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Short review

RIFM fragrance ingredient safety assessment, α-Isobutylphenethyl alcohol, CAS Registry Number 7779-78-4

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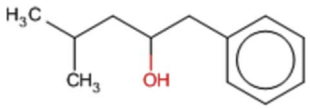
Name: α-Isobutylphenethyl alcohol

CAS Registry Number: 7779-78-4



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; Safford et al., 2017; Comiskey et al., 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- Organization for Economic Co-operation and Development
OECD TG- Organization 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
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- 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 RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.

Each endpoint discussed in this safety assessment, reviews the relevant data that was 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 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 guidance relevant to human health and environmental protection.

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

The material (α-isobutylphenethyl alcohol) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from read across analog alpha-propylphenethyl alcohol (CAS # 705-73-7) show that α-isobutylphenethyl alcohol is not genotoxic. Data on α-isobutylphenethyl alcohol provided a MOE > 100 for the repeated dose endpoint. Data from the read across analog benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2) show that α-isobutylphenethyl alcohol does not have skin sensitization potential. The reproductive and developmental toxicity, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day, 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, α-isobutylphenethyl alcohol 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. (Wild et al., 1983; RIFM, 2015; ECHA REACH Dossier: α-methylbenzyl alcohol)

Repeated Dose Toxicity: NOEL = 40 mg/kg/day (Ford et al., 1983)

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: Not sensitizing (RIFM, 2003; RIFM, 2000a; RIFM, 2000b)

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: 2.9 (Biowin 3) (US EPA, 2012a)

Bioaccumulation: Screening Level: 44 L/kg (US EPA, 2012a)

Ecotoxicity: Screening Level: LC50: 15.15 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: LC50: 15.15 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.015 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:** α-Isobutylphenethyl alcohol
2. **CAS Registry Number:** 7779-78-4
3. **Synonyms:** Benzyl isoamyl alcohol; Benzyl isobutyl carbinol; Isobutyl benzyl carbinol; α-Isobutylphenethyl alcohol; 4-Methyl-1-phenyl-2-pentanol; 2-Methylpropyl benzyl carbinol; 2-Pentanol, 4-methyl-1-phenyl-; ﾌｪﾆﾙｱﾙｷﾙ(C = 6～8)ｱﾙｺｰﾙ; 4-Methyl-1-phenylpentan-2-ol
4. **Molecular Formula:** $C_{12}H_{18}O$
5. **Molecular Weight:** 178.28
6. **RIFM Number:** 5023

2. Physical data

1. **Boiling Point:** 268.42 °C [US EPA, 2012a]
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.38 [US EPA, 2012a]
4. **Melting Point:** 26.08 °C [US EPA, 2012a]
5. **Water Solubility:** 234 mg/L [US EPA, 2012a]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000504 mmHg @ 20 °C [US EPA, 2012a], 0.02 mm Hg 20C [FMA database], 0.00098 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless, slightly oily liquid with a green-floral, fresh and slightly sweet odor. The material has very good tenacity.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0016% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000035 mg/kg/day or 0.0027 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00059 mg/kg/day (RIFM, 2016)

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

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

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also 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:** α-Propylphenethyl alcohol (CAS # 705-73-7); α-methylbenzyl alcohol (CAS# 98-85-1)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Benzenepropanol, a,β-dimethyl (CAS # 56836-93-2)
   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)

α-Isobutylphenethyl alcohol 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, 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 11/30/2010; no dossier available as of 08/03/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, α-isobutylphenethyl alcohol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

α-Isobutylphenethyl alcohol was tested using the BlueScreen assay and found to be non-genotoxic with and without S9 metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic potential of α-isobutylphenethyl alcohol. Read across material α-

propylphenethyl alcohol (CAS # 705-73-7; see Section 5) was assessed in an Ames assay conducted equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with α-propylphenethyl alcohol in DMSO (dimethyl sulfoxide) at concentrations up to 3.6 mg/plate in the presence and absence of exogenous metabolically active microsomal mix (S-9 mix). No increase in the number of revertant colonies was observed in the tester strains at any concentration (Wild et al., 1983). Under the conditions of the study, α-propylphenethyl alcohol was considered not mutagenic in the Ames test and this can be extended to α-isobutylphenethyl alcohol. As an additional weight of evidence, read-across analog α-methylbenzyl alcohol (CAS # 98-85-1; see Section 5) was assessed in mammalian cell gene mutation assay conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary (CHO) cells were treated with α-methylbenzyl alcohol in DMSO at concentrations of 0, 0.5, 1, 2.5 or 5 mM (as determined in a preliminary toxicity assay), for 3 h. Effects were evaluated both with and without metabolic activation. No toxicologically significant increases in the frequency of mutant colonies were observed with any dose, with or without metabolic activation (ECHA REACH Dossier). α-Methylbenzyl alcohol was also negative when tested in Ames assay using *S. typhimurium* TA98, TA100, TA1535 and TA1537 strains (ECHA REACH Dossier). Taken together it can be considered that α-isobutylphenethyl alcohol does not have any mutagenic potential.

There are no studies assessing the clastogenic activity of α-isobutylphenethyl alcohol. Read across material α-propylphenethyl alcohol (CAS # 705-73-7; see Section 5) was assessed 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 α-propylphenethyl alcohol at concentrations up to 600 μg/ml in the presence and absence of metabolic activation. No statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at any evaluated concentration in any treatment condition, with or without S9 (RIFM, 2015). Under the conditions of the study, α-propylphenethyl alcohol was considered negative for the induction of micronuclei in human lymphocytes and this can be extended to α-isobutylphenethyl alcohol.

Based on the available data, α-propylphenethyl alcohol and α-methylbenzyl alcohol do not present a concern for genotoxic potential and this can be extended to α-isobutylphenethyl alcohol.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.3. Repeated dose toxicity

The margin of exposure is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are sufficient repeated dose toxicity data on α-isobutylphenethyl alcohol. In a 13-week GLP feeding study (Ford et al., 1983; RIFM, 1981), groups of 15 Sprague-Dawley rats/sex received 0, 10, 40 & 160 mg/kg/day α-isobutylphenethyl alcohol in the diet. No effects were observed at 10 mg/kg/day. At 40 mg/kg/day, decreased serum glucose levels (males) were reported. At 160 mg/kg/day, reduced weight gain, mild proteinuria (females), increased caecal weights, increased relative liver weight (males), reduced serum glucose, and a lower reticulocyte count were reported. There were no treatment-related histopathological findings. The NOEL of α-isobutylphenethyl alcohol is 10 mg/kg/day. The NOAEL is 40 mg/kg/day, based on decreased serum glucose levels in the male rats and increased organ weight and lower reticulocyte counts at the higher dose level.

Therefore, the α-isobutylphenethyl alcohol MOE for the repeated dose toxicity endpoint can be calculated by dividing the α-isobutylphenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to α-isobutylphenethyl alcohol, 40/0.00059 or 67797.

In addition, the total systemic exposure to α-isobutylphenethyl alcohol (0.59 μg/kg/day; Kroes et al., 2007) is below the TTC (9 μg/kg bw/day) 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: 2/23/2017.

10.1.4. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on α-isobutylphenethyl alcohol or any read across materials. The exposure is below the threshold of toxicological concern at the current level of use.

10.1.4.1. Risk assessment. There are no developmental or reproductive toxicity data on α-isobutylphenethyl alcohol or any read across materials that can be used to support the developmental and reproductive toxicity endpoint. The total systemic exposure to α-isobutylphenethyl alcohol (0.59 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) 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: 2/23/2017.

10.1.5. Skin sensitization

Based on existing data and read across to benzenepropanol, a,β-dimethyl (CAS # 56836-93-2), α-isobutylphenethyl alcohol does not present a concern for skin sensitization.

10.1.5.1. Risk assessment. Based on existing data and read across to benzenepropanol, a,β-dimethyl (CAS # 56836-93-2; see Section 5), α-isobutylphenethyl alcohol does not present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In the murine local lymph node assay, this material was reported to be a non-sensitizer up to 40% (greater than 10,000 μg/cm^2) (RIFM, 2003). No human studies are available for α-isobutylphenethyl alcohol, however, up to 6% or 3000 μg/cm2 of read across benzenepropanol, a,β -dimethyl- in 3:1 alcohol SD39C: diethyl phthalate did not cause sensitization reactions in human repeated insult patch tests (RIFM, 2000a; RIFM, 2000b). Based on weight of evidence from structural analysis, animal data and read across to benzenepropanol, a,ß-dimethyl-, α-isobutylphenethyl alcohol does not present a concern for skin sensitization.

Additional References: RIFM, 1962.

Literature Search and Risk Assessment Completed on: 2/22/17.

10.1.6. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, α-isobutylphenethyl alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.6.1. Risk assessment. There are no phototoxicity data available for α-isobutylphenethyl alcohol. The available UV/Vis spectra (OECD test guideline 101) for α-isobutylphenethyl alcohol indicate no significant absorbance between 290 and 700 nm. Molar absorption coefficient for wavelengths between 290 and 700 nm is below the benchmark (1000 L · mol-1 · cm-1) considered to be of concern for phototoxic effects (Henry et al., 2009). Based on UV/Vis absorption spectra, α-isobutylphenethyl

alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/09/17.

10.1.7. Respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, α-isobutylphenethyl alcohol, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment. There are no inhalation data available on α-isobutylphenethyl alcohol. Based on the Creme RIFM model, the inhalation exposure is 0.0027 mg/day. This exposure is 174 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.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/22/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of α-isobutylphenethyl alcohol 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; US EPA, 2012b) 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 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, α-isobutylphenethyl alcohol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify α-isobutylphenethyl alcohol as either being possibly persistent nor 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 EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), α-isobutylphenethyl alcohol does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.4. Ecotoxicity

No data available.

10.2.5. Other available data

α-Isobutylphenethyl alcohol has been pre-registered for REACH with no additional data at this time.

10.2.6. Risk assessment refinement

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

Endpoints used to calculate PNEC are highlighted.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	15.15 mg/l			1,000,000	0.015 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.38	3.38
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 additional assessment is necessary.

The RIFM PNEC is 0.015 μg/l. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening level, therefore does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 8/18/14.

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.

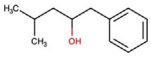
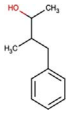
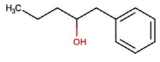
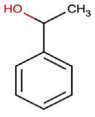
This is not an exhaustive list.

Appendix

Read across justification

Methods

- The identified read across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analog were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), 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 v.2.1.7 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		Weight of Evidence (WoE)
Principal Name	α-Isobutylphenethyl alcohol	Benzenepropanol, a,ß-dimethyl-	α-Propylphenethyl alcohol	α-Methylbenzyl alcohol
CAS No.	7779-78-4	56836-93-2	705-73-7	98-85-1
Structure				
Similarity (Tanimoto score)		0.62	0.78	0.73
Read across endpoint		• Skin sensitization	• Genotoxicity	• Genotoxicity
Molecular Formula	$C_{12}H_{18}O$	$C_{11}H_{16}O$	$C_{11}H_{16}O$	$C_8H_{10}O$
Molecular Weight	178.28	164.25	164.25	122.17
Melting Point (°C, EPISUITE)	26.08	15.49	26	−6.87
Boiling Point (°C, EPISUITE)	268.42	251.46	261.79	207.10
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.131	0.395	0.198	7.27
Log Kow (KOWWIN v1.68 in EPISUITE)	3.38	2.89	2.97	1.42
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	234	716.5	620.1	14700
J_{max} (mg/cm^2/h, SAM)	40.837	110.394	87.541	259.209
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	8.96E-007	6.75E-007	6.75E-007	2.89E-007
Genotoxicity				
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found		• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition		• Michael addition	• Michael addition
Carcinogenicity (genotoxity and non-genotoxity) alerts (ISS)	• Non-carcinogen (low reliability)		• Non-carcinogen (low reliability)	• Carcinogen (Experimental value)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found		• No alert found	• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found		• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found		• No alert found	• No alert found

Oncologic Classification	• Not classified		• 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 (good reliability)	• Sensitizer (good reliability)		
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	Supplemental Data 1	Supplemental Data 2	Supplemental Data 3	Supplemental Data 4

Summary

There are insufficient toxicity data on the target material α-isobutylphenethyl alcohol (CAS # 7779-78-4). Hence *in silico* evaluation was conducted to determine a read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2), α-propylphenethyl alcohol (CAS # 705-73-7) and α-methylbenzyl alcohol (CAS # 98-85-1) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- Benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2) was used as a read across analog for the target material α-isobutylphenethyl alcohol (CAS # 7779-78-4) for the skin sensitization endpoint.
  - ○ The target substance and the read across analog are structurally similar and belong to the structural class of secondary aliphatic alcohols with remote aryl moiety.
  - ○ The target substance and the read across analogs share a hydroxyl group on a secondary carbon with an isolated aromatic moiety.
  - ○ The key difference between the target substance and the read across analog is that the target substance, α-isobutylphenethyl alcohol, has an isopropyl group at the secondary carbon. The read across analog, benzenepropanol, a,ß-dimethyl- has methyl group on the secondary carbon. The structural differences between the target substance and the read across analog does not affect consideration of the toxicological endpoint.
  - ○ Similarity between the target substance and the read across analogs is indicated by the Tanimoto scores in the above table.
  - ○ The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoint are consistent between the target substance and the read across analog.
  - ○ The target substance and the read across analog are predicted to be sensitizers by the CAESAR model. Other protein binding alerts for skin sensitization are negative. The data described in the skin sensitization section above shows that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alerts will be superseded by the availability of data.
  - ○ The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.
- α-propylphenethyl alcohol (CAS # 705-73-7) and α-methylbenzyl alcohol (CAS # 98-85-1) were used as a read across analog and weight of evidence (WoE) respectively, for the target material α-isobutylphenethyl alcohol (CAS # 7779-78-4) for the genotoxicity endpoint.
  - ○ The target substance, read across analog and weight of evidence material are structurally similar and belong to the structural class of secondary aliphatic alcohols with remote aryl substituents.
  - ○ The target substance, read across analog and weight of evidence material share a hydroxyl group on a secondary carbon with an isolated aromatic moiety.
  - ○ The key difference between the target substance and the read across analog is that the target substance, α-isobutylphenethyl alcohol, has an isopropyl group at the secondary carbon. While the read across analog, α-propylphenethyl alcohol, has an n-propyl group at the secondary carbon connected to he hydroxyl group and the weight of evidence material, α-methylbenzyl alcohol, has a methyl group at the secondary carbon. The structural differences between the target substance and the read across analogs do not affect consideration of the toxicological endpoint.
  - ○ Similarity between the target substance, read across analog and weight of evidence material is indicated by the Tanimoto scores in the above table.
  - ○ The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoint are consistent between the target substance and the read across analog.
  - ○ The target substance, read across analog and weight of evidence material have a Michael addition DNA binding alert by OECD. The weight of evidence material, α-methylbenzyl alcohol, is predicted to be a carcinogen by the ISS model, whereas the target and read across analog are predicted to be non-carcinogens. The data described in the genotoxicity section above shows that the read across analog and the weight of evidence material do not pose a concern for the genotoxicity endpoint. Therefore, the alerts will be superseded by the availability of data.
  - ○ The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

Explanation of Cramer classification

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? **No**
Q17. Readily hydrolyzed to a common terpene? **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? **No**
Q18. One of the list? (Question 18 examines the terpenes, and later the open-chain and mononuclear substances by reference, to determine whether they contain certain structural features generally thought to be associated with some enhanced toxicity) **Yes Class Moderate (Class II)**

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.10.012.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.012.

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