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Short review

RIFM fragrance ingredient safety assessment, benzenepropanol, a,ß-dimethyl-, CAS Registry Number 56836-93-2

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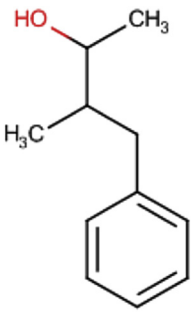

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

(*continued on next page*)

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(*continued*)

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 (benzenepropanol, a,ß-dimethyl-) 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 the read across analogs α-propylphenethyl alcohol (CAS # 705-73-7) and α-methylbenzyl alcohol (CAS # 98-85-1) show that benzenepropanol, a,ß-dimethyl- is not genotoxic. Data from the read across analog α-methylbenzyl alcohol (CAS # 98-85-1) provided a MOE > 100 for the repeated dose endpoint. Data from the read across analog α-isobutylphenethyl alcohol (CAS # 7779-78-4) show that this material 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, benzenepropanol, a,ß-dimethyl- 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) (NTP, 1990)

(*continued*)

Repeated Dose Toxicity: 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: 2.9 (Biowin 3)	(US EPA, 2012a)
Bioaccumulation: Screening Level: 20.9 l/kg	(US EPA, 2012a)
Ecotoxicity: Screening Level: 48-hr *Daphnia magna* LC50: 13.12 mg/l	(US EPA, 2012a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-hr *Daphnia magna* LC50: 13.12	(US EPA, 2012a)

RIFM PNEC is: 1.312 μg/l

- Revised PEC/PNECs (2011 IFRA Volume of Use): North America and Europe: <1

1. Identification

1. **Chemical Name:** Benzenepropanol, a,ß-dimethyl-
2. **CAS Registry Number:** 56836-93-2
3. **Synonyms:** Benzenepropanol, a,ß-dimethyl-; 3-Methyl-4-phenylbutan-2-ol; 3-methyl-4-phenylbutane-2-ol; 4-fenil-3-metilbutan-2-ol; Benzenepropanol,-dimethyl; Mugesia
4. **Molecular Formula**: $C_{11}H_{16}O$
5. **Molecular Weight**: 164.25
6. **RIFM Number**: 6661

2. Physical data

1. **Boiling Point:** 251.46 °C [US EPA, 2012a]
2. **Flash Point**: >93 °C [GHS]
3. **Log K_{OW}**: 2.89 [US EPA, 2012a]
4. **Melting Point**: 15.49 °C [US EPA, 2012a]
5. **Water Solubility:** 716.5 mg/l [US EPA, 2012a]
6. **Specific Gravity**: Not Available
7. **Vapor Pressure:** 0.0017 mmHg @ 20 °C [US EPA, 2012a], 0.00296 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} cm^{-1})
9. **Appearance/Organoleptic:** colorless to pale yellow clear liquid (est); floral muguet green rose mentholic*

*http://www.thegoodscentscompany.com/data/rw1012661.html, retrieved 03/01/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 10 to 100 metrics tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.60% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00051 mg/kg/day or 0.036 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.0061 mg/kg/day (RIFM, 2014)

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

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

2. **Analogues Selected:**
   a. **Genotoxicity:** α-propylphenethyl alcohol (CAS # 705-73-7); α-methylbenzyl alcohol (CAS# 98-85-1)
   b. **Repeated Dose Toxicity:** α-methylbenzyl alcohol (CAS # 98-85-1)
   c. **Reproductive Toxicity**: None
   d. **Skin Sensitization:** α-Isobutylphenethyl alcohol (CAS # 7779-78-4)
   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)

Benzenepropanol, a,ß-dimethyl- 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

Available, accessed 8/4/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzenepropanol, a,ß-dimethyl- does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Benzenepropanol, a,ß-dimethyl- was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of benzenepropanol, a,ß-dimethyl- however, read across can be made to α-propylphenethyl alcohol (CAS # 705-73-7; see Section 5). The mutagenic potential of α-propylphenethyl alcohol 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 (S9 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 benzenepropanol, a,ß-dimethyl-. As an additional weight of evidence, read-across analog α-methylbenzyl alcohol (CAS # 98-85-1) 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 benzenepropanol, a,ß-dimethyl- does not have any mutagenic potential.

There are no studies assessing the clastogenic activity of benzenepropanol, a,ß-dimethyl- however, read across can be made to α-propylphenethyl alcohol (CAS # 705-73-7; see Section 5). The clastogenic activity of α-propylphenethyl alcohol 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 benzenepropanol, a,ß-dimethyl-.

Based on the available data on read across material, it can be concluded that benzenepropanol, a,ß-dimethyl- does not present a concern for genotoxic potential.

Additional References: None.

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

10.1.2. Repeated dose toxicity

The margin of exposure for benzenepropanol, a,ß-dimethyl- is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on benzenepropanol, a,ß-dimethyl-. There are sufficient repeated dose toxicity data on read across material α-methylbenzyl alcohol (CAS # 98-85-1; see section 5). A 13-week gavage study was conducted on F344/N rats to help select doses for a 2-year study. Groups of 10 rats/sex/dose were administered α-methylbenzyl alcohol in corn oil at 0, 93, 187, 375, 750 or 1500 mg/kg by oral gavage, 5 days/week for 13 weeks. Throughout the study, rats receiving 750 or 1500 mg/kg 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 or more, however there was no dose response. Minimal to mild increases in brown pigment, characteristic of hemosiderin, were seen in macrophages in the spleen of 10/10 males receiving 750 mg/kg and 9/10 males receiving 1500 mg/kg, but none were seen in males receiving 375 mg/kg. A similar pigment was seen in the spleen of 6/10 females receiving 1500 mg/kg, but none was seen in females receiving 750 mg/kg. Final mean body weights were reduced in 1500 mg/kg animals. Because there were no deaths or life-threatening histopathologic lesions at 375 or 750 mg/kg, these doses were selected for the 2-year study. The NOAEL of this study was considered to be 187 mg/kg/day, based on the increased liver weights and spleen effects at the higher dose levels. 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 is considered insufficiently robust. In another study, α-methylbenzyl alcohol was administered via gavage to groups of 10 B6C3F1 mice/sex/dose group 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 of this study is 750 mg/kg/day, the highest dose tested, based on the lack of any significant adverse effects at this 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 (NTP, 1990).

10.1.2.2. Carcinogenicity. A 2-year gavage study in male and female F344/N rats was conducted with the primary purpose of detecting neoplastic and nonneoplastic lesions potentially related to treatment with α-methylbenzyl alcohol (NTP, 1990). Groups of 50 rats/sex were administered 0, 375 or 750 mg/kg/day of the material in corn oil by gavage 5 days/week for 103 weeks. A 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) compared with controls. An age-related spontaneous nephropathy was observed in nearly all male rats including controls, but was considered to be more severe in dosed 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 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 compared to controls in the male rats dosed at both levels. 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, decreased body weight gains among treated animals of both sex and increase in the incidence of renal tubular cell adenomas or adenocarcinomas (combined) were observed in male rats. 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). In another study, Groups of 50 B6C3F1 mice/sex/group were administered α-methylbenzyl alcohol at doses of 0, 375 or 750 mg/kg 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 final survival rates in mice were similar among 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 administration in mice of either sex (NTP, 1990).

The most conservative NOAEL of 37.5 mg/kg/day from the 2-year study conducted on rats was selected for the repeated dose toxicity endpoint.

Therefore, the benzenepropanol, a,ß-dimethyl- MOE for the repeated dose toxicity endpoint can be calculated by dividing the α-methylbenzyl alcohol NOAEL in mg/kg/day by the total systemic exposure to benzenepropanol, a,ß-dimethyl-, 37.5/0.0061 or 6148.

In addition, the total systemic exposure to benzenepropanol, a,ß-dimethyl- (6.1 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/23/2017.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on benzenepropanol, a,ß-dimethyl- or any read across materials. The exposure is below the TTC for the developmental and reproductive toxicity endpoints.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on benzenepropanol, a,ß-dimethyl- or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to benzenepropanol, a,ß-dimethyl- (6.1 μg/kg/day) is below the TTC (9 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the reproductive toxicity endpoint of

a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/23/2017.

10.1.4. Skin sensitization

Based on the existing data and read across to α-isobutylphenethyl alcohol (CAS # 7779-78-4), benzenepropanol, a,ß-dimethyl- 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; see Section 5), benzenepropanol, a,ß-dimethyl- 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, read across analog α-isobutylphenethyl alcohol material was reported to be a non-sensitizer up to 40% (greater than 10,000 μg/cm^2) (RIFM, 2003). Up to 6% or 3000 μg/cm^2 of benzenepropanol, a,ß-dimethyl- in 3:1 alcohol SD39C:diethyl phthalate did not cause sensitization reactions in human repeat insult patch tests (RIFM, 2000b; RIFM, 2000a). Based on weight of evidence from structural analysis, human data and read across to α-isobutylphenethyl alcohol, benzenepropanol, a,ß-dimethyl- alcohol does not present a concern for skin sensitization.

Additional References: RIFM, 1962.

Literature Search and Risk Assessment Completed on: 02/22/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, benzenepropanol, a,ß-dimethyl- 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 benzenepropanol, a,ß-dimethyl- 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 (Henry et al., 2009). Based on lack of absorbance, benzenepropanol, a,ß-dimethyl- 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, benzenepropanol, a,ß-dimethyl-, exposure level 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 benzenepropanol, a,ß-dimethyl-. Based on the Creme RIFM model, the inhalation exposure is 0.036 mg/day. This exposure is 13.1 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 benzenepropanol, a,ß-dimethyl- 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, benzenepropanol, a,ß-dimethyl- was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did not identify benzenepropanol, a,ß-dimethyl- as possibly persistent or 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 v4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), benzenepropanol, a,ß-dimethyl- presents 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. Benzenepropanol, a,β-dimethyl has been pre-registered for REACH with no additional data at this time.

10.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	37.25 mg/L			1,000,000	0.03725 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	21.29 mg/L	13.12 mg/L	13.75 mg/L	10,000	1.312 µg/L	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.89	2.89
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	10–100
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 1.312 µg/l. The revised PEC/PNECs for EU and NA are < 1 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.2017.09.009.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.009.

Appendix

Read across justification

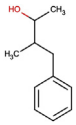
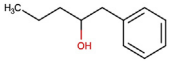
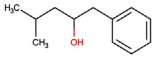
Methods:

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

- In essence, materials were first clustered based on their structure similarity. In the second step, data availability and data quality on the selected cluster was examined. Finally, the appropriate read across analogs from the cluster were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of the target substance and the read across analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 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).

used as a read across analog for genotoxicity, α-isobutylphenethyl alcohol (CAS # 7779-78-4) was used as a read across analog for skin senzitization and α-methylbenzyl alcohol (CAS # 98-85-1) was used as a read across analog and weight of evidence for the repeated dose toxicity endpoint and genotox-

	Target material	Read across material		
Principal Name	Benzenepropanol, a,ß-dimethyl-	α-Propylphenethyl alcohol	α-Isobutylphenethyl alcohol	α-Methylbenzyl alcohol
CAS No.	56836-93-2	705-73-7	7779-78-4	98-85-1
Structure				
Similarity (Tanimoto score)		0.59	0.62	0.73
Read across endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose • Genotoxicity
Molecular Formula	$C_{11}H_{16}O$	$C_{11}H_{16}O$	$C_{12}H_{18}O$	$C_8H_{10}O$
Molecular Weight	164.25	164.25	178.28	122.17
Melting Point (°C, EPISUITE)	15.49	26	26.08	−6.87
Boiling Point (°C, EPISUITE)	251.46	261.79	268.42	207.10
Vapor Pressure (Pa @ 25°C, EPISUITE)	0.395	0.198	0.131	7.27
Log Kow (KOWWIN v1.68 in EPISUITE)	2.89	2.97	3.38	1.42
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	716.5	620.1	234	14700
J_{max} (mg/cm^2/h, SAM)	110.394	87.541	40.837	259.209
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	6.75E-007	6.75E-007	8.96E-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 (genotoxicity and non-genotoxicity) alerts (ISS)	• Carcinogen (moderate 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
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized			• Not categorized
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)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4
Rat liver S9 metabolism simulator and structural alerts for metabolites				

Summary:

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

Conclusion/Rationale:

- For the target material, benzenepropanol, a,ß-dimethyl- (CAS # 56836-93-2), α-propylphenethyl alcohol (CAS # 705-73-7) was

icity endpoint, respectively.

o The target substance and the read across analogs are structurally similar and belong to the structural class of secondary aryl alkyl alcohols.

o The target substance and the read across analogs share a hydroxyl group on the secondary alkyl carbon with isolated aromatic substituent.

o The key differences between the target substance and the read across analogs are as follows: analog, α-propylphenethyl alcohol, has an n-propyl group at the secondary carbon connected to the hydroxyl group, and the target substance benzenepropanol, a,ß-dimethyl- has a methyl group on the secondary carbon while the read across analog, α-isobutylphenethyl alcohol, has an isopropyl group at the secondary carbon. This structural difference between the target

substance and the read across analog 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 analogs are sufficiently similar to enable comparison of their toxicological properties.
- o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read across analog.
- o 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.
- o The target substance, read across analog α-propylphenethyl alcohol and weight of evidence α-methylbenzyl alcohol have a Michael addition DNA binding alert by OECD. The weight of evidence material, α-methylbenzyl alcohol, and the target substance are predicted to be carcinogens by ISS the model, whereas read across analog, α-propylphenethyl alcohol, is predicted to be a non-carcinogen. The data described in the genotoxicity section above shows that the read across analog and the weight of evidence material does not pose a concern for the genotoxicity endpoint. Therefore, the alerts will be 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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