Short review

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


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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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Abbreviation list:

- **2-Box Model** – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
- **97.5th percentile** - The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
- **AF** - Assessment Factor
- **BCF** - Bioconcentration factor
- **DEREK** - Derek nexus is an *in silico* tool used to identify structural alerts
- **DST** - Dermal Sensitization Threshold
- **ECHA** - European Chemicals Agency
- **EU** - Europe/European Union
- **GLP** - Good Laboratory Practice
- **IFRA** - The International Fragrance Association
- **LOEL** - Lowest Observable Effect Level
- **MOE** - Margin of Exposure
- **MPPD** - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
- **NA** - North America
- **NESIL** - No Expected Sensitization Induction Level
- **NOAEC** - No Observed Adverse Effect Concentration
- **NOAEL** - No Observed Adverse Effect Level
- **NOEC** - No Observed Effect Concentration
- **OECD** - Organisation for Economic Co-operation and Development
- **OECD TG** - Organisation for Economic Co-operation and Development Testing Guidelines
- **PBT** - Persistent, Bioaccumulative, and Toxic
- **PEC/PNEC** - Predicted Environmental Concentration/Predicted No Effect Concentration
- **QRA** - Quantitative risk assessment
- **REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals
- **RIFM** - Research Institute for Fragrance Materials
- **RQ** - Risk Quotient
- **TTC** - Threshold of Toxicological Concern
- **UV/Vis Spectra** - Ultra Violet/Visible spectra
- **VCF** - Volatile Compounds in Food
- **VoU** - Volume of Use
- **vPvB** - (very) Persistent, (very) Bioaccumulative
- **WOE** - Weight of Evidence
RIFM's Expert Panel concludes that this material is safe under the limits described in this safety assessment. This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and should be referred to for clarifications.

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

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
Developmental and Reproductive Toxicity: NOAEL – 300 mg/kg/day
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
Critical Ecotoxicity Endpoint: 48 h Daphnia LC50: 13.38 mg/L
RIFM PNEC is: 1.3 ɪ/L

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

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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

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree 2.6</th>
<th>OECD QSAR Toolbox 3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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) and Thom |
| Camomile | Grape brandy |
| Cheese, various types | Honey |
| Cinnamomum species | Mastic (Pistacia lentiscus) |
| Curcuma species | Ocimum species |
| Eucalyptus oil (Eucalyptus globulus) and Labili | Papaya (Carica papaya L.) |
| Rooibos tea (Aspalathus linearis) | Salvia species |
| Rosemary (Rosmarinus officinalis L) | Thyme (Thymus species) |

8. **Ifra standard**

None.

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 Blue-screen 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 WP2uvR were treated with l-borneol in DMSO (dimethyl sulfoxide) at concentrations up to 1000 µg/ml 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 vivo 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 (MNBN) cells was increased compared to vehicle control in the non-S9-activated 4h 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.

   **AdditionalReferences**: 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 increasing 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.

   **AdditionalReferences**: 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; Wagnerich 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.

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\(^1\) VCF Volatile Compounds in Food: database/NIJSSEN, L.M.; INGEN-VISCHER, C.A. van; Donders, 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.
Based on the available data and application of the non-reactive DST, below the DST for non-reactive materials when evaluated in QRA current dermal exposure from hydroalcoholic products, 0.04%, is not be expected to react directly with skin proteins (Roberts et al., 2000). Therefore, the MOE for phototoxicity in the parental generation was determined to be 300 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 OECD 415 gavage 1-generation reproductive toxicity study that was conducted in rats. The NOAEL was determined to be 1000 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; Belisio et al., 2008; Green, 1996; Buchbauer et al., 1993; Leblanc, 1973; Longenecker et al., 1939; Bhatia et al., 2008b; Wu et al., 2005; Wagerich 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.


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.


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.


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 RIFM survey results for hydroalcohols, 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 RIFM 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.


2. Environmental Endpoint Summary:

Analogues Identified/Justification:
I-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 Kow 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 Kow 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 BCDFBAF 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.  

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

<table>
<thead>
<tr>
<th>RIFM Framework</th>
<th>L50 (Fish) (mg/l)</th>
<th>EC50 (Daphnia)/EC50 (Algae) (mg/l)</th>
<th>AF</th>
<th>PNEC (µg/l)</th>
<th>Chemical Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Level (Tier 1)</td>
<td>37.90 mg/l</td>
<td>1,000,000</td>
<td>0.0379 µg/L</td>
<td>Neutral Organics</td>
<td></td>
</tr>
<tr>
<td>ECOSAR Acute Endpoints (Tier 2) Ver 1.11</td>
<td>21.78 mg/l</td>
<td>13.38 mg/l</td>
<td>13.79 mg/l</td>
<td>10,000</td>
<td>1.3 µg/l</td>
</tr>
</tbody>
</table>

> 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**  
- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS  
- ECHA: http://echa.europa.eu/  
- OECD Toolbox  
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf  
- 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 Robust Summary: http://cfpub.epa.gov/hpv-s/  
- Japan Existing Chemical DataBase: http://dra4.nih.go.jp/mhlw_data.jsp/SearchPageENG.jsp  
- Google: https://www.google.com/webhp?tab=ww&ei=KMSolUpiQK-arsQS324GwBg&ved=0CBQQ1S4

This is not an exhaustive list.

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2 Information sources outside of RIFM’s database are noted as appropriate in the safety assessment.
Appendix

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)

<table>
<thead>
<tr>
<th>Principal Name</th>
<th>Target material</th>
<th>Read across material</th>
<th>Read-across endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS No.</td>
<td>Isoborneol</td>
<td>l-Borneol</td>
<td>Isobornyl acetate</td>
</tr>
<tr>
<td>Structure</td>
<td>124-76-5</td>
<td>464-45-9</td>
<td>125-12-2</td>
</tr>
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</table>

3D Structure
http://www.thegoodscentscompany.com/opl/124-76-5.html
http://www.thegoodscentscompany.com/opl/125-12-2.html

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>C10H18O</th>
<th>C10H18O</th>
<th>C12H20O2</th>
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<tr>
<td>Molecular Weight</td>
<td>154.25</td>
<td>154.25</td>
<td>196.29</td>
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<tr>
<td>Melting Point</td>
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<td>26.56</td>
<td>34.11</td>
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<tr>
<td>Boiling Point</td>
<td>209.58</td>
<td>209.58</td>
<td>225.89</td>
</tr>
<tr>
<td>Log Kow (v1.68)</td>
<td>2.85</td>
<td>2.85</td>
<td>3.86</td>
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<tr>
<td>Water Solubility</td>
<td>1.186</td>
<td>1.186</td>
<td>9.721</td>
</tr>
<tr>
<td>Jmax (mg/cm²/h)</td>
<td>43.96656395</td>
<td>43.96656395</td>
<td>18.65520626</td>
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<tr>
<td>Henry's Law (Pa m²/mol)</td>
<td>0.679384</td>
<td>0.679384</td>
<td>44.228362</td>
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<tr>
<td>Similarity (Tanimoto score)</td>
<td>100%</td>
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In silico Results for Target and Analogs

<table>
<thead>
<tr>
<th>Genotoxicity</th>
<th>DNA binding (OASIS v1.1)</th>
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<th>No alert found</th>
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<tbody>
<tr>
<td>Carcinogenicity</td>
<td>DNA binding (OEC)</td>
<td>No alert found</td>
<td>No alert found</td>
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<tr>
<td>(genox and non-genox) alerts (ISS)</td>
<td>DNA alerts for Ames, MN, CA (OASIS v1.1)</td>
<td>No alert found</td>
<td>No alert found</td>
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<tr>
<td></td>
<td>In vivo mutagenicity (Ames test) alerts (ISS)</td>
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<td>No alert found</td>
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<td>In vivo mutagenicity (Microtiter wells) alerts (ISS)</td>
<td>No alert found</td>
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<td></td>
<td>Oncologic classification (OECD)</td>
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</tr>
<tr>
<td>Repeated Dose Toxicity</td>
<td>Repeated dose (HESS)</td>
<td>Not categorized</td>
<td>Not categorized</td>
</tr>
<tr>
<td>Developmental and Reproductive Toxicity</td>
<td>ER binding (OECD)</td>
<td>Weak binder, OH group</td>
<td>Non binder, without OH or NH2 group</td>
</tr>
<tr>
<td></td>
<td>Developmental toxicity model (CAESAR v2.1.6)</td>
<td>Toxicant (good reliability)</td>
<td>NON-Toxicant (low reliability)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Rat liver S9 metabolism simulator (OECD)</td>
<td>Supplemental data 1</td>
<td>Supplemental data 2</td>
</tr>
</tbody>
</table>

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.
Conclusion/Rationale.

- I-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.

- Iso Bornyl acetate (analog) was used as a read-across for iso borneol (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.

References


