Food and Chemical Toxicology 84 (2015) S33–S41

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short review

RIFM fragrance ingredient safety assessment, Isoborneol, CAS Registry Number 124-76-5

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ARTICLE INFO

Article history:
Received 22 June 2015
Accepted 11 August 2015
Available online 17 August 2015

Keywords:
Genotoxicity
Repeated dose toxicity/developmental and reproductive toxicity
Skin sensitization
Phototoxicity/Photoallergenicity
Local respiratory toxicity
Environmental toxicity

ABSTRACT

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential as well as environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NOAEL of 15 mg/kg/day based on a gavage 13-week subchronic toxicity study conducted in rats on a read across analog resulting in a MOE of 1000 considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

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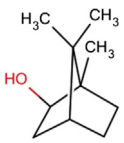
http://dx.doi.org/10.1016/j.fct.2015.08.011
0278-6915/

Version: 050515. This version replaces any previous versions.
Name: Isoborneol
CAS Registry Number: 124-76-5



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th **percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

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

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

Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria such as, acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential as well as environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NOAEL of 15 mg/kg/day based on a gavage 13-week subchronic toxicity study conducted in rats on a read across analog resulting in a MOE of 1000 considering 100% absorption from skin contact and inhalation. A MOE of > 100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013b; RIFM, 2013c)
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.	(RIFM, 1977)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 83% (Method C.4D) Read-across to l-Borneol CAS# 464-45-9	(RIFM, 2000)
Bioaccumulation: Screening Level: 27.7 L/Kg	(EPISUITE ver 4.1)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48 h Daphnia LC50: 13.38 mg/L	(ECOSAR ver 1.11)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) > 1	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48 h Daphnia LC50: 13.38 mg/L	(ECOSAR ver 1.11)
RIFM PNEC is: 1.3 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe<1	

[a] 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.

1. Identification

1. **Chemical Name:** Isoborneol
2. **CAS Registry Number:** 124-76-5
3. **Synonyms:** Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, exo-, exo-2-Bornanol, Borneol(iso), exo-2-Camphanol, iso-Camphol, Isoborneol, Isobornyl alcohol, 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:** 902

2. Physical data

1. **Boiling Point:** 212 °C (sub.) [FMA database], 209.98 °C [EPI Suite]
2. **Flash Point:** 200 °F; CC [FMA database]
3. **Log K_{OW}:** 2.85 [EPI Suite]
4. **Melting Point**: 212 °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 mmHg @ 20 °C [EPI Suite 4.0], 0.8 mm Hg 20C [FMA database], 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 (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic:** White granular or crystal flakes with a camphoraceous and slightly woody odor.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year	[IFRA, 2011a, b]
2. **Average Maximum Concentration in Hydroalcoholics**: 0.04%	[IFRA, 2011a, b]
3. **97.5**th **Percentile**: 0.55%	[IFRA, 2006]
4. **Dermal Exposure*:** 0.0140 mg/kg/day	[IFRA, 2006]
5. **Oral Exposure:** Not available	
6. **Inhalation Exposures**:** 0.00085 mg/kg/day	[IFRA, 2006]
7. **Total Systemic Exposure (Dermal + Inhalation)**: 0.015 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., anti-perspirant, 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 = 0.015 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree 2.6	OECD QSAR Toolbox 3.2
I	I	I

2. **Analogues Selected:**
   a. **Genotoxicity:** *l*-Borneol (CAS # 464-45-9)
   b. **Repeated Dose Toxicity:** Isobornyl acetate (CAS # 125-12-2)
   c. **Developmental and Reproductive Toxicity**: Isobornyl acetate (CAS # 125-12-2)
   d. **Skin Sensitization**: None
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity:** *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)

Isoborneol is reported to occur in the following foods[1] and in some natural complex substances (NCS):

Ashanti pepper (Piper guineense Schum and Thom)	Ginger (Zingiber species)
Camomile	Grape brandy
Cheese, various types	Honey
Cinnamomum species	Mastic (Pistacia lentiscus)
Curcuma species	Ocimum species
Eucalyptus oil (Eucalyptus globulus Labill)	Papaya (Carica papaya L.)
Rooibos tea (Aspalathus linearis)	Raspberry, blackberry and boysenberry
Rosemary (Rosmarinus officinalis L.)	Salvia species
	Thyme (Thymus species)

8. Ifra standard

None.

[1] VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. Reach dossier

Pre-Registered for 2010; No dossier available as of 4/20/15.

10. Summary

1. **Human Health Endpoint Summaries**:

Genotoxicity:

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

Risk Assessment:

Isoborneol, was assessed for genotoxic potential in the Bluescreen assay and was found negative for genotoxicity and cytotoxicity in the presence and absence of metabolic activation (S9) (RIFM, 2013a). There are no data assessing the genotoxic risk of isoborneol, however, read across analog *l*-borneol (CAS # 464-45-9; see Section V) was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA102 and TA100 and *Escherichia coli* strain WP2uvrA were treated with *l*-borneol in DMSO (dimethyl sulfoxide) at concentrations up to 1000 μg/plate in the presence and absence of S9 mix. No increase in the number of revertant colonies was observed at any of the doses tested in any strain (RIFM, 2013b) and therefore was considered not mutagenic in bacteria.

The clastogenic potential of the read across material, *l*-borneol, was assessed 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 up to 55 μg/ml for 24 h without metabolic activation. A significant, non-dose-dependent increase in micronucleated binucleated (MNBN) cells was increased compared to vehicle control in the non-S9-activated 4hr exposure group at doses of 100 and 400 μg/ml. However, the percentage of MNBN cells was within the historical solvent control range; this increase was not considered biologically relevant (RIFM, 2013c). Under the conditions of the study, *l*-borneol was concluded to be negative for the induction of micronuclei in the micronucleus test.

Taken together, *l*-borneol does not present a concern for genotoxic potential and this can be applied to the target material, isoborneol.

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/07/14.

Repeated Dose Toxicity:

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

Risk Assessment:

There are no repeated dose toxicity data on isoborneol. Read across material isobornyl acetate (CAS # 125-12-2; see Section V) 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, 15/0.015 or 1000.**

Additional References: Bhatia et al., 2008a; Belsito et al., 2008; Green and Tephly, 1996; Buchbauer et al., 1993; Leibman and Ortiz, 1973; Longenecker et al., 1939; Bhatia et al., 2008b; Wu et al., 2005; Wagreich et al., 1941; Quick, 1928, 1927; Boutin et al., 1985; Tamura et al., 1962; Robertson and Hussain, 1969; Pryde and Williams, 1934; Lehman-McKeeman and Caudill, 1999; Leclerc et al., 2002; Boutin et al., 1984; Pinching and Doving, 1974; Schafer and Schafer, 1982.

Literature Search and Risk Assessment Completed on: 11/22/13.

Developmental and Reproductive Toxicity:

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

Risk Assessment:

There are no developmental toxicity data on isoborneol. Read across material isobornyl acetate (CAS # 125-12-2; see Section V) has an OECD 414 gavage developmental toxicity limit dose study that was conducted in rats. The NOAEL was determined to be 1000 mg/kg/day, the only dosage tested (ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl acetate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-b8dd69b0-4345-07f7-e044-00144f67d031/DISS-b8dd69b0-4345-07f7-e044-00144f67d031_DISS-b8dd69b0-4345-07f7-e044-00144f67d031.html, retrieved 11/22/2013, 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, 1000/0.015 or 66667.**

There are no reproductive toxicity data on isoborneol. Read across material isobornyl acetate (CAS # 125-12-2) has an enhanced OECD 415 gavage 1-generation reproductive toxicity study that was conducted in rats. The NOAEL for reproductive toxicity in the parental generation was determined to be 300 mg/kg/day, the highest dosage tested (RIFM, 2011). **Therefore, the MOE for reproductive toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.015 or 20000.**

Additional References: Bhatia et al., 2008a; Belsito et al., 2008; Green, 1996; Buchbauer et al., 1993; Leibman, 1973; Longenecker et al., 1939; Bhatia et al., 2008b; Wu et al., 2005; Wagreich et al., 1941; Quick, 1928, 1927; Boutin et al., 1985; Tamura et al., 1962; Robertson, 1969; Politano et al., 2013; Pryde, 1934; Lehman-McKeeman, 1999; Leclerc et al., 2002; Boutin et al., 1984; Pinching, 1974; Schafer, 1982;

Literature Search and Risk Assessment Completed on: 11/22/13.

Skin Sensitization:

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

Risk Assessment:

The chemical structure of this material indicates that it would not be expected to react directly with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In a human maximization test, no reactions indicative of sensitization were observed with 10% isoborneol in petrolatum (RIFM, 1977). Finally, as there are no predictive tests available in animal models, the dermal exposure to isoborneol was benchmarked utilizing the non-reactive DST. The current dermal exposure from hydroalcoholic products, 0.04%, 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). Based on the available data and application of the non-reactive DST, isoborneol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/22/13.

Phototoxicity/Photoallergenicity:

Based on the UV/Vis absorption spectra, isoborneol does not present a concern for phototoxicity or photoallergenicity.

Risk Assessment:

The available UV/Vis absorption spectra for isoborneol indicate no significant absorption in the region of 290–700 nm, with a corresponding molar absorption coefficient below the benchmark of concern for phototoxic effects (1000 L mol^{-1} cm^{-1}) (Henry et al., 2009). Based on the UV spectra, isoborneol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/22/13.

Local Respiratory Toxicity:

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

Risk Assessment:

There are no inhalation data available on isoborneol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.55%. 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 0.051 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; Duchamp, 1982; Revial et al., 1982.

Literature Search and Risk Assessment Completed on: 11/22/13.

2. **Environmental Endpoint Summary**:

Analogues Identified/Justification:

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

Screening-Level Assessment:

A screening level risk assessment of isoborneol 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, isoborneol 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 isoborneol as being possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below

and summarized in the Environmental Safety Assessment section prior to Section I.

Risk Assessment:

Based on current VoU from 2011, isoborneol does present a risk to the aquatic compartment in the screening level assessment.

Key Studies:

Biodegradation: Not Available.

Ecotoxicity: Not Available.

Other available data: Isoborneol 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).

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	1.3 μg/	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 1.3 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 11/22/13.

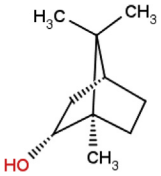
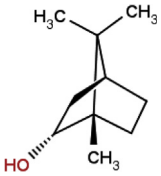
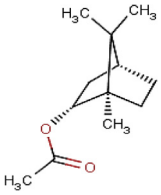
11. Literature Search[2]

- **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 DataBase:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

This is not an exhaustive list.

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

Appendix

	Target material	Read across material	
Principal Name	Isoborneol	l-Borneol	Isobornyl acetate
CAS No.	124-76-5	464-45-9	125-12-2
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/124-76-5.html	http://www.thegoodscentscompany.com/opl/464-45-9.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		• Genotoxicity • 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)[1]		100%[3]	NA[2]
In silico Results for Target and Analogs			
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)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	Supplemental data 1	Supplemental data 2	Supplemental data 3

1 Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).
2 The target is the major metabolite of the analog.
3 The Tanimoto coefficient is calculated by determining the number of common fragments in target and the analog. A Tanimoto score of 100% means that two chemical structures are very similar but not necessarily identical.

Summary:

There are insufficient toxicity data on Isoborneol (RIFM # 902, CAS # 124-76-5). 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 US EPA
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale.

- *l*-Borneol (CAS # 464-45-9) is a stereoisomer and was determined to be a suitable analog based on structural similarity, physicochemical properties, metabolism and expert judgment. 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 isoborneol (target) based on:
  - The target is a metabolite of the analog. The target and the analog are terpenes. The target belongs to the generic class of cyclic terpene alcohol while the analog belongs to cyclic esters terpenes.
  - Both have the common structure of isoborneol. The analog is the acetate ester form of the target. The analog will rapidly hydrolyze into the target and acetic acid. Therefore, the toxicity profiles are expected to be that of the analog.
  - They both also show similar alerts for Repeated Dose (HESS) Categorization. The target is predicted to be a weak binder, while the analog is predicted to be a non-binder. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - As per the OECD Toolbox, the target is one of the metabolites of the analog, (metabolites # 3).

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.08.011.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.08.011.

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