Update to RIFM fragrance ingredient safety assessment, fenchyl alcohol, CAS Registry Number 1632-73-1


Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA
Member Expert Panel for Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA
Member Expert Panel for Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden
Member Expert Panel for Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA
Member Expert Panel for Fragrance Safety, 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
Member Expert Panel for Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA
Member Expert Panel for Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA
Member Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center in Molecular Toxicology, 1316 Biomedical Research Building (BBB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA
Member Expert Panel for Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA
Member Expert Panel for Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA
Member Expert Panel for Fragrance Safety, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

Handling Editor: Dr. Jose Luis Domingo

Version: 121421. This safety assessment is an updated version and replaces the previous version at http://doi.org/10.1016/j.fct.2015.08.022 (RIFM, 2015). All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

**Name:** Fenchyl alcohol  
**CAS Registry Number:** 1632-73-1

**Abbreviation/Definition List:**
- AF: Assessment Factor
- BCF: Bioconcentration Factor
- 2-Box Model: A RIFM, Inc. proprietary in silico tool used to calculate fragrance air exposure concentration

*Corresponding author. E-mail address: gsullivan@rifm.org (G. Sullivan).*

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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 with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Fenchyl alcohol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog borneol (CAS # 464-45-9) show that fenchyl alcohol is not expected to be genotoxic. Data on read-across material isobornyl acetate (CAS # 125-12-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; fenchyl alcohol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material and the exposure to fenchyl alcohol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; fenchyl alcohol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC)), are <1.

### Environmental Safety Assessment

**Hazard Assessment:**
- **Persistence:** Critical Measured Value: 74% (OECD 301F) (RIFM, 1997b)
- **Bioaccumulation:** Screening-level: 57.35 L/kg (EPI Suite v4.11); US EPA, 2012a
- **Ecotoxicity:** Screening-level: 48-h Daphnia magna LC50: 13.38 mg/L (EPI Suite; US EPA, 2012b)
- **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards

**Risk Assessment:**
- **Screening-level:** PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvin, 2002)
- **Critical Ecotoxicity Endpoint:** 48-h Daphnia magna LC50: 13.38 mg/L (EPI Suite; US EPA, 2012b)
- **RIFM PNEC in:** 1.338 μg/L
  - **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe <1

### 1. Identification

- **Chemical Name:** Fenchyl alcohol
  - **CAS Registry Number:** 1632-73-1
  - **Synonyms:** Bicyclo[2.2.1]heptan-2-ol, 1,3,3-trimethyl-, (1S-endo)-; 2-Fenchanol; Fenchol; α-Fenchyl alcohol; 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethyl-2-norbornanol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethyl-2-norbornanol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trime-thylbicyclo[2.2.1]heptan-2-ol; Fenchyl alcohol
  - **Molecular Formula:** C10H16O
  - **Molecular Weight:** 154.26 g/mol
  - **RIFM Number:** 718

- **Chemical Name:** (−)-α-Fenchol
  - **CAS Registry Number:** 512-13-0
  - **Synonyms:** (−)-α-Fenchol; (15-endo)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol; 1,3,3-trimethyl-2-bicyclo[2.2.1]heptan-2-ol
  - **Molecular Formula:** CaHoO
  - **Molecular Weight:** 154.53 g/mol
  - **RIFM Number:** 5183

### 2. Physical data*

1. **Boiling Point:** 209.98 °C (EPI Suite)
2. **Flash Point:** 73 °C (Globally Harmonized System), 163 °F (CC (Fragrance Materials Association (FMA))
3. **Log Kow:** 3.0 (RIFM, 1997a), 2.85 (EPI Suite)
4. **Melting Point:** 48 °C (EPI Suite)
5. **Water Solubility:** 461.4 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0126 mm Hg at 20 °C (EPI Suite v4.0), 0.1 mm Hg at 20 °C (FMA Database), 0.0247 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ cm⁻¹)
9. **Appearance/Organoleptic:** A solid colorless crystalline mass

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(continued on next column)
*Physical data for both materials included in this assessment are identical.

3. Volume of use (worldwide band)
1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)*
1. 95th Percentile Concentration in Fine Fragrance: 0.0012% (RIFM, 2017)
2. Inhalation Exposure**: 0.00016 mg/kg/day or 0.011 mg/day (RIFM, 2017)
3. Total Systemic Exposure***: 0.00048 mg/kg/day (RIFM, 2017)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015a, 2017).

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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 have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

5. Derivation of systemic absorption
1. Dermal: Assumed 100%
2. Oral: Assumed 100%
3. Inhalation: Assumed 100%

6. Computational toxicology evaluation
1. Cramer Classification: Class I, Low* (Expert Judgment)

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v3.1</th>
<th>OECD QSAR Toolbox v4.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>i</td>
<td>iii</td>
</tr>
</tbody>
</table>

*See Appendix below for further details.

2. Analogs Selected:
   a. Repeated Dose Toxicity: Isobornyl acetate (CAS #: 125-12-2); Weight of evidence (WoE): 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (CAS #: 76-22-2)
   b. Reproductive Toxicity: Isobornyl acetate (CAS #: 125-12-2); WoE: 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (CAS #: 76-22-2)
   c. Skin Sensitization: None
   d. Phototoxicity/Photoallergenicity: None
   e. Local Respiratory Toxicity: None
   f. Environmental Toxicity: None
   g. Read-across Justification: See Appendix below

7. Metabolism
   No relevant data available for inclusion in this safety assessment.

8. Natural occurrence
   Fenchyl alcohol is reported to occur in the following foods by the

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VCF*:

<table>
<thead>
<tr>
<th>Material</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>Eucalyptus oil (Eucalyptus globulus Labill)</td>
</tr>
<tr>
<td>Fenchyl's heart (Artemisia recuticulata)</td>
<td>Fennel (Foeniculum vulg., var. capillaceum)</td>
</tr>
<tr>
<td>Copra (Capparis spinosa)</td>
<td>Mastic (Pistacia lentiscus)</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>Ocimum species</td>
</tr>
<tr>
<td>Pistachio oil (Pistacia vera)</td>
<td>Thyme (Thymus species)</td>
</tr>
</tbody>
</table>

(—)-α-Fenchol is not reported to occur in foods by the VCF*.


9. REACH dossier
   Fenchyl alcohol and (—)-α-fenchol are pre-registered for 2010; no dossiers available as of 12/14/21.

10. Conclusion
   The existing information supports the use of this material as described in this safety assessment.

11. Summary
11.1. Human health endpoint summaries
11.1.1. Genotoxicity
   Based on the current existing data, fenchyl alcohol does not present a concern for genotoxicity.

11.1.1.1. 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) (RIFM, 2013c). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. There are no data assessing the mutagenicity of fenchyl alcohol. Read-across can be made to l-bornel (CAS #: 464-45-9; see Section VI), which has been assessed for mutagenicity in a GLP-compliant bacterial reverse mutation assay and in accordance with OECD TG 471 using the plate incorporation method. Salmonella typhi murium strains TA1535, TA1537, TA98, TA102, TA100, and Escherichia coli strain WP2uvrA were treated with l-bornel in dimethyl sulfoxide (DMSO) at concentrations up to 1000 μg/plate in the presence and absence of S9 mix (RIFM, 2013b). Under the conditions of the study, l-bornel 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-bornel, in accordance with OECD TG 487. Human peripheral blood lymphocytes were exposed to varying concentrations of l-bornel in DMSO up to 600 μg/mL for 4 h with and without metabolic activation and for 24 h without metabolic activation. Under the conditions of the study, l-bornel was considered not clastogenic (RIFM, 2013d). l-bornel does not present a concern for genotoxicity, and this can be applied to fenchyl alcohol.

   Additional References: None.

11.1.2. Repeated dose toxicity
   The MOE for fenchyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.
11.1.2.1. Risk assessment. There are no repeated dose toxicity data on fenchyl alcohol. Read-across material isobornyl acetate (CAS # 125-12-2; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a subchronic toxicity study, 15 CFE strain rats/sex/dose were administered isobornyl acetate via gavage at dose levels of 0, 15, 90, or 270 mg/kg/day for 13 weeks (once daily). Animals were observed for clinical signs, hematology, clinical chemistry, and macroscopic and microscopic findings. There were no differences between treated and control animals in the rate of bodyweight gain, food intake, or the results of hematological investigations. At 90 mg/kg/day, increased urinary cell excretion was noted. At 270 mg/kg/day there was a decrease in renal concentrating ability, increased water intake, and increased organ weights (liver, kidney, and cecum). Microscopic changes seen at the high dose included an increased incidence of focal tubular degeneration and atrophy in the kidney and, in males, vacuolation of the tubular epithelium. There was also vacuolation of the epithelial cells of the intrahepatic bile ducts in males. The NOAEL was determined to be 15 mg/kg/day (Gaunt, 1971).

Therefore, the fenchyl alcohol MOE is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure to fenchyl alcohol, 15/0.00048 or 31250.

In addition, the total systemic exposure for fenchyl alcohol (0.48 μg/g/day) is below the TTC (30 μg/g/day; Kroes, 2007) for the repeated dose toxicity endpoint at the current level of use.

Data on metabolite 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) are provided as WoE. Dermal 13-week subchronic toxicity studies were conducted in rats and mice. Ten Fisher 344 rats/sex/dose were treated with 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one at 0, 16, 32, 64, 125, or 250 mg/kg/day in an ethanol vehicle. Dermal treatment was 5 days per week for 13 weeks. There were no treatment-related adverse effects on body weights, clinical signs, hematology, or clinical chemistry. Relative lung weights were reduced in female rats at 64 mg/kg/day, while relative kidney weights were increased in males at 64 mg/kg/day. However, these effects were not dose-dependent. Based on no treatment-treated adverse effects observed up to the highest dose, the NOAEL was determined to be 250 mg/kg/day (ECHA, 2013).

In another study, a group of 10 B6C3F1 mice/sex/dose were treated dermally with 0, 200, 400, 600, 800, or 1000 mg/kg/day 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one in an ethanol vehicle. Dermal treatment was 5 days per week for 13 weeks. Minimal epidermal hyperplasia was observed at the application site at 1000 mg/kg/day in males and 800 and 1000 mg/kg/day in females; however, this is a local effect. No other test material-related alteration was reported (mortality, clinical signs, body weights, organ weights, hematology). Thus, the systemic NOAEL was determined to be 1000 mg/kg/day, the highest dosage tested (ECHA, 2013).

Therefore, the MOE for development toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 1000/0.00048, or 2083333.

There are no fertility 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. Isobornyl acetate was administered to male and female Sprague Dawley rats (25 rats/sex/dose) at dosages of 0, 30, 100, and 300 mg/kg/day via oral gavage. No test material-related adverse effects were seen in P and F1 generation 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 RIFM, 2013a). Therefore, the MOE for fertility is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.00048, or 625000.

In addition, the total systemic exposure to fenchyl alcohol (0.48 μg/kg/day) is below the TTC (30 μg/g/day; Kroes, 2007; Lauwersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.


11.1.4. Skin sensitization

Based on existing data and the application of DST, fenchyl alcohol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for fenchyl alcohol. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a human maximization test, no skin sensitization reactions were observed with 4% fenchyl alcohol (2760 μg/cm²) in petrolatum (RIFM, 1976). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm² (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 below provides the maximum acceptable concentrations for fenchyl alcohol that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.


11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. 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. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, fenchyl alcohol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ • cm⁻¹ (Henry, 2009).

Additional References: None.


11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of fenchyl alcohol was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material’s volume of use in a region, its log Kow, and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted 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 is > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify fenchyl alcohol as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic, or very persistent and very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECH, 2012a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCPIABF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material’s physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA’s BIOWIN and BCPIABF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current volume of use (2015), fenchyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. RIFM, 1997b: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. The rate of degradation after 28 days was 74%.

Table 1

<table>
<thead>
<tr>
<th>IFRA Category</th>
<th>Description of Product Type</th>
<th>Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST</th>
<th>Reported 95th Percentile Use Concentrations in Finished Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Products applied to the lips</td>
<td>0.069%</td>
<td>5.3 × 10⁻⁴%</td>
</tr>
<tr>
<td>2</td>
<td>Products applied to the axillae</td>
<td>0.021%</td>
<td>0.0025%</td>
</tr>
<tr>
<td>3</td>
<td>Products applied to the face using fingertips</td>
<td>0.41%</td>
<td>0.0013%</td>
</tr>
<tr>
<td>4</td>
<td>Fine fragrance products</td>
<td>0.39%</td>
<td>0.0012%</td>
</tr>
<tr>
<td>5</td>
<td>Products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.10%</td>
<td>0.0029%</td>
</tr>
<tr>
<td>6</td>
<td>Products with oral and lip exposure</td>
<td>0.23%</td>
<td>0.0029%</td>
</tr>
<tr>
<td>7</td>
<td>Products applied to the hair with some hand contact</td>
<td>0.79%</td>
<td>0.0015%</td>
</tr>
<tr>
<td>8</td>
<td>Products with significant anogenital exposure</td>
<td>0.041%</td>
<td>No Data</td>
</tr>
<tr>
<td>9</td>
<td>Products with body and hand exposure, primarily rinse-off</td>
<td>0.75%</td>
<td>0.027%</td>
</tr>
<tr>
<td>10</td>
<td>Household care products with mostly hand contact</td>
<td>2.7%</td>
<td>0.027%</td>
</tr>
<tr>
<td>11</td>
<td>Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate</td>
<td>1.5%</td>
<td>No Data</td>
</tr>
<tr>
<td>12</td>
<td>Products not intended for direct skin contact, minimal or insignificant transfer to skin</td>
<td>No Restriction</td>
<td>0.62%</td>
</tr>
</tbody>
</table>
**Ecotoxicity:** No data available.

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

### 11.2.3. 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.

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

<table>
<thead>
<tr>
<th>Exposure Information</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log K_{ow} Used</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band</td>
<td>10-100</td>
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</tr>
<tr>
<td>Risk Characterization: PEC/PNEC</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 08/23/20.

### 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine’s Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nih.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM’s database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 12/14/21.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112897.
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were 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 material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{\text{max}} \text{ 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- To keep continuity and compatibility with in silico alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

<table>
<thead>
<tr>
<th>Target Material</th>
<th>Read-across Material</th>
<th>Read-across Material</th>
<th>WoE Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Name</td>
<td>Fenchyl alcohol</td>
<td>l-Borneol</td>
<td>1,7,7-Trimethyl bicyclo[2.2.1]heptan-2-one</td>
</tr>
<tr>
<td>CAS No.</td>
<td>1632-73-1</td>
<td>464-45-9</td>
<td>76-22-2</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C_{10}H_{18}O</td>
<td>C_{10}H_{18}O</td>
<td>C_{12}H_{20}O_{2}</td>
</tr>
<tr>
<td>Molecular Weight (g/mol)</td>
<td>154.25</td>
<td>154.25</td>
<td>196.29</td>
</tr>
<tr>
<td>Melting Point (°C, EPI Suite)</td>
<td>43.50</td>
<td>207.00</td>
<td>29.00</td>
</tr>
<tr>
<td>Boiling Point (°C, EPI Suite)</td>
<td>209.98</td>
<td>210.00</td>
<td>221.00</td>
</tr>
<tr>
<td>Vapor Pressure (Pa @ 25°C, EPI Suite)</td>
<td>15.07</td>
<td>6.69</td>
<td>30.40</td>
</tr>
<tr>
<td>Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)</td>
<td>826.00</td>
<td>738.00</td>
<td>9.72</td>
</tr>
<tr>
<td>Log K_{OW}</td>
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<td>2.69</td>
<td>4.30</td>
</tr>
<tr>
<td>J_{\text{max}} (μg/cm²/h, SAM)</td>
<td>77.62</td>
<td>40.10</td>
<td>1.22</td>
</tr>
<tr>
<td>Henry’s Law (Pa m³/mol, Bond Method, EPI Suite)</td>
<td>2.81</td>
<td>1.40</td>
<td>44.28</td>
</tr>
<tr>
<td>Similarity (Tanimoto Score)</td>
<td>1.00</td>
<td>0.52</td>
<td>0.37</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Genotoxicity</td>
<td>Reproductive toxicity</td>
<td>Reproductive toxicity</td>
</tr>
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<td>DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)</td>
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<td>No alert found</td>
<td>Not classified</td>
</tr>
<tr>
<td>DNA Binding (OECD QSAR Toolbox v4.2)</td>
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<td>No alert found</td>
<td>Not classified</td>
</tr>
<tr>
<td>Carcinogenicity (ISS)</td>
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</tr>
<tr>
<td>DNA Binding (Ames, MN, CA, OASIS v1.1)</td>
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<td>No alert found</td>
<td>Not classified</td>
</tr>
<tr>
<td>In Vitro Mutagenicity (Ames, ISS)</td>
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</tr>
<tr>
<td>Oncologic Classification</td>
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<td>Not classified</td>
</tr>
<tr>
<td>Repeated Dose Toxicity</td>
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<td>Not categorized</td>
<td>Not categorized</td>
</tr>
<tr>
<td>Repeated Dose (HESS)</td>
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<td>Not categorized</td>
<td>Not categorized</td>
</tr>
<tr>
<td>Reproductive ER Binding (OECD QSAR Toolbox v4.2)</td>
<td>Non-binder, impaired OH or NH2 group</td>
<td>Non-binder, without OH or NH2 group</td>
<td>Toxicant (experimental value)</td>
</tr>
<tr>
<td>Developmental Toxicity (CAESAR v2.1.6)</td>
<td>Toxicant (low reliability)</td>
<td>Non-toxicant (low reliabilty)</td>
<td>Non-toxicant (low reliabilty)</td>
</tr>
</tbody>
</table>

Genotoxicity

Metabolism

See Supplemental Data 1 See Supplemental Data 2 See Supplemental Data 3 See Supplemental Data 4
Summary
There are insufficient toxicity data on fenchyl alcohol (CAS # 1632-73-1). Hence, in silico evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical-chemical properties, and expert judgment, l-borneol (CAS # 464-45-9) and isobornyl acetate (CAS # 125-12-2) were identified as read-across analogs, and 1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) was identified as a WoE material, with sufficient data for toxicological evaluation.

Metabolism
There are no metabolism data on fenchyl alcohol (CAS # 1632-73-1). Metabolism of the target material was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The read-across material isobornyl acetate (CAS # 125-12-2) is predicted to be metabolized via ester hydrolysis to fenchyl alcohol (CAS # 1632-73-1) and acetic acid (CAS # 64-19-7) in the first step with 0.511 pre-calculated 0.95 intrinsic probability. The target material fenchyl alcohol (CAS # 1632-73-1) is predicted to be metabolized via dehydrogenation to 1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) in the first step. Hence, isobornyl acetate (CAS # 125-12-2) and 1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) can be used as read-across analogs for the target material. Fenchyl alcohol was out of domain for the in vivo rat and in vitro rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model’s domain exclusion was overridden, and a justification was provided.

Conclusion
- l-Borneol (CAS # 464-45-9) was used as a read-across analog for the target material fenchyl alcohol (CAS # 1632-73-1) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the generic class of alcohols; specifically, cyclic terpene alcohol/bicyclic bridged secondary alcohols.
  - The key difference between the target material and the read-across analog 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). These structural differences are toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Isobornyl acetate (CAS # 125-12-2) was used as a read-across analog for the target material fenchyl alcohol (CAS # 1632-73-1) for the repeated dose and reproductive toxicity endpoints.
  - The read-across l-borneol is an ester, which generates an alcohol upon hydrolysis. This alcohol is structurally very similar to the target material.
  - That is why the ester is used as a read-across analog for the target alcohol for the endpoints indicated in the table.
  - The target material is a major metabolite or analog of the major metabolites of the target.
  - Structural differences between the target material and the read-across analog are mitigated by the fact that the read-across could be metabolically hydrolyzed to the target analog. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analog have similar physical-chemical properties. Any differences in the physical-chemical properties of the target material and the read-across analog are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 1,7,7-Trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) was used as a WoE material for the target material fenchyl alcohol (CAS # 1632-73-1) for the repeated dose and reproductive toxicity endpoints.
  - The target material fenchyl alcohol gives rise to a ketone upon dehydrogenation, which is structurally similar to the WoE analog used. That is why 1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) is used as a WoE analog for the target alcohol for the endpoints indicated in the table.
  - The WoE material is a major metabolite or analog of the major metabolites of the target.
  - Structural differences between the target material and the WoE analog are mitigated by the fact that the target could be metabolically oxidized to the WoE analog. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target material and the read-across analog have similar physical-chemical properties. Any differences in the physical-chemical properties of the target material and the WoE analog are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the WoE analog.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification
Due to potential discrepancies between 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.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No

Conclusion
- l-Borneol (CAS # 464-45-9) was used as a read-across analog for the target material fenchyl alcohol (CAS # 1632-73-1) for the genotoxicity endpoint.
- Isobornyl acetate (CAS # 125-12-2) was used as a read-across analog for the target material fenchyl alcohol (CAS # 1632-73-1) for the genotoxicity endpoint.
- 1,7,7-Trimethyl bicyclo[2.2.1]heptan-2-one (CAS # 76-22-2) was used as a WoE material for the target material fenchyl alcohol (CAS # 1632-73-1) for the genotoxicity endpoint.
Q3. Contains elements other than C, H, O, N, and divergent S? No
Q43. Possibly harmful divalent sulfur (not detected via Q3) No
Q4. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q5. Benzene derivative with certain substituents? No
Q42. Possibly harmful analog of benzene? No
Q7. Heterocyclic? No
Q4. Possibly harmful analog of benzene? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? Yes
Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? No, Low (Class I)

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RIFM (Research Institute for Fragrance Materials, Inc), 2008a. A Toxicologic and Dermatologic Assessment of Cyclic and Non-cyclic Terpene Alcohols When Used as Fragrance Ingredients. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 56372.


RIFM (Research Institute for Fragrance Materials, Inc), 2013a. One-generation Reproduction Study of Isobornyl Acetate in Rats, with an Evaluation following Exposure to Different Odours. Brain Res. 82 (2), 195–204.


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