Food and Chemical Toxicology 182 (2023) 114247

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 2-methoxy-3-methylpyrazine, CAS Registry Number 2847-30-5

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], J. Muldoon [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Expert Panel for Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Expert Panel for Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[k] *Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

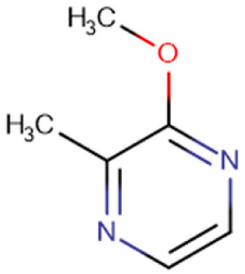
ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

https://doi.org/10.1016/j.fct.2023.114247
Received 15 February 2023; Received in revised form 7 November 2023; Accepted 20 November 2023
Available online 26 November 2023

Version: 021023. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.



Name: 2-Methoxy-3-methylpyrazine
CAS Registry Number: 2847-30-5
Additional CAS Numbers:
63450-30-6 Methoxymethylpyrazine
68378-13-2 2,5 or 6-Methoxy-3-methylpyrazine (mixture of isomers)
25680-58-4 Pyrazine, 2-ethyl-3-methoxy-

Abbreviation/Definition List:

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

(*continued on next column*)

(*continued*)

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

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

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

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

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

2-Methoxy-3-methylpyrazine was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-methoxy-3-(1-methylpropyl)pyrazine (CAS # 24168-70-5) show that 2-methoxy-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 III material, and the exposure to 2-methoxy-3-methylpyrazine is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The photoirritation endpoint was evaluated based on data; 2-methoxy-3-methylpyrazine is not expected to be photoirritating. 2-Methoxy-3-methylpyrazine has not been evaluated for photoallergenic potential. The environmental endpoints were evaluated; 2-methoxy-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 (VoU) 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, 1983; RIFM, 2014b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Photoirritation/Photoallergenicity: Not photoirritating. Photoallergy has not been evaluated. RIFM (2017)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.79 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 3.05 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 495 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: 495 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.495 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

Chemical Name: 2-Methoxy-3-methylpyrazine **CAS Registry Number:** 2847-30-5 **Synonyms:** Pyrazine, 2-methoxy-3-methyl-; 2-Methoxy-3-methylpyrazine **Molecular Formula:** $C_6H_8N_2O$ **Molecular Weight:** 124.14 g/mol **RIFM Number:** 5286 **Stereochemistry:** No stereocenter present and no stereoisomer possible.	**Chemical Name**: Methoxymethylpyrazine **CAS Registry Number:** 63450-30-6 **Synonyms:** Pyrazine, methoxymethyl-; Methoxymethylpyrazine **Molecular Formula:** $C_6H_8N_2O$ **Molecular Weight:** 124.14 g/mol **RIFM Number:** 7222 **Stereochemistry:** No stereocenter present and no stereoisomer possible.
Chemical Name: 2,5 or 6-Methoxy-3-methylpyrazine (mixture of isomers) **CAS Registry Number:** 68378-13-2 **Synonyms:** 2,5 or 6-Methoxy-3-methyl-pyrazine (mixture of isomers); methoxy methyl pyrazine; methyl methoxy pyrazine **Molecular Formula:** $C_6H_8N_2O$ **Molecular Weight:** 124.14 g/mol **RIFM Number:** 6832 **Stereochemistry:** No stereocenter present and no stereoisomer possible.	**Chemical Name**: Pyrazine, 2-ethyl-3-methoxy- **CAS Registry Number:** 25680-58-4 **Synonyms:** Pyrazine, 2-ethyl-3-methoxy- **Molecular Formula:** $C_7H_{10}N_2O$ **Molecular Weight:** 138.17 g/mol **RIFM Number:** 6955 **Stereochemistry:** No stereocenter present and no stereoisomer possible.

1.1. Physical data

CAS # 2847–30–5 **Boiling Point:** 190.27 °C (EPI Suite v4.11) **Flash Point:** 56 °C (Globally Harmonized System [GHS]) **Log K_{OW}:** 1.46 (EPI Suite v4.11) **Melting Point**: 20.19 °C (EPI Suite v4.11) **Water Solubility:** 8457 mg/L (EPI Suite v4.11) **Specific Gravity:** Not Available **Vapor Pressure:** 0.401 mm Hg at 20 °C (EPI Suite v4.0), 0.584 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** Significant absorbance between 290 and 700 nm, with distinct peaks at 290 nm and returning to the baseline by 350 nm. Maximum molar absorption coefficients within this range (3656, 4420, and 3821 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not available	**CAS # 63450–30–6** **Boiling Point:** 190.28 °C **Flash Point:** Not available **Log K_{OW}:** 0.28 (EPI Suite v4.11) **Melting Point**: 23.61 °C (EPI Suite v4.11) **Water Solubility:** 167300 mg/L (EPI Suite v4.11) **Specific Gravity:** Not available **Vapor Pressure:** 0.401 mm Hg at 20 °C (EPI Suite v4.0), 0.584 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** Not available **Appearance/Organoleptic:** Not available
CAS # 68378–13–2 **Boiling Point:** 190.27 °C (EPI Suite v4.11) **Flash Point:** 56 °C (GHS) **Log K_{OW}:** 1.46 (EPI Suite v4.11) **Melting Point**: 20.19 °C (EPI Suite v4.11) **Water Solubility:** 8457 mg/L (EPI Suite v4.11) **Specific Gravity:** Not Available **Vapor Pressure:** 0.401 mm Hg at 20 °C (EPI Suite v4.0), 0.584 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** Significant absorbance between 290 and 700 nm, with distinct peaks at 291 nm (under neutral and basic conditions) and 298 nm (under acidic conditions) and returning to the baseline by 350 nm. Maximum molar absorption coefficients within this	**CAS # 25680–58–4** **Boiling Point:** 210.16 °C **Flash Point:** Not available **Log K_{OW}:** 1.95 (EPI Suite v4.11) **Melting Point**: 31.72 °C (EPI Suite v4.11) **Water Solubility:** 2474 mg/L (EPI Suite v4.11) **Specific Gravity:** Not available **Vapor Pressure:** 0.105 mm Hg at 20 °C (EPI Suite v4.0), 0.174 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** Significant absorbance between 290 and 700 nm, with distinct peaks at 290 nm (under neutral and acidic conditions) and returning to the baseline by 350 nm. Maximum molar absorption coefficients within this range (3729 and 4357 L mol^{-1} • cm^{-1} under

(*continued on next column*)

(*continued*)

range (3992, 5411, and 3921 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Not available	neutral and acidic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1}). No absorbance between 290 and 700 nm under basic conditions **Appearance/Organoleptic:** Not available

2. Volume of use (Worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0018% (RIFM, 2020)
2. **Inhalation Exposure**:** 0.000011 mg/kg/day or 0.00077 mg/day (RIFM, 2020)
3. **Total Systemic Exposure***:** 0.000099 mg/kg/day (RIFM, 2020)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**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; 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; Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. **Analogs Selected**:

a. **Genotoxicity:** 2-Methoxy-3-(1-methylpropyl)pyrazine (CAS # 24168-70-5)
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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

7. Natural occurrence

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

Krill.

Sherry.

Pyrazine, 2-ethyl-3-methoxy- is reported to occur in the following foods by the VCF:

Sherry.

Methoxymethylpyrazine and 2,5 or 6-methoxy-3-methylpyrazine (mixture of isomers) are not reported to occur in foods by the VCF.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. Reach dossier

All 4 materials have been pre-registered for 2010; no dossiers available as of 02/10/23.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-methoxy-3-methylpyrazine does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2-Methoxy-3-methylpyrazine was assessed in the BlueScreen assay and found negative for genotoxicity without metabolic activation and positive for genotoxicity with metabolic activation. These positive results were observed at cytotoxic concentrations that were within the acceptable range for the BlueScreen assay (positive: <80% relative cell density) (RIFM, 2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). While the BlueScreen assay on the target material showed positive results, data from additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of 2-methoxy-3-methylpyrazine; however, read-across can be made to 2-methoxy-3-(1-methylpropyl)pyrazine (CAS # 24168-70-5; see Section VI).

The mutagenic activity of 2-methoxy-3-(1-methylpropyl)pyrazine has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 2-methoxy-3-(1-methylpropyl)pyrazine in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. Slight increases in the mean number of revertant colonies were observed in strains TA1535 and TA1537 in the presence or absence of S9 (RIFM, 1983). However, the increases are not statistically significant. Under the conditions of the study, 2-methoxy-3-(1-methylpropyl)pyrazine was not mutagenic in the Ames test, and this can be extended to 2-methoxy-3-methylpyrazine.

The clastogenic activity of 2-methoxy-3-(1-methylpropyl)pyrazine 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-methoxy-3-(1-methylpropyl)pyrazine in DMSO at concentrations up to 1660 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 500 μg/mL in the presence and absence of metabolic activation. 2-Methoxy-3-(1-methylpropyl)pyrazine did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, 2-methoxy-3-(1-methylpropyl)pyrazine was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-methoxy-3-methylpyrazine.

Based on the data available, 2-methoxy-3-(1-methylpropyl)pyrazine does not present a concern for genotoxic potential, and this can be extended to 2-methoxy-3-methylpyrazine.

Additional References: None.

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

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-methoxy-3-methylpyrazine or any read-across materials. The total systemic exposure to 2-methoxy-3-methylpyrazine is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-methoxy-3-methylpyrazine or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-methoxy-3-methylpyrazine (0.099 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/21/22.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-methoxy-3-methylpyrazine or any read-across materials. The total systemic exposure to 2-methoxy-3-methylpyrazine is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-methoxy-3-methylpyrazine or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-methoxy-3-methylpyrazine (0.099 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/21/22.

10.1.4. Skin sensitization

Based on existing data and the application of DST, 2-methoxy-3-methylpyrazine does not present a safety concern for skin sensitization under the current declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization data are available for 2-methoxy-3-methylpyrazine; see table below (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 v4.5). 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 2 provides the supported concentrations for 2-methoxy-3--methylpyrazine that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent supported concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

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

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

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction) μg/cm^2	WoE NESIL[3] μg/cm^2	LLNA[4] Weighted Mean EC3 Value μg/cm^2	GPMT[5]	Buehler[5]
Human potency category unknown; Current exposure level below the DST for non-reactive materials.	NA	NA	NA	NA	NA	NA	NA
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		No alert found	No alert found	Schiff base formation

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = 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]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Table 2
Supported concentrations for 2-methoxy-3-methylpyrazine that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069	7.1×10^{-5}
2	Products applied to the axillae	0.021	0.0043
3	Products applied to the face using fingertips	0.41	0.0013
4	Fine fragrance products	0.39	0.0018
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	0.0043
6	Products with oral and lip exposure	0.23	1.4×10^{-5}
7	Products applied to the hair with some hand contact	0.79	5.3×10^{-5}
8	Products with significant ano-genital exposure	0.041	No Data[d]
9	Products with body and hand exposure, primarily rinse-off	0.75	0.0021
10	Household care products with mostly hand contact	2.7	0.0014
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data[d]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.031

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

10.1.5. Photoirritation/photoallergenicity

Based on *in vitro* study data, 2-methoxy-3-methylpyrazine does not present a concern for photoirritation. 2-methoxy-3-methylpyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 2-methoxy-3-methylpyrazine.

10.1.5.1. Risk assessment. UV/Vis absorbance spectra indicate significant absorbance in the range of 290–700 nm, with distinct peaks at 290 nm and returning to the baseline by 350 nm. Molar absorption coefficients are above the benchmark of concern for photoirritation/photoallergenicity (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red Uptake photoirritation assay (OECD 432), 2-methoxy-3-methylpyrazine was not predicted to have photoirritating potential according to the prediction model presented in the test guidelines (RIFM, 2017). Based on available *in vitro* study data, 2-methoxy-3-methylpyrazine does not present a concern for photoirritation. 2-Methoxy-3-methylpyrazine was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of fragrance materials.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were generated for 2-methoxy-3-methylpyrazine. The spectra demonstrate significant absorbance between 290 and 700 nm, with distinct peaks at 290 nm and returning to the baseline by 350 nm. Molar absorption coefficients (3656, 4420, and 3821 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/30/22.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-methoxy-3-methylpyrazine is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-methoxy-3-methylpyrazine. Based on the Creme RIFM Model, the inhalation exposure is 0.00077 mg/day. This exposure is 610.4 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/22.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methoxy-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. 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, 2-methoxy-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, 2012a) did not identify 2-methoxy-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, 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 ≥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).

10.2.1.1. Risk assessment. Based on the current VoU (2019), 2-methoxy-3-methylpyrazine does not a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies. ***Biodegradation***:

No data available.

Ecotoxicity:

No data available.

10.2.1.3. Other available data. 2-Methoxy-3-methylpyrazine has been pre-registered for REACH with no additional data at this time.

10.2.2. 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 Framework: Salvito et al., 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.46	1.46
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1*	<1*
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined volumes for CAS # 2847-30-5 and CAS # 63450-30-6.

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

The RIFM PNEC is 0.495 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/30/22.

11. 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/
- **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 02/10/23.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	495			1000000	0.495	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114247.

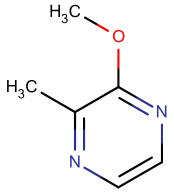
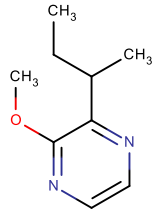
Appendix

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, 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 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 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
Principal Name	2-Methoxy-3-methylpyrazine	2-Methoxy-3-(1-methylpropyl)pyrazine
CAS No.	2847-30-5	24168-70-5
Structure		
Similarity (Tanimoto Score)		0.65
Endpoint		Genotoxicity
Molecular Formula	$C_6H_8N_2O$	$C_9H_{14}N_2O$
Molecular Weight (g/mol)	124.14	166.22
Melting Point (°C, EPI Suite)	20.19	45.12
Boiling Point (°C, EPI Suite)	190.27	236.45
Vapor Pressure (Pa @ 25°C, EPI Suite)	77.86	4.64
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	8457.00	229.60
Log K_{OW}	1.24	2.86
J_{max} (μg/cm^2/h, SAM)	105.59	12.10
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	0.18	0.41
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	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)**	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-methoxy-3-methylpyrazine (CAS # 2847-30-5). Hence, *in silico* evaluation was conducted to determine read-across analogs. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, 2-methoxy-3-(1-methylpropyl)pyrazine (CAS # 24168-70-5) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- 2-Methoxy-3-(1-methylpropyl)pyrazine (CAS # 24168-70-5) was used as a read-across analog for the target material, 2-methoxy-3-methylpyrazine (CAS # 2847-30-5), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to the class of pyrazines.
  - o The key difference between the target material and read-across analog is that the target material has a methyl group at the 3rd position while the read-across analog has a methylpropyl group at the 3rd position. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - 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 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82 (Suppl. l), S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 32, 248–260. Apr.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718, 2020.

ECHA, 2017a. Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2021. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of 2-Methoxy-3-(1-Methylpropyl) pyrazine. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 45733.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Report on the Testing of 2-Methoxy-3-Methylpyrazine in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 66846. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. 2-Methoxy-3-(1-methylpropyl)pyrazine: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM Report Number 68492. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 2-Methoxy-3-methylpyrazine: Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts. RIFM Report Number 71506. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Exposure Survey 28. August 2020.

Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.

Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.
Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23, 2022.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.