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Short review

RIFM fragrance ingredient safety assessment, Fenchyl alcohol, CAS registry number 1632-73-1

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ABSTRACT

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 15 mg/kg/day. A gavage 13-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 10,714 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

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Version: 071615. This version replaces any previous versions.
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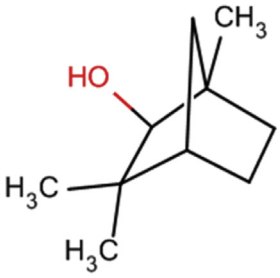
CAS Registry Number: 1632-73-1



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration.
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor.
BCF – Bioconcentration Factor.
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.
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.

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews the relevant data that 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*RIFM's Expert Panel 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 use conditions is supported by the existing information.

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 15 mg/kg/day. A gavage 13-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 10714 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(RIFM, 2013c; RIFM, 2013b)
Repeated dose toxicity: NOAEL = 15 mg/kg/day	(Gaunt, 1971)
Developmental and reproductive toxicity: NOAEL = 300 mg/kg/day	(RIFM, 2011)
Skin sensitization: Not a sensitization concern. Exposure is below the DST	(RIFM, 1976)
Phototoxicity/photoallergenicity: Not phototoxic/photoallergenic	(UV spectra, RIFM Database)
Local respiratory toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 74% (OECD 301F)	(RIFM, 1997a)
Bioaccumulation: Screening Level: 57.35 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Screening Level: 48 h *Dapnia magna* LC50: 13.38 mg/l	(EPISUITE ver 4.1)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48 h *Dapnia magna* LC50: 13.38 mg/l	(EPISUITE ver 4.1)
RIFM PNEC is: 1.338 μg/l	

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Fenchyl alcohol
2. **CAS Registry Number:** 1632-73-1
3. **Synonyms:** Bicyclo[2.2.1]heptan-2-ol, 1,3,3-trimethyl-, 2-Fenchanol, Fenchol, α-Fenchyl alcohol, Fenchyl alcohol, 1,3,3-Trimethylbicyclo(2.2.1)heptan-2-ol, 1,3,3-Trimethyl-2-norbornanol, 1,3,3-ﾄﾘﾒﾁﾙ-2-ﾋﾞｼｸﾛ〔2.2.1〕ﾍﾌﾟﾀﾉｰﾙ, 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 718

2. Physical data

1. **Boiling Point:** 209.98 °C [EPI Suite]
2. **Flash Point:** 163 °F; CC [FMA database]
3. **Log K_{OW}:** Log Pow = 3.0 [RIFM, 1997b], 2.85 [EPI Suite]
4. **Melting Point**: 48 °C [FMA database], (calculated) 26.56 °C [EPI Suite]
5. **Water Solubility:** 461.4 mg/L [EPI Suite]
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0136 mm Hg @ 20 °C [EPI Suite 4.0], 0.1 mm Hg 20 °C [FMA database], 0.0247 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Does not significantly absorb in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic:** A crystalline solid that is colorless to pale yellow with a medium balsamic, camphor, borneol pine, woody, dry, sweet, and lemon odor.[1]

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year [IFRA, 2011]
2. **Average Maximum Concentration in Hydroalcoholics:** 0.001% [IFRA, 2011]
3. **97.5**th **Percentile:** 0.05% [IFRA, 2004]
4. **Dermal Exposure**[a]**:** 0.0013 mg/kg/day [IFRA, 2004]
5. **Oral Exposure:** Not available
6. **Inhalation Exposures**[b]**:** 0.000077 mg/kg/day [IFRA, 2004]
7. **Total Systemic Exposure (Dermal + Inhalation):** 0.0014 mg/kg/day

[a] Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). (Cadby, 2002; Ford, 2000).

[b] Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.0014 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert judgment	Toxtree (v. 2.6)	Toolbox (v. 3.2)
I[a]	I	II

[a] See Appendix below for explanation.

2. **Analogues selected**:
   a. **Genotoxicity:** *l*-Borneol (CAS # 464-45-9)
   b. **Repeated Dose Toxicity:** Isobornyl acetate (CAS # 125-12-2)
   c. **Developmental and Reproductive Toxicity**: Isobornyl acetate (CAS # 125-12-2)
   d. **Skin Sensitization**: None
   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)

Fenchyl alcohol is reported to occur in the following foods[2] and in some natural complex substances (NCS):

Beer	Fennel (Foeniculum vulg., ssp. capillaceum; var.)
Bullock's heart (Annona reticulata L.)	Ginger (Zingiber species)
Citrus fruitsEucalyptus oil (Eucalyptus globulus Labill)	Grape (Vitis species)
	Grape brandy
Hop (Humulus lupulus)	Pepper (Piper nigrum L.)
Litchi (Litchi chinensis Sonn.)	Pistachio oil (Pistacia vera)
Malt	Rosemary (Rosmarinus officinalis L.)
Mangifera species	Sweetsop, sugar apple (Annona squamosa L.)
Mastic (Pistacia lentiscus)	Tea
Nutmeg (Myristica fragrans Houttuyn)	Thyme (Thymus species)
Ocimum species	

8. IFRA standard:

None.

[1] http://www.thegoodscentscompany.com/data/rw1011531.html, retrieved 12/4/13.

[2] 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.

9. REACH dossier:

Pre-registered for 2010; No dossier available as of 7/16/2015.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, Fenchyl alcohol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

Fenchyl alcohol was assessed for genotoxic potential in the Bluescreen assay and was found to be negative for genotoxicity and cytotoxicity in the presence and absence of metabolic activation (S9 mix). There are no data assessing the genotoxic risk of fenchyl alcohol. Read across can be made to l-borneol (CAS # 464-45-9; see Section 5) which has been assessed for mutagenicity in a GLP compliant bacterial reverse mutation assay in accordance with OECD TG 471 using the plate incorporation method. Salmonella typhimurium strains TA1535, TA1537, TA98, TA102, and TA100 and *Escherichia coli* strain WP2uvrA were treated with l-borneol in DMSO (dimethyl sulfoxide) at concentrations up to 1000 μg/plate in the presence and absence of S9 mix (RIFM, 2013b). Under the conditions of the study, l-borneol is considered not mutagenic in bacteria.

There are no clastogenicity data for fenchyl alcohol. A GLP in vitro micronucleus study was conducted on the read across material, l-borneol, in accordance with OECD TG 487. Human peripheral blood lymphocytes were exposed to varying concentration of l-borneol in DMSO up to 600 μg/ml for 4 h, with and without metabolic activation and 24 h without metabolic activation. Under the conditions of the study, l-borneol was considered not clastogenic (RIFM, 2013c).

l-borneol does not present a concern for genotoxicity and this can be applied to the target material, fenchyl alcohol.

Additional references: RIFM, 2013a.

Literature search and risk assessment completed on: 11/22/13.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on fenchyl alcohol. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has a gavage 13-week subchronic toxicity study that was conducted in rats. The NOEL was determined to be 15 mg/kg/day, based on increased urinary cell excretion (Gaunt et al., 1971). Therefore, the MOE is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 15/0.0014 or 10,714.

Additional references: Bhatia, 2008a; Belsito, 2008; Boutin, 1985; Bhatia, 2008b; Wu et al., 2005; Buchbauer, 1993; Wagreich, 1941; Quick, 1928, 1927; Tamura, 1962; Robertson, 1969; Pryde, 1934; Leibman and Ortiz, 1973; Lehman-McKeeman and Caudill, 1999; Leclerc, 2002; Boutin, 1984; Bhatia, 2008c; Antoine, 1984; Green, 1996; Boutin, 1981, 1983; Pinching and Doving, 1974; Schafer, 1982.

Literature search and risk assessment completed on: 11/22/13.

10.1.5. Developmental and reproductive toxicity

The margin of exposure for Fenchyl alcohol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.6. Risk assessment

There are no developmental toxicity data on fenchyl alcohol. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has an OECD 414 gavage developmental toxicity limit dose study that was conducted in rats. The NOAEL was determined to be 1000 mg/kg/day, the only dosage tested (ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl acetate Exp Key Developmental toxicity/teratogenicity.001 (accessed 08/12/13)). Therefore, the MOE for developmental toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.0014 or 7,14,286.

There are no repeated dose toxicity data on fenchyl alcohol. Read across material isobornyl acetate (CAS # 125-12-2) has an enhanced OECD 415 gavage 1-generation reproductive toxicity study that was conducted in rats. The NOAEL for reproductive toxicity in the parental generation was determined to be 300 mg/kg/day, the highest dosage tested (RIFM, 2011; data also available in Politano, 2013). Therefore, the MOE for reproductive toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0014 or 2,14,286.

Additional references: Bhatia et al., 2008a; Belsito et al., 2008; Boutin, 1985; Bhatia et al., 2008b; Wu, 2005; Buchbauer et al., 1993; Wagreich, 1941; Quick, 1928, 1927; Tamura et al., 1962; Robertson, 1969; Pryde, 1934; Leibman and Ortiz, 1973; Lehman-McKeeman and Caudill, 1999; Leclerc et al., 2002; Boutin et al., 1984; Bhatia et al., 2008c; Antoine et al., 1984; Green and Tephly, 1996; Boutin, 1981, 1983; Pinching and Doving, 1974; Schafer, 1982.

Literature search and risk assessment completed on: 11/22/13.

10.1.7. Skin sensitization

Based on the available data and application of the non-reactive DST, fenchyl alcohol does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the available data and application of the non-reactive DST, fenchyl alcohol does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts, 2007; Toxtree 2.5.0; OECD toolbox v3.1). In the human maximization test, no reactions (0/25) indicative of sensitization were observed to fenchyl alcohol at 4% in petrolatum (RIFM, 1976). As there are no predictive tests available in animal models, the dermal exposure to fenchyl alcohol was benchmarked utilizing the non-reactive DST. The dermal exposure from hydroalcoholic products is 0.001% which is below the DST for non-reactive materials when evaluated in QRA categories 3 and 4 (DST levels of 0.14% and 0.41%, respectively).

Additional references: None.

Literature search and risk assessment completed on: 11/22/13

10.1.9. Phototoxicity/photoallergenicity

Based on the UV spectra, fenchyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for fenchyl alcohol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009).

Based on lack of absorbance, fenchyl alcohol does not present a concern for phototoxicity or photoallergenicity.

Additional references: None.

Literature search and risk assessment completed on: 11/22/13.

10.1.11. Local respiratory toxicity

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

10.1.12. Risk assessment

There are no inhalation data available on fenchyl alcohol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.05%. If the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) the inhalation combined exposure would be 0.005 mg/day, as calculated using the 97.5th percentile IFRA survey hydroalcoholic use value by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model. This value is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009) and is deemed safe for use at the reported use level.

Additional References: Helmig, 1999a; Helmig, 1999b.

Literature search and risk assessment completed on: 07/7/15.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of fenchyl 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) 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, fenchyl alcohol 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 EPISUITE ver 4.1 did identify fenchyl alcohol as being possibly persistent but not 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 EPISUITE ver.4.1). 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 VoU (as of 2011), fenchyl alcohol does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. **RIFM, 1997a:** Biodegradation was determined by the Manometric Respirometry Test according to the OECD 301F method. The rate of degradation after 28 days was 74%.

Ecotoxicity: No data available.

Other available data: Fenchyl alcohol has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	28.06 mg/l			1,000,000	0.028 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	21.78 mg/l	13.38 mg/l	13.79 mg/l	10,000	1.338 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	3.0	3.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	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 1.338 µg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment completed on: 11/22/13.

11. Literature search[3]

- **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

This is not an exhaustive list.

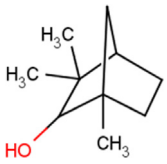
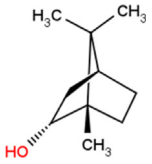
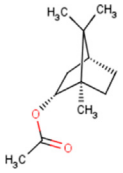
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.08.022.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.08.022.

Appendix

	Target material	Read across materials	
Principal name	Fenchyl alcohol	l-Borneol	Isobornyl acetate
CAS No.	1632-73-1	464-45-9	125-12-2
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/1632-73-1.html	http://www.thegoodscentscompany.com/opl/464-45-9.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		• Genotoxicity	• Repeated Dose • Devel/Repro
Molecular formula	C10H18O	C10H18O	C12H20O2
Molecular weight	154.25	154.25	196.29
Melting point (°C, EPISUITE)	26.56	26.56	34.11
Boiling Point (°C, EPISUITE)	209.98	209.98	225.89
Vapor pressure (Pa @ 25 °C, EPISUITE)	3.293	0.0572	14.27
Log Kow (KOWWIN v1.68 in EPISUITE)	2.85	2.85	3.86
Water solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	461.4	1186	9.721
J_{max} (mg/cm^2/h, SAM)	102.9671013	43.96956395	18.65520626
Henry's law (Pa m^3/mol, Bond method, EPISUITE)	0.679384	0.679384	44.228362
Similarity (Tanimoto score)[a]		57%	NA[b]
Genotoxicity			
DNA binding (OASIS v1.1)	•No alert found	• No alert found	
DNA binding (OECD)	•No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	•No alert found	• No alert found	
DNA alerts for Ames, MN, CA (OASIS v1.1)	•No alert found	• No alert found	
In vitro mutagenicity (Ames test) alerts (ISS)	•No alert found	• No alert found	
	•No alert found	• No alert found	

[3] Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

(*continued*)

	Target material	Read across materials	
Principal name	Fenchyl alcohol	l-Borneol	Isobornyl acetate
In vivo mutagenicity (Micronucleus) alerts (ISS)			
Oncologic classification (OECD)	•Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized		Not categorized
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non binder, impaired OH or NH2 group		Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (low reliability)		NON-Toxicant (low reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See Supplemental data 1	See Supplemental data 2	See Supplemental data 3

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
[b] The metabolite of the read-across materials is an analog of the target.

12. Summary

There are insufficient toxicity data on fenchyl alcohol (RIFM # 718, CAS # 1632-73-1). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

13. Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012).

14. Conclusion/rationale

- l-Borneol and isobornyl acetate (analogs) were used as a read-across for fenchyl alcohol (target) based on:
  - The target and analog (l-borneol) belong to the generic class of alcohols, specifically, cyclic terpene alcohol/bicyclic bridged secondary alcohols.
  - The target and analog (l-borneol) have a [2.2.1] bridged ring system and an alcohol functional group. l-Borneol is the hydrolysis metabolite of the isobornyl acetate.
  - The only difference is in the position of the dimethyl group. The target has the dimethyl group in the C3 atom, while l-borneol has the dimethyl group attached in the bridge (C7 atom). The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and read-across material show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - As per the OECD Toolbox, the target and analog are expected to be metabolized similarly. Isobornyl acetate is predicted to be metabolized to l-Borneol (metabolite # 3).

15. 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? **Yes** – Low (Class I).

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