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Short review

RIFM fragrance ingredient safety assessment, isobornyl propionate, CAS Registry Number 2756-56-1

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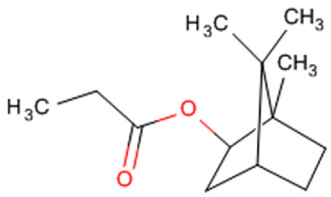

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th 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
EC_{50}- Half Maximal Effective Concentration
ECHA-European Chemicals Agency
ECOSAR- Ecological Structure - Activity Relationships Program
EPISUITE- Essential Estimation Programs Interface (EPI) SuiteTM
EU – Europe/European Union
FMA- Fragrance Material Association
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LC_{50}- Lethal Concentration 50
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure

(*continued on next page*)

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(*continued*)

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
NOEL- No Observed Effect Level
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
QSAR- Quantitative structure–activity relationship
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 the RIFM Criteria Document (Api et al., 2015) which 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 conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class II material (0.47 mg/day). The repeated dose, developmental and reproductive toxicity endpoints were completed using isobornyl acetate (CAS # 125-12-2) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework along with data from the suitable read across analog isobornyl acetate (CAS # 125-12-2).

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (Wild et al., 1983)
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 sensitizing (RIFM, 2007; RIFM, 2008; Klecak, 1985; RIFM, 1979)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment

(*continued*)

Hazard Assessment:
Persistence: Critical Measured Value: (RIFM, 1994)
OECD 301B: 104.7% (OECD 301B)
Read-across to Isobornyl Acetate (CAS # 125-12-2)
Bioaccumulation: Screening Level: (EPISUITE ver 4.1)
343 L/Kg
Ecotoxicity: Critical Ecotoxicity Endpoint: 96 h Algae EC50: 0.567 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 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96 h Algae EC50: 0.567 mg/L (ECOSAR ver 1.11)
RIFM PNEC is: 0.0567 μg/L
•**Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe <1

1. Identification

1 **Chemical Name**: Isobornyl propionate
2 **CAS Registry Number**: 2756-56-1
3 **Synonyms**: Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, propanoate, exo-; exo-2-Bornyl propionate; exo-2-Camphanyl propionate; Isobornyl propionate; exo-1,7,7-Trimethylbicyclo(2.2.1)hept-2-ylpropionate; 1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl propionate
4. **Molecular Formula**: $C_{13}H_{22}O_2$
5. **Molecular Weight**: 210.32
6. **RIFM Number**: 404

2. Physical data

1. **Boiling Point**: 245 °C [FMA database], (calculated) 244.14 °C [EPI Suite]
2. **Flash Point**: >200 °F; CC [FMA database]
3. **Log KOW**: 4.35 [EPI Suite]
4. **Melting Point**: 44.97 °C [EPI Suite]
5. **Water Solubility**: 7.491 mg/L [EPI Suite]
6. **Specific Gravity**: 0.970 [FMA database]
7. **Vapor Pressure:** 0.01 mm Hg 20 °C [FMA database], 0.0136 mm Hg @ 20 °C [EPI Suite 4.0], 0.0236 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1}) (RIFM DB)
9. **Appearance/Organoleptic:** A colorless oily liquid. Sweeter, fruitier and less harsh than the acetate. The turpentine odor type is still there, but it is softer and combined with almost lavender-like herbaceous notes.

3. Exposure

1 **Volume of Use (worldwide band)**: 10–100 metric tons per year (IFRA, 2011)
2 **Average Maximum Concentration in Hydroalcoholics**: 0.018% (IFRA, 2008)
3 **97.5th Percentile**: 0.075% (IFRA, 2008)
4 **Dermal Exposure***: 0.0019 mg/kg/day (IFRA, 2008)
5 **Oral Exposure**: Not available
6 **Inhalation Exposures****: 0.00012 mg/kg/day or 0.0070 mg/day (IFRA, 2008)
7 **Total Systemic Exposure (Dermal + Inhalation)**: 0.0020 mg/kg/day

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* 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 = 0.0020 mg/kg/day

5. Computational toxicology evaluation

1. **Cramer Classification**: Class II, Intermediate

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

*See Appendix below for explanation.

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

Benzyl butyrate is reported to occur in the following foods* and in some natural complex substances (NCS):

Citrus fruits.

*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.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 8/18/16.

10. Summary

1. Human Health Endpoint Summaries:

10.1. Genotoxicity

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

10.1.1. Risk assessment

The mutagenic potential of isobornyl propionate was assessed in a bacterial reverse mutagenicity assay conducted in compliance with GLP regulation and in accordance with OECD TG 471 using the standard plate incorporation method. *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with the test substance in DMSO (dimethyl sulfoxide) at concentrations up to 3600 μg/plate in the presence and absence of metabolically activated mitochondrial fraction (S9 mix) (Wild et al., 1983). There was no increase in revertant colonies in any strain with or without S9 metabolic stimulation, concluding it as non-mutagenic in the Ames test.

The clastogenic potential of isobornyl propionate was assessed in an *in vivo* micronucleus test equivalent or similar to OECD TG 474. The test material was administered in olive oil via intraperitoneal injection, at doses of 841, 1893 and 2944 mg/kg body weight. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (Wild et al., 1983). Under the conditions of the study, isobornyl propionate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the existing data, isobornyl propionate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.2. Repeated dose toxicity

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

10.2.1. Risk assessment

There are no repeated dose toxicity data on isobornyl propionate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has a gavage 13-week subchronic toxicity study 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, 15/0.0020 or 7500.**

In addition, the total systemic exposure to isobornyl propionate (2.0 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the repeated dose toxicity endpoint.

Additional References: Pinching and Doving, 1974; Schafer and Schafer, 1982; Bhatia et al., 2008; Belsito et al., 2008; Wu et al., 2005; Buchbauer et al., 1993; Wagreich et al., 1941; Quick, 1928; Quick, 1927; Boutin et al., 1985; Tamura et al., 1962; Robertson and Hussain, 1969; Pryde and Williams, 1934; Leibman and Ortiz,

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1973; Lehman-McKeeman and Caudill, 1999; Leclerc et al., 2002; Boutin et al., 1984.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.3. Developmental and reproductive toxicity

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

10.3.1. Risk assessment

There are no developmental toxicity data on isobornyl propionate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has an OECD 414 gavage developmental toxicity limit dose study 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, 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, 1000/0.0020 or 500,000.

There are no reproductive toxicity data on isobornyl propionate. Read across material isobornyl acetate (CAS # 125-12-2) has an enhanced OECD 415 gavage 1-generation reproductive toxicity study 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; data also available in Politano et al., 2013). Therefore, the MOE for reproductive toxicity is equal to the isobornyl acetate NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0020 or 150,000.

In addition, the total systemic exposure to isobornyl propionate (2.0 μg/kg/day) is below the TTC (9 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoint.

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

Literature Search and Risk Assessment Completed on: 01/31/14.

10.4. Skin sensitization

Based on existing data specific to isobornyl propionate and the read across material, isobornyl acetate (CAS # 125-12-2), isobornyl propionate does not present a concern for skin sensitization.

10.4.1. Risk assessment

Based on existing data specific to isobornyl propionate and the read across material, isobornyl acetate (CAS # 125-12-2; see Section 5), isobornyl propionate does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to significantly react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). In guinea pig sensitization studies and a murine local lymph node assay no reactions indicative of sensitization were observed for isobornyl acetate (RIFM, 2007; Klecak, 1985; and Klecak, 1979; RIFM, 1979). In human confirmatory studies no sensitization reactions were observed for isobornyl acetate or isobornyl propionate (RIFM, 2008; RIFM, 1970; RIFM, 1973).

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, isobornyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

There are no phototoxicity studies available for isobornyl propionate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, isobornyl propionate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/18/16.

10.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, isobornyl propionate, exposure level is below the Cramer Class III* TTC value for inhalation exposure local effects.

10.6.1. Risk assessment

There are no inhalation data available on isobornyl propionate. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.075%. Assuming 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 combined inhalation exposure would be 0.0070 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 67.1 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al., 2009, Cramer Class II materials default to Cramer Class III.

Additional References: None.

Literature Search and Risk Assessment Completed on: 7/20/2016.

2. Environmental Endpoint Summary:

10.7. Screening-level assessment

A screening level risk assessment of isobornyl propionate was performed following the RIFM Environmental Framework (Salvito et al., 2002) that 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). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most

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recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, isobornyl propionate was identified as a fragrance material with 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 isobornyl propionate as 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).

10.7.1. Risk assessment

Based on current Volume of Use (2011) isobornyl propionate presents a risk to the aquatic compartment in the screening level assessment.

Key Studies:

10.8. Biodegradation

No data available.

10.9. Ecotoxicity

No data available.

10.9.1. Other available data

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

There are 2 biodegradation studies for isobornyl acetate (CAS # 125-12-2) in RIFM Database:

RIFM, 1997: The ready biodegradability of isobornyl acetate was evaluated using the Manometric Respirometry Test according to the OECD 301F guideline. Biodegradation after 28 days was 75%.

RIFM, 1994: The ready and ultimate biodegradability of the test material was determined using a CO_2 production test based on OECD 301B guideline. Biodegradation of the test material after 28 days was 104.7%.

10.9.2. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.35	4.35
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**

Based on available data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 0.0567 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: 01/31/14.

11. Literature Search*

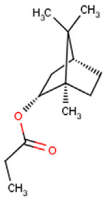
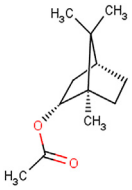
- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **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=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

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

This is not an exhaustive list.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.92 mg/l			1,000,000	0.00292 μg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.545 mg/l	1.079 mg/l	1.893 mg/l	10,000	0.1079 μg/l	Neutral organics

Appendix

	Target Material	Read across Material
Principal Name	Isobornyl propionate	Isobornyl acetate
CAS No.	2756-56-1	125-12-2
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/2756-56-1.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		• Repeated Dose • Devel/Repro • Skin sensitization • Environmental
Molecular Formula	C13H22O2	C12H20O2
Molecular Weight	210.32	196.29
Melting Point (°C, EPISUITE)	44.97	34.11
Boiling Point (°C, EPISUITE)	244.14	225.89
Vapor Pressure(Pa @ 25°C, EPISUITE)	3.146	14.27
Log Kow (KOWWIN v1.68 in EPISUITE)	4.35	3.86
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	7.491	9.721
J_{max} (mg/cm^2/h, SAM)	12.05675887	18.65520626
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	58.717838	44.228362
Similarity (Tanimoto score)[1]		80%
In silico Results for Target and Analogs		
Repeated Dose Toxicity		
Repeated dose (HESS)	Not categorized	Not categorized
Developmental and Reproductive Toxicity		
ER binding (OECD)	Non binder, without OH or NH2 group	Non binder, without OH or NH2 group
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (moderate reliability)	NON-Toxicant (low reliability)
Skin Sensitization		
Protein binding (OASIS v1.1)	•No alert found	•No alert found
Protein binding (OECD)	•Acylation •Acylation >> Direct Acylation Involving a Leaving group •Acylation >> Direct Acylation Involving a Leaving group >> Acetates	•Acylation •Acylation >> Direct Acylation Involving a Leaving group •Acylation >> Direct Acylation Involving a Leaving group >> Acetates
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 Data 2

[1] Values calculated using JChem with FCFP4 1024 bits fingerprint. J. Chem. Inf. Model. Rogers and Hahn, 2010.

Summary:

There are insufficient toxicity data on Isobornyl propionate (RIFM # 404, CAS # 2756-56-1). 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 (USEPA, 2012)
- 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)

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- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/Rationale

- Isobornyl acetate (analog) was used as a read-across for Isobornyl propionate (target) based on:
- The target and analog both belong to the generic class of esters, specifically, cyclic alcohol simple acid esters/bicyclic.
- Both have the same alcohol part and similar acid part.
- The only difference is that the target is a propanoic acid ester, while the analog has an acetic acid ester. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the repeated dose toxicity profiles are expected to be similar.
- The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. 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.
- The target and analog show similar alerts for protein binding.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

Explanation of Cramer Class:

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (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? No.

Q17.Readily hydrolysed to a common terpene? No.

Q19.Open chain? No.

Q23.Aromatic? No.

Q24.Monocarbocyclic with simple substituents? No.

Q25.Cyclopropane, etc. (see explanation)? No.

Q26.Monocycloalkanone or a bicyclocompound? Yes Class Intermediate (Class II).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.10.008.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.10.008.

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