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RIFM fragrance ingredient safety assessment, methyl phenethyl ether, CAS Registry Number 3558-60-9

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Name: Methyl phenethyl ether

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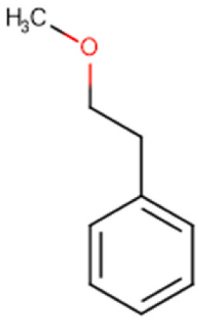

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly

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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.

Methyl phenethyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl phenethyl ether is not 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 methyl phenethyl ether is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). Data from read-across analog (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) show that there are no safety concerns for methyl phenethyl ether for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl phenethyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl phenethyl ether was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 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 under the current, declared levels of use. RIFM (1995)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 45% (OECD 301 D) (ECHA REACH Dossier: Methyl phenethyl ether; ECHA, 2013)

Bioaccumulation:
Screening-level: 14.52 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: 96-h Algae EC50: 30.975 mg/L (ECOSAR; US EPA, 2012b)
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: 96-h Algae EC50: 30.975 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 3.0975 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Methyl phenethyl ether
2. **CAS Registry Number:** 3558-60-9
3. **Synonyms:** Benzene, (2-methoxyethyl)-; (2-Methoxyethyl)benzene; Phenylethyl methyl ether; Pandanol; Methyl phenethyl ether
4. **Molecular Formula:** $C_9H_{12}O$
5. **Molecular Weight:** 136.19
6. **RIFM Number:** 992
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 187 °C (Fragrance Materials Association [FMA]), 191.55 °C (EPI Suite)
2. **Flash Point:** 57 °C (Globally Harmonized System), 150 °F; CC (FMA)
3. **Log K_{OW}:** 2.27 (EPI Suite)
4. **Melting Point**: 17.57 °C (EPI Suite)
5. **Water Solubility:** 1008 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.376 mm Hg at 20 °C (EPI Suite v4.0), 0.5 mm Hg at 20 °C (FMA), 0.549 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless mobile liquid with a powerful, dissuasive, and penetrating odor with a warm floral note (Arctander, 1969)

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.042% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.010 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2020b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High* (Expert Judgment)

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

*See Appendix below.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** (3-Methoxy-2-methylpropyl)benzene (CAS # 120811-92-9)
   e. **Phototoxicity/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

Methyl phenethyl ether is reported to occur in the following foods by the VCF*:

Litchi (*Litchi chinensis* Sonn.)

Mentha oils.

*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; accessed 12/21/20 (ECHA, 2013).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, methyl phenethyl ether does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Methyl phenethyl ether 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, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of methyl phenethyl ether 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 methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with methyl phenethyl ether 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, 2016a). Under the conditions of the study, methyl phenethyl ether was not mutagenic in the Ames test.

The clastogenic activity of methyl phenethyl ether 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 methyl phenethyl ether in DMSO at concentrations up to 1362 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1362 μg/mL in the presence and absence of metabolic activation. Methyl phenethyl ether did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, methyl phenethyl ether was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, methyl phenethyl ether does not present

a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/10/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl phenethyl ether or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl phenethyl ether (1.3 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 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: 01/06/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl phenethyl ether or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl phenethyl ether (1.3 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 01/14/21.

11.1.4. Skin sensitization

Based on the existing data and the read-across material (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9), methyl phenethyl ether does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available on methyl phenethyl ether. Therefore, data on the read-across material (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9; see section VI) were considered in addition to the existing data on the target material. Based on the chemical structure, both methyl phenethyl ether and (3-methoxy-2-methylpropyl)benzene are not predicted to react with skin proteins directly *in silico* (Toxtree v3.1.0; OECD Toolbox v4.2). The existing data on methyl phenethyl ether include an open epicutaneous test (OET) in guinea pigs and 2 confirmatory human studies. In the OET with methyl phenethyl ether, no sensitization reactions were reported (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed in 24 subjects when 5520 μg/cm2 methyl phenethyl ether in petrolatum was used (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 775 μg/cm2 of methyl phenethyl ether in SDA39C, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1972). In a guinea pig maximization test, the read-across material (3-methoxy-2-methylpropyl)benzene did not lead to skin sensitization reactions when 100% was used for topical induction and challenge (RIFM, 1995).

Based on the weight of evidence (WoE) from structural analysis as well as animal and human studies on the target material and the read-across material, methyl phenethyl ether does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1971; ECETOC, 2003.

Literature Search and Risk Assessment Completed On: 01/21/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl phenethyl ether would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for methyl phenethyl ether in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, methyl phenethyl ether does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level for methyl phenethyl ether 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 methyl phenethyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.010 mg/day. This exposure is 47 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/08/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl phenethyl ether was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, methyl phenethyl ether was identified as a fragrance material with the 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) identified methyl phenethyl ether as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl phenethyl ether presents a risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

Methyl phenethyl ether has been registered for REACH with the following additional information available at this time (ECHA, 2013):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D guideline. Biodegradation of 45.12% was observed after 42 days.

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301 B guideline. Biodegradation of 50.36% was observed after 28 days.

The acute fish (*Danio rerio*) toxicity test was conducted according to the OECD 203 guideline under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be $>$ 50 mg/L.

The acute fish (*Cyprinus carpio*) toxicity test was conducted according to the OECD 203 guideline under static conditions. The 96-h LC50 value based on nominal test concentration was reported to be $>$ 100 mg/L.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on nominal test concentration was reported to be $>$ 100 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 values based on nominal test concentration for growth rate and biomass were reported to be 70 mg/L and 42.3 mg/L, respectively.

11.2.4.1. Risk assessment refinement. Since methyl phenethyl ether has passed the screening criteria (Tier II), measured data is included for completeness only and has not been used in PNEC derivation.

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, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.27	2.27
Biodegradation Factor Used	0.1	0.1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 3.0975 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: 01/11/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission

RIFM Framework Screening-level **(Tier 1)**	107			1000000	0.107	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	64.559	37.568	30.975	10000	3.0975	Neutral Organics

- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/31/21.

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.2021.112718.

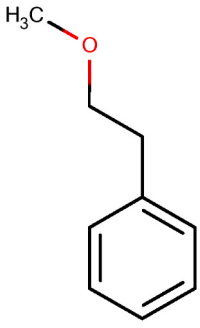
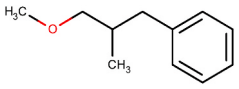
Appendix

Read-across Justification

Methods

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

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

	Target Material	Read-across Material
Principal Name	Methyl phenethyl ether	(3-Methoxy-2-methylpropyl)benzene
CAS No.	3558-60-9	120811-92-9
Structure		
Similarity (Tanimoto Score)		0.50
Endpoint		Skin Sensitization
Molecular Formula	$C_9H_{12}O$	$C_{11}H_{16}O$
Molecular Weight	136.19	164.25
Melting Point (°C, EPI Suite)	−17.57	−5.78

(*continued on next page*)

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	Target Material	Read-across Material
Boiling Point (°C, EPI Suite)	191.55	219.02
Vapor Pressure (Pa @ 25°C, EPI Suite)	73.19	18.40
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1008.00	127.30
Log K_{OW}	2.27	3.17
J_{max} (μg/cm^2/h, SAM)	46.08	10.06
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.36	16.52
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.
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 methyl phenethyl ether (CAS # 3558-60-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusion

- (3-Methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was used as a read-across analog for the target material methyl phenethyl ether (CAS # 3558-60-9) for skin sensitization.
  - o The target material and the read-across analog belong to the structural class of ethers.
  - o The key difference between the target material and the read-across analog is that the target material has a phenylethyl group in the ether functionality, whereas the read-across analog has a methyl-substituted phenylpropyl group in the ether functionality. This structure difference between the target material and the read-across analog does not affect consideration of the toxic endpoint.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for toxicity 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.

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? No.
Q16 Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17 Readily hydrolyzed to a common terpene? No.
Q19 Open chain? No.
Q23 Aromatic? No.
Q27 Rings with substituents? No.
Q28 More than one aromatic ring? No.
Q30 Aromatic ring with complex substituents? No.
Q31 Is the substance an acyclic acetal or ester of substances defined in Q30? No.
Q32 It contains 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>=4) on the aromatic or aliphatic side chain? No.
Q22 A common component of food? No.
Q33 Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No. Class High (Class III)

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