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Short review

RIFM fragrance ingredient safety assessment, α-methylbenzyl alcohol, CAS registry number 98-85-1

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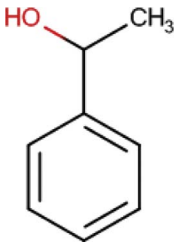
Name: α-Methylbenzyl alcohol
CAS Registry Number: 98-85-1



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 the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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-methylbenzyl alcohol) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that α-methylbenzyl alcohol is not genotoxic and provided a MOE > 100 for the repeated dose toxicity endpoint. Data from the read across analogs α-isobutylphenethyl alcohol (CAS # 7779-78-4) and benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2) show that α-methylbenzyl alcohol does not have skin sensitization potential. The reproductive 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 and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, α-methylbenzyl 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. (ECHA REACH Dossier)
Repeated Dose Toxicity: (NTP, 1990)
NOAEL = 37.5 mg/kg/day.
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: 3.11 mg/L (US EPA, 2012a)
Bioaccumulation: Screening Level: 2.23 L/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: Fish LC50: 457.7 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: 457.7 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.4577 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening level

1. Identification

1. **Chemical Name:** α-Methylbenzyl alcohol
2. **CAS Registry Number:** 98-85-1
3. **Synonyms:** Benzenemethanol,.α.-methyl-; α-Methylbenzyl alcohol; Methyl phenyl carbinol; 1-Phenylethanol; 1-Phenylethan-1-ol; α-Phenylethyl alcohol; secondary-Phenylethyl alcohol; 1-Phenyl-1-hydroxyethane; Phenyl methyl carbinol; Styralyl alcohol; アルキル（C = 1 ~ 3 ）ベンジルアルコール; α-メチルベンジルアルコール; α - ヒドロキシエチルベンゼン
4. **Molecular Formula:** $C_8H_{10}O$
5. **Molecular Weight:** 122.17
6. **RIFM Number:** 468

2. Physical data

1. **Boiling Point:** 205 °C [FMA Database], 207.1 °C [US EPA, 2012a]
2. **Flash Point:** 70 °C [GHS]
3. **Log K_{OW}:** 1.49 [US EPA, 2012a]
4. **Melting Point:** −6.87 °C [US EPA, 2012a]
5. **Water Solubility:** 19540 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 1.0112 [RIFM Database], 1.011–1.016 [FMA Database], 1.0102 [RIFM Database], 1.009–1.014 [FMA Database]
7. **Vapor Pressure:** 0.2 mm Hg 20 °C [FMA Database], 0.0338 mmHg @ 20 °C [US EPA, 2012a], 0.0545 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 to pale yellow liquid with mild hyacinth and gardenia odor which congeals below room temperature (Arctander, Volume II 1969)

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA , 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00043% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.0000059 mg/kg/day or 0.00043 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00017 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate 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 I, Low

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

2. **Analogues Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** α-isobutylphenethyl alcohol (CAS# 7779-78-4) and benzenepropanol, a,ß-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-methylbenzyl alcohol is reported to occur in nature in the following*:

Allium speciesBeansCheese, various typesCloudberry (*Rubus chamaemorus* L.)Cocoa
Endive (*Cichorium endivia* L.)Filbert, hazelnut (*Corylus avellano*)Grape (*Vitis* species)Grape brandyHoneyKumazasa (*Sasa albo-marginata*)Mentha oilsMushroomPlum (*Prunus* species)Swiss cheesesTea*Vaccinium* speciesWine

*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

Available, accessed 08/08/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, α-methylbenzyl alcohol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenicity of α-methylbenzyl alcohol was assessed in a mammalian cell gene mutation assay conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary (CHO) cells were treated with α-methylbenzyl alcohol (1-phenylethanol) in DMSO (dimethyl sulfoxide) 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). Under the conditions of the study, α-methylbenzyl alcohol 1-phenylethanol was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of α-methylbenzyl alcohol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in 10 ml of olive oil, via oral gavage to groups of 40 male NMRI mice (10 mice/exposure group). Doses of 0, 187.5, 375 or 700 mg/kg were administered. Mice from each dose level were euthanized at 24 h (all exposure groups) or 48 h (top dose and control only), the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA REACH Dossier). Under the conditions of the study, α-methylbenzyl alcohol 1-phenylethanol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, α-methylbenzyl alcohol does not present a concern for genotoxic potential.

Additional References: NTP, 1990; Szybalski, 1958; Fluck et al., 1976; Zeiger et al., 1987.

Literature Search and Risk Assessment Completed on: 2/12/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for α-methylbenzyl alcohol is adequate for the repeated dose toxicity endpoint.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on α-methylbenzyl alcohol. α-Methylbenzyl alcohol was administered via gavage to groups of 10 B6C3F1 mice/sex/dose at doses of 0, 46.9, 93.8, 187.5, 375 or 750 mg/kg/day for 13-weeks. Mice receiving 375 or 750 mg/kg/day exhibited labored breathing, ataxia, and lethargy for up to 30 min after dosing. There were no other effects reported among treated mice. The NOAEL was considered to be 750 mg/kg/day, based on the lack of any significant adverse effects at the highest dose level. However, this study lacked information on food and water consumption, hematology, clinical chemistry, urinalysis and organ weights, and histopathology results other than the liver. In the follow-up 2-year study, groups of 50 B6C3F1 mice/sex/group were administered α-methylbenzyl alcohol at doses of 0, 375 or 750 mg/kg/day, 5 days/week for 103 weeks. A significant reduction in body weight gain was apparent in the high dose groups of males and females, and the final survival rates in mice were similar among the groups. The NOAEL was considered to be 750 mg/kg/day, based on the lack of any neoplastic or non-neoplastic lesions attributed to α-methylbenzyl alcohol the administration of the test material in mice of either sex (NTP, 1990). In another study, Groups of 10 F344/N rats/sex/dose were administered test material, α-methylbenzyl alcohol in corn oil at 0, 93, 187, 375, 750 or 1500 mg/kg/day by via oral gavage, 5 days/week for 13 weeks. The study was conducted to help select doses for a 2-year study. Throughout the study, rats receiving 750 or 1500 mg/kg/day exhibited ataxia, rapid breathing, and lethargy for up to 30 min after dosing. After 30 min, these clinical effects subsided. Relative liver weight was significantly greater than solvent controls for all females (up to ~40%) and all males dosed at 375 mg/kg/day or more, however there was no dose response. Minimal-to-mild increase in brown pigment, characteristic of hemosiderin, was seen in macrophages in the spleen of 10/10 males receiving 750 mg/kg/day and 9/10 males receiving 1500 mg/kg/day, but none was seen in males receiving 375 mg/kg/day. A similar pigment was seen in the spleen of 6/10 females receiving 1500 mg/kg/day, but none was seen in females receiving 750 mg/kg/day. Final mean body weights were reduced in 1500 mg/kg/day animals. Since there were no deaths or life-threatening histopathological lesions observed at 375 or 750 mg/kg/day, these doses were selected for the 2-year study. The NOAEL of the 13-week study was considered to be 187 mg/kg/day, based on the increased liver weights and spleen effects at the higher dose levels (NTP, 1990). However, this study lacked information on food and water consumption, hematology, clinical chemistry, urinalysis, organ weights and histopathology other than the liver and spleen. Therefore, this study by itself was considered insufficiently robust. A follow-up 2-year gavage study in male and female F344/N rats was conducted with the primary purpose of detecting neoplastic and non-neoplastic lesions potentially related to treatment with α-methylbenzyl alcohol. Groups of 50 rats/sex/dose were administered 0, 375 or 750 mg/kg/day of test material in corn oil via gavage, 5 days/week for 103 weeks. Necropsy was performed on all animals, and histological examination of approximately 29 different organs and tissues were performed on all rats. Examination of kidney tissue from male rats indicated a dose related increase in renal tubular cell adenoma or adenocarcinoma (combined) when compared with controls. An age-related spontaneous nephropathy was observed in nearly all male rats including the controls, but was considered to be more severe in dosed treated male rats. Hyperplasia of the transitional epithelium overlying the renal pelvis was increased in male rats. The tubular cell hyperplasia, adenoma, and carcinoma of the kidneys appeared to encompass a morphologic continuum. Other non-neoplastic lesions occurring in an increased incidence in male rats included parathyroid hyperplasia, calcification of the heart and stomach, and fibrous osteodystrophy of bone. These changes were believed to be a secondary response stemming from a mineral imbalance caused by renal toxicity. Centrilobular necrosis of the liver was observed at increased incidences in the male rats dosed at both levels (8/50 low dose and 8/50 high dose) when compared to controls (0/50). No evidence of carcinogenic activity was observed for female rats. In summary, the non-neoplastic lesions appeared to be either a continuum of the changes leading to the neoplastic lesions of the kidneys, or secondary effects due to mineral imbalance caused by renal toxicity. The centrilobular necrosis of the liver observed in treated male rats was not mentioned in the 13-week gavage study, including rats given higher dose levels. Thus the LOAEL in this study was considered to be 375 mg/kg/day, based on decreased survival. Thus the NOAEL was derived by dividing the LOAEL by a safety factor of 10, 375/10 or 37.5 mg/kg/day (NTP, 1990 > ; Eustis et al., 1994). The most conservative NOAEL of 37.5 mg/kg/day from the 2-year study conducted on rats (NTP, 1990) was considered for the repeated dose toxicity endpoint.

Therefore, the α-methylbenzyl alcohol MOE can be calculated by dividing the α-methylbenzyl alcohol NOAEL in mg/kg/day by the total systemic exposure to α-methylbenzyl alcohol, 37.5/0.00017 or 220588.

In addition, the total systemic exposure to α-methylbenzyl alcohol (0.17 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 08/07/2017.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on α-methylbenzyl alcohol or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure

to α-methylbenzyl alcohol (0.17 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

10.1.4. Skin sensitization

Based on the existing data and read across to α-isobutylphenethyl alcohol (CAS # 7779-78-4) and benzenepropanol, a,ß-dimethyl (CAS # 56836-93-2), α-methylbenzyl alcohol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on existing data and read across to α-isobutylphenethyl alcohol (CAS # 7779-78-4) and benzenepropanol, a,ß-dimethyl (CAS # 56836-93-2; see Section 5), α-methylbenzyl 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 a guinea pig open epicutaneous test, α-methylbenzyl alcohol was reported to be negative (Klecak, 1985). Moreover, in the murine local lymph node assay, read across analog α-isobutylphenethyl alcohol was reported to be a non-sensitizer up to 40% (greater than 10,000 μg/cm^2) (RIFM, 2003). In a human maximization test, 8% or (2760 μg/cm^2) α-methylbenzyl alcohol in petrolatum did not induce sensitization reactions in any of the subjects (RIFM, 1973). Similarly, up to 6% or 3000 μg/cm^2 of read across analog benzenepropanol, a,b-dimethyl- in 3:1 alcohol SD39C:diethyl phthalate did not cause sensitization reactions in human repeat insult patch tests (RIFM, 2000a; RIFM, 2000b).

Additional References: Klecak, 1979; Sharp, 1978; RIFM, 1962

Literature Search and Risk Assessment Completed on: 02/23/17.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for α-methylbenzyl alcohol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, α-methylbenzyl alcohol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are insufficient inhalation data available on α-methylbenzyl alcohol. Based on the Creme RIFM model, the inhalation exposure is 0.00043 mg/day. This exposure is 3256 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Smyth and Carpenter, 1944; Engstrom, 1984.

Literature Search and Risk Assessment Completed on: 4/25/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of α-methylbenzyl 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, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, α-methylbenzyl 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-methylbenzyl alcohol as either being possibly persistent nor 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 criteria used in the EU for REACH (ECHA, 2016). For persistence, if the EPI Suite models BIOWIN 2 or BIOWIN 6 < 0.5 and BIOWIN 3 < 2.2, then the material is considered as potentially persistent. A material would be considered potentially bioaccumulative if the EPISUITE model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening level risk assessment. Should additional assessment be required, based on these model outputs (Step 1), a weight-of-evidence based review is 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., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

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

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. α-Methylbenzyl alcohol is registered under REACH and the following data is available:

96-hr Fish (Zebra fish) acute toxicity study was conducted according to the OECD 203 method under static conditions and the LC50 was reported to be 100 mg/L.

Algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50, based on growth rate was reported to be > 200 mg/L.

10.2.3. Risk assessment refinement

Since α-methylbenzyl alcohol has passed the screening criteria measured data is included for completeness only and has not been used in PNEC derivations.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	457.7 mg/L			1,000,000	0.4577 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.49	1.49
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 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 0.4577 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: 2/16/17.

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

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.09.045.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.045.

Appendix

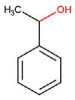
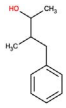
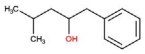
Read across justification

Methods

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

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, the appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints. (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} were calculated using RIFM skin absorption model (SAM), and the parameters were calculated using consensus model (Shen et al., 2014).

- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR 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	
Principal Name	α-Methylbenzyl alcohol	Benzenepropanol, a,ß-dimethyl-	α-Isobutylphenethyl alcohol
CAS No.	98-85-1	56836-93-2	7779-78-4
Structure			
Similarity (Tanimoto score)		0.61	0.53
Read across endpoint		• Skin sensitization	• Skin sensitization
Molecular Formula	$C_8H_{10}O$	$C_{11}H_{16}O$	$C_{12}H_{18}O$
Molecular Weight	122.17	164.25	178.28
Melting Point (°C, EPISUITE)	−6.87	15.49	26.08
Boiling Point (°C, EPISUITE)	207.10	251.46	268.42
Vapor Pressure (Pa @ 25°C, EPISUITE)	7.27	0.395	0.131
Log Kow (KOWWIN v1.68 in EPISUITE)	1.42	2.89	3.38
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	14700	716.5	234
J_{max} (mg/cm^2/h, SAM)	259.209	110.394	40.837
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.89E-007	6.75E-007	8.96E-007
Repeated dose toxicity			
Repeated Dose (HESS)	• Not categorized		
Skin Sensitization			
Protein binding by OASIS v1.4	• No alert found	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)	• Sensitizer (good reliability)	• Sensitizer (good reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1. RIFM, 1996.
2. RIFM, 2011.

Summary

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

Conclusion/Rationale

- Benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2), α-isobutylphenethyl alcohol (CAS # 7779-78-4) and α-ethylbenzyl alcohol (CAS # 98-85-1) were used as a read across analogs for the skin senzitization and repeated dose toxicity endpoints.
  - o The target substance and the read across analogs are structurally similar and belong to the structural class of secondary aryl alcohols.
  - o The target substance and the read across analogs share short chain branched secondary alkyl alcohol structures with a phenyl substituent.
  - o The key differences between the target substance and the read across analog are in the length of the alkyl chain, position of the alcohol, and the methyl and phenyl substituents. These structural differences between the target substance and the read across analogs does not affect

consideration of the toxicological endpoints.

- o Similarity between the target substance and the read across analogs is indicated by the Tanimoto scores in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoints.
- o The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
- o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read across analogs.
- o The target substance and the read across analogs are predicted to be sensitizers by the CAESAR model. Other protein binding alerts for the skin sensitization endpoint are negative. The data described in the skin sensitization section above show that the read across analogs do not pose a concern for the skin sensitization endpoint. Therefore, the alerts are superseded by the availability of data.
- o The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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