Food and Chemical Toxicology 122 (2018) S422–S430

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, isobutyl butyrate, CAS Registry Number 539-90-2

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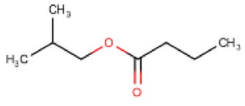
Version: 073118. This version replaces any previous versions.
Name: Isobutyl butyrate
CAS Registry Number: 539-90-2



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

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https://doi.org/10.1016/j.fct.2018.09.073
Received 23 August 2018; Accepted 28 September 2018
Available online 01 October 2018

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 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 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 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 use of this material under current conditions is supported by existing information.

Isobutyl butyrate (CAS # 539-90-2) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from isobutyl acetate (CAS # 110-19-0) show that isobutyl butyrate is not expected to be genotoxic. Data from the target material and the read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for isobutyl butyrate for skin sensitization under the current declared levels of use. The repeated dose and reproductive endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to isobutyl butyrate is below the TTC (0.03 mg/kg/day and 0.03 mg/kg/day, respectively). For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across analog butyl acetate (CAS # 123-86-4). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; isobutyl butyrate is not expected to be phototoxic/photoallergenic. For the environmental endpoints, isobutyl butyrate 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: NOAEC = 2375 mg/m^3.	(ECHA REACH Dossier: Butyl acetate, accessed on 11/30/17 data also available in David et al., 2001)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 3.0 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 30.54 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 42.44 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: 42.44 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.04244 μg/L	
•Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Isobutyl butyrate
2. **CAS Registry Number:** 539-90-2
3. **Synonyms:** Butanoic acid, 2-methylpropyl ester; Isobutyl butanoate; 2-Methyl-1-propyl butyrate; 2-Methylpropanyl butyrate; ﾌﾞﾀﾝ酸ｱﾙｷﾙ (C = 1–7); Isobutyl butyrate
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21
6. **RIFM Number:** 678
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 157 °C (FMA Database), 157.09 °C (US EPA, 2012a)
2. **Flash Point:** 46 °C (GHS), 115 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.76 (US EPA, 2012a)
4. **Melting Point:** -43.92 °C (US EPA, 2012a)
5. **Water Solubility:** 356.7 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.858–0.863 (FMA Database), 0.860–0.865 (FMA Database)
7. **Vapor Pressure:** 2.08 mm Hg @ 20 °C (US EPA, 2012a), 2.8 mm Hg 20 °C (FMA Database), 2.91 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} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless to pale yellow liquid with fruity odor reminiscent of apple or pineapple*

*http://www.thegoodscentscompany.com/data/rw1012391.html, 07/31/18.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.017% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000012 mg/kg/day or 0.00086 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0013 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:** Butyl acetate (CAS # 123-86-4)
   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 butyrate is reported to occur in the following foods by the VCF*:

Apple brandy (*Calvados*)	Kiwifruit (*Actinidia chinensis,* syn. *A. deliciosa*)
Apple fresh (*Malus* species)	*Mangifera* species
Apricot (*Prunus armeniaca* L.)	Melon
Artocarpus species	Mushroom
Banana (*Musa sapientum* L.)	Olive (*Olea europaea*)
Beans	Passion fruit (*Passiflora* species)
Blue cheeses	Pear (*Pyrus communis* L.)
Cheese, various types	Plum (*Prunus* species)
Cherimoya (*Annona cherimolia* Mill.)	Quince, marmelo (*Cydonia oblonga* Mill.)
Chinese quince (*Pseudocydonia sinensis* Schneid)	Strawberry (*Fragaria* species)
Citrus fruits	Tapereba, caja fruit (*Spondias lutea* L.)
Grape brandy	Wine
Honey	

*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 07/31/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Isobutyl butyrate 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 mutagenic activity of isobutyl butyrate; 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 REACH Dossier, 1989). Under the conditions of the study, isobutyl acetate was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of isobutyl butyrate; 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 REACH Dossier, 1996). Under the conditions of the study, isobutyl acetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

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

The clastogenicity of isobutyl acetate (CAS # 110-19-0) was assessed in an *in vitro* mammalian chromosome aberration test using Chinese hamster lung fibroblasts (V79 cells) and conducted according to OECD TG 473 and GLP guidelines. The assay was conducted in the presence and absence of an S9 fraction from Aroclor 1254–induced rats (species not specified). The mitotic index was used to assess cytotoxicity and select concentrations for metaphase analysis. The test material was dissolved in MEM culture medium and assessed in a dose range finding (DRF) study at concentrations ranging from 25 to 5000 μg/mL to assess cytotoxicity. Cytotoxicity of the test substance resulting in a clear reduction of the mitotic index was not observed. From the DRF study, concentrations of 600, 3000, and 5000 μg/mL were assessed for 18 and 28 h in the presence and absence of metabolic activation. All positive and vehicle control values were within acceptable ranges. Isobutyl acetate did not induce any statistically significant increases in the frequency of cells with chromosomal aberrations either in the presence and absence of metabolic activation. It was concluded that isobutyl acetate has shown no evidence of clastogenic activity under the conditions of this study.

Additional References: OECD SIDS Database.

Literature Search and Risk Assessment Completed On: 9/11/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isobutyl butyrate or any read-across materials. The total systemic exposure to isobutyl butyrate 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 butyrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isobutyl butyrate (1.3 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: 11/22/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on isobutyl butyrate or any read-across materials. The total systemic exposure to isobutyl butyrate 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 butyrate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isobutyl butyrate (1.3 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: 11/22/17.

10.1.4. Skin sensitization

Based on the existing data and read-across isoamyl acetate (CAS # 123-92-2), isobutyl butyrate 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 butyrate. Based on the existing data and read-across isoamyl acetate (CAS # 123-92-2; see Section V), isobutyl butyrate 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 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 butyrate and read-across 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 isoamyl acetate, isobutyl butyrate 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 butyrate 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 butyrate 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 butyrate 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: 10/27/17.

10.1.6. Local respiratory toxicity

There are no inhalation data available on isobutyl butyrate; however, in a 13-week inhalation study for the analog butyl acetate (CAS # 123-86-4; see section V), a NOAEC of 2375 mg/m^3 is reported (ECHA REACH Dossier Accessed Last 08/03/2017; David et al., 2001).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE for local respiratory toxicity. In a 13-week whole-body inhalation study conducted in rats, a NOAEC of 2375 mg/m^3 (500 ppm) was reported (ECHA REACH Dossier, accessed 11/30/2017; David et al., 2001). Whole-body inhalation exposure of read-across material, butyl acetate was administered at target concentrations (0 [sham], 2375, 7126, and 14253 mg/m^3) to both male and female Sprague Dawley rats (15 animals/sex/concentration). Clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross pathology, and histopathology were all considered. Body weights and food consumption decreased among animals in mid- and high-concentration treatment groups. Organ weight changes were also dependent upon treatment and concentration. Lung weights increased among males exposed to 14253 mg/m^3 butyl acetate compared to the control group. Additionally, histopathology for both the mid- and high-concentration treatment groups demonstrated degenerated olfactory epithelial tissue as well as dorsal medial meatus and ethmotubinates of the nasal passages. Severity of the histopathological findings ranged from mild to moderate for the high-concentration group, but minimal to mild for the mid-concentration group. As there were no observable adverse effects documented for the low-concentration treatment group, the NOAEC was determined to be 2375 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (2375 mg/m^3) (1m^3/1000 L) = 2.375 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (2.375 mg/L) (61.2 L/day) = 145.35 mg/day
- (145.35 mg/day)/(0.0016 kg lung weight of rat*) = 90844 mg/kg lung weight/day

The 95th percentile calculated exposure to isobutyl butyrate was reported to be 0.00086 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0013 mg/kg lung weight/day resulting in an MOE of 69880000 (i.e., [90844 mg/kg lung weight/day]/[0.0013 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.00086 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed. 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy,” subsection, “Comparative Airway Anatomy.”

10.1.6.2. Additional references. Smyth et al., 1954; Smyth and Smyth, 1928; Haglund et al., 1980; Nelson et al., 1943; McOmie and Anderson, 1949; Burleigh-Flayer et al., 1991; Querci and Mascia, 1970a; Ambrosio and D'Arrigo, 1962a; Ambrosio et al., 1962b; Frantik et al., 1994; Querci et al., 1970b; Osina, 1959; Sayers et al., 1936; Iregren et al., 1993; Ashley and Prah, 1997; Bowen and Balster, 1997; Norris et al., 1997; Silver, 1992; Prah et al., 1998; David et al., 1998; Saillenfait et al., 2007.

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 butyrate 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 butyrate 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 v4.11 (US EPA, 2012a) did not identify isobutyl butyrate 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 v4.11). 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 butyrate does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.3. Other available data

Isobutyl butyrate has been pre-registered for REACH with no additional data at this time.

10.2.4. 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>42.44</u>			1,000,000	0.04244	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.76	2.76
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.04244 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. Th 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: 11/27/17.

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 07/31/2018.

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.2018.09.073.

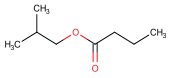
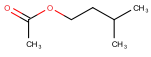
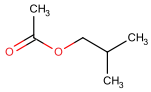
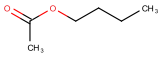
Appendix

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	Read-across Material
Principal Name	Isobutyl butyrate	Isoamyl acetate	Isobutyl acetate	Butyl acetate
CAS No.	539-90-2	123-92-2	110-19-0	123-86-4
Structure				
Similarity (Tanimoto Score)		0.78	0.71	0.59
Read-across Endpoint		• Skin sensitization	• Genotoxicity	• Local Respiratory toxicity
Molecular Formula	$C_8H_{16}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$	$C_6H_{12}O_2$
Molecular Weight	144.22	130.19	116.16	116.16
Melting Point (°C, EPI Suite)	−43.92	−56.05	−68.43	−56.83
Boiling Point (°C, EPI Suite)	157.09	134.87	111.74	125.79
Vapor Pressure (Pa @ 25°C, EPI Suite)	387	7.47E+002	2.44E+003	1.59E+003
Log Kow (KOWWIN v1.68 in EPI Suite)	2.76	2.25	1.78	1.78
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	356.7	2000	6300	8400
J_{max} (mg/cm^2/h, SAM)	231.986	101.618	225.843	301.124
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.33E+001	5.52E+001	4.16E+001	4.16E+001
Genotoxicity				
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	
Skin Sensitization				
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		
Local Respiratory Toxicity				
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• 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	See Supplemental Data 4

Summary

There are insufficient toxicity data on Isobutyl butyrate (CAS # 539-90-2). 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), isoamyl acetate (CAS # 123-92-2), and butyl acetate (CAS # 123-86-4) 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 butyrate (CAS # 539-90-2) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of branched saturated esters.
  - The target substance and the read-across analog share similar structures as esters of aliphatic acids with branched alcohols.
  - The key structural differences between the target substance and the read-across analog are that the target substance is an isobutyl alcohol ester of butyric acid, whereas the read-across material is an isoamyl alcohol ester of acetic acid. These structural differences are toxicologically insignificant.
  - Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects the high similarity of these straight chain esters of similar branched alcohols. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - 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 butyrate (CAS # 539-90-2) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of saturated branched esters.
  - The target substance and the read-across analog share an isobutyl alcohol portion.
  - The key structural difference between the target substance and the read-across analog is that the target substance is an isobutyl ester of butyric acid, whereas the read-across analog is an isobutyl ester of acetic acid. This structural difference is toxicologically insignificant.
  - 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.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - 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 compared to 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.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material isobutyl butyrate (CAS # 539-90-2) for the local respiratory toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of saturated aliphatic esters.
  - The target substance and the read-across analog share similar aliphatic ester structures.
  - The key structural difference between the target substance and the read-across analog is that the target substance is an isobutyl alcohol ester of butyric acid, whereas the read-across analog is a butyl alcohol ester of acetic acid. This structural difference is toxicologically insignificant.
  - 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 butyl alcohol esters. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the

read-across analog.

- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- 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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