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Short review

RIFM fragrance ingredient safety assessment, isobornyl isovalerate, CAS registry number 7779-73-9

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ABSTRACT

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, as well as, environmental safety. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material is not genotoxic, provided a MOE > 100 for the repeated dose, developmental and reproductive endpoints, and 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 phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

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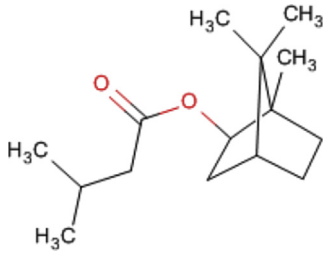
CAS Registry Number: 7779-73-9



Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) compared to a deterministic aggregate approach.
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 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.

(*continued*)

This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, as well as, environmental safety. Data from the suitable read across analog isobornyl acetate (CAS # 125-12-2) show that this material is not genotoxic, provided a MOE > 100 for the repeated dose, developmental and reproductive endpoints, and 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 phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (ECHA REACH Dossier, exo-1,7,7-trimethylbicyclo [2.2.1]hept-2-yl acetate, accessed 6/24/2015)
Repeated Dose Toxicity: NOEL = 15 mg/kg/day (Gaunt et al., 1971)
Developmental and Reproductive Toxicity: NOAEL = 1000 and 300 mg/kg/day, respectively (ECHA REACH Dossier; RIFM, 2011)
Skin Sensitization: Not sensitizing (RIFM, 2008)
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:** Screening Level: 81% (OECD 301F) (Catalogic v.5.11.15; OECD Toolbox)

Bioaccumulation: Screening Level: 1366 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 0.468 mg/L (RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 0.468 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.000468 μg/L

- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not Applicable; Cleared at screening level

1. Identification

1 **Chemical Name:** Isobornyl isovalerate
2 CAS Registry Number: 7779-73-9
3 **Synonyms:** *exo*-Bornyl isovalerate; Butanoic acid, 3-methyl-, 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl ester, exo-; Isobornyl isopentanoate; Isobornyl isovalerate; Isobornyl 3-methylbutanoate; 1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl 3-methylbutanoate
4 Molecular Formula: $C_{15}H_{26}O_2$
5 Molecular Weight: 238.37
6 RIFM Number: 5044

2. Physical data

1 **Boiling Point:** 268.12 °C [EPI Suite]
2 **Flash Point:** 230.00 °F TCC (110.00 °C)*
3 **Log K_{OW}:** 5.26 [EPI Suite]
4 **Melting Point**: 56.81 °C [EPI Suite]
5 **Water Solubility:** 0.8885 mg/L [EPI Suite]
6 **Specific Gravity:** 0.90000 to 0.90600 @ 25.00 °C*
7 **Vapor Pressure:** 0.0114 mmHg @ 20 °C [EPI Suite 4.0], 0.0182 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})

9 **Appearance/Organoleptic:** A colorless liquid with a herbaceous-camphorceous, warm and slightly green-woody odor.

*http://www.thegoodscentscompany.com/data/rw1012821.html, retrieved on 04/02/15.

3. Exposure

1 Volume of Use (worldwide band): <0.1 metric tons per year (IFRA , 2011)
2 95th Percentile Concentration in Hydroalcoholics: 0.0018% (RIFM, 2014)
3 Inhalation Exposure*: <0.00001 mg/kg/day or 0.0000024 mg/day (RIFM, 2014)
4 Total Systemic Exposure**: 0.000069 mg/kg/day (RIFM, 2014)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015).

4. Derivation of systemic absorption

1 **Dermal:** Assumed 100%
2 **Oral:** Assumed 100%
3 Inhalation: Assumed 100%

5. Computational toxicology evaluation

1 **Cramer Classification:** Class II, Intermediate (Expert Judgment)

2 Analogs Selected:
a **Genotoxicity:** Isobornyl acetate (CAS # 125-12-2)
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: None
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.

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II*	I	I

*See Appendix below for explanation.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Isobornyl isovalerate is reported to occur in the following foods*:

Lovage (Levisticum officinale Koch).

*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 08/31/16

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Isobornyl isovalerate was found to be negative for both cytotoxicity and genotoxicity when tested in the BlueScreen assay indicating a lack for genotoxic potential (RIFM, 2013). There are no data assessing the mutagenic activity of the target material, however read across can be made to its analog, isobornyl acetate (CAS # 125-12-2) which was assessed in a GLP compliant study in accordance with OECD TG 471 using the plate incorporation method. *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were treated with isobornyl acetate in DMSO (dimethyl sulfoxide) at concentrations up to 500 μg/plate in the presence and absence of S9 mix (ECHA REACH Dossier: exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acetate). Under the conditions of the study, isobornyl acetate was considered not mutagenic in bacteria.

There are no studies assessing the clastogenic activity of isobornyl isovalerate. Read across material isobornyl acetate was assessed for clastogenicity in an *in vivo* mouse micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 474. Male and female NMRI mice were treated with isobornyl acetate dissolved in sesame oil via a single oral administration of 2000 mg/kg bodyweight. Peripheral blood was harvested 24, 48 and 72 h after administration. The number of polychromatic and normochromatic erythrocytes containing micronuclei was not increased (ECHA REACH Dossier: exo-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl acetate). Under the conditions of the study, isobornyl acetate was considered negative for induction of clastogenic and aneugenic activity in mice.

Based on the available data, isobornyl acetate does not present a concern for genotoxic potential and this can be extended to isobornyl isovalerate.

Additional References: RIFM, 2013.

Literature Search and Risk Assessment Completed on: 04/24/15.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on isobornyl isovalerate. 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, 15/0.000069 or 217391.**

In addition, the total systemic exposure for isobornyl isovalerate (0.069 μg/kg/day) is below the TTC (9 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

Additional References: Pinching and Doving, 1974; Schafer and Schafer, 1982; ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo [2.2.1]hept-2-yl acrylate; ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl methacrylate; SIAM, 2011: Isobornyl methacrylate (IBOMA).

Literature Search and Risk Assessment Completed on: 04/24/15.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on isobornyl isovalerate. Read across material isobornyl acetate (CAS # 125-12-2; see Section 5) has an OECD 414 gavage 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 (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, 1000/0.000069 or 14 492 754.**

There are no reproductive toxicity data on isobornyl isovalerate. 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, 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, 300/0.000069 or 4 347 826.**

In addition, the total systemic exposure to isobornyl isovalerate (0.069 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; ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo [2.2.1]hept-2-yl acrylate; ECHA REACH Dossier: exo-1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl methacrylate; SIAM, 2011: Isobornyl methacrylate (IBOMA).

Literature Search and Risk Assessment Completed on: 04/24/15.

10.1.4. Skin sensitization

Based on the existing data on read across materials isobornyl acetate (CAS # 125-12-2), Isobornyl isovalerate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization studies exist for isobornyl isovalerate. Based on the existing data on the read across material (isobornyl acetate CAS # 125-12-2; see Section 5), isobornyl isovalerate does not present a concern for skin sensitization. The chemical structure of isobornyl isovalerate indicates that it would not be expected to significantly react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In guinea pig sensitization studies and the murine local lymph node assay no reactions indicative of sensitization were observed with isobornyl acetate (RIFM, 2007; Klecak, 1979, 1985). In human confirmatory studies no sensitization reactions were observed to isobornyl acetate (RIFM, 1970; RIFM, 2008). Based on the existing animal and human data on isobornyl acetate, isobornyl isovalerate is considered a non-sensitizer.

The conclusion of isobornyl isovalerate being a non-sensitizer is further supported by the weight of evidence from the animal (Klecak, 1985) and human maximization tests (RIFM, 1971; RIFM, 1972; RIFM, 1973) performed on structurally similar materials Bornyl isovalerate (endo-) (CAS # 76-50-6); Isobornyl propionate (CAS # 2756-56-1); Bornyl acetate (CAS # 76-49-3) and laevo-Bornyl acetate (CAS # 5655-61-8).

Additional References: None.

Literature Search and Risk Assessment Completed on: 04/24/15.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for isobornyl isovalerate 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 phototoxic and photoallergenic effects, 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009). Based on lack of absorbance, isobornyl isovalerate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 07/19/16.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on isobornyl isovalerate. Based on the Creme RIFM model, the inhalation exposure is 0.0000024 mg/day. This exposure is 195 833 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.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isobornyl isovalerate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic

Table 1
PNEC derivation.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.468 mg/l			1,000,000	0.000468 µg/l	

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 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 isovalerate was identified as a fragrance material with no 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 and OECD Toolbox (Catalogic v.5.11.16) did not identify isobornyl isovalerate as either being possibly persistent nor 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).

10.2.2. Risk assessment

Based on current Volume of Use (2011), isobornyl isovalerate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

Table 2
Exposure information and PEC calculation.

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.26	5.26
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

10.2.3.3. Other available data. Isobornyl isovalerate has been pre-registered for REACH with no additional data at this time.

11. 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 in Table 1.

Exposure information and PEC calculation in Table 2 (following RIFM Environmental Framework: Salvito et al., 2002).

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

The RIFM PNEC is 0.000468 µg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening level 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: 4/23/15.

12. 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.

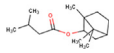
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.10.029.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.10.029.

Appendix

	Target Material	Read across Material
Principal Name	Isobornyl isovalerate	Isobornyl acetate
CAS No.	7779-73-9	125-12-2
Structure		
3D Structure	http://www.thegoodscentscompany.com/opl/7779-73-9.html	http://www.thegoodscentscompany.com/opl/125-12-2.html
Read-across endpoint		• Genotoxicity • Repeated Dose • Devel/Repro • Skin sensitization
Molecular Formula	C15H26O2	C12H20O2
Molecular Weight	238.37	196.29
Melting Point (°C, EPISUITE)	56.81	34.11
Boiling Point (°C, EPISUITE)	268.12	225.89
Vapor Pressure(Pa @ 25°C, EPISUITE)	2.426	14.27
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	5.26	3.86
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	0.8885	9.721
J_{max} (mg/cm^2/h, SAM)	3.328115159	18.65520626
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	103.452825	44.228362
Similarity (Tanimoto score)[1]		83%
Genotoxicity		
DNA binding (OASIS v1.1)	•No alert found	• Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers • Schiff base formers ≫ Direct acting Schiff base formers ≫ Specific Acetate Esters • SN1 • SN1 ≫ Carbenium ion formation • SN1 ≫ Carbenium ion formation ≫ Specific Acetate Esters • SN2 • SN2 ≫ Acylating agents • SN2 ≫ Acylating agents ≫ Specific Acetate Esters • SN2 ≫ SN2 at sp3-carbon atom • SN2 ≫ SN2 at sp3-carbon atom ≫ Specific Acetate Esters
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)	•H-acceptor-path3-H-acceptor	•H-acceptor-path3-H-acceptor
Oncologic classification (OECD)	•Not classified	•Not classified
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)	NON-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 v2.1.6)	NON-Sensitizer (low 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 (Rogers and Hahn, 2010).

Summary:

There are insufficient toxicity data on isobornyl isovalerate (RIFM# 5044, CAS# 7779-73-9). 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 J_{max} 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 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)
- 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 analog for isobornyl isovalerate (target) based on:
  - o The target and analog belong to the generic class of aliphatic esters, specifically, esters/cyclic alcohol/bicyclic/secondary alcohols/saturated.
  - o The target and analog have the same alcohol part and similar carboxylic acid part.
  - o The key differences between target and analog are the carboxylic acid part. The target is an isovalerate, while the analog is an acetate. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification. An exception was noted for DNA binding alerts generated by Oasis v1.1 for isobornyl acetate.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog show similar alerts for protein binding.
  - o 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? Yes
Q19. Open chain? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane, cyclobutane with substituents in Q24 or a mono or bicyclic sulphide or mercaptan? No
Q26. Monocycloalkanone or a bicyclocompound? Yes Class Intermediate (Class II)

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