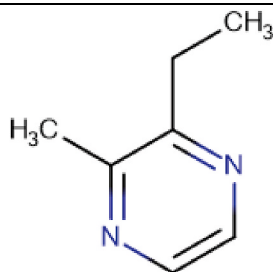
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Name: 2-Ethyl-3-methylpyrazine
CAS Registry Number: 15707-23-0

**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)
Crete RIFM Model - The Crete 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

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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 material has not been fully evaluated for photoallergenicity.

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 photoallergenicity.

2-Ethyl-3-methylpyrazine was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog 2,3,5-trimethylpyrazine (CAS # 14667-55-1) show that 2-ethyl-3-methylpyrazine is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 2-ethyl-3-methylpyrazine is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Data show that there are no safety concerns for 2-ethyl-3-methylpyrazine for skin sensitization under the current declared levels of use. The photoirritation endpoint was evaluated based on data; 2-ethyl-3-methylpyrazine is not expected to be photoirritating. 2-Ethyl-3-methylpyrazine has not been fully evaluated for photoallergenicity. The environmental endpoints were evaluated; 2-Ethyl-3-methylpyrazine 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 expected to be genotoxic. (RIFM, 2017f; RIFM, 2016a, RIFM, 2016b)

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. (RIFM, 2018; RIFM, 2017h; RIFM, 2017g)

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

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

Environmental Safety Assessment

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Hazard Assessment:		
Persistence:		
Critical Measured Value: 7% (OECD 301D)		RIFM (2002)
Bioaccumulation:		
Screening-level: 2.36 L/kg		(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:		
Screening-level: Fish LC50: 422.5 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: 422.5		(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.4225 µg/L		
• Revised PEC/PNECs (2019 IFRA VoU): North America and Europe: Not applicable; cleared at screening-level		

1. Identification

- 1. **Chemical Name:** 2-Ethyl-3-methylpyrazine
- 2. **CAS Registry Number:** 15707-23-0
- 3. **Synonyms:** 3-Ethyl-2-methylpyrazine; Pyrazine, 2-ethyl-3-methyl-; シアルキル(C = 1~4)ピラジン; Methyl ethylpyrazine-2,3; PB-Mischung neu; 2-Ethyl-3-methylpyrazine
- 4. **Molecular Formula:** C₇H₁₀N₂
- 5. **Molecular Weight:** 122.17 g/mol
- 6. **RIFM Number:** 5100
- 7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

- 1. **Boiling Point:** 70 °C at 16 mm Hg (Fragrance Materials Association [FMA]), 189.48 °C (EPI Suite), 171.8 °C (corrected to normal atmospheric pressure of 1013 hPa) (RIFM, 2017a)
- 2. **Flash Point:** 54 °C (Globally Harmonized System), 129 °F; CC (FMA), 62.5 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2017b)
- 3. **Log K_{OW}:** 1.53 (EPI Suite), 1.42 at a pH mean value of 13.4 (RIFM, 2017c)
- 4. **Melting Point:** 17.11 °C (EPI Suite), -33.1 °C (at atmospheric pressure of 997 and 1003 hPa, respectively) (RIFM, 2017a)
- 5. **Water Solubility:** 12020 mg/L (EPI Suite)
- 6. **Specific Gravity:** 0.982 (FMA)
- 7. **Vapor Pressure:** 0.417 mm Hg at 20 °C (EPI Suite v4.0), 1.3 mm Hg at 20 °C (FMA), 0.608 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 (3072, 9531, and 2971 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)
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4. IV.Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1.95th Percentile Concentration in Fine Fragrance: 0.0000094%	RIFM (2020)
2. Inhalation Exposure*: 0.0000066 mg/kg/day or 0.00049 mg/day	RIFM (2020)
3. Total Systemic Exposure**: 0.000037 mg/kg/day	RIFM (2020)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; 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, 2015; Safford, 2015; Safford, 2017; 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: 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:** 2,3,5-Trimethylpyrazine (CAS # 14667-55-1)
- 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: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None

8. Natural occurrence

2-Ethyl-3-methylpyrazine is reported to occur in the following foods by the VCF*:

Allium species	Egg
Beef	Maize (<i>Zea mays</i> L.)
Cashew nut (<i>Anacardium occidentale</i>)	Rye
Chicken	Soybean (<i>Glycine max.</i> L. merr.)
Cocoa category	Tea

*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

Available (ECHA, 2017a); accessed 05/31/22.

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, 2-ethyl-3-methylpyrazine does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Ethyl-3-methylpyrazine was assessed in the BlueScreen 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 on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-ethyl-3-methylpyrazine has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-ethyl-3-methylpyrazine 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, 2017f). Under the conditions of the study, 2-ethyl-3-methylpyrazine was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-ethyl-3-methylpyrazine; however, read-across can be made to 2,3,5-trimethylpyrazine (CAS # 14667-55-1; see Section VI).

The clastogenic activity of 2,3,5-trimethylpyrazine was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2,3,5-trimethylpyrazine in water at concentrations up to 1220 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1220 µg/mL in the presence and absence of metabolic activation. 2,3,5-Trimethylpyrazine 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, 2016b). Under the conditions of the study, 2,3,5-trimethylpyrazine was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-ethyl-3-methylpyrazine.

Based on the available data, 2,3,5-trimethylpyrazine does not present a concern for genotoxic potential, and this can be extended to 2-ethyl-3-methylpyrazine.

Additional References: None

Literature Search and Risk Assessment Completed On: 05/20/22

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-ethyl-3-methylpyrazine or any read-across materials. The total systemic exposure to 2-ethyl-3-methylpyrazine 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 2-ethyl-3-methylpyrazine or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-ethyl-3-methylpyrazine (0.037 µg/kg/day) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material

(9 µg/kg/day; Kroes et al., 2007) at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 03/15/22

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-ethyl-3-methylpyrazine or any read-across materials. The total systemic exposure to 2-ethyl-3-methylpyrazine 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 2-ethyl-3-methylpyrazine or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-ethyl-3-methylpyrazine (0.037 µg/kg/day) is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material (9 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) at the current level of use.

Additional References: None

Literature Search and Risk Assessment Completed On: 03/15/22

11.1.4. Skin sensitization

Based on the existing data, 2-ethyl-3-methylpyrazine presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, 2-ethyl-3-methylpyrazine is not considered a skin sensitizer. The data are summarized in 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). 2-Ethyl-3-methylpyrazine is predicted *in vitro* to be a non-sensitizer when evaluated following the OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021). 2-Ethyl-3-methylpyrazine was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT) (RIFM, 2018; RIFM, 2017h; RIFM, 2017g).

Based on weight of evidence (WoE) from structural analysis and *in vitro* studies, 2-ethyl-3-methylpyrazine does not present a concern for skin sensitization.

Additional References: None

Literature Search and Risk Assessment Completed On: 05/18/22

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vitro* study data, 2-ethyl-3-methylpyrazine would not be expected to present a concern for phototoirritation. 2-Ethyl-3-methylpyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 2-ethyl-3-methylpyrazine.

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), 2-ethyl-3-methylpyrazine was not predicted to have photoirritating effects (RIFM, 2016b). Based on the available *in vitro* study data, 2-ethyl-3-methylpyrazine would not be expected to present a concern for photoirritation. 2-Ethyl-3-methylpyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 2-ethyl-3-methylpyrazine.

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 (3072, 9531, and 2971 L mol⁻¹ • cm⁻¹ under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating

Table 1
Summary of existing data on 2-ethyl-3-methylpyrazine.

WoE Skin Sensitization Potency Category ¹	Human Data				Animal Data		
	NOEL-CNIH (induction) $\mu\text{g}/\text{cm}^2$	NOEL-HMT (induction) $\mu\text{g}/\text{cm}^2$	LOEL ² (induction) $\mu\text{g}/\text{cm}^2$	WoE NESIL ³ $\mu\text{g}/\text{cm}^2$	LLNA Weighted Mean EC3 Value $\mu\text{g}/\text{cm}^2$	GPMT ⁴	Buehler ⁴
No evidence of sensitization ⁶	NA	NA	NA	NA	NA	NA	NA
	<i>In vitro</i> Data ⁵				<i>In silico</i> protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3	Target Material	Autoxidation simulator	Metabolism simulator	
	Negative	Negative	Negative	No alert found	No alert found	No alert found	

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

¹WoE 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).

²Data derived from CNIH or HMT

³WoE NESIL limited to 2 significant figures

⁴Studies conducted according to the OECD TG 406 are included in the table.

⁵Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

⁶Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al. 2015).

effects, 1000 L mol⁻¹ • cm⁻¹ (Henry et al., 2009).
Additional References: None
Literature Search and Risk Assessment Completed On: 04/14/22

11.1.6. Local respiratory toxicity
The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-Ethyl-3-methylpyrazine is below the Cramer Class III TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-Ethyl-3-methylpyrazine. Based on the Creme RIFM Model, the inhalation exposure is 0.00049 mg/day. This exposure is 959.2 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human

lung weight of 650 g; Carthew, 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: 05/19/22

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment
A screening-level risk assessment of 2-ethyl-3-methylpyrazine 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. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-ethyl-3-methylpyrazine 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,

test was conducted according to the OECD 201 method. Under the test conditions and based on nominal concentrations, the 72-h EC50 values for inhibition of both growth rate and yield were >100 mg/L. The 72-h NOEC for inhibition of both growth rate and yield was 10 mg/L.

RIFM, 2017e: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Under the conditions of this study and based on nominal concentrations, the 48-h EC50 and NOEC values were >100 and ≥ 100 mg/L, respectively.

11.2.1.2.3. Other available data. 2-Ethyl-3-methylpyrazine does have been registered for REACH with no additional data at this time.

11.2.1.3. Risk assessment refinement. Since 2-ethyl-3-methylpyrazine has passed the screening criteria (Tier 1), measured data are included for completeness only and have not been used in PNEC derivation.

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>422.5</u>			1000000	0.4225	

2012a) did not identify 2-ethyl-3-methylpyrazine 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, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), 2-ethyl-3-methylpyrazine 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. RIFM, 2002: The ready biodegradability of the test material in an aerobic aqueous medium was evaluated using a closed bottle method according to the OECD 301D guidelines. Biodegradation of 7% was observed after 28 days.

11.2.1.2.2. Ecotoxicity. RIFM, 2017d: An algae growth inhibition

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.53	1.53
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 0.4225 $\mu\text{g/L}$. 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 volumes of use.

Literature Search and Risk Assessment Completed On: 05/17/22

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 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 links listed above were active as of 10/14/22.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2023.114360>.

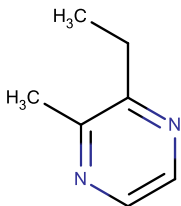
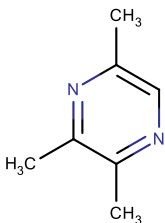
Appendix

Read-across Justification:

Methods

The read-across analog was 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 Chemical Agency read-across assessment framework (ECHA, 2017c).

- 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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 v4.2 (OECD, 2018).
- 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.

Principal Name	Target Material	Read-across Material
	2-Ethyl-3-methylpyrazine	2,3,5-Trimethylpyrazine
CAS No.	15707-23-0	14667-55-1
Structure		
Similarity (Tanimoto Score)		0.64
SMILES	CCc1nccn1C	Cc1cnc(C)c(C)n1
Endpoint		Genotoxicity (Clastogenicity)
Molecular Formula	C ₇ H ₁₀ N ₂	C ₇ H ₁₀ N ₂

(continued on next page)

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

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.

(continued)

Principal Name	Target Material	Read-across Material
	2-Ethyl-3-methylpyrazine	2,3,5-Trimethylpyrazine
Molecular Weight (g/mol)	122.171	122.171
Melting Point (°C, EPI Suite)	17.11	20.23
Boiling Point (°C, EPI Suite)	189.48	171.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	8.11E+01	1.93E+02
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.20E+04	1.52E+04
Log KOW	1.07	0.95
J _{max} (µg/cm ² /h, SAM)	119.05	123.13
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	4.78E-01	3.97E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	H-acceptor-path3-H-acceptor	H-acceptor-path3-H-acceptor
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-ethyl-3-methylpyrazine (CAS # 15707-23-0). 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, 2,3,5-trimethylpyrazine (CAS # 14667-55-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2,3,5-Trimethylpyrazine (CAS # 14667-55-1) was used as a read-across analog for the target material, 2-ethyl-3-methylpyrazine (CAS # 15707-23-0), for the genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to the pyrazine group.
 - o The key difference between the target material and the read-across analog is an additional methyl substituent in the read-across analog and the presence of the ethyl group in the target material. These structural differences are considered 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 v4.2, 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 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. 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. Common component of food? Yes, Class Intermediate (Class II)

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