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Short review

RIFM fragrance ingredient safety assessment, Isoamyl butyrate, CAS Registry Number 106-27-4

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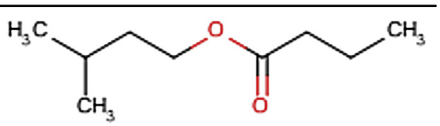

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Abbreviation list:

2-Box Model - a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration.
AF - Assessment Factor.
BCF - Bioconcentration Factor.
Creme RIFM model - The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015) compared to a deterministic aggregate approach.
DEREK - Derek nexus is an *in silico* tool used to identify structural alerts.
DST - Dermal Sensitization Threshold.
ECHA - European Chemicals Agency.
EU - Europe/European Union.
GLP - Good Laboratory Practice.
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level.
MOE - Margin of Exposure.
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition.
NA - North America.
NESIL - No Expected Sensitization Induction Level.
NOAEC - No Observed Adverse Effect Concentration.
NOAEL - No Observed Adverse Effect Level.

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NOEC - No Observed Effect Concentration.
OECD - Organisation for Economic Co-operation and Development.
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines.
PBT - Persistent, Bioaccumulative, and Toxic.
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration.
QRA - Quantitative risk assessment.
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals.
RIFM - Research Institute for Fragrance Materials.
RQ - Risk Quotient.
TTC - Threshold of Toxicological Concern.
UV/Vis Spectra - Ultra Violet/Visible spectra.
VCF - Volatile Compounds in Food.
VoU - Volume of Use.
vPvB - (very) Persistent, (very) Bioaccumulative.
WOE - Weight of Evidence.
RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred for clarifications.
Each endpoint discussed in this safety assessment reviews relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the target material and suitable read across analogs isoamyl alcohol (CAS# 123-51-3) and butyric acid (CAS# 107-92-6) show that this material is not genotoxic. Data from the suitable read across analog isoamyl acetate (CAS# 123-92-2) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was evaluated using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoints were evaluated using isoamyl alcohol (CAS# 123-51-3) and butyric acid (CAS# 107-92-6) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was evaluated based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.
Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2015c; Ishidate et al., 1984; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day. (Schilling et al., 1997)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day. (ECHA REACH Dossier: 3-methylbutan-1-ol)
Skin Sensitization: Not a sensitization concern. (RIFM, 1987)
Phototoxicity and Photoallergenicity: Not phototoxic and photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening Level: 92.1% (OECD 301B) (RIFM, 1994)
Bioaccumulation: Screening Level: 64.3 l/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 96 h Algae EC50: 2.51 mg/l (EpiSuite ver 4.1)
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 (EpiSuite ver 4.1)
Endpoint: 96 h Algae EC50: 2.51 mg/l
RIFM PNEC is: 0.251 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: <1

1. Identification

1. **Chemical Name:** Isoamyl butyrate
2. **CAS Registry Number:** 106-27-4
3. **Synonyms**: Butanoic acid, 3-methylbutyl ester; Isoamyl butanoate; Isoamyl butyrate; Isopentyl butanoate; Isopentyl butyrate; 3-methylbutyl butanoate; ブタン酸アルキル(C = 1~7); 3-methylbutyl butyrate
4. **Molecular Formula:** $C_9H_{18}O_2$
5. **Molecular Weight:** 158.24
6. **RIFM Number:** 804

2. Physical data

1. **Boiling Point:** 178.41 °C [EPI Suite]
2. **Flash Point**: 57 °C [GHS], 135 °F; CC [FMA database]
3. **Log K_{OW}**: 3.25 [EPI Suite]
4. **Melting Point**: −32.06 °C [EPI Suite]
5. **Water Solubility:** 117.8 mg/L [EPI Suite]
6. **Specific Gravity**: 0.8639 [RIFM database], 0.862 [FMA database]
7. **Vapor Pressure**: 0.705 mm Hg @ 20 °C [EPI Suite 4.0], 0.8 mm Hg 20 °C [FMA database], 1.01 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorption between 290 and 400 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with aromatic pear-like odor or fruity odor

3. Exposure

1. **Volume of Use (Worldwide Band)**: 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.033% (RIFM, 2016)
3. **Inhalation Exposure***: 0.00049 mg/kg/day or 0.037 mg/day (RIFM, 2016)
4. **Total Systemic Exposure****: 0.0024 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral

and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogues Selected:
   a. **Genotoxicity:** Isoamyl alcohol (CAS# 123-51-3) and butyric acid (CAS# 107-92-6).
   b. **Repeated Dose Toxicity:** Isoamyl alcohol (CAS# 123-51-3) and butyric acid (CAS# 107-92-6).
   c. **Developmental and Reproductive Toxicity:** Isoamyl alcohol (CAS# 123-51-3) and butyric acid (CAS# 107-92-6).
   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

See Appendix below

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

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

Acerola (*Malpighia*)	Blue cheeses
Apple brandy (Calvados)	Camomile
Apple fresh (*Malus* species)	*Capsicum* species
Apricot (*Prunus armeniaca* L.)	Cashew apple (*Anacardium occidentale*)
Artocarpus species	Cheese, various types
Banana (*Musa sapientum* L.)	Cherimoya (*Annona cherimolia Mill.*)
Bilberry wine	Cider (apple wine)
Citrus fruits	Passion fruit (*passiflora* species)
Dalieb, palmyra paml fruit (*Borassus aethiopum* L.)	Plum (*Prunus* species)
Grape (*Vitis* species)	Plum wine
Grape brandy	Pomegranate wine (*Punica granatum* L.)
Guava and feyoa	Rum
Honey	Spineless monkey orange (*Strychnos madagasc.*)
Mangifera species	Strawberry (*Fragaria* species)
Mastic (*Pistacia* lentiscus)	Tapereba, caja fruit (*Spondias lutea* L.)
Melon	Tomato (*Lycopersicon esculentum Mill.*)
Mountain papaya (*C. candamarcensis, C. pubescens*)	Whisky
Muruci (*Byrsonima* crassifolia)	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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None

9. REACH Dossier

Pre-registered for 2010, no dossier available as of 3/3/2017

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, isoamyl butyrate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of isoamyl butyrate (CAS # 106-27-4) 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/preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA were treated with isoamyl butyrate in DMSO (dimethyl sulfoxide) 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 S9 (RIFM, 2015c). Under the conditions of the study, isoamyl butyrate was not mutagenic in the Ames test.

The clastogenicity of isoamyl butyrate was assessed in an *in vitro* chromosome aberration study. Chinese hamster lung cells were treated with isoamyl butyrate in DMSO at concentrations up to 2 mg/mL in the 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, without S9 metabolic activation (Ishidate et al., 1984). Under the conditions of the study, isoamyl butyrate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Due to lack of additional clastogenicity data in presence of metabolic activation, and considering isoamyl butyrate will readily hydrolyze into isoamyl alcohol (CAS # 123-51-3; see section 5) and butyric acid (CAS# 107-92-6; see Section 5). Metabolite, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient genotoxicity data. The clastogenic activity of isoamyl alcohol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). There are no studies in presence of metabolic activation for the acid part of the ester. However, an *in vivo* mouse micronucleus test conducted with n-butanol (a butyric acid precursor; CAS # 107-92-6; see section 5) administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight did

not produce any chromosome-damaging (clastogenic) effect (ECHA REACH Dossier: butyric acid, accessed 08/30/2016). Under the conditions of the study, isoamyl alcohol was considered to be non-clastogenic in the *in vivo* micronucleus test, which can be extended to isoamyl butyrate based on metabolism.

Based on the data available, isoamyl butyrate does not present a concern for genotoxic potential.

Additional References: Kuroda et al., 1984.

Literature Search and Risk Assessment Completed on: 06/23/2016

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on isoamyl butyrate. Isoamyl butyrate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section section 5) and butyric acid (CAS# 107-92-6; see section 5). The metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on a group of 12 male and female Sprague-Dawley rats/group administered the test material, isoamyl alcohol via gavage at doses of 0, 30, 100 and 300 mg/kg/day, an additional satellite recovery group of 5 animals/sex/group were administered test material at doses of 0 and 300 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day, based on reduced body weight gain in males (ECHA REACH Dossier: 3-methylbutan-1-ol, accessed 07/09/14). In another study, an OECD/GLP 408 study was conducted on a group of 10 SPF-Wistar, Chbb:THOM rats/sex/group administered test material, isoamyl alcohol via drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day) & 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters, the NOAEL was determined to be 1600 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment related (Schilling et al., 1997; data also available in RIFM, 1991). In another study, a group of 15 rats/sex/group were gavaged with the test material, isoamyl alcohol at doses of 0, 150, 500 and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to the test material administration up to the highest dose tested. Thus the NOAEL was determined to be 1000 mg/kg/day (Carpaninini et al., 1973). Since no adverse effects were reported among the animals during the 13 and 17 week studies, the NOAEL was determined to be 1250 mg/kg/day.

Therefore, the MOE for repeated dose toxicity is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 1250/0.0024 or 520833.

In addition, the total systemic exposure for isoamyl butyrate (2.4 μg/kg/day) is below the TTC (30 μg/kg bw/day).

Additional References: ECHA REACH Dossier: 3-methylbutan-1-ol

Literature Search and Risk Assessment Completed on: 6/23/2016

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on isoamyl butyrate. Isoamyl butyrate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and butyric acid (CAS# 107-92-6; see Section 5). Metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient developmental toxicity data. There is an OECD 414 developmental toxicity study conducted on 15 female pregnant Himalayan rabbits/dose group administered test material, isoamyl alcohol via inhalation at doses of 0, 0.5, 2.5 and 10 mg/l equivalent to 0, 68, 341 and 1365 mg/kg/day, respectively, according to standard minute volume and body weight parameters of New Zealand rabbits. The NOAEL for developmental toxicity was determined to be 10 mg/l or 1365 mg/kg/day the highest dose tested (RIFM, 1990b). In another study, an OECD 414 developmental toxicity study was conducted on a group of 25 female pregnant Wistar rats/group administered test material, isoamyl alcohol at doses of 0, 0.5, 2.5 and 10 mg/l, equivalent to 0, 135, 674 and 2695 mg/kg/day according to standard minute volume and body weight parameters of Wistar rats. The NOAEL for developmental toxicity was determined to be 10 mg/l or 2695 mg/kg/day the highest dose tested (RIFM, 1990a). Subsequently, an OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group administered test material, isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the development of the fetus up to the highest dose tested (ECHA REACH Dossier: 3-Methylbutan-1-ol). Thus, the NOAEL was determined to be 300 mg/kg/day the highest dose tested. In addition, metabolite, butyric acid (CAS# 107-92-6; see section 5) had a developmental toxicity screening assay (Chernoff/Kavlock) conducted in rats. Decreased pup viability occurred only in the presence of significant maternal toxicity. But The LOAEL for maternal toxicity was determined to be 100 mg/kg/day due to mortality and clinical signs at the higher dose level. The NOAEL for fetal toxicity was determined to be 133 mg/kg/day the highest dose tested (Narotsky et al., 1994). The most conservative NOAEL of 300 mg/kg/day was selected for the developmental toxicity endpoint.

There are no reproductive toxicity data on isoamyl butyrate. The metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient reproductive toxicity data. An OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group administered the test material, isoamyl alcohol, at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). The NOAEL for reproductive toxicity was determined to be 300 mg/kg/day the highest dose tested.

Therefore, the MOE is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 300/0.0024 or 125000.

In addition, the total systemic exposure for isoamyl butyrate (2.4 μg/kg/day) is below the TTC (30 μg/kg bw/day).

Additional References: Narotsky et al., 1994.

Literature Search and Risk Assessment Completed on: 6/23/2016

10.1.4. Skin sensitization

Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2), isoamyl butyrate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2; see section 5), isoamyl butyrate does not present a concern for skin sensitization. The

chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, read across material isoamyl acetate was found to be negative in the guinea pig Open Epicutaneous Test (OET) (Klecak, 1979, 1985). In human maximization tests, no skin sensitization reactions were observed with 3% isoamyl butyrate (2760 μg/cm^2) or 8% (5520 μg/cm^2) isoamyl acetate (RIFM, 1976; RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm^2 isoamyl acetate in 75:25 Ethanol:Diethyl phthalate (DEP), no reactions of sensitization were observed in any of the 197 volunteers (RIFM, 1987). Based on the available data and read across to isoamyl acetate, isoamyl butyrate does not present a concern for skin sensitization.

Additional References: None

Literature Search and Risk Assessment Completed on: 10/11/16

10.1.5. Phototoxicity/Photoallergenicity

Based on available UV spectra, isoamyl 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 isoamyl butyrate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, isoamyl butyrate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None

Literature Search and Risk Assessment Completed on: 06/30/16

10.1.6. Local respiratory toxicity

The Margin of Exposure could not be calculated due to lack of appropriate data. The material, isoamyl butyrate, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There is limited inhalation data available on isoamyl butyrate. Based on the Creme RIFM model, the inhalation exposure is 0.037 mg/day. This exposure is 37.8 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: Frederick et al., 2009.

Literature Search and Risk Assessment Completed on: 07/08/2016

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isoamyl butyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, isoamyl butyrate 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 EPISUITE ver 4.1 did not identify isoamyl butyrate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate 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 (2011), isoamyl butyrate presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. **RIFM, 1992a**: The ready biodegradation test has been conducted according to the Commission Directive 79/831/EWG annex V part C. Biodegradation of 23% was observed after 28 days.

RIFM, 1994: Biodegradability was evaluated by the sealed vessel test based on OECD 301B guidelines. Vessels containing mineral salts medium were inoculated with filtered activated sludge plant secondary effluent. Amyl butyrate (10 mg/l) was added directly to the vessels. The vessels were sealed and were incubated for 28 days. The biodegradation rate was 92.1%.

RIFM, 2015b: Ready biodegradability of the test material was evaluated according to the OECD 310 method. Biodegradation of 63% was observed after 28 days.

10.2.2.2. Ecotoxicity. **RIFM, 2015a**: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48 h EC50 was reported to be 8.12 mg/l.

RIFM, 1992b: A 96-h acute toxicity study was conducted with Zebra fish. The LC50 was reported to be 21 mg/l.

10.2.3. Other available data

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

11. Risk assessment refinement

Since isoamyl butyrate has passed the screening criteria, measured volumes are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	4.7 mg/L			1,000,000	0.0047 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.96 mg/L	7.2 mg/L	2.51 mg/L	10,000	0.251 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	9.87 mg/L	6.29 mg/L	7.54 mg/L			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.9	3.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 0.251 µg/L. The revised PEC/PNECs for EU and NA are <1 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: 6/20/2016

12. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww%26ei%3dKMSoUpiQK-arsQS324GwBg%26ved%3d0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.05.016

Transparency document

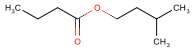
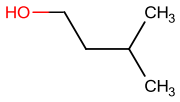
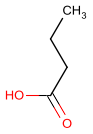
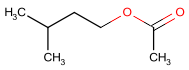
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.05.016

Appendix

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen, 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano, 2010).
- Protein binding was estimated 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		
Principal Name	Isoamyl butyrate	Isoamyl alcohol	Butyric acid	Isoamyl acetate
CAS No.	106-27-4	123-51-3	107-92-6	123-92-2
Structure				
Similarity (Tanimoto score)	1.0	0.68	0.46	0.83
Read across endpoint		• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Genotoxicity • Repeated dose, • Developmental and reproductive	• Skin sensitization
Molecular Formula	$C_9H_{18}O_2$	$C_5H_{12}O$	$C_4H_8O_2$	$C_7H_{14}O_2$
Molecular Weight	158.24	88.15	88.11	130.19
Melting Point (°C, EPISUITE)	-32.06	-61.49	3.02	-56.05
Boiling Point (°C, EPISUITE)	178.41	123.17	166.84	134.87
Vapor Pressure (Pa @ 25°C, EPISUITE)	135	512	281	756
Log Kow (KOWWIN v1.68 in EPISUITE)	3.25	1.16	0.79	2.25
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	117.8	4.158e+004	6.606e+004	1100
J_{max} (mg/cm^2/h, SAM)	11.16992	1142.301	998.7874	55.89014
Henry's Law (Pa·m^3/mol, Bond	9.73E+001	1.34E+000	9.78E-002	5.52E+001

Method, EPISUITE)				
		Genotoxicity		
DNA binding (OASIS v 1.1 QSAR Toolbox 3.1)	• No alert found	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.1)	• No alert found	• No alert found	• No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	
***In-vitro* Mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found	• No alert found	
***In-vivo* mutagenicity (Micronucleus) alerts by ISS**	• No alert found	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	• Not classified	
		Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Carboxylic acids (Hepatotoxicity) No rank • Valproic acid (Hepatotoxicity) Alert	

Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.1)	• Non binder, non-cyclic structure	• Non binder, non-cyclic structure	• Non binder, non-cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Toxicant (good reliability)	• Toxicant (good reliability)	
Sensitization				
Protein binding by OASIS v1.1	• No alert found			• No alert found
Protein binding by OECD	• No alert found			• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)			• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found			• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)			• Sensitizer (good reliability)
Metabolism				
OECD QSAR Toolbox (3.1) Rat liver S9 metabolism simulator	See Supplemental data 1 • 8 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation.	See Supplemental data 2 • 8 metabolites from Rat S9 simulator. • Aldehydes, Schiff base formation.	See Supplemental data 3 • 4 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, Schiff base formation.	See Supplemental data 4 • 5 metabolites from Rat S9 simulator. Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.

Summary

There are insufficient toxicity data on isoamyl butyrate (CAS # 106-27-4). Hence *in silico* evaluation was conducted to determine suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs isoamyl alcohol (CAS # 123-51-3), butyric acid (CAS # 107-92-6), and isoamyl acetate (CAS # 123-92-2) were identified as read across materials with data for their respective toxicity end points.

Metabolism

There are no metabolism data on isoamyl butyrate (CAS # 106-27-4). Metabolism of the material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (See table above). Isoamyl butyrate (CAS # 106-27-4) is metabolized to isoamyl alcohol and butyric acid in the first step with 0.950 probability. Hence, isoamyl alcohol (CAS # 123-51-3) and butyric acid (CAS # 107-92-6) can be use as read across for isoamyl butyrate (CAS # 106-27-4). Isoamyl alcohol (CAS # 123-51-3) and butyric

acid (CAS # 107-92-6) were out of domain for *in vivo* rat and out of domain for *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification will be provided.

Conclusion/Rationale

- Isoamyl alcohol (CAS # 123-51-3) is used as a structurally similar read across analog for isoamyl butyrate (CAS # 106-27-4) for clastogenicity, repeated dose, developmental, and reproductive toxicological end points.
  - o The target belongs to a class of esters, and the read across analog belongs to a class of alcohols. The read across materal is a direct metabolite of the target.
  - o The target and read across analog have a Tanimoto score of 0.68.
  - o The physical chemical properties of the target and the read across analog are very similar.
  - o The structural alerts for the toxicological end points are consistent between the target as well as the read across material.
  - o The read across analog isoamyl alcohol is predicted to be toxicant by CAESAR model for developmental toxicity. This shows that the read across analogs be more reactive compared to the target substance. The data described in the developmental toxicity section above shows that the read across analog have adequate margin of exposure at current level of use. The ER binding alert is negative for isoamyl alcohol. Therefore the alert will be superseded by the availability of data.
  - o The structural alerts show that the read across material is similarly reactive for the toxicity end points as compared to the target material.
  - o The structural differences between target and the read across analog appear to be toxicologically insignificant.
- Butyric acid (CAS # 107-92-6) is used as a structurally similar read across analog for isoamyl butyrate (CAS # 106-27-4) for clastogenicity, repeated dose, developmental, reproductive toxicological end points.
  - o The target belongs to a class of esters, but the analog is an organic acid and a direct metabolite of the target.
  - o The target and read across analog have a Tanimoto score of 0.46.
  - o The physical chemical properties of the target and the read across analog are very similar.
  - o The structural alerts for the toxicological end points are consistent between the target and the read across material.
  - o The read across analog is categorized as a carboxylic acid with hepatoxicity alert by HESS categorization. The structural alerts show that the read across material is more reactive for the toxicity end points as compared to the target material. From the data described in the repeated dose section above, it is shown that the read across analog butyric acid is excreted from body without toxic effects. Therefore this alert will be superseded by the data.
  - o The read across analog butyric acid is predicted to be toxicant by CAESAR model for developmental toxicity. This shows that the read across analogs be more reactive compared to the target substance. The data described in the developmental toxicity section above shows that the read across analog has and adequate margin of exposure at current level of use. The ER binding alert is negative for butyric acid. Therefore, the alert will be superseded by the availability of data.
  - o The structural differences between target and the read across analog appear to be toxicologically insignificant.
- Isoamyl acetate (CAS # 123-92-2) is used as a structurally similar read across analog for isoamyl butyrate (CAS # 106-27-4) for skin sensitization end point.
  - o The target and analog are structurally similar and belong to a class of esters.
  - o The key difference between the target material and the read across is the aliphatic group on acid portion of the ester. The target has butyrate group while the read across has an acetate group.
  - o The target and read across analog have a Tanimoto score of 0.83721 which is mainly driven by isoamyl fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from toxicological end point perspective.
  - o The physical chemical properties of the target and the read across analog are very similar.
  - o The structural alerts for the skin sensitization end points are consistent between the target and the read across material.
  - o The read across analog isoamyl acetate is predicted to be sensitizer by CAESAR model for skin sensitization. The structural alerts show that the predicted metabolites of read across material are more reactive as compared to the target material. Other protein binding alerts for skin sensitization are negative for the read across. The data described in skin sensitization section shows that the read across analog does not pose a concern for skin sensitization endpoint. Hence, the alert will be superseded by the availability of data.
  - o The target and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read across metabolites show no structural alerts for mutagenicity and clastogenicity toxicity.
  - o The structural differences between target and the read across analog appear to be toxicologically insignificant.

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