

Short Review

RIFM fragrance ingredient safety assessment, isobutyl phenylacetate, CAS Registry Number 102-13-6



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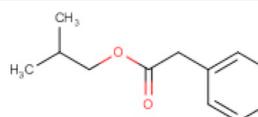
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Version 073018. This version replaces any previous versions.

Name: Isobutyl phenylacetate

CAS Registry Number: 102-13-6

**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

Crete RIFM Model - The Crete 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

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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
 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 phenylacetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog methyl phenylacetate (CAS # 101-41-7) show that isobutyl phenylacetate is not expected to be genotoxic. Data on isobutyl phenylacetate and read-across analog methyl benzoate (CAS # 93-58-3) show that isobutyl phenylacetate is not a safety concern at the current, declared levels of use for the skin sensitization endpoint. 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 phenylacetate 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 phenylacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; isobutyl phenylacetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1 .

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2001; RIFM, 2015)
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. (ECHA REACH Dossier: Methyl benzoate, accessed 12/1/17)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.8 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 91.9 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: 96-h Algae EC50: 2.096 mg/L (ECOSAR; US EPA, 2012b)
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: 2.096 mg/L (ECOSAR; US EPA, 2012b)
 RIFM PNEC is: 0.2096 $\mu\text{g/L}$
 • Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

- 1. Chemical Name:** Isobutyl phenylacetate
- 2. CAS Registry Number:** 102-13-6
- 3. Synonyms:** Benzeneacetic acid, 2-methylpropyl ester; Isobutyl α -toluate; 2-Methylpropyl phenylacetate; 7-イソブチルフェニルアセテート (C = 2 ~ 5) 7-イソブチルフェニルアセテート (C = 1 ~ 8); Isobutyl phenylacetate
- 4. Molecular Formula:** $\text{C}_{12}\text{H}_{16}\text{O}_2$
- 5. Molecular Weight:** 192.26
- 6. RIFM Number:** 432
- 7. Stereochemistry:** Isomer not specified. No stereocenters and no

stereoisomers possible.

2. Physical data

- 1. Boiling Point:** 253 °C (FMA Database), 258.98 °C (EPI Suite)
- 2. Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA Database)
- 3. Log K_{ow} :** 3.48 (EPI Suite)
- 4. Melting Point:** 21.57 °C (EPI Suite)
- 5. Water Solubility:** 51.02 mg/L (EPI Suite)
- 6. Specific Gravity:** 0.984–0.988 (FMA Database), 0.986–0.990 (FMA Database)

7. **Vapor Pressure:** 0.0203 mm Hg @ 20 °C (EPI Suite v4.0), 0.01 mm Hg @ 20 °C (FMA Database), 0.032 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 clear, colorless to pale yellow liquid having a rose honey-like character

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcohols:** 0.015% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00016 mg/kg/day or 0.012 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0012 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:** Methyl phenylacetate (CAS # 101-41-7)
 - b. **Repeated Dose Toxicity:** None
 - c. **Reproductive Toxicity:** None
 - d. **Skin Sensitization:** Methyl benzoate (CAS # 93-58-3)
 - 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.

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

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

Cocoa

*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

Dossier available, accessed 07/27/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, isobutyl phenylacetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Isobutyl phenylacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenicity of isobutyl phenylacetate. The mutagenic activity of read-across material methyl phenylacetate (CAS # 101-41-7; see Section V) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, and TA102 were treated with methyl phenylacetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of an S9 activation system (RIFM, 2001). Under the conditions of the study, methyl phenylacetate was not mutagenic in the Ames test, and this can be extended to isobutyl phenylacetate.

There are no studies assessing the clastogenicity of isobutyl phenylacetate. The clastogenic activity of read-across material methyl phenylacetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with methyl phenylacetate in DMSO at concentrations up to 1500 µg/mL in the presence and absence of an S9 metabolic activation system for 4 and 24 h. Methyl phenylacetate did not induce binucleated cells with micronuclei when tested up to the maximum concentration either in the presence or absence of S9 metabolic activation (RIFM, 2015). Under the conditions of the study, methyl phenylacetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to isobutyl phenylacetate.

Based on the available data, isobutyl phenylacetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/13/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isobutyl phenylacetate or any read-across materials. The total systemic exposure to isobutyl phenylacetate 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 phenylacetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isobutyl phenylacetate (1.2 µg/kg/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: 11/28/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on isobutyl phenylacetate or any read-across materials. The total systemic exposure to isobutyl phenylacetate 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 phenylacetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isobutyl phenylacetate (1.2 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: 11/28/17.

10.1.4. Skin sensitization

Based on the existing data and read-across analog methyl benzoate (CAS # 93-58-3), isobutyl phenylacetate 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 phenylacetate. Based on the existing data and read-across analog methyl benzoate (CAS # 93-58-3; see Section V), isobutyl phenylacetate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay, read-across analog methyl benzoate was found to be negative up to maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 2.98 (ECHA REACH Dossier: Methyl benzoate, accessed 12/1/17). In guinea pigs, open epicutaneous tests with isobutyl phenylacetate and read-across analog methyl benzoate did not present reactions indicative of sensitization (Klecek, 1985). In a Freund's complete adjuvant test, read-across analog methyl benzoate did not present reactions indicative of sensitization (Hausen et al., 1995). In human maximization tests, no skin sensitization reactions were observed with isobutyl phenylacetate and read-across analog methyl benzoate (RIFM, 1973; RIFM, 1970). Based on weight of evidence from structural analysis, animal and human studies, and read-across analog methyl benzoate, isobutyl phenylacetate 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: 12/1/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, isobutyl phenylacetate 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 phenylacetate 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 phenylacetate 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 phenylacetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.7.1. Risk assessment. There are no inhalation data available on isobutyl phenylacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 117 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: 12/01/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of isobutyl phenylacetate 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 phenylacetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.1 did not identify isobutyl phenylacetate 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 phenylacetate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. *Biodegradation*. No data available.

10.2.2.2. *Ecotoxicity*. No data available.

10.2.2.3. *Other available data*. Isobutyl phenylacetate 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)	<u>13.35</u>			1,000,000	0.01335	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	3.510	6.226	<u>2.096</u>	10,000	0.2096	Esters
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	7.390	4.811	6.307			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.9	3.9

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.04.025>.

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.,](#)

Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	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 0.2096 µg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/1/17.

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/oppphpv/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.

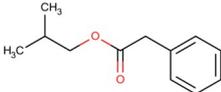
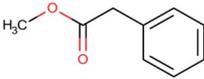
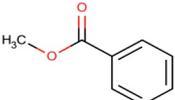
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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 Materials	
Principal Name	Isobutyl phenylacetate	Methyl phenylacetate	Methyl benzoate
CAS No.	102-13-6	101-41-7	93-58-3
Structure			
Similarity (Tanimoto Score)		0.60	0.43
Read-Across Endpoint		• Genotoxicity	• Skin sensitization
Molecular Formula	C ₁₂ H ₁₆ O ₂	C ₉ H ₁₀ O ₂	C ₈ H ₈ O ₂
Molecular Weight	192.26	150.18	136.15
Melting Point (°C, EPI Suite)	21.57	-0.50	-11.87
Boiling Point (°C, EPI Suite)	258.98	215.57	195.93
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.26	20.9	50.6
Log Kow (KOWWIN v1.68 in EPI Suite)	3.48	1.83	2.12
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	51.02	2072	2100
J_{max} (mg/cm²/h, SAM)	28.042	78.176	77.618
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	3.36E+000	1.43E+000	3.52E+000
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition	• Michael addition	
Carcinogenicity (ISS)			
	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate 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	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found		• Acylation
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
Metabolism			
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 phenylacetate (CAS # 102-13-6). 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, methyl phenylacetate (CAS # 101-41-7), and methyl benzoate (CAS # 93-58-3) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Methyl phenylacetate (CAS # 101-41-7) was used as a read-across analog for the target material isobutyl phenylacetate (CAS # 102-13-6) for the genotoxicity endpoint.
 - o The target substance and the read-across analog are structurally similar and belong to the class of aromatic alkyl esters.
 - o The target substance and the read-across analog share a phenylacetyl structure.
 - o The key structural difference between the target substance and the read-across analog is that the target substance is an isobutyl ester of phenylacetic acid, whereas the read-across analog is a methyl ester. 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 phenylacetyl 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 target substance and the read-across analog have a Michael addition alert by the DNA binding model in OECD. According to these predictions, the target substance and the read-across analog are expected to have comparable reactivity. As described in the genotoxicity

- section above, based on current existing data the read-across analog does not pose a concern for genotoxicity. Therefore, data superseded predictions in this case.
- 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.
 - Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material isobutyl phenylacetate (CAS # 102-13-6) for the skin sensitization endpoint.
 - o The target substance and the read-across analog are structurally similar and belong to the class of aromatic alkyl esters.
 - o The target substance and the read-across analog share aryl alkyl ester structures.
 - o The key structural difference between the target substance and the read-across analog is that the target substance is the isobutyl alcohol ester of phenylacetic acid, whereas the read-across analog is the methyl ester of benzoic 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 aryl alkyl 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 protein 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. As described in the skin sensitization section above, the read-across analog does not present a safety concern for skin sensitization under the current, declared levels of use. Therefore, data superseded predictions in this case.
 - 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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