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Short Review

RIFM fragrance ingredient safety assessment, isobutyl hexanoate, CAS Registry Number 105-79-3

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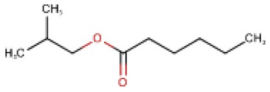
Version: 080218. This version replaces any previous versions.

Name: Isobutyl hexanoate CAS Registry Number: 105-79-3



Abbreviation/Definition 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, 2017; Safford et al., 2015, 2017) 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
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

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Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test.
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultraviolet/Visible Spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety × concludes that this material is safe as 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 includes 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 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., 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 endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety 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 with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment. Isobutyl hexanoate (CAS # 105-79-3) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from isobutyl acetate (CAS # 110-19-0) show that isobutyl hexanoate is not expected to be genotoxic. Data from the target material and read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for isobutyl hexanoate for skin sensitization under the current declared levels of use. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to isobutyl hexanoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; isobutyl hexanoate is not expected to be phototoxic/photoallergenic. For the environmental endpoints, isobutyl hexanoate is not PBT as per the IFRA Environmental Standards, and its risk quotients (i.e., PEC/PNEC) for the aquatic environment based on the screening-level are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (ECHA REACH Dossier: Isobutyl acetate)	
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns at current, declared use levels.	RIFM (1987)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC is available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 135 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: Fish LC50: 7.-709 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: 7.709 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.007709 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** Isobutyl hexanoate
2. **CAS Registry Number:** 105-79-3
3. **Synonyms:** Hexanoic acid, 2-methylpropyl ester; Isobutyl caproate; 2-Methyl-1-propyl caproate; ｱﾙｶﾝ酸(C = 6 ~ 10)ｱﾙｷﾙ(C = 1 ~ 10); Isobutyl hexanoate
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.27
6. **RIFM Number:** 634
7. **Stereochemistry:** Isomer not specified. One stereocenter and total 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 198.83 °C (US EPA, 2012a)
2. **Flash Point:** 169 °F; CC (FMA)
3. **Log K_{OW}:** 3.74 (EPI Suite)
4. **Melting Point**: 20.47 °C (US EPA, 2012a)
5. **Water Solubility:** 38.59 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.856 (FMA Database)
7. **Vapor Pressure:** 0.259 mm Hg @ 20 °C (US EPA, 2012a), 0.2 mm Hg 20 °C (FMA), 0.382 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid with a fruity odor.*

* http://www.thegoodscentscompany.com/data/rw1013501.html, 12/7/17.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** no reported use in hydroalcoholics (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.0098 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00027 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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; Safford et al., 2017; and Comiskey et al., 2017).

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 I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** Isobutyl acetate (CAS # 110-19-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Isoamyl acetate (CAS # 123-92-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

Isobutyl hexanoate is reported to occur in the following foods by the VCF*:

Apple brandy (*Calvados*)	Guava and feyoa
Apple fresh (*Malus* species)	*Mangifera* species
Apple processed (*Malus* species)	Passion fruit (*Passiflora* species)
Apricot (*Prunus armeniaca* L.)	Plum wine
Banana (*Musa sapientum* L.)	Quince, marmelo (*Cydonia oblonga* Mill.)
Beer	Rum
Blue cheeses	Sea buckthorn (*Hippophaë rhamnoides* L.)
Cheese, various types	Sherry
Chinese quince (*Pseudocydonia sinensis* Schneid)	Spineless monkey orange (*Strychnos madagasc.*)
Cider (apple wine)	Whisky
Grape brandy	Wine

*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 containing information on published volatile compounds that 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 11/30/2010; no dossier available as of 08/02/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Isobutyl hexanoate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

There are no studies assessing the mutagenic activity of isobutyl hexanoate; however, read-across can be made to isobutyl acetate (CAS # 110-19-0; see Section V). The mutagenic activity of isobutyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and according to guidelines similar to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with isobutyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, isobutyl acetate was not mutagenic in the Ames test, and this can be extended to isobutyl hexanoate.

There are no data assessing the clastogenic activity of isobutyl hexanoate; however, read-across can be made to isobutyl acetate (CAS # 110-19-0; see Section V). The clastogenicity of isobutyl acetate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung fibroblasts (V79 cells) were treated with isobutyl acetate in MEM culture medium at concentrations up to 5000 μg/mL in the presence and absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, isobutyl acetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to isobutyl hexanoate.

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

Additional References: OECD SIDS Database.

Literature Search and Risk Assessment Completed On: 12/5/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isobutyl hexanoate or any read-across materials. The total systemic exposure to isobutyl hexanoate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on isobutyl hexanoate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isobutyl hexanoate (0.27 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/29/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on isobutyl hexanoate or any read-across materials. The total systemic exposure to isobutyl hexanoate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on isobutyl hexanoate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isobutyl hexanoate (0.27 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/29/17.

10.1.4. Skin sensitization

Based on the existing data and read-across material isoamyl acetate (CAS # 123-92-2), isobutyl hexanoate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for isobutyl hexanoate. Based on the existing data and read-across material isoamyl acetate (CAS # 123-92-2; see Section V), isobutyl hexanoate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, maximization tests and an open epicutaneous test with read-across material isoamyl acetate did not present reactions indicative of sensitization (Ballantyne et al., 1986; Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with isobutyl hexanoate and read-across material isoamyl acetate (RIFM, 1976; RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 23622 μg/cm^2 of read-across material isoamyl acetate, no reactions indicative of sensitization were observed in any of the 197 volunteers (RIFM, 1987).

Based on weight of evidence from structural analysis, animal and human studies, and read-across material isoamyl acetate, isobutyl hexanoate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/15/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, isobutyl hexanoate 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 isobutyl hexanoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, Isobutyl hexanoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/19/17.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on isobutyl hexanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0098 mg/day. This exposure is 143 times lower than the Cramer Class I TTC value of 1.4 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of isobutyl hexanoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, isobutyl hexanoate 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 EPI Suite v4.1 (US EPA, 2012a) did not identify isobutyl hexanoate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), isobutyl hexanoate does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.2.1. Other available data. Isobutyl hexanoate has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	7.709			1,000,000	0.007709	

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

Exposure	Europe	North America
Log K_{ow} used	3.7	3.7
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	Not reported
Risk Characterization: PEC/PNEC	**< 1**	**N/A**

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

The RIFM PNEC is 0.007709 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the 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: 11/30/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- 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://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 08/02/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.014.

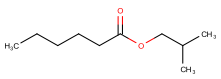
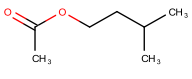
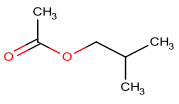
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material
Principal Name	Isobutyl hexanoate	Isoamyl acetate	Isobutyl acetate
CAS No.	105-79-3	123-92-2	110-19-0
Structure			

Similarity (Tanimoto Score)		0.55	0.42
Read-across Endpoint		• Skin sensitization	• Genotoxicity
Molecular Formula	$C_{10}H_{20}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$
Molecular Weight	172.27	130.19	116.16
Melting Point (°C, EPI Suite)	−20.47	−56.05	−68.43
Boiling Point (°C, EPI Suite)	198.83	134.87	111.74
Vapor Pressure (Pa @ 25 °C, EPI Suite)	51	7.47 E+002	2.44 E+003
Log Kow (KOWWIN v1.68 in EPI Suite)	3.74	2.25	1.78
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	38.59	2000	6300
J_{max} (mg/cm^2/h, SAM)	65.245	101.618	225.843
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.29 E+002	5.52 E+001	4.16 E+001
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found		• AN2 - Schiff base formation • SN1 - Nucleophilic attack • Acylation
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found		• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)		• Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found		• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found		• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found		• No alert found
Oncologic Classification	• Not classified		• Not classified
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	
Protein Binding (OECD)	• No alert found	• No alert found	
Protein Binding Potency	• Not possible to classify	• Not possible to classify	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found	
Metabolites			
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• No alert found		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on isobutyl hexanoate (CAS # 105-79-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, isobutyl acetate (CAS # 110-19-0) and isoamyl acetate (CAS # 123-92-2) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Isoamyl acetate (CAS # 123-92-2) was used as a read-across analog for the target material isobutyl hexanoate (CAS # 105-79-3) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - o The target substance and the read-across analog are both esters of straight chain acids with branched chain alcohols.
  - o The key structural difference between the target substance and the read-across analog is that the target substance is the ester of isobutanol and hexanoic acid, whereas the read-across analog is the ester of isoamyl alcohol and acetic acid. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these branched chain ester structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Isobutyl acetate (CAS # 110-19-0) was used as a read-across analog for the target material isobutyl hexanoate (CAS # 105-79-3) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of saturated branched esters.
  - o The target substance and the read-across analog are both isobutyl alcohol esters.
  - o The key structural difference between the target substance and the read-across analog is that the target substance is the hexanoate ester of isobutanol, whereas the read-across analog is the acetate ester of isobutanol. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the similarity of these isobutyl alcohol esters. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog has a DNA binding alert by the OASIS model. The target substance does not have any such alert. According to these

predictions, the read-across analog is expected to be more reactive than the target substance. The data described in the genotoxicity section above show that, based on the current existing data, the read-across analog does not pose a concern for genotoxicity. Therefore, the predictions are superseded by data.

- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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