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Update to RIFM fragrance ingredient safety assessment, borneol, CAS Registry Number 507-70-0

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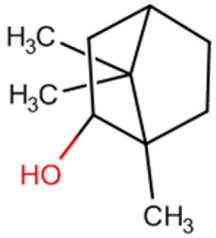

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Name: Borneol
CAS Registry Number: 507-70-0
Additional CAS*
464-45-9 *l*-Borneol
124-76-5 Isoborneol
*Included because the materials are isomers

Abbreviation/Definition List:

(*continued on next page*)

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(*continued*)

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
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, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed 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
NOEL - No Observed Effect Level
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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/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 as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 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 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., 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 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.

Borneol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that borneol is not 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 limited data on the additional materials and the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; borneol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material and the exposure to borneol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; borneol 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2013a; RIFM, 2013b)
Repeated Dose Toxicity: NOAEL = 15 mg/kg/day. Gaunt (1971)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1000 mg/kg/day; Fertility: NOAEL = 300 mg/kg/day. (ECHA REACH Dossier: Isobornyl acetate; ECHA, 2012b; RIFM, 2011)
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 100% (OECD 301F) from CAS # 507-70-0 RIFM (2014)
Bioaccumulation: Screening-level: 27.66 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* EC50: 13.38 mg/L (ECOSAR; 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; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 13.38 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 1.338 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1

1. Identification

Chemical Name: Borneol	Chemical Name: *l*-Borneol	Chemical Name: Isoborneol
CAS Registry Number: 507-70-0	**CAS Registry Number:** 464-45-9	**CAS Registry Number:** 124-76-5
Synonyms: Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, endo-; Borneocamphor; dl-borneol; Bornyl alcohol; 2-Camphanol; d-Camphanol; 2-Hydroxycamphane; 1,7,7-Trimethylbicyclo(2.2.1)heptan-2-ol; Bicyclo(2.2.1)heptan-2-ol, 1,7,7-trimethyl-endo-; Camphol; ﾎﾞﾙﾈｵｰﾙ及びｲｿﾎﾞﾙﾈｵｰﾙ; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol; Borneol Crystals; 2-Borneol; 2-endo-Bornyl alcohol; Borneol	**Synonyms:** l-2-Camphanol; l-Borneol; l-Bornyl alcohol; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol; Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, (1S-endo)-; Borneol-laevo; ﾎﾞﾙﾈｵｰﾙ及びｲｿﾎﾞﾙﾈｵｰﾙ	**Synonyms:** exo-2-Bornanol; 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol; Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, (1R,2R,4R)-rel-; Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, exo-; Borneol(iso); Isoborneol; Isobornyl alcohol; ﾎﾞﾙﾈｵｰﾙ及びｲｿﾎﾞﾙﾈｵｰﾙ
Molecular Formula: $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$	**Molecular Formula:** $C_{10}H_{18}O$
Molecular Weight: 154.25	**Molecular Weight:** 154.25	**Molecular Weight:** 154.25
RIFM Number: 6257	**RIFM Number:** 325	**RIFM Number:** 902

2. Physical data*

1. **Boiling Point:** 212 °C (Fragrance Materials Association [FMA] Database), 209.98 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System [GHS]), >200 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.85 (EPI Suite)
4. **Melting Point**: 204 °C (FMA Database), 26.56 °C (EPI Suite)
5. **Water Solubility:** 1186 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000214 mm Hg at 20 °C (EPI Suite v4.0), 0.3 mm Hg at 20 °C (FMA Database), 0.000429 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:** Hexagonal plates or leaflets with dry-camphoraceous, woody-peppery odor and burning taste somewhat resembling that of mint

*Physical data for all 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. **95**th **Percentile Concentration in Fine Fragrance:** 0.0098% (RIFM, 2017)
2. **Inhalation Exposure**:** 0.00024 mg/kg/day or 0.018 mg/day (RIFM, 2017)
3. **Total Systemic Exposure***:** 0.00089 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 include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015a, 2017).

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 II, Intermediate* (Expert Judgment)

Expert Judgment	Toxtree v 3.1	OECD QSAR Toolbox v 3.2
II	I	I

*See the Appendix below for details.

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

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

Borneol is reported to occur in the following foods by the VCF*:

Alpinia species	Origanum (Spanish) (*Coridothymus cap.*(L.) Rchb.)
Ginger (*Zingiber* species)	Pistacia atlantica
Mastic (*Pistacia lentiscus*)	Rosemary (*Rosmarinus officinalis* L.)
Mentha oils	*Salvia* species
Ocimum species	Thyme (*Thymus* species)

l-Borneol is not reported to occur in foods by the VCF*.

Isoborneol is reported to occur in the following foods by the VCF*:

Ashanti pepper (*Piper guineense* Schum and Thom)	Ginger (*Zingiber species*)
Camomile	Mastic (*Pistacia lentiscus*)
Cinnamomum species	Rosemary (*Rosmarinus officinalis* L.)
Curcuma species	*Salvia* species
Eucalyptus oil (*Eucalyptus globulus* Labill)	Thyme (*Thymus* species)

*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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. These are partial lists.

9. REACH Dossier

Dossiers available for borneol (ECHA, 2018a) and *l*-borneol (ECHA, 2018b); accessed 12/14/21. Dossier available for isoborneol; accessed 12/14/21 (ECHA, 2017a).

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 and use levels, borneol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenicity data on borneol are

insufficient. The additional material, *l*-borneol (CAS # 464-45-9), 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 typhimurium* strains TA1535, TA1537, TA98, TA102, TA100, and *Escherichia coli* strain WP2uvrA were treated with *l*-borneol in dimethyl sulfoxide (DMSO) at concentrations up to 1000 μg/plate in the presence and absence of S9 mix (RIFM, 2013a). Under the conditions of the study, *l*-borneol is considered not mutagenic in bacteria.

There are no data assessing the clastogenicity of borneol. The additional material included in this assessment, *l*-borneol (CAS # 464-45-9), was assessed for clastogenic potential in a GLP in vitro micronucleus study conducted in accordance with OECD TG 487. Human peripheral blood lymphocytes were exposed to varying concentrations of *l*-borneol in DMSO up to 600 μg/mL for 4 h with and without metabolic activation and for 24 h without metabolic activation (RIFM, 2013b). Under the conditions of the study, *l*-borneol was considered non-clastogenic. *l*-Borneol does not present a concern for genotoxic potential, and this can be extended to borneol.

Based on the available data, borneol does not present a concern for genotoxic potential.

Additional References: Simmon (1977); Azizan (1995).

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for borneol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. The repeated dose toxicity data on borneol are insufficient for the repeated dose toxicity endpoint. Read-across material isobornyl acetate (CAS # 125-12-2; see Section VI) has sufficient data to support the repeated dose endpoint. A gavage 13-week subchronic toxicity study was conducted in rats with isobornyl acetate. Rats (CFE Strain, 15/sex/group) were administered the test compound in corn oil by oral gavage once daily at dose levels of 0, 15, 90, or 270 mg/kg/day. 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, a 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 borneol MOE is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure to borneol, 15/0.00089, or 16853.

In addition, the total systemic exposure for borneol (0.89 μg/kg/day) is below the TTC (9 μg/kg/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-related adverse effects seen up 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 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 at 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).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

The MOE for borneol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on borneol. Read-across material isobornyl acetate (CAS # 125-12-2; see Section VI) has an OECD 414 gavage developmental toxicity limit dose study that was conducted in rats. A group of 20 female Wistar rats were administered the test article once daily via gavage at a dose of 1000 mg/kg/day. No test material-related adverse effects were seen in pups. The NOAEL for developmental toxicity was determined to be 1000 mg/kg/day, the only dosage tested (ECHA, 2012b).

In addition, a metabolite of the target material (borneol), which is 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (CAS # 76-22-2), was also used as an additional weight of evidence. Groups of 20 pregnant Sprague Dawley rats per dose group were administered 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one in propylene glycol by gavage at doses of 0, 216, 464, and 1000 mg/kg/day from gestation day (GD) 6–17. No treatment-related effect on prenatal fetal development was observed. Thus, the NOAEL for developmental toxicity was determined to be 1000 mg/kg/day (Leuschner, 1997). In another study, groups of 12 pregnant Himalayan rabbits per dose group were administered 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one in propylene glycol by gavage at doses of 147, 316, and 681 mg/kg/day from GD 6–18. No treatment-related effect on prenatal fetal development was observed up to the highest dose tested. Thus, the NOAEL was determined to be 681 mg/kg/day, the highest dose tested (Leuschner, 1997).

Therefore, the MOE for developmental toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure for borneol, 1000/0.00089, or 1123596.

There are no fertility data on borneol. 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 substance-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, 2013c). **Therefore, the MOE for fertility is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure for borneol, 300/0.00089, or 337079.**

In addition, the total systemic exposure to borneol (0.89 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on existing data for the additional materials (*l*-borneol, CAS # 464-45-9 and isoborneol, CAS # 124-76-5) and application of DST, borneol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for borneol, while limited data are available for additional material (*l*-borneol, CAS # 464-45-9). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v 4.2). In a human maximization test, 2 reactions were observed in a panel of 25 subjects to additional material *l*-borneol at 20% (13800 μg/cm^2) in petrolatum; however, these were considered questionable due to the presence of concurrent test materials for which numerous strong reactions were observed (RIFM, 1972). The human maximization test was repeated, utilizing the same concentration; no reactions (0/23) indicative of sensitization were observed to *l*-borneol (RIFM, 1973). In another human maximization test, no reactions indicative of sensitization were observed with 8% (5520 μg/cm^2) *l*-borneol in petrolatum (RIFM, 1972). Additionally, a human maximization test with additional material isoborneol resulted in no sensitization reactions at 10% (6900 μg/cm^2) in petrolatum. Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (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 borneol 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, borneol 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 borneol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, borneol 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.

Literature Search and Risk Assessment Completed On: 08/07/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for borneol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on borneol. Based on the Creme RIFM Model, the inhalation exposure is 0.018 mg/day. This exposure is 77.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Table 1
Maximum acceptable concentrations for borneol that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	0.0011%
2	Products applied to the axillae	0.021%	0.0058%
3	Products applied to the face using fingertips	0.41%	0.0031%
4	Fine fragrance products	0.39%	0.0098%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0066%
6	Products with oral and lip exposure	0.23%	0.0010%
7	Products applied to the hair with some hand contact	0.79%	0.0012%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.014%
10	Household care products with mostly hand contact	2.7%	0.024%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.98%

Note.
[b]No reported use.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Additional References: Regnault-Roger (1995); Buchbauer (1993); Leclerc (2002); Helmig (1999a); Helmig (1999b).

Literature Search and Risk Assessment Completed On: 08/19/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of borneol 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 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, borneol 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 borneol 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 (ECHA, 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 BCFBAF 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 BCFBAF 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.

11.2.1.1. Risk assessment. Based on the current VoU (2015), borneol does present a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. For CAS # 507-70-0.

RIFM, 2014: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 100% was observed after 34 days.

For CAS # 464-45-9.

RIFM, 2000a: Biodegradation was evaluated by the manometric respirometry test, which was conducted according to Council Directive 92/69/EEC Method C.4-D guidelines. Under the conditions of this study, the test material had a biodegradation of 83% after 28 days.

11.2.2.2. Ecotoxicity. For CAS # 464-45-9.

RIFM, 2000b: The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on mean measured concentration was reported to be 25.9 mg/L.

11.2.2.3. Other available data. Borneol has been registered for REACH with the following additional data available at this time:

For CAS # 507-70-0.

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 77% was observed after 28 days (ECHA, 2018a).

The ready biodegradability of the test material was evaluated using the CO_2 evolution test according to the OECD 301B guideline. Biodegradation of 85% was observed after 28 days (ECHA, 2018a).

For CAS # 464-45-9:

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301 F guideline. Biodegradation of 79.8% was observed after 28 days (ECHA, 2018b).

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 value based on mean measured concentrations for growth rate was reported to be 11.69 mg/L (95% CI: 10.27–13.30 mg/L) (ECHA, 2018b).

For CAS # 124-76-5:

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline, under static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 14.85 mg/L (95% CI: 12.34–17.87 mg/L) (ECHA, 2017a).

11.2.2.4. Risk assessment refinement. Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.85	2.85
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volumes of Use for all the CAS #s.

Based on available data, the RQ for this material is < 1 for EU and NA. No further 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=0&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.nihs.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.

	(Fish) (mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	37.90			1000000	0.0379	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	21.78	13.38	13.79	10000	1.338	Neutral Organics

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.2022.113025.

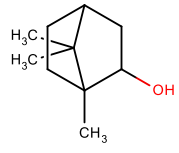
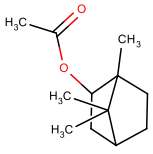
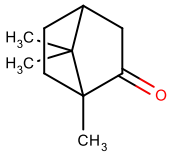
Appendix

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, 2017b).

- 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 substance and the read-across analogs were calculated using EPI Suite 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, 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.

	Target Material	Read-across Material	WoE Material
Principal Name	Borneol	Isobornyl acetate	1,7,7-Trimethylbicyclo[2.2.1] heptan-2-one
CAS No.	507-70-0	125-12-2	76-22-2
Structure			
Similarity (Tanimoto Score)		0.52	0.37

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	WoE Material
Endpoint		• Reproductive toxicity • Repeated dose toxicity	• Reproductive toxicity • Repeated dose toxicity
Molecular Formula	$C_{10}H_{18}O$	$C_{12}H_{20}O_2$	$C_{10}H_{16}O$
Molecular Weight	154.25	196.29	152.24
Melting Point (°C, EPI Suite)	207.00	29.00	176.00
Boiling Point (°C, EPI Suite)	210.00	221.00	204.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.69	30.40	9.60
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	738.00	9.72	100.00
Log K_{OW}	2.69	4.30	2.74
J_{max} (μg/cm2/h, SAM)	40.10	1.22	6.04
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	1.40	44.28	8.40
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Not categorized	Not categorized
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Weak binder, OH group	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)	Non-toxicant (low reliability)	Toxicant (EXPERIMENTAL value)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on borneol (CAS # 507-70-0). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, isobornyl acetate (CAS # 125-12-2) was identified as a read-across analog, and 1,7,7-trimethylbicyclo[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 borneol (CAS # 507-70-0). 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 borneol (CAS # 507-70-0) 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. Borneol 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 is provided.

Conclusions

- Isobornyl acetate (CAS # 125-12-2) was used as a read-across analog for the target material borneol (CAS # 507-70-0) for the repeated dose and reproductive toxicity endpoints.
  - o The read-across 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.
  - o The target material is a major metabolite or analog of the major metabolites of the target.
  - o Structural differences between the target substance 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.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analog are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.
- 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 borneol (CAS # 507-70-0) for the repeated dose and reproductive toxicity endpoints.
  - o The target material 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.
  - o The WoE material is a major metabolite or analog of the major metabolites of the target.
  - o Structural differences between the target substance 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.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the WoE analog are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target substance and the WoE analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q43. Possibly harmful divalent sulfur (not detected via Q3) No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q42. Possibly harmful analog of benzene? No
Q7. Heterocyclic? 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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