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Short Review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, [2-Isopropoxyethyl]benzene, CAS Registry Number 68039-47-4

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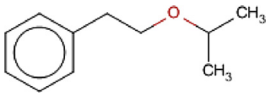

Abbreviation/Definition List:

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

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QRA - Quantitative Risk Assessment
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 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 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 use of this material under current conditions is supported by existing information.

[2-Isopropoxyethyl]benzene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog phenylethyl isoamyl ether (CAS# 56011-02-0) show that [2-isopropoxyethyl]benzene is not expected to be genotoxic. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2/day); exposure is below the DST. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class III material, and the exposure to [2-isopropoxyethyl]benzene is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra and data; [2-isopropoxyethyl]benzene is not phototoxic/photoallergenic. The environmental endpoints were evaluated; [2-isopropoxyethyl]benzene was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

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: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB; RIFM, 1981)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.7 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 57.7 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 24.49 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: 24.49 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02449 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** [2-Isopropoxyethyl]benzene
2. CAS Registry Number: 68039-47-4
3. Synonyms: Benzene, [2-(1-methylethoxy)ethyl]-; [2-(1-Methylethoxy)ethyl]benzene; 1-Phenyl-4-methyl-3-oxapentane; Petiole; (2-Isopropoxyethyl)benzene; [2-Isopropoxyethyl]benzene
4. Molecular Formula: $C_{11}H_{16}O$
5. Molecular Weight: 164.48
6. RIFM Number: 5880

2. Physical data

1. **Boiling Point:** 219.02 °C (EPI Suite)
2. **Flash Point:** 79 °C (GHS)
3. **Log K_{ow}:** 3.1 (RIFM, 2013b), 3.17 (EPI Suite)
4. **Melting Point**: −5.78 °C (EPI Suite)
5. **Water Solubility:** 127.3 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.091 mm Hg @ 20 °C (EPI Suite v4.0), 0.138 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 450 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium green, rose, plastic, metallic, spicy, foliage odor*

*http://www.thegoodscentscompany.com/data/rw1020111.html#toorgano retrieved 3/22/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.029% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0081 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00093 mg/kg/day (RIFM, 2016)

*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 IV. 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).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	II	II

*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). See Appendix below for further detail.

2. Analogs Selected:
   a. **Genotoxicity:** Phenylethyl isoamyl ether (CAS # 56011-02-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   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)

[2-Isopropoxyethyl]benzene is not reported to occur in food 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 that contains information on published volatile compounds that 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 05/15/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, [2-isopropoxyethyl]benzene does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. [2-Isopropoxyethyl]benzene was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013a). There are no studies assessing the mutagenic activity of [2-isopropoxyethyl]benzene; however, read-across can be made to phenylethyl isoamyl ether (CAS # 56011-02-0; see Section V). 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, and this can be extended to phenylethyl isoamyl ether.

There are no studies assessing the clastogenic activity of [2-isopropoxyethyl]benzene; however, read-across can be made to phenylethyl isoamyl ether (CAS # 56011-02-0). 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 metabolic activation (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, and this can be extended to phenylethyl isoamyl ether.

Based on the data available, phenylethyl isoamyl ether does not present a concern for genotoxic potential, and this can be extended to [2-isopropoxyethyl]benzene.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/14/2017.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on [2-isopropoxyethyl]benzene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to [2-isopropoxyethyl]benzene (0.93 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on [2-

isopropoxyethyl]benzene or any read-across materials. The total systemic exposure to [2-isopropoxyethyl]benzene is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on [2-isopropoxyethyl]benzene or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to [2-isopropoxyethyl]benzene (0.93 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

There are no fertility data on [2-isopropoxyethyl]benzene or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to [2-isopropoxyethyl]benzene (0.93 μg/kg/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.4. Skin sensitization

Based on application of DST, [2-isopropoxyethyl]benzene does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive or confirmatory skin sensitization studies are available for [2-isopropoxyethyl]benzene. Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. [2-Isopropoxyethyl]benzene does not present a concern for skin sensitization. Table 1 provides the acceptable concentrations for [2-isopropoxyethyl]benzene, which present no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/20/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra along with existing data, [2-isopropoxyethyl]benzene would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. 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). In a rat phototoxicity study, undiluted [2-isopropoxyethyl]benzene did not result in phototoxic reactions (RIFM, 1981). Based on lack of absorbance and *in vivo* study data, [2-isopropoxyethyl]benzene does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV absorption spectra were obtained. The spectra indicate no significant absorbance in the range of 290–450 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: 04/26/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for [2-isopropoxyethyl]benzene is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on [2-isopropoxyethyl]benzene. Based on the Creme RIFM Model, the inhalation exposure is 0.0081 mg/day. This exposure is 58.0 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/20/2016.

10.2. .Environmental endpoint summary:

10.2.1. Screening-level assessment

A screening-level risk assessment of [2-isopropoxyethyl]benzene 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

Table 1
Acceptable concentration limits for [2-isopropoxyethyl]benzene based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.000%
2	Products applied to the axillae	0.021%	0.011%
3	Products applied to the face using fingertips	0.41%	0.012%
4	Fine Fragrance products	0.39%	0.029%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.012%
6	Products with oral and lip exposure	0.23%	0.000%
7	Products applied to the hair with some hand contact	0.79%	0.003%
8	Products with significant ano-genital exposure	0.04%	0.000%
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.004%
10	Household care products with mostly hand contact	2.70%	0.048%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	0.000%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.231%

Note: [a]For a description of the categories, refer to the QRA Informational Booklet. (www.rifm.org/doc).

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, [2-isopropoxyethyl]benzene was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify [2-isopropoxyethyl]benzene 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), [2-isopropoxyethyl]benzene does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data

[2-Isopropoxyethyl]benzene has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.1	3.1
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 material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.02449 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 3/7/17.

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
- 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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	24.49			1,000,000	0.02449	

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.07.037

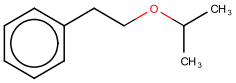
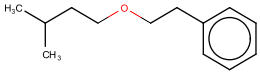
Appendix

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). The strategy is also 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, 2016).

- 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).
- Jmax values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted 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
Principal Name	[2-Isopropoxyethyl]benzene	Phenylethyl isoamyl ether
CAS No.	68039-47-4	56011-02-0
Structure		
Similarity (Tanimoto score)		0.75
Read-across endpoint		• Genotoxicity
Molecular Formula	$C_{11}H_{16}O_1$	$C_{13}H_{20}O$
Molecular Weight	164.25	192.30
Melting Point (°C, EPI Suite)	−5.78	16.07
Boiling Point (°C, EPI Suite)	219.02	255.27
Vapor Pressure (Pa @ 25°C, EPI Suite)	18.4	2.74
Log Kow (KOWWIN v1.68 in EPI Suite)	3.1[1]	4.8[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	127.3	13.49
J_{max} (mg/cm^2/h, SAM)	72.87	33.924
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.65E + 001	2.91E + 001
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)	• Michael addition	• Michael addition
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
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
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2

1. RIFM, 2013a,b
2. RIFM, 1999.

Summary

There are insufficient toxicity data on the target material [2-isopropoxyethyl]benzene (CAS # 68039-47-4). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenylethyl isoamyl ether (CAS # 56011-02-0) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

Phenylethyl isoamyl ether (CAS # 56011-02-0) was used as a read-across analog for target material [2-isopropoxyethyl]benzene (CAS # 68039-47-4) for the genotoxicity endpoint.

- The target substance and the read-across analog are structurally similar and belong to the structural class of aromatic ethers.
- The target substance and the read-across analog share an alkyl phenethyl ether structure.
- The key difference between the target substance and the read-across analog is that the phenethyl ether in the target is an isopropyl ether, whereas it is an isoamyl ether in the read-across material. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicological evaluation.
- Similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score are not toxicologically significant.
- According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicity endpoints are consistent between the target substance and the read-across analog.
- OECD QSAR Toolbox DNA binding alert system shows a Michael addition alert for the target substance and the read-across analog. The data described in the genotoxicity section show that the target substance does not pose a concern for the genetic toxicity endpoint. Therefore, the alert will be superseded by the availability of the data.
- The target substance 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 between 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.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation)? No
Q19. Open chain? No
Q23. Aromatic? Yes
Q27. Rings with substituents? Yes
Q28. More than one aromatic ring? No
Q30. Aromatic ring with complex substituents? Yes
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q32. 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 ($n \geq 4$) on the aromatic or aliphatic side chain? No
Q22. Common component of food? No
Q33. Has sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulfonate or sulfamate? No, Class III (Class High)

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