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Short review

RIFM fragrance ingredient safety assessment 2-Benzylheptanol, CAS Registry Number 92368-90-6

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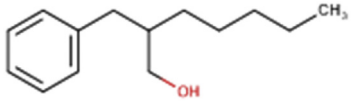

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Abbreviation/Definition list:

2-Box Model - a RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; 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
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 includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 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.

2-Benzylheptanol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 2-benzylheptanol and read across analog 2-methyl-5-phenylpentanol (CAS # 25634-93-9) show that 2-benzylheptanol is not expected to be genotoxic and has no safety concerns for skin sensitization under the current, levels of use. Data from read across analog β-methylphenethyl alcohol (CAS # 1123-85-9) provided a calculated MOE > 100 for the repeated dose toxicity endpoint. The reproductive and local respiratory toxicity endpoints were evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.009 mg/kg/day and 0.47 mg/day, respectively). The developmental toxicity endpoint was evaluated using phenethyl alcohol (CAS # 60-12-8) as a read across analog, which provided a calculated MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra along with data on 2-benzylheptanol; 2-benzylheptanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, 2-benzylheptanol was found not to be PBT as per the IFRA Environmental Standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2001; RIFM, 1988e)
Repeated Dose Toxicity: NOEL = 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, 1985b; RIFM, 1988c; 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: Critical Measured Value: 16% (OECD 301D) (RIFM, 2000a)
Bioaccumulation: Screening Level: 219 .1 L/kg (US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-hr *Daphnia magna* EC50: 1.7 mg/L (RIFM, 2000b)

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* EC50: 1.7 mg/L (RIFM, 2000b)

RIFM PNEC is: 0.34 µg/L

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

1. Identification

1 **Chemical Name:** 2-Benzylheptanol
2 **CAS Registry Number:** 92368-90-6
3 **Synonyms:** Benzenepropanol,.β.-pentyl-; 2-ベンジルヘプタノール; Jasmol; 2-Benzylheptanol
4 **Molecular Formula:** $C_{14}H_{22}O$
5 **Molecular Weight:** 206.29
6 **RIFM Number:** 5572

2. Physical data

1. **Boiling Point:** 312.88 °C [US EPA, 2012a]
2. **Flash Point:** 252.00 °F. TCC (122.10 °C)*
3. **Log K_{OW}:** 4.44 [US EPA, 2012a]
4. **Melting Point:** 57.82 °C [US EPA, 2012a]
5. **Water Solubility:** 21.23 mg/L [US EPA, 2012a]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 2.92e-005 mm Hg @ 25 °C [US EPA, 2012a], 0.0000149 mmHg @ 20 °C [US EPA, 2012a]
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Not Available

*http://www.thegoodscentscompany.com/data/rw1383631.html, retrieved 8/9/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.11% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.00063 mg/kg/day or 0.041 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.0088 mg/kg/day (RIFM, 2015b)

*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; 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:** 77%, read across from phenethyl alcohol (CAS # 60-12-8)

RIFM, 2013b **(data also available in** RIFM, 1986a; RIFM, 1987; RIFM, 1988a; RIFM, 1988b; 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, the amount unaccounted for among humans was attributed to evaporation from the treatment site).

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate (Expert Judgment)

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

*Due to potential discrepancies with the current in silico tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further detail.

2. Analogs Selected:
   a. **Genotoxicity:** 2-Methyl-5-phenylpentanol (CAS # 25634-93-9)
   b .**Repeated Dose Toxicity:** β-Methylphenethyl alcohol (CAS # 1123-85-9)
   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:** None

3. **Read across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

2-Benzylheptanol is not reported to occur in food by the VFC*.
*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 8/9/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-benzylheptanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic potential of 2-benzylheptanol was assessed in an Ames study conducted in compliance with GLP regulations in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 were treated with 2-benzylheptanol in DMSO (dimethyl sulfoxide) at concentrations up to 500 μg/plate in the presence and absence of metabolic activation. No increase was observed in the number of revertants in any strain in the presence or absence of S9 (RIFM, 2001). Under the conditions of the study, 2-benzylheptanol was not mutagenic to bacteria.

There are no studies assessing the clastogenic potential of 2-benzylheptanol. Read across material 2-methyl-5-phenylpentanol (CAS # 25634-93-9; see Section 5) was assessed for clastogenicity in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of male and female NMRI mice (5/sex/dose) were treated 2-methyl-5-phenylpentanol in arachis oil once via oral gavage at the concentrations of 250, 500 and 1000 mg/kg b.w. Animals in the low and intermediate dosage groups were euthanized at 24 h after dosing while the animals in the high dose group were divided into 3 groups to be euthanized at 24, 48 and 72 h after dosing. Compared to the vehicle controls, no significant increase in the number of micronucleated polychromatic erythrocytes was observed (RIFM, 1988e). Under the conditions of the study, 2-methyl-5-phenylpentanol was considered not clastogenic in the *in vivo* micronucleus test and this can be extended to 2-benzylheptanol.

Based on the available data, 2-benzylheptanol does not present a concern for genotoxic potential.

Additional References: RIFM, 1988d.

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

10.1.2. Repeated dose toxicity

The margin of exposure for 2-benzylheptanol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-benzylheptanol. Read across material, β-methylphenethyl alcohol (CAS # 1123-85-9; see section 5) has sufficient repeated dose toxicity data. 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 in terminal body weights among the treated females. However, this was not considered to be a treatment-related adverse effect, since there was no parallel effect reported among the treated males. The difference in terminal body weights among the treated females were small (7–9% decrease) as compared to the control. There was also no dose-response relationship. 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 in both sexes and increased kidney weights at the two highest doses in the 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 2-benzylheptanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the β-methylphenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 2-benzylheptanol, 40/0.0088 or 4545.**

When correcting for skin absorption, the total systemic exposure to 2-benzylheptanol (8.8 μg/kg/day) is below (close to) 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: 2/17/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-benzylheptanol is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient reproductive toxicity data on 2-benzylheptanol or any read across materials. The total systemic exposure to 2-benzylheptanol is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 2-benzylheptanol. 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 10000 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 the treated animals. Thus, the NOAEL for maternal and developmental toxicity was determined to be 10000 ppm or 799 mg/kg/day, the highest dose tested (RIFM, 2013a). 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. Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day. A dose related increase in skeletal abnormalities was reported among the animals of the mid- and high-dose group animals, thus, the NOAEL for developmental toxicity was determined to be 140 mg/kg/day (RIFM, 2013a). In another dermal developmental toxicity study, 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 decreases in fetal body weights for litters of the 140 mg/kg/day and higher dose groups. 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 (RIFM, 2013a). 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. The NOAEL for developmental toxicity was determined to be 70 mg/kg/day, based on increased incidences of fetal skeletal ossifications among the mid- and high-dose group animals, and gross, soft tissue and skeletal alterations among the high dose group animals (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, 2013b; data also in RIFM, 1985a, 1986b, 1988f; Ford, 1987a; Burdock et al., 1987; Ford, 1990a, 1990b; 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 2-benzylheptanol 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 2-benzylheptanol, 54/0.0088 or 6136.**

When correcting for skin absorption, the total systemic exposure to 2-benzylheptanol (8.8 μg/kg/day) is below (close to) the TTC (9 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class II material at the current level of use.

There are no reproductive toxicity data on 2-benzylheptanol 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 2-benzylheptanol (8.8 μg/kg/day) is below **(close to)** the TTC (9 μg/kg bw/day; Kroes et al., 2007; 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: 02/16/2017.

10.1.4. Skin sensitization

Based on the available data and read across to 2-methyl-5-phenylpentanol (CAS # 25634-93-9); 2-benzylheptanol 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), 2-benzylheptanol 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 (OECD Toolbox 3.4; Toxtree 2.6.13). In a Guinea pig maximization test 2-benzylheptanol and read across material 2-methyl-5-phenylpentanol were reported to be non-sensitizers (RIFM, 1985b; RIFM, 1988c). Moreover, in a human confirmatory study no sensitization reactions were observed to 2-methyl-5-phenylpentanol (RIFM, 1997). Based on weight of evidence from structural analysis, animal studies and read across to 2-methyl-5-phenylpentanol, 2-benzylheptanol does not present a concern for skin sensitization.

Additional References: RIFM, 1985d.

Literature Search and Risk Assessment Completed on: 2/17/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra and available study data, 2-benzylheptanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity, $1000\,L\,mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Phototoxicity and photoallergenicity of 2-benzylheptanol were evaluated in Dunkin Hartley guinea pigs and there were no observed effects (RIFM, 1985c). Based on the lack of absorbance in the critical range and the available *in vivo* studies, 2-benzylheptanol would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/07/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-benzylheptanol, 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 2-benzylheptanol. Based on the Creme RIFM model, the inhalation exposure is 0.041 mg/day. This exposure is 11.5 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: 02/03/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2-benzylheptanol 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 (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. 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, 2-benzylheptanol 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 v4.11 (US EPA, 2012a) did not identify 2-benzylheptanol 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 v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), 2-benzylheptanol presents a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 2000a: A closed bottle biodegradation test was conducted with 2-benzylheptanol according to the OECD 301D method. After 28 days, biodegradation of 16% was observed.

10.2.3.2. Ecotoxicity. RIFM, 2000b: A 48-h *Daphnia magna* acute toxicity test was conducted following the OECD 202 I guidelines. Under the conditions of this study, the EC50 value was 1.7 mg/L calculated as the geometric mean of EC0/EC100 values.

RIFM, 2015a: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-hr ErC50 and EyC50 based on geometric mean measured concentrations was 5.29 mg/L and 2.08 mg/L, respectively.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.10 mg/L			1,000,000	0.00210 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.09 mg/L	0.78 mg/L	1.47 mg/L	10,000	0.078 µg/L	Neutral Organics

Tier 3: Measured Data Including Read across data

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		1.7 mg/L		5000	0.34 µg/L	
Algae		2.08 mg/L				

10.2.3.3. Other available data. 2-Benzylheptanol has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.44	4.44
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 class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.34 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: 9/22/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/

- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&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.2018.01.040.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.040.

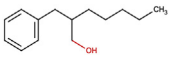
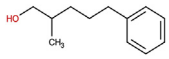
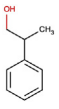
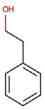
Appendix

Read across justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target substance and the read across analogs were calculated using EPI SuiteTM v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read across material		
Principal Name	2-Benzylheptanol	2-Methyl-5-phenylpentanol	beta-Methylphenethyl alcohol	Phenethyl alcohol
CAS No.	92368-90-6	25634-93-9	1123-85-9	60-12-8
Structure				
Similarity (Tanimoto score)		0.78	0.69	0.62
Read across endpoint		• Skin sensitization • Genotoxicity	• Repeated dose	• Developmental
Molecular Formula	$C_{14}H_{22}O$	$C_{12}H_{18}O$	$C_9H_{12}O$	$C_8H_{10}O$
Molecular Weight	206.33	178.28	136.20	122.17
Melting Point (°C, EPISUITE)	57.82	54.4	6.10	5.81
Boiling Point (°C, EPISUITE)	312.88	292.61	232.23	224.85
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.00389	0.0154	1.35	3.24
Log Kow (KOWWIN v1.68 in EPISUITE)	4.0[1]	2.9[3]	1.98	1.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	29.6[2]	412.8[4]	5677	2.22E+004
J_{max} (mg/cm^2/h, SAM)	2.641	17.736	293.535	355.140

Henry's Law ($Pa \cdot m^3$/mol, Bond Method, EPISUITE)	1.58E-006	7.45E-007	3.83E-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)	• Structural alert for non-genotoxic carcinogenicity Substituted n-alkylcarboxylic acids (nongentox)	• 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		
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH orNH_2 group			• Non-binder without OH orNH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (good reliability)			• Toxicant (good reliability)
Skin Sensitization				
Protein binding by OASIS v1.4	• No alert found	• No alert found		
Protein binding by OECD	• No alert found	• No alert found		
Protein binding potency	• Not possible to classify	• Not possible to classify		
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found		
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Sensitizer (good reliability)		
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4

1.RIFM, 2016b.
2. RIFM, 2016a.
3. RIFM, 2012.
4. RIFM, 1989.

Summary

There are insufficient toxicity data on the target material 2-benzylheptanol (CAS # 92368-90-6). 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, 2-methyl-5-phenylpentanol (CAS # 25634-93-9), beta-methylphenethyl alcohol (CAS # 1123-85-9) 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 2-benzylheptanol (CAS # 92368-90-6), 2-methyl-5-phenylpentanol (CAS # 25634-93-9) was used as a read across analog for the skin senzitization and genotoxicity endpoints, beta-methylphenethyl alcohol (CAS # 1123-85-9) was used as a read across analog for the repeated dose toxicity endpoint and phenethyl alcohol (CAS # 60-12-8) was used as a read across analog for the developmental toxicity endpoint.
  - o The target substance and the read across analogs are structurally similar and belong to the structural class of primary alcohol with aromatic moiety.
  - o The target substance and the read across analogs are all phenyl-substituted primary alkyl alcohols.
  - o The key difference between the target substance and the read across analogs is that they have different chain length of branching in the aliphatic extended fragment of the structure. The target substance has a five-carbon chain branch in the 2-position, while the read across analogs 2-methyl-5-phenylpentanol and beta-methylphenethyl alcohol have methyl group branching in the 2-postiion, whereas phenethyl

alcohol lacks branching all together. These structural differences between the target substance and the read across analogs do 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. Differences are predicted for J_{max}, which estimates skin absorption. The J_{max} values translate to 10% skin abrorption for the target substance and 80% absorption for all of the read across analogs. While percentage skin absorption estimated from J_{max} values indicate exposure of the substance, they do not represent hazard or toxicity parameters. Thererfore, the J_{max} of the target substance and the appropriate read across analog material are not used directly in comparing substance hazard or toxicity. However, these parameters provide context to assess the impact of bioavailability on toxicity comparisons between the individual materials.
- 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 According to the ISS model, the target substance has a non-genotoxic carcinogenicity alert whereas the read across analog 2-methyl-5-phenylpentanol does not have this alert. Also, the target substance as well as the read across analog 2-methyl-5-phenylpentanol are alerted for Michael addition reaction. Other in silico models of genotoxicity do not give any alerts for the read across analog. The data described in the genotoxicity section above shows that the read across analog 2-methyl-5-phenylpentanol does not pose a concern for genetic toxicity, and therefore these alerts will be superseded by the data.
- o According to the CAESAR model for developmental toxicity, the target substance and the read across analog are predicted to be toxicants with good reliability. The ER binding alert is negative for both of the substances. The data described in the developmental toxicity section shows that the margin of exposure is adequate at the current level of use of the read across analog. Therefore, this alert can be ignored.
- o According to the CAESAR model for skin sensitization, the target substance as well as the read across analog are predicted to be sensitizers with good reliability. All other protein binding alerts are negative for both of the substances. The data described in the skin sensitization section shows that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alerts will be superseded by the data.
- o The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

Explanation of Cramer Class

Due to potential discrepancies with the current in silico tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1.Normal constituent of the body **No**
Q2.Contains functional groups associated with enhanced toxicity **No**
Q3.Contains elements other than C,H,O,N, divalent S **No**
Q5.Simply branched aliphatic hydrocarbon or a common carbohydrate **No**
Q6.Benzene derivative with certain substituents **No**
Q7.Heterocyclic **No**
Q16.Common terpene **No**
Q17.Readily hydrolysed to a common terpene **No**
Q19.Open chain **No**
Q23.Aromatic **Yes**
Q27.Rings with substituents **Yes**
Q28.More than one aromatic ring **No**
Q30.Aromatic Ring with complex substituents **Yes** Class Intermediate (Class II).

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