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RIFM fragrance ingredient safety assessment, borneol, CAS registry number 507-70-0

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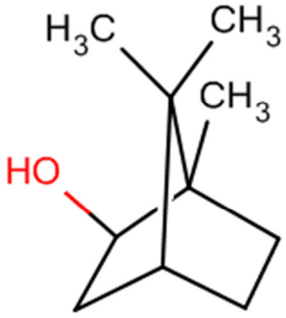

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Abbreviation/Definition list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5 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
DEREK – Derek nexus is an *in silico* tool to predict whether a chemical will be toxic
DST – Dermal Sensitization Threshold
ECHA – European Chemicals Agency
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
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

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., 2014) 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 assessment. Repeated Dose toxicity was determined using read across analog to have the most conservative systemic exposure derived NO[A]EL of 15 mg/kg/day, based on a gavage 13-week subchronic toxicity study conducted in rats, that resulted in an MOE of 3409, considering 100% absorption from skin contact and inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013; Simmon et al., 1978)
Repeated Dose Toxicity: NOEL = 15 mg/kg/day	(Gaunt et al., 1971)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day	(RIFM, 2011)
Skin Sensitization: Not a sensitization concern. Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not phototoxic	(UV spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 83% (Method C.4D) Read-across to l-Borneol CAS # 464-45-9	(RIFM, 2000)
Bioaccumulation: Screening Level: 27.66 L/kg	(EPISUITE ver 4.1)
Ecotoxicity: Screening Level (Default – Measured Data Available): Daphnia 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: Daphnia 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:** Borneol
2. **CAS Registry Number:** 507-70-0
3. **Synonyms:** Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, endo-, Borneocamphor, Borneol, 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, ボルネオール及びイソボルネオール, 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-ol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25
6. **RIFM Number:** 6257

2. Physical data

1. **Boiling Point:** 212 °C [FMA], (calculated) 209.98 °C [EPI Suite]
2. **Flash Point:** > 200 °F;CC [FMA]
3. **Log K_{OW}:** 2.85 [EPI Suite]
4. **Melting Point**: 204 °C [FMA], (calculated) 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 @ 20°C [EPI Suite 4.0], 0.3 mm Hg 20 °C [FMA], 0.000429 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
9. **Appearance/Organoleptic:** Hexagonal plates or leaflets with dry-camphoraceous, woody-peppery odor and burning taste somewhat resembling that of mint.

3. Exposure

1. Volume of Use (worldwide band): 10 to 100 metric tons per year	(IFRA, 2011)
2. Average Maximum Concentration in Hydroalcoholics: 0.09%	(IFRA, 2004)
3. 97.5th Percentile: 0.16%	(IFRA, 2004)
4. Dermal Exposure*: 0.0041 mg/kg/day	(IFRA, 2004)
5. Oral Exposure: Not available	
6. Inhalation Exposures:** 0.00025 mg/kg/day	(IFRA, 2004)
7. Total Systemic Exposure (Dermal + Inhalation): 0.0044 mg/kg/day	

*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., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

**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 = 0.0044 mg/kg/day

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v. 3.1
I*	I	II

* See Appendix below for explanation.

2. **Analogs 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:** *l*-Borneol (CAS # 464-45-9)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** *l*-Borneol (CAS # 464-45-9)
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)

Borneol is reported to occur in the following foods*:

Alpina species
Chekur (Alpinia sessilis = Kaempferia galanga)
Ginger (Zingiber officinale Rosc.)
Mastic (Pistacia lentiscus L.) gum oil
Mastic (Pistacia lentiscus)
Ocimum basilicum varieties
Ocimum species
Origanum (Spanish) (Coridothymus cap. (L.) Rchb.)
Pistacia atlantica
Pistacia atlantica, fruit oil
Pistacia palaestina (Pistacia terebinthus L.)
Rosemary (Rosmarinus officinalis L.)
Sage (Salvia officinalis L.)
Salvia species
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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 01/22/15.

10. Summary

10.1. Human Health Endpoint Summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic potential of borneol was assessed in an Ames study following experimental outlines similar to those in OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with borneol at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation (S9 mix; Simmon et al., 1978). Other studies confirming a lack of mutagenic potential in *S. typhimurium* strains TA98 and TA100 have been published (Azizan and Blevins, 1995). Under the conditions of the study, borneol is considered not mutagenic in bacteria.

There are no data assessing the clastogenicity of borneol. Read across material *l*-borneol (CAS # 464-45-9; see Section 5), was assessed for clastogenic potential in a GLP compliant *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 24 h without metabolic activation (RIFM, 2013). Under the conditions of the study, *l*-borneol was considered non-clastogenic. Taken together, *l*-borneol does not present a concern for genotoxic potential and this can be extended to borneol.

Taken together, borneol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/15/13.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on borneol are insufficient for the repeated dose toxicity endpoint. 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 NOEL in mg/kg/day divided by the total systemic exposure, 15/0.0044 or 3409.**

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

Literature Search and Risk Assessment Completed on: 11/15/13.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on borneol. 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, based on 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, 1000/0.0044 or 227273.**

There are no reproductive toxicity 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. The NOAEL for reproductive toxicity in the parental generation was determined to be 300 mg/kg/day, based on the highest dosage tested (RIFM, 2011). **Therefore, the MOE for reproductive toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0044 or 68182.**

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

Literature Search and Risk Assessment Completed on: 11/15/13.

10.1.4. Skin sensitization

Based on the available data for the read across material (l-borneol, CAS # 464-45-9) and application of the non-reactive DST, borneol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data for the read across material (l-borneol, CAS # 464-45-9; see Section 5) and application of the non-reactive DST, borneol does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In the human maximization test, two reactions were observed in a Panel of 25 subjects to l-borneol; 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 (0/25) indicative of sensitization were observed to l-borneol (RIFM, 1973). In another human maximization test, no reactions indicative of sensitization were observed with 8% l-borneol in petrolatum (RIFM, 1972). Finally, as there are no predictive tests available in animal models for either l-borneol or borneol, the dermal exposure to borneol was benchmarked utilizing the non-reactive DST. The current dermal exposure from hydroalcoholic products, 0.09%, 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: 11/15/13.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. The available UV absorption spectra for borneol demonstrate that this material does not significantly absorb in the region of 290–700 nm. The molar absorption coefficient at all wavelengths between 290 and 700 nm is well below the benchmark (1000 L mol^{-1} cm^{-1}) considered to be of concern for phototoxic effects (Henry et al., 2009). Based on the UV spectra, borneol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/15/13.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on borneol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.16%. 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 0.015 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value. This value is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

Additional References: Buchbauer et al., 1993; Helmig et al., 1999a, 1999b; Leclerc et al., 2002; Regnault-Roger et al., 1995.

Literature Search and Risk Assessment Completed on: 11/15/13.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of borneol 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, 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 >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did identify borneol as being possibly persistent but not bio-accumulative 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.

10.2.1.1. Risk assessment. Based on current VoU (2011), borneol does present a risk to the aquatic compartment in the screening level assessment.

Biodegradation: Not Available.

Ecotoxicity: Not Available.

10.2.2. Other available data

Borneol has been pre-registered for REACH with no additional data at this time.

There is one biodegradation study in RIFM Database for l-borneol (CAS # 464-45-9):

Biodegradation was evaluated by the Manometric Respirometry Test which was conducted according to Council Directive 92/69/EEC Method C.4-D guidelines. Under conditions of this study, test material at 100 mg per liter had a biodegradation level of 59% after 10 days, 67% after 14 days, 75% after 20 days and 83% after 28 days (RIFM, 2000).

10.2.3. Risk assessment refinement

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (Daphnia) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC(μg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	37.90 mg/L			1,000,000	0.0379 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	2.85	2.85
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**

The RIFM PNEC is 1.338 μg/L. The revised PEC/PNECs for EU and NA are <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/15/13.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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

This is not an exhaustive list.

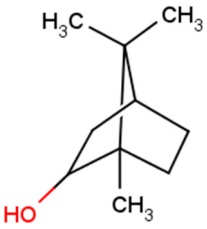
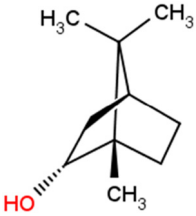
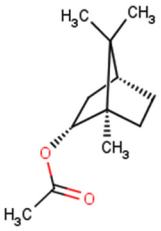
Conflict of interest

A.M. Api, S. Bhatia, L. Kromidas, S. La Cava, J.F. Lalko, A. Lapczynski, V.T. Politano, G. Ritacco, D. Salvito, J. Shen, B. Wall, D.K. Wilcox are employees of the Research Institute for Fragrance Materials, Inc. (RIFM); D. Belsito, M. Bruze, P. Calow, M.L. Dagli, W. Dekant, A.D. Fryer, D.C. Liebler, Y. Miyachi, T.W. Schultz, I.G. Sipes are members of the RIFM Expert Panel.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix

	Target Material	Read across Material	
Principal Name	Borneol	l-Borneol	Isobornyl acetate
CAS No.	507-70-0	464-45-9	125-12-2
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/507-70-0.html	http://www.thegoodscentscompany.com/opl/464-45-9.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		•Genotoxicity •Skin sensitization •Environmental	•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)	0.0572	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)	1186	1186	9.721
J_{max} (mg/cm^2/h, SAM)	43.96956395	43.96956395	18.65520626
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	0.679384	0.679384	44.228362
Similarity (Tanimoto score) [a]		100%	N/A[b]
In silico Results for Target and Analog			
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	
In vivo mutagenicity (Micronucleus) alerts (ISS)	•No alert found	•No alert found	
Oncologic classification (OECD)	•Not classified	•Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized		Not categorized
Developmental and Reproductive Toxicity			
ER binding (OECD)	Weak binder, OH group		Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (good reliability)		NON-Toxicant (low reliability)
Skin Sensitization			
Protein binding (OASIS v1.1)	•No alert found	•No alert found	
Protein binding (OECD)	•No alert found	•No alert found	
Protein binding potency (OECD)	•Not possible to classify according to these rules (GSH)	•Not possible to classify according to these rules (GSH)	
Protein binding alerts for skin sensitization (OASIS v1.1)	•No alert found	•No alert found	
Skin sensitization model (CAESAR v2.1.5)	Sensitizer (good reliability)	Sensitizer (good reliability)	
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data2	See supplemental data 3

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
[b] Target is the metabolite of the analog.

Summary

There are insufficient toxicity data on Borneol (RIFM # 6257, CAS # 507-70-0). 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.

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 USEPA (2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using the 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)

Conclusion/Rationale

- l-borneol (CAS # 464-45-9 (analog) is a stereoisomer of the target. Stereoisomers have the same atomic connectivity but differ in spatial arrangement of atoms or functional groups and usually behave in a similar chemical and toxicological manner.
- Isobornyl acetate (analog) was used as a read-across for Borneol (target) based on:
  - The target is the major metabolite of the read-across material.
  - The target is an ester formed by Borneol and acetic acid. The difference between target and read-across material could be mitigated since the analog is expected to be readily hydrolyzed into the target and acetic acid. Besides, the differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the developmental and reproductive toxicity profiles are expected to be similar.
  - The target and read-across material show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is a 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 read-across material is predicted to be metabolized to the target (metabolite # 3).

Environmental analogs identified/Justification

- l-Borneol (CAS # 464-45-9) has been identified as a structurally related isomer of borneol. Both materials are terpene cyclic alcohols with molecular weight of 154.25 and predicted K_{ow} of 2.85 for both. Available biodegradation data for l-borneol show that it is not persistent; therefore it is assumed that borneol will also not be persistent.

Explanation of Cramer class

The Cramer class of the target material was determined based on 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**, Class Low (Class I)

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.04.012.

References

Antoine, B., Magdalou, J., Siest, G., 1984. Kinetic properties of UDP-glucuronosyltransferase (s) in different membranes of rat liver cells. Xenobiotica 14 (7), 575–579.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., et al., 2014. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. pii: S0278-6915(14)00481-5. doi:10.1016/j.fct.2014.11.014.

Azizan, A., Blevins, R.D., 1995. Mutagenicity and antimutagenicity testing of six chemicals associated with the pungent properties of specific spices as revealed by the Ames Salmonella/microsomal assay. Arch. Environ. Contam. Toxicol. 28 (2), 248–258.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., et al., 2008. A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food Chem. Toxicol. 46 (11), S1–S71.

Bhatia, S.P., McGinty, D., Letizia, C.S., Api, A.M., 2008. Fragrance material review on l-borneol. Food Chem. Toxicol. 46 (11), S81–S84.

Boutin, J.A., Lepage, C., Batt, A.M., Siest, G., 1981. The activity of hepatic UDP-glucuronosyltransferase from control and induced pigs towards 17 hydroxylated aglycones. IRCS Med. Sci. Biochem. 9 (7), 633–634.

Boutin, J.A., Siest, G., Batt, A.M., Solheim, E., Scheline, R.R., 1983. Studies of UDP-glucuronosyltransferase activity toward eugenol, using a gas chromatographic method of measurement. Anal. Biochem. 135 (1), 201–207.

Boutin, J.A., Thomassin, J., Siest, G., Batt, A.M., 1984. Inhibition studies of microsomal UDP-glucuronosyltransferase activities by furosemide and salicylamide. Pharmacol. Res. Commun. 16 (3), 227–241.

Boutin, J.A., Thomassin, J., Siest, G., Cartier, A., 1985. Heterogeneity of hepatic microsomal UDP-glucuronosyltransferase activities: Conjugations of phenolic and monoterpenoid aglycones in control and induced rats and guinea pigs. Biochem. Pharmacol. 34 (13), 2235–2249.

Buchbauer, G., Jirovetz, L., Jäger, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. J. Pharm. Sci. 82 (6), 660–664.

Cadby, P.A., Troy, W.R., Vey, M.G., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regul. Toxicol. Pharmacol. 36 (3), 246–252.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (ttC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., et al., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard – a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000–2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Research 20 (6), 482–487. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regul. Toxicol. Pharmacol. 31 (2), 166–181.

Gaunt, I.F., Agrelo, C.E., Colley, J., Lansdown, A.B.G., Grasso, P., 1971. Short-term toxicity of isobornyl acetate in rats. Food Cosmet. Toxicol. 9 (3), 355–366.

Green, M.D., Tephly, T.R., 1996. Glucuronidation of amines and hydroxylated xenobiotics and endobiotics catalyzed by expressed human UGT1. 4 protein. Drug Metab. Dispos. 24 (3), 356–363.

Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999a. Biogenic volatile organic compound emissions (BVOCs) I. Identifications from three continental sites in the US. Chemosphere 38 (9), 2163–2187.

Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999b. Biogenic volatile organic compound emissions (BVOCs) II. Landscape flux potentials from three continental sites in the US. Chemosphere 38 (9), 2189–2204.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B. 96 (1), 57–62.

IFRA (International Fragrance Association), 2004. Use level survey, September 2004.

IFRA (International Fragrance Association), 2011. Volume of use survey, February 2011.

Leclerc, S., Heydel, J.M., Amossé, V., Gradinaru, D., Cattarelli, M., Artur, Y., et al., 2002. Glucuronidation of odorant molecules in the rat olfactory system. Activity, expression and age-linked modifications of UDP-glucuronosyltransferase isoforms, UGT1A6 and UGT2A1, and relation to mitral cell activity. Mol. Brain Res. 107 (2), 201–213.

Lehman-McKeeman, L.D., Caudill, D., 1999. Development of an in vitro competitive binding assay to predict alpha2u-globulin nephropathy. In Vitr. Mol. Toxicol. 12 (2), 83–95.

Leibman, K.C., Ortiz, E., 1973. Mammalian metabolism of terpenoids I. Reduction and hydroxylation of camphor and related compounds. Drug Metab. Dispos. 1 (2), 543–551.

O'Boyle, N., Banck, M., James, C., Morley, C., Vandermeersch, T., Hutchison, G., 2011. Open Babel: an open chemical toolbox. J. Cheminform. 3 (1), 33.

OECD, 2012. The OECD QSAR toolbox, v 3.1. http://www.qsartoolbox.org/.

Pinching, A.J., Døving, K.B., 1974. Selective degeneration in the rat olfactory bulb following exposure to different odours. Brain Res. 82 (2), 195–204.

Pryde, J., Williams, R.T., 1934. The biochemistry and physiology of glucuronic acid.(a) The occurrence of conjugated glucuronic acids in the animal body.(b) Observations on the conjugation of d-and l-borneol. Biochem. J. 28 (1), 131.

Quick, A.J., 1927. The preparation of borneol glycuronic acid and glycuronic acid. J. Biol. Chem. 74 (2), 331–341.

Quick, A.J., 1928. Quantitative studies of beta-oxidation. IV. The metabolism of conjugated glycuronic acids. J. Biol. Chem. 80, 535–541.

Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say)(Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L.). J. Stored Prod. Res. 31 (4), 291–299.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The Contact-sensitization Potential of Fragrance Materials by Maximization Testing in Humans. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. RIFM Report Number 1803. RIFM, Woodcliff Lake, NJ.
RIFM (Research Institute for Fragrance Materials, Inc.), 2000. l-Borneol: biodegradation. Unpublished Report from Symrise. RIFM report number 55011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2011. Oral (Gavage) One-generation Reproduction Study of Isobornyl Acetate in Rats, with an Evaluationthrough Sexual Maturity in the F1 Generation. RIFM Report Number 62950. RIFM, Woodcliff Lake, NJ.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. l-Borneol: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM Report Number 66358. RIFM, Woodcliff Lake, NJ.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., et al., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Robertson, J.S., Hussain, M., 1969. Metabolism of camphors and related compounds. Biochem. J. 113, 57–65.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schafer, R., Schafer, W., 1982. Percutaneous-absorption of various terpenes menthol, camphene, limonene, isoborneolacetate, alpha-pinene from foam baths. Arzneimittel-Forschung/Drug Research 32 (1), 56–58.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An in silico skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
Simmon, V.F., Kauhanen, K., Mortelmans, K., Tardiff, R., 1978. Mutagenic activity of chemicals identified in drinking water. Mutat. Res./Environ. Mutagen. Relat. Subj. 53 (2), 262.
Tamura, S.S., Tsutsumi, S., Kizu, K., 1962. Studies on glucuronic acid metabolism. I. The influence of borneol, ionone and carvone on the urinary excretion of glucuronic acid and ascorbic acid. Nippon Yakurigaku Zasshi 58, 323–336.
USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC.
Wagreich, H., Bernstein, A., Pader, M., Harrow, B., 1941. Detoxication of Borneo1 by Glucuronic acid in humans. Exp. Biol. Med. 46 (4), 582–586.
Wu, C.J., Huang, Q.W., Qi, H.Y., Hou, S., 2005. Ocular toxicity of borneol in rabbits. Chin. Pharm. J. 40 (22), 1710.