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RIFM fragrance ingredient safety assessment, phenylethyl isoamyl ether, CAS Registry Number 56011-02-0

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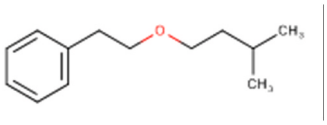

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Name: Phenylethyl isoamyl ether CAS Registry Number: 56011-02-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
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 et al., 2015), which should be referred to for clarifications.

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

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

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

Phenylethyl isoamyl ether was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenylethyl isoamyl ether is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to phenylethyl isoamyl ether is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). Based on the existing data and read-across (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9), phenylethyl isoamyl ether presents no concern for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were completed based on ultraviolet/visible (UV/Vis) spectra. The environmental endpoints were evaluated; phenylethyl isoamyl 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.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2014a; 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 current, declared levels of use.	RIFM (1995a)
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: 76% (OECD 301F)	RIFM (1999a)
Bioaccumulation: Screening-level: 256 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 1.265 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 et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 1.265 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1265 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** Phenylethyl isoamyl ether
2. **CAS Registry Number:** 56011-02-0
3. **Synonyms:** Anther; Benzene, (2-(3-methylbutoxy)ethyl)-; Isopentyl phenethyl ether; ﾌｪﾈﾁﾙｱﾐﾙｴｰﾃﾙ; [2-(3-Methylbutoxy)ethyl]benzene; Isoamyl phenethyl ether; Phenethyl isoamyl ether; 2-Phenylethyl isoamyl ether; [2-(3-Methylbutoxy)ethyl] benzene; Phenylethyl isoamyl ether
4. **Molecular Formula:** $C_{13}H_{20}O$
5. **Molecular Weight:** 192.3
6. **RIFM Number:** 1119
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 255.27 °C (EPI Suite), 244 °C (517 K) (RIFM, 2016b)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (Fragrance Materials Association [FMA]), 117.5 °C (mean rounded off to the nearest 0.5 °C) (RIFM, 2016c)
3. **Log K_{OW}:** 4.8 at 35 °C (RIFM, 1999b), 4.16 (EPI Suite)
4. **Melting Point**: 16.07 °C (EPI Suite)
5. **Water Solubility:** 13.49 mg/L (EPI Suite)
6. **Specific Gravity:** 0.900 (FMA)
7. **Vapor Pressure:** 0.0129 mm Hg at 20 °C (EPI Suite v4.0), 0.01 mm Hg at 20 °C (FMA), 0.0205 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 liquid

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 v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.084% (RIFM, 2016a)
2. **Inhalation Exposure*:** 0.00025 mg/kg/day or 0.019 mg/day (RIFM, 2016a)
3. **Total Systemic Exposure**:** 0.0032 mg/kg/day (RIFM, 2016a)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
II	II	II

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

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

7.1. Additional References

None.

8. Natural occurrence

Phenylethyl isoamyl ether is 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.

9. REACH dossier

Available; accessed 08/17/20 (ECHA, 2017).

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 and use levels, phenylethyl isoamyl ether does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. Phenylethyl isoamyl ether was assessed in the BlueScreen assay and found negative for 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. The mutagenic activity of phenylethyl isoamyl 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with phenylethyl isoamyl 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 dose in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, phenylethyl isoamyl ether was not mutagenic in the Ames test.

The clastogenic activity of phenylethyl isoamyl 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 phenylethyl isoamyl ether in DMSO at concentrations up to 250 μg/mL in the presence and absence of S9 for 3 and 24 h. Phenylethyl isoamyl ether did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, phenylethyl isoamyl ether was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data available, phenylethyl isoamyl ether does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenylethyl isoamyl ether or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to phenylethyl isoamyl ether (3.2 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/17/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on phenylethyl isoamyl ether or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phenylethyl isoamyl ether (3.2 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/29/20.

11.1.4. Skin sensitization

Based on the existing data and read-across to (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9), phenylethyl isoamyl ether presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for phenylethyl isoamyl ether. Based on the existing data and read-across material (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9; see Section VI), phenylethyl isoamyl ether is not considered a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In guinea pig maximization test conducted on 10 test-group animals, no reactions indicative of skin sensitization were observed with phenylethyl isoamyl ether (RIFM, 1982; European Centre for Ecotoxicology and Toxicology of Chemicals, 2003). In another guinea pig maximization test conducted with the read-across material (3-methoxy-2-methylpropyl)benzene, no sensitization reactions were observed in the 20 test group animals (RIFM, 1995a; European Centre for Ecotoxicology and Toxicology of Chemicals, 2003). Undiluted test materials (100%) were used for the topical induction in both guinea pig maximization studies. In human maximization tests, no reactions were observed when 2% or 1380 μg/cm^2 phenylethyl isoamyl ether in petrolatum was used for induction and challenge (RIFM, 1979; RIFM, 1980).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material (3-methoxy-2-methylpropyl)benzene, phenylethyl isoamyl ether does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/03/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, phenylethyl isoamyl 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 phenylethyl isoamyl ether in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, phenylethyl isoamyl 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/21/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for phenylethyl isoamyl 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 phenylethyl isoamyl ether. Based on the Creme RIFM Model, the inhalation exposure is 0.019 mg/day. This exposure is 24.7 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/30/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of phenylethyl isoamyl ether was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio 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, phenylethyl isoamyl 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) did not identify phenylethyl isoamyl ether as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening

criteria applied are the same as those used in the EU for REACH (ECHA, 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 ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1997:** The inherent biodegradability of phenylethyl isoamyl ether was determined in a sealed vessel CO_2 production test according to the OECD 302A method, using an acclimatized inoculum from a modified semi-continuous activated sludge test. Phenylethyl isoamyl ether (13.2 mg/L) was incubated with filtered activated sludge for 28 days. The average extent of mineralization in the sealed vessel test using an acclimatized inoculum was 39.6%.

RIFM, 1993: Biodegradation of the test material was evaluated by the modified sealed vessel test according to the OECD 301B method. 10 mg/L of phenylethyl isoamyl ether was incubated with filtered activated sludge for 56 days. Biodegradation of 71.6% was observed after 56 days.

RIFM, 1996: Biodegradation was evaluated by the sealed vessel test according to the OECD 301B method. 10 mg/L of phenylethyl isoamyl ether was incubated with filtered activated sludge for 28 days. The rate of degradation after 28 days was 39.2%.

RIFM, 1999a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Phenylethyl isoamyl ether at a nominal concentration of 100 mg/L was incubated for 34 days. Under the conditions of this study, biodegradation of 76% was observed.

11.2.2.1.2. Ecotoxicity. **RIFM, 1995b:** A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 value based on nominal test concentration was reported to be 5.2 mg/L.

RIFM, 1994: An algae growth inhibition test was conducted according to the OECD 201 guideline. The 72-h EC50 value based on nominal test concentration for growth rate was reported to be greater than 32 mg/L.

11.2.2.1.3. Other available data. Phenylethyl isoamyl ether has been registered under REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

Since phenylethyl isoamyl ether has passed the screening criteria, 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 et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	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 0.1265 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: 10/03/20.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.951			1000000	0.000951	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.826	1.265	2.148	10000	0.1265	Neutral Organic SAR (Baseline toxicity)

- **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
- **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 09/17/21.

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.2022.112954.

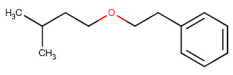
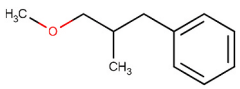
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). 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 substance 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, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), 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, 2020).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material
Principal Name	Phenylethyl isoamyl ether	(3-Methoxy-2-methylpropyl)benzene
CAS No.	56011-02-0	120811-92-9
Structure		
Similarity (Tanimoto Score)		0.51
Endpoint		Skin sensitization
Molecular Formula	$C_{13}H_{20}O$	$C_{11}H_{16}O$
Molecular Weight	192.302	164.248
Melting Point (°C, EPI Suite)	16.07	−5.78
Boiling Point (°C, EPI Suite)	255.27	219.02
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.73E+00	1.84E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.35E+01	1.27E+02
Log K_{OW}	4.16	3.17
J_{max} (μg/cm^2/h, SAM)	1.63	10.06
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.91E+01	1.65E+01
Skin Sensitization		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
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 phenylethyl isoamyl ether (CAS # 56011-02-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, (3-methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- (3-Methoxy-2-methylpropyl)benzene (CAS # 120811-92-9) was used as a read-across analog for the target material phenylethyl isoamyl ether (CAS # 56011-02-0) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of aromatic ethers.
  - The key difference between the target substance and the read-across analog is that the target substance has a branched alkyl chain on the ether, while the read-across analog has a methyl on the ether. This structural difference is toxicologically insignificant. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - There are no *in silico* alerts for the target substance or the read-across analog for the skin sensitization endpoint. The predictions are consistent with data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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