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Short review

RIFM fragrance ingredient safety assessment, 1-methyl-3-methoxy-4-isopropylbenzene, CAS Registry Number 1076-56-8

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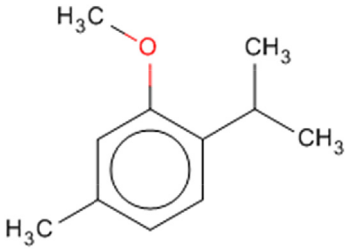


Abbreviation list:
2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015, 2017) compared to a deterministic aggregate approach.
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable 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
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
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
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 - Ultra Violet/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 under the limits described in this safety assessment.

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

Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

The material (1-methyl-3-methoxy-4-isopropylbenzene) was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog 4-isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3) show that 1-methyl-3-methoxy-4-isopropylbenzene is not genotoxic. Data from the read across analog *p*-methylanisole (CAS # 104-93-8) show that 1-methyl-3-methoxy-4-isopropylbenzene does not present a concern for skin sensitization. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03, 0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated and the material was not found to be PBT as per IFRA environmental standards; the material was cleared at the screening level (PEC/PNEC North America and Europe <1).

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2016a,b)
Repeated Dose Toxicity: No NOAEL available.	Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available.	Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization.	(ECHA Dossier: 4-methylanisole; Klecak, 1985; Klecak, 1979)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available.	Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening Level: 2.62 (Biowin 3)	(EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 227.6 l/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 3.435 mg/l	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 3.435 mg/l	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.003435 μg/l	

- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; cleared at screening level

1. Identification

1. **Chemical Name:** 1-Methyl-3-methoxy-4-isopropylbenzene
2. **CAS Registry Number:** 1076-56-8
3. **Synonyms:** Benzene, 2-methoxy-4-methyl-1-(1-methylethyl)-; 2-Isopropyl-5-methylanisole; 3-Methoxy-*para*-cymene; 1-Methyl-3-methoxy-4-isopropylbenzene; Thymol methylether; 1-Isopropyl-2-methoxy-4-methylbenzene; Methyl thymol
4. **Molecular Formula:** $C_{11}H_{16}O$
5. **Molecular Weight:** 164.25
6. **RIFM Number:** 6265

2. Physical data

1. **Boiling Point:** 219 °C [EPI Suite]
2. **Flash Point:** 197.00 °F. TCC (91.67 °C)*
3. **Log K_{OW}:** 4.08 [EPI Suite]
4. **Melting Point**: 6.74 °C [EPI Suite]
5. **Water Solubility:** 21.57 mg/L [EPI Suite]
6. **Specific Gravity:** 0.93600 to 0.94000 @ 25.00 °C*
7. **Vapor Pressure:** 0.0911 mmHg @ 20 °C [EPI Suite 4.0], 0.138 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Arctander Volume II 1969: Colorless oily liquid. Practically insoluble in water, soluble in alcohol and oils. Warm spicy rooty, herbaceous odor with practically no trace of medicinal or "phenolic" notes, but rather a dry-leafy character. The odor of this material is rather pleasant but lacks character and the type of odor is not frequently wanted in perfumery.

*http://www.thegoodscentscompany.com/data/rw1036161.html#tophyp, retrieved 10/21/2015.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00033% (RIFM, 2016a,b)
3. **Inhalation Exposure*:** 0.0000018 mg/kg/day or 0.00013 mg/day (RIFM, 2016a,b)
4. **Total Systemic Exposure**:** 0.000012 mg/kg/day (RIFM, 2016a,b)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015 and Safford et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015 and Safford 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 I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** 4-Isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** *p*-Methylanisole (CAS# 104-93-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. Natural occurrence (discrete chemical) or Composition (NCS)

1-Methyl-3-methoxy-4-isopropylbenzene is reported to occur in the following foods* and in some natural complex substances (NCS):

Chamomile	Mastic (*Pistacia lentiscus*)
Citrus fruits	Passion fruit (*Passiflora* species)
Cloves (*Eugenia caryophyllata Thunberg*)	Sweet marjoram (*Origanum majorana* L.)
Ginger (*Zingiber* species)	Thyme (*Thymus* species)
Macadamia nut (*Macadamia integrifolia*)	Wild marjoram (*Origanum vulgare* L.)

*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 07/05/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, 1-methyl-3-methoxy-4-isopropylbenzene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment.
1-Methyl-3-methoxy-4-isopropylbenzene was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of 1-methyl-3-methoxy-4-isopropylbenzene, however, read across can be made to 4-isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3; see Section 5). The mutagenic activity of 4-isopropyl-2-methoxy-1-methylbenzene 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 *Escherichia coli* strain WP2uvrA were treated with 4-isopropyl-2-methoxy-1-methylbenzene in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any dose tested in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, 4-isopropyl-2-methoxy-1-methylbenzene was not mutagenic in the Ames test and this can be extended to 1-methyl-3-methoxy-4-isopropylbenzene.

There are no studies assessing the clastogenic activity of 1-methyl-3-methoxy-4-isopropylbenzene however, read across can be made to 4-isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3; see Section 5). The clastogenic activity of 4-isopropyl-2-methoxy-1-methylbenzene 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 4-isopropyl-2-methoxy-1-methylbenzene in solvent DMSO (dimethyl sulfoxide) at concentrations up to 2000 μg/ml in the presence and absence of metabolic activation (S9) for 4 and 24 h 4-Isopropyl-2-methoxy-1-methylbenzene did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016b). Under the conditions of the study, 4-isopropyl-2-methoxy-1-methylbenzene was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to 1-methyl-3-methoxy-4-isopropylbenzene.

Based on the data available, 4-isopropyl-2-methoxy-1-methylbenzene does not present a concern for genotoxicity and this can be extended to 1-methyl-3-methoxy-4-isopropylbenzene.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/16/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1-methyl-3-methoxy-4-isopropylbenzene or any read across materials. The total systemic exposure to 1-methyl-3-methoxy-4-isopropylbenzene is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1-methyl-3-methoxy-4-isopropylbenzene or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1-methyl-3-methoxy-4-isopropylbenzene (0.012 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/22/2017.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 1-methyl-3-methoxy-4-isopropylbenzene or any read across materials. The total systemic exposure to 1-methyl-3-methoxy-4-isopropylbenzene is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 1-methyl-3-methoxy-4-isopropylbenzene or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to 1-methyl-3-methoxy-4-isopropylbenzene (0.012 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints for a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/22/2017.

10.1.4. Skin sensitization

Based on read across to *p*-methylanisole (CAS # 104-93-8), 1-methyl-3-methoxy-4-isopropylbenzene does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on read across to *p*-methylanisole (CAS # 104-93-8), 1-methyl-3-methoxy-4-isopropylbenzene does not present a concern for skin sensitization. The chemical structures for these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), *p*-methylanisole was found to be non-sensitizing up to 50% (ECHA Dossier: 4-methylanisole). In a guinea pig open epicutaneous test, *p*-methylanisole did not present reactions indicative of sensitization (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed when 2% or 1380 μg/cm2 p-methylanisole in petrolatum was used for induction and challenge. (RIFM, 1971). Based on the weight of evidence from structural analysis, animal and human studies, *p*-methylanisole does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/23/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 1-methyl-3-methoxy-4-isopropylbenzene would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 1-methyl-3-methoxy-4-isopropylbenzene in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 1-methyl-

3-methoxy-4-isopropylbenzene does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/28/2017.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The material, 1-methyl-3-methoxy-4-isopropylbenzene, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1-methyl-3-methoxy-4-isopropylbenzene. Based on the Creme RIFM model, the inhalation exposure is 0.00013 mg/day. This exposure is 10 769 times lower than the Cramer Class I TTC value of 1.4 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: 12/16/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 1-methyl-3-methoxy-4-isopropylbenzene was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 1-methyl-3-methoxy-4-isopropylbenzene 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 EPISUITE v4.1 identified 1-methyl-3-methoxy-4-isopropylbenzene as possibly persistent but not bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.1.1. Risk assessment. Based on the current Volume of Use (2011), 1-methyl-3-methoxy-4-isopropylbenzene does not present a risk to the aquatic compartment in the screening level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.1.2. Other available data.

1-Methyl-3-methoxy-4-isopropylbenzene has been pre-registered for REACH with no additional data at this time.

10.2.1.3. 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	3.435 mg/L			1,000,000	0.003435 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.08	4.08
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.003435 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at screening level and, therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 03/20/2017.

11. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS

- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr/)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.08.042.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.08.042.

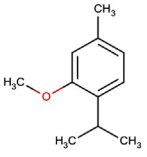
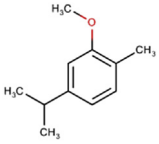
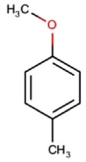
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015) and is consistent with the guidance provided by OECD on the reporting of defined approached used within Integrated Approaches for Testing and Assessment or IATA (OECD, 2015) and the European Chemical Agency (ECHA) read across assessment framework or RAAF (ECHA, 2016).

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, the appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), and the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v2.1.7 and 2.1.6, respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material	Read across material
Principal Name	1-Methyl-3-methoxy-4-isopropylbenzene	4-Isopropyl-2-methoxy-1-methylbenzene	*p*-Methylanisole
CAS No.	1076-56-8	6379-73-3	104-93-8
Structure			
Similarity (Tanimoto score)		0.92	0.62
Read across endpoint		• Genotoxicity	• Skin sensitization
Molecular Formula	$C_{11}H_{16}O$	$C_{11}H_{16}O$	$C_8H_{10}O$
Molecular Weight	164.25	164.25	122.17
Melting Point (°C, EPISUITE)	6.74	6.74	−23.00
Boiling Point (°C, EPISUITE)	219.00	219.00	170.8
Vapor Pressure (Pa @ 25 °C, EPISUITE)	18.4	18.4	160
Log Kow (KOWWIN v1.68 in EPISUITE)	4.08	4.08	2.66
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	21.57	21.57	527.1
J_{max} (mg/cm^2/h, SAM)	25.297	25.251	177.912
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	6.84E-004	6.84E-004	3.52E-004
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-Carcinogen (low reliability)	• Non-Carcinogen (moderate reliability)	

(*continued*)

	Target material	Read across material	Read across material
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Skin Sensitization			
Protein binding by OASIS v1.4	• No alert found		• No alert found
Protein binding by OECD	• No alert found		• No alert found
Protein binding potency	• Not possible to classify		• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found		• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)		• Sensitizer (good reliability)
Metabolism			
OECD QSAR Toolbox (3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3
Rat liver S9 metabolism simulator and structural alerts for metabolites			

Summary

There are insufficient toxicity data on the target material, 1-methyl-3-methoxy-4-isopropylbenzene (CAS # 1076-56-8). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, 4-isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3) and *p*-methylanisole (CAS # 104-93-8) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- For target material, 1-methyl-3-methoxy-4-isopropylbenzene (CAS # 1076-56-8), 4-isopropyl-2-methoxy-1-methylbenzene (CAS # 6379-73-3) was used as a read across analog for the genotoxicity endpoint and *p*-methylanisole (CAS # 104-93-8) was used as a read across analog for the skin senzitization endpoint.
  - The target material and the read across analogs are structurally similar and belong to the structural class of alkyl substituted anisoles.
  - The target material and the read across analogs share an anisole substructure.
  - The key difference between the target material and the read across analogs are that the target has an isopropyl substitution at the ortho-position, while the read across analog 4-isopropyl-2-methoxy-1-methylbenzene has an isopropyl substitution at the meta-position, and read across analog *p*-methylanisole has a methyl substitution at the para-position of the anisole structure. The structural differences between the target material and the read across analogs do not affect consideration of toxicological endpoints.
  - Similarity between the target material and the read across analogs are indicated by the Tanimoto scores in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of toxicological endpoints.
  - The physical chemical properties of the target material and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target material and the read across analogs.
  - The target material and the read across analog, *p*-methylanisole (CAS # 104-93-8), are predicted to be sensitizers by the CAESAR model for skin sensitization. No other protein binding alerts for the skin sensitization endpoint are found. Data described in the skin sensitization section shows that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the prediction is superseded by the availability of the data.
  - The target material and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

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