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Short review

RIFM fragrance ingredient safety assessment, β-methylphenethyl alcohol, CAS Registry Number 1123-85-9

A.M. Api[a,*], D. Belsito[b], D. Botelho[a], D. Browne[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], M. Francis[a], A.D. Fryer[h], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], D.C. Liebler[i], D. O'Brien[a], R. Parakhia[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], Y. Thakkar[a], E.H. Theophilus[a], A.K. Tiethof[a], Y. Tokura[m], S. Tsang[a], J. Wahler[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan*

[*] Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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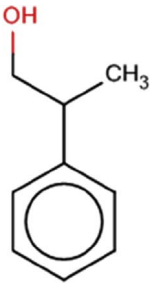
Name: β-Methylphenethyl alcohol

CAS Registry Number: 1123-85-9



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- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
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 (β-methylphenethyl 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 the read across analog phenethyl alcohol (CAS # 60-12-8) show that β-methylphenethyl alcohol is not genotoxic and provided a MOE > 100 for the developmental toxicity endpoint. Data from the read across analog 2-methyl-5-phenylpentanol (CAS # 25634-93-9) show that β-methylphenethyl 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). Data on β-methylphenethyl alcohol provided a MOE > 100 for the repeated dose toxicity endpoint. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, β-methylphenethyl 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: NOAEL = 40 mg/kg/day. (Gaunt et al., 1982)

Developmental and Reproductive Toxicity: Developmental NOAEL = 54 mg/kg/day. No reproductive NOAEL. Exposure is below the TTC. (RIFM, 2010)

Skin Sensitization: Not sensitizing. (RIFM, 1964; RIFM, 1974; RIFM, 1988a; RIFM, 1997)

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: Complete biodegradation based on read –across to phenethyl alcohol (CAS# 60-12-8) (RIFM, 1994)

Bioaccumulation: Screening Level: 5.255 L/kg (US EPA, 2012a)

Ecotoxicity: Screening Level: Fish LC50: 191.22 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: Fish LC50: 191.22 mg/L (US EPA, 2012a)

RIFM PNEC is: 0.191 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe Not Applicable

1. Identification

1. **Chemical Name:** β-Methylphenethyl alcohol
2. **CAS Registry Number:** 1123-85-9
3. **Synonyms:** Benzeneethanol, α.-methyl-; Hydratropic alcohol; Hydratropyl alcohol; β-Methylphenethyl alcohol; 2-Phenyl-1-propanol; 2-Phenylpropyl alcohol; ﾌｪﾆﾙｱﾙｷﾙ(C = 3～5)ｱﾙｺｰﾙ; 2-Phenylpropan-1-ol
4. **Molecular Formula:** $C_9H_{12}O$
5. **Molecular Weight:** 136.19
6. **RIFM Number:** 547

2. Physical data

1. **Boiling Point:** 219 °C [FMA database], (calculated) 232.23 °C (US EPA, 2012a)
2. **Flash Point:** > 200 °F; CC [FMA database]
3. **Log K_{OW}:** 1.98 (US EPA, 2012a)
4. **Melting Point:** 6.1 °C (US EPA, 2012a)
5. **Water Solubility:** 5677 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 1.003 [FMA database]
7. **Vapor Pressure:** 0.00599 mm Hg @ 20 °C (US EPA, 2012a), 0.02 mm Hg 20 °C [FMA database], 0.0101 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 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Organoleptic:** Colorless liquid. Sweet-floral, but rather heavy odor of lilac-hyacinth type.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0024% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0089 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00032 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 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:** 77%, read across from phenethyl alcohol (CAS # 60-12-8) RIFM, 2013c **(data also available in** RIFM, 1986b; RIFM, 1987; RIFM, 1988b; RIFM, 1988c; RIFM, 1990; Ford et al., 1987b, 1990a): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA) by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg body weight [bw]), gavage (430 mg/kg bw), or dietary (430 mg/kg bw) administration of PEA to rats, plasma concentrations of PEA were found to be low regardless of the route of administration. The plasma concentrations of phenylacetic acid (PAA, the major metabolite of PEA) greatly exceeded the concentrations of PEA and were highest after gavage, followed by dermal then dietary administration. The pharmacokinetic parameters were compared following topical application of [14]C-labeled PEA to rats, rabbits and humans (specific activities of dosing solutions: 58-580, 164, and 50 μCi/ml, respectively). In rabbits, the plasma concentration–time profile for PAA was markedly prolonged compared to rats or humans. In humans, only 7.6% of the applied dose of PEA was absorbed, versus 77% in rats and 50% in rabbits. Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation from the human study (87.4% in rats compared to 10.8% in humans).
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
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2. Analogues Selected:
   a. **Genotoxicity:** Phenethyl alcohol (CAS # 60-12-8)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8)
   d. **Skin Sensitization:** 2-Methyl-5-phenylpentanol (CAS # 25634-93-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** Phenylethyl alcohol (CAS # 60-12-8)
3. **Read Across Justification:** See appendix below

6. Metabolism

Not relevant 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)

β-Methylphenethyl 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 2010; no dossier available as of 08/2/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. β-Methylphenethyl alcohol was tested using the BlueScreen assay and found negative for both cytotoxicity and genotoxicity (RIFM, 2013a). There are no studies assessing the mutagenic activity of β-methylphenethyl alcohol. Read across material phenethyl alcohol (CAS # 60-12-8; see Section 5) was assessed in an Ames study conducted in compliance with GLP regulations in accordance with to OECD TG 471 using both the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA were treated with phenylethyl alcohol in DMSO (dimethyl sulfoxide) at the concentrations 50, 150, 500, 1500 and 5000 μg/plate both in the presence and absence of metabolic activation. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test item, either with or without metabolic activation (ECHA REACH Dossier). Under the conditions of the study, phenethyl alcohol was considered not mutagenic in the Ames test and this can be extended to β-methylphenethyl alcohol.

There are no studies assessing the clastogenic potential of the target material, β-methylphenethyl alcohol, however the clastogenic activity of read across material phenethyl alcohol was assessed in an *in vitro* chromosome aberration study in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with phenethyl alcohol for 4-hr with S9 at concentrations 38.13, 76.25, 152.5, 305, 610 and 1220 μg/ml; 4hr without S9 mix at 38.13, 76.25, 152.5, 305, 610 and 1220 μg/ml and 24-hr without S9 mix at 38.13, 76.25, 152.5, 305, 610 and 1220 μg/ml. Phenethyl alcohol did not induce any statistically significant increases in the frequency of cells with aberrations either in the absence or presence of metabolic activation (ECHA REACH Dossier). Under the conditions of the study, phenethyl alcohol was considered not clastogenic in the *in vitro* chromosome aberration test and this can be extended to β-methylphenethyl alcohol.

Based on the available data, phenethyl alcohol does not present a concern for genotoxic potential and this can be extended to β-methylphenethyl alcohol.

Additional References: Florin et al., 1980; Tachibana and Yonei, 1985; Norppa and Vainio, 1983; Urban and Wyss, 1969; Brunner and Treick, 1982; Rosenkranz and Leifer, 1980; Tomiyama et al., 1986; Mendelson and Fraser, 1965; Cleaver and Painter, 1975; Lilley and Brewer, 1953; Wild et al., 1983; RIFM, 2013a; Tachibana et al., 1982.

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

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on β-methylphenethyl alcohol are sufficient for the repeated dose toxicity endpoint. β-Methylphenethyl alcohol was added to the diet of groups of 15 male and female Wistar rats to provide intakes of 0, 10, 40 or 160 mg/kg/day for 13 weeks. There was a significant decrease (7–9%) in terminal body weights among treated females when compared to the controls, which was not dose related and not observed in males. Thus, this was not considered to be a treatment related adverse effect. There were no treatment related effects on food intake, water intake, hematology, serum chemistry, semi-quantitative analysis of urine, renal concentration and dilution tests, or histology. Increased liver weights at the highest dose level (160 mg/kg/day) in both sexes and increased kidney weights at the two highest doses (40 and 160 mg/kg/day) in males were considered to be related to treatment, however the significance of such alterations remained unknown in the absence of related histopathological alterations. It was concluded that the NOAEL in this study was 40 mg/kg/day (Gaunt et al., 1982; data also available in RIFM, 1979). Therefore, the β-methylphenethyl alcohol MOE for the repeated dose toxicity endpoint can be calculated by dividing the β-methylphenethyl NOAEL in mg/kg/day by the total systemic exposure to β-methylphenethyl alcohol, 40/0.00032 or 125,000.

When correcting for skin absorption, the total systemic exposure to β-methylphenethyl alcohol (0.32 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: 2/17/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for β-methylphenethyl alcohol is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on β-methylphenethyl alcohol or any read across materials. The total systemic exposure to β-methylphenethyl 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 developmental toxicity data on β-methylphenethyl alcohol. Read across material, phenethyl alcohol (CAS # 60-12-8; see Section 5) has several developmental toxicity studies in rats. A dietary developmental toxicity study conducted on groups of 28 pregnant rats were fed diets containing test material, phenethyl alcohol, at doses of 0, 1000, 3000 or 10,000 ppm, equivalent to 0, 83, 266 or 799 mg/kg/day according to calculated food intake from Gestation Days (GDs) 6–15. There were no maternal or fetal developmental toxicity effects reported among treated animals. Thus, the NOAEL for maternal and developmental toxicity was determined to be 10,000 ppm or 799 mg/kg/day, the highest dose tested (RIFM, 2013b, data also in RIFM, 1985; RIFM, 1986a; RIFM, 1988b; Ford et al., 1987a, 1990a, 1990b; Burdock et al., 1987). In another study, a dermal developmental toxicity study conducted on groups of 25–35 pregnant female rats were administered test material, phenethyl alcohol at doses of 0, 140, 430 or 1400 mg/kg/day from GDs 6–15. There was significant maternal toxicity reported among the high dose animals (1400 mg/kg/day). Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day. Dose related increase in skeletal abnormalities was reported among the animals of the mid and high dose group animals (430 and 1400 mg/kg/day), thus the NOAEL for developmental toxicity was determined to be 140 mg/kg/day (RIFM, 2013b, data also in RIFM, 1985; RIFM, 1986a; RIFM, 1988b; Ford et al., 1987a, 1990a, 1990b; Burdock et al., 1987). In another dermal developmental toxicity study conducted on test material, phenethyl alcohol was administered at doses of 0, 70, 140, 280, 430 and 700 mg/kg/day to groups of 10 rats/sex/group from GDs 6–15. Fetal effects included dose-dependent decrease in fetal body weights for litters of the 140 mg/kg/day and higher dose groups (280, 430 and 700 mg/kg/day). Dosages as high as 700 mg/kg/day did not adversely affect average litter sizes, numbers of implantations, live fetuses, or post-implantation loss. Thus, the NOAEL for developmental toxicity was determined to be 70 mg/kg/day, based on a decrease in body weights of litters among the higher dose groups (140, 280, 430 and 700 mg/kg/day) (RIFM, 2013b, data also in RIFM, 1985; RIFM, 1986a; RIFM, 1988b; Ford et al., 1987a, 1990a, 1990b; Burdock et al., 1987). Another study was conducted to determine the reversibility of skeletal alterations (e.g., rudimentary cervical ribs and vertebral irregularities) and delays in skeletal ossification following

exposure of pregnant rats to the test material during the gestation period, and to evaluate any safety concerns relating to human health. Dosages of 0 (water), 140, 430 or 1400 mg/kg/day phenylethyl alcohol were percutaneously administered once daily on GDs 7–20. Twenty rats per dosage group were caesarean-sectioned on GD 21. The remaining twenty rats per dosage group were allowed to deliver naturally; the dams and pups were euthanized on Postpartum Day (PPD) 21. Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day, based on increased incidences of altered clinical observations and mortality among the high dose group animals (1400 mg/kg/day). The NOAEL for developmental toxicity was determined to be 140 mg/kg/day, based on increased incidences of fetal skeletal ossifications among the mid and high dose group animals (430 and 1400 mg/kg/day), and gross, soft tissue and skeletal alterations among the high dose group animals (1400 mg/kg/day) (RIFM, 2010, data also available in RIFM, 2011). The most conservative NOAEL of 70 mg/kg/day from the dermal studies on phenethyl alcohol was selected for the developmental toxicity endpoint. To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013c; see Section 4) was used to revise the NOAEL of 70 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 54 mg/kg/day. **Therefore, the β-methylphenethyl alcohol MOE for the developmental toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to β-methylphenethyl alcohol, 108/0.00032 or 337,500.**

When correcting for skin absorption, the total systemic exposure to β-methylphenethyl alcohol (0.32 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on β-methylphenethyl alcohol or any read across materials that can be used to support the reproductive toxicity endpoint. When correcting for skin absorption (see Section 4), the total systemic exposure to β-methylphenethyl alcohol (0.32 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: 02/16/2017.

10.1.4. Skin sensitization

Based on the existing data and read across to 2-methyl-5-phenylpentanol (CAS # 25634-93-9), β-methylphenethyl alcohol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data and read across to 2-methyl-5-phenylpentanol (CAS # 25634-93-9; see Section 5), β-methylphenethyl alcohol would not be expected to present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react directly with skin proteins (OECD Toolbox 3.4; Toxtree 2.6.13). In a Guinea pig maximization test, read across material 2-methyl-5-phenylpentanol was reported to be a non-sensitizer (RIFM, 1988a). In human studies, no sensitization was observed at the maximum tested concentration of 6.25% in the human repeat insult patch test and 6% in the human maximization test with β-methylphenethyl alcohol (RIFM, 1988d; RIFM, 1974). Similarly, in a human repeat insult patch test no sensitization reactions were observed to 2-methyl-5-phenylpentanol (RIFM, 1997). Based on weight of evidence from structural analysis, human data and read across to 2-methyl-5-phenylpentanol, β-methylphenethyl alcohol does not present a concern for skin sensitization.

Additional References: None.

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

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity data available for β-methylphenethyl alcohol. The available UV/Vis spectra (OECD test guideline 101) for spectra available β-methylphenethyl alcohol indicate no 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) of concern for phototoxic effects (Henry et al., 2009). Based on UV/Vis absorption spectra, β-methylphenethyl alcohol would not be expected to present a concern for phototoxicity or photoallergencitiy.

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, β-methylphenethyl alcohol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on β-methylphenethyl alcohol. Based on the Creme RIFM model, the inhalation exposure is 0.0089 mg/day. This exposure is 157 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: None.

Literature Search and Risk Assessment Completed on: 2/16/2017.

10.2. Environmental endpoint summary

10.2.1. Analogs identified/justification

Phenethyl alcohol CAS # 60-12-8 was identified as structurally related material for biodegradation read across. Both chemicals have similar ECOSAR predictions for persistent (both not P and not B), and since phenethyl alcohol available data confirms that it is not a persistent molecule, β-methylphenethyl alcohol is expected not be persistent.

10.2.2. Screening-level assessment

A screening level risk assessment of β-methylphenethyl 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). Following the RIFM Environmental Framework β-methylphenethyl 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 β-methylphenethyl alcohol as being 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 v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.3. Risk assessment

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

10.2.4. Key studies

10.2.4.1. Biodegradation. No data available. See other available data section for read across.

10.2.4.2. Ecotoxicity. No data available.

10.2.4.3. Other available data. β-Methylphenethyl alcohol has been pre-registered for REACH with no additional data at this time.

There is one biodegradation study available for the read across material phenethyl alcohol CAS # 60-12-8.

A biodegradation study was conducted using activated sludge according to the OECD 301B method. Phenylethyl alcohol as 10 mg/L organic carbon was incubated with activated sludge for 28 days. The test material underwent complete biodegradation in the 28-day course of the study (RIFM, 1994).

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)**	191.2 mg/L			1,000,000	0.1912 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.98	1.98
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.1912 μg/L. The revised PEC/PNECs for EU and NA are Not Applicable.

Literature Search and Risk Assessment Completed on: 08/07/13.

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

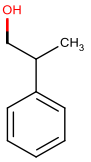
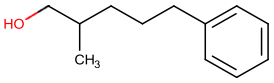
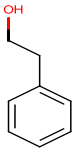
Read across justification

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).

- Jmax 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	
Principal Name	β-Methylphenethyl alcohol	2-Methyl-5-phenylpentanol	Phenethyl alcohol
CAS No.	1123-85-9	25634-93-9	60-12-8
Structure			
Similarity (Tanimoto score)		0.73	0.89
Read across endpoint		• Skin sensitization	• Genotoxicity • Developmental and Reproductive • Environmental
Molecular Formula	$C_9H_{12}O$	$C_{12}H_{18}O$	$C_8H_{10}O$
Molecular Weight	136.20	178.28	122.17
Melting Point (°C, EPISUITE)	6.10	54.4	5.81
Boiling Point (°C, EPISUITE)	232.23	292.61	224.85
Vapor Pressure (Pa @ 25 °C, EPISUITE)	1.35	0.0154	3.24
Log Kow (KOWWIN v1.68 in EPISUITE)	1.98	2.9[a]	1.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	5677	412.8[b]	2.22E+004
J_{max} (mg/cm^2/h, SAM)	293.535	17.736	355.140
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	3.83E-007	7.45E-007	2.89E-007
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found		• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition		• Michael addition
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• No alert found		• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found		• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found		• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found		• No alert found
Oncologic Classification	• Not classified		• Not classified
Reproductive and developmental toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH or NH2 group		• Non-binder, without OH or NH2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (good reliability)		• Toxicant (good reliability)
Skin Sensitization			
Protein binding by OASIS v1.1	• 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 v1.1	• 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	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

[a] RIFM, 2012.
[b] RIFM, 1989.

Summary

There are insufficient toxicity data on the β-methylphenethyl alcohol (CAS # 1123-85-9). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, 2-methyl-5-phenylpentanol (CAS # 25634-93-9) and phenethyl alcohol (CAS # 60-12-8) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/rationale

- For the target material β-methylphenethyl alcohol (CAS # 1123-85-9), 2-methyl-5-phenylpentanol (CAS # 25634-93-9) was used as a read across analog for the skin senzitization endpoint and phenethyl alcohol (CAS # 60-12-8) was used as a read across analog for the genotoxicity and developmental and reproductive and environmental toxicity endpoints.
  - o The target substance and the read across analogs are structurally similar and belong to the structural class of primary aryl alcohols.
  - o The target substance and the read across analogs share a primary alcohol and distant aromatic ring fragment.
  - o The key difference between the target substance and the read across analogs is the length of the carbon chain between the primary alcohol and aromatic ring. The target substance has a shorter chain with a methyl substituent, whereas the read across analog, 2-methyl-5-phenylpentanol, has a longer chain with a methyl substituent and read across analog, phenethyl alcohol, has a shorter chain with no methyl substitution. This structural difference between the target substance and the read across analogs does 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 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 scores do not affect consideration of the toxicological endpoints.
  - o The physical-chemical properties of the target substance and the read across analogs do not differ by a magnitude that it will differentiate 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 analogs.
  - o According to the CAESAR model, the target substance as well as the read across analog, phenethyl alcohol, are predicted to be toxicants with good reliability. ER binding alerts for both of the substances are negative. The data described above in the developmental toxicity section show that the margin of exposure of the read across substance is adequate at the current level of use. In this case, the *in silico* prediction can be ignored.
  - o According to the CAESAR model, the target substance as well as the read across analog, 2-methyl-5-phenylpentanol, are predicted to be sensitizers. All other protein binding alerts for skin sensitization are negative. From the data described in the skin sensitization section, it is shown that the read across analog does not present a concern for the skin sensitization endpoint. Therefore, the *in silico* prediction is superseded with data.
  - o The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.09.056.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.09.056.

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