Food and Chemical Toxicology 127 (2019) S81–S89

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, butyric acid, CAS Registry Number 107-92-6

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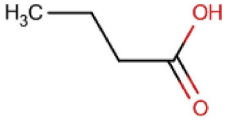
Version: 091118. This version replaces any previous versions.
Name: Butyric acid
CAS Registry Number: 107-92-6



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https://doi.org/10.1016/j.fct.2019.01.030
Received 13 September 2018; Accepted 28 January 2019
Available online 31 January 2019

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., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and 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.

Butyric acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from butyric acid and read-across analog isobutyric acid (CAS # 79-31-2) show that butyric acid is not expected to be genotoxic. The repeated dose and reproductive toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to butyric acid is below the TTC (0.03 mg/kg/day and 0.03 mg/kg/day, respectively). The skin sensitization endpoint was completed using data from butyric acid and application of the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; butyric acid is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across analog acetic acid (CAS # 64-19-7) The environmental endpoints were evaluated; butyric acid 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.	(ECHA REACH Dossier, RIFM, 2014)
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. Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOEC = 12.3 mg/m^3.	(Ernstgard et al., 2006)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 100% (EU Directive 84/449/EEC C.3	(ECHA REACH Dossier, accessed 7/18)
Bioaccumulation: Screening-level: 3.16 L kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 880 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: 880 - mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.880 μg/L	

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

1. Identification

1. **Chemical Name:** Butyric acid
2. **CAS Registry Number:** 107-92-6
3. **Synonyms:** Butanoic acid; *n*-Butyric acid; 1-Propanecarboxylic acid; Propylformic acid; Ethylacetic acid; ｱﾙｶﾝ酸(C = 4 ~ 30); Butyric acid
4. **Molecular Formula:** $C_4H_8O_2$
5. **Molecular Weight:** 88.11
6. **RIFM Number:** 940
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 176 °C (FMA Database), 166.84 °C (EPI Suite)
2. **Flash Point:** 71 °C (GHS), 160°F; CC (FMA Database)
3. **Log K_{ow}:** 0.79 (Patel et al., 2002; #41492), 1.07 (EPI Suite)
4. **Melting Point**: 3.02 °C (EPI Suite)
5. **Water Solubility:** 66060 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.5 mm Hg @ 20 °C (EPI Suite v4.0), 0.7 mm Hg 20 °C (FMA Database), 2.11 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:** Colorless liquid with an unpleasant, penetrating, spoiled, butter-like, putrid odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0011% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000024 mg/kg/day or 0.0018 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00036 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., 2015a; 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., 2015a; 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
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2. Analogs Selected:
   a. **Genotoxicity:** Isobutyric acid (CAS # 79-31-2)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Acetic acid (CAS # 64-19-7)
   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)

Butyric acid is reported to occur in the following foods by the VCF*:
Acerola (*Malpighia*)
Allium species
Apple brandy (calvados)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Banana (*Musa sapientum* L.)
Beef
Beer
Black choke berry juice (*Aronia melanocarpa* Ell.)
Black currants (*Ribes nigrum* L.)
Blue cheeses
Bread and bread preferment
Buckwheat
Calamus (sweet flag) (*Acorus calamus* L.)
Cape gooseberry (*Physalis peruviana* L.)
Capers (*Capparis spinoza*)
Capsicum species
Cardamom (*Ellettaria cardamomum* Maton.)
Cashew apple (*Anacardium occidentale*).
Cheddar cheese
Cheese, various types
Cherimoya (*Annona cherimolia* Mill.)
Cherry (*prunus avium* [sweet], *pr. Cerasus* [sour])
Chicken
Chinese liquor (baijiu)
Chinese quince (*Pseudocydonia sinensis* Schneid)
Cider (apple wine)
Citrus fruits
Cloudberry (*Rubus chamaemorus* L.)
Cocoa category
Coconut (*Cocos nucifera* L.)
Coffee
Crispbread.
Crowberry (*Empetrum nigrum* Coll.)
Cupuacu (*Theobroma grandiflorum* Spreng.)
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)
Dill (*Anethum* species)
Durian (*Durio zibethinus*)
Elderberry (*Sambucus nigra* L.)
Filbert, hazelnut (*Corylus avellano*)
Fish
Gabiroba (*Campomanesia xanthocarpa*)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Hog plum (*Spondias mombins* L.)
Honey
Hop (*Humulus lupulus*)
Katsuobushi (dried bonito)
Kiwifruit (*Actinidia chinensis, syn. A. Deliciosa*)
Kumazasa (Sasa albo-marginata)
Lamb and mutton
Licorice (*Glycyrrhiza* species)
Litchi (*Litchi chinensis* Sonn.)
Lobster
Loganberry juice (*Rubus ursinus var. Loganobaccus*).
Loquat (*Eriobotrya japonica* Lindl.)
Maize (*Zea mays* L.)
Malt
Mangifera species
Mate (*Ilex paraguayensis*)
Melon
Milk and milk products
Mountain papaya (*C. Candamarcensis, c. Pubescens*)
Mulberry spirit (mouro)
Mushroom
Mussel
Mustard (*Brassica* species)
Naranjilla fruit (*Solanum quitoense* Lam.)
Noni (*Morinda citrifolia* L.)
Oats (*Avena sativa* L.)
Olive (*Olea europaea*)
Oysters
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Peanut (*Arachis hypogaea* L.)
Pear (*Pyrus communis* L.)
Pear brandy
Pecan (*Carya illinoensis* Koch)
Pepper (*Piper nigrum* L.)
Pineapple (*Ananas comosus*)
Pistachio nut (*Pistacia vera*)
Plum (*Prunus* species)
Plum brandy
Pork

Potato (*Solanum tuberosum* L.)
Potato chips (American)
Rambutan (*Nephelium lappaceum* L.)
Rapeseed
Raspberry, blackberry, and boysenberry
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Rum
Rye bread
Sake
Salami
Sauerkraut
Scallop
Sea buckthorn (*Hippophaë rhamnoides* L.)
Sherry
Shoyu (fermented soya hydrolysate)
Shrimps (prawn)
Soursop (*Annona muricata* L.)
Soybean (*glycine max. L.* Merr.)
Spineless monkey orange (*Strychnos madagasc*.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Sugar molasses
Sukiyaki
Swiss cheeses
Tapereba, caja fruit (*Spondias lutea* L.)
Tarragon (*Artemisia dracunculus* L.)
Tea
Tequila (agave tequilana)
Tomato (*Lycopersicon esculentum* Mill.)
Trassi (cooked)
Truffle
Vaccinium species
Vanilla
Vinegar
Wheaten bread
Whey protein hydrolysate
Whisky
Wine
Wood apple (*Feronia limonia*)

*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

Available; accessed on 04/20/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, butyric acid does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT assay) was conducted according to OECD TG 476/GLP guidelines. Chinese hamster ovary cells were treated with butyric acid in media at concentrations of 13.75–440 μg/mL (as determined in a preliminary toxicity assay) for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test item, either with or without metabolic activation (ECHA REACH Dossier). Under the conditions of the study, butyric acid was not mutagenic to mammalian cells *in vitro*.

There are no studies assessing the clastogenicity of butyric acid. The clastogenic activity of read-across material isobutyric acid (CAS # 79-31-2) 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 isobutyric acid in dimethyl sulfoxide (DMSO) at concentrations up to 880 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Isobutyric acid did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, isobutyric acid was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to butyric acid.

Based on the available data, butyric acid does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/18.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on butyric acid or on any read-across materials. The total systemic exposure to butyric acid 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 butyric acid or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to butyric acid (0.36 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: 07/06/2018.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on butyric acid or on any read-across materials. The total systemic exposure to butyric acid 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 insufficient data on butyric acid for the developmental toxicity endpoint. In an *in vivo* study for developmental toxicity, butyric acid in corn oil was administered via oral gavage to groups of 15 pregnant female Sprague Dawley rats at doses of 0 (corn oil, 20 rats), 100, or 133.3 mg/kg/day on gestation days 6–15. Dams demonstrated significant weight reduction in treated groups throughout gestation as well as higher incidences of mortality (3/15 and 7/15 for the low- and high-dose groups, respectively, versus 0/20 in controls). Other signs of toxicity included vocalization and respiratory distress such as rales and dyspnea. Dyspnea was associated with cases of mortality in the low- and high-dose groups. Gas in the gastrointestinal tract was noted at necropsy for most of the animals as well as gastric ulceration in 2 animals of the high-dose group. Additionally, gross and visceral examinations of the progeny revealed sporadic alterations only. Skeletal examinations demonstrated increased incidences of lumbar ribs. Due to the high mortality of dams and progeny, the number of specimens examined was small; therefore, the data was considered inconclusive. A decrease in postnatal

viability in the lower-dose group as well as reduced weight of pups in the high-dose group on postnatal day 6 was attributed to severe respiratory effects on dams. No malformations were observed at any dose level due to test material administration. The LOAEL for maternal toxicity was 100 mg/kg/day, and the NOAEL for fetal toxicity was determined to be 133 mg/kg/day, the highest dose tested. The corrosive effects of butyric acid as seen with maternal toxicity at the site of administration was responsible for the mortality among the dams (Narotsky et al., 1994). There were no incidences of teratogenicity among fetuses at any dose group. Since the data available is of low quality, no NOAEL was selected for the developmental toxicity endpoint. The total systemic exposure to butyric acid (0.36 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on butyric acid or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to butyric acid (0.36 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/06/2018.

10.1.4. Skin sensitization

Based on existing data and the application of DST, butyric acid does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for butyric acid. However, in a human maximization test, no skin sensitization reactions were observed (RIFM, 1977). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for butyric acid that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, butyric acid 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 butyric acid 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, butyric acid 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: 04/11/18.

10.1.6. Local respiratory toxicity

There are no inhalation data available on butyric acid; however, in a 2-h inhalation study in humans for the analog acetic acid (CAS # 64-19-7), a NOEC of 12.3 mg/m^3 is reported by Ernstgard et al. (2006).

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 from inhalation exposure when used in perfumery. In an inhalation study to evaluate potential acute irritation during controlled exposure to vapors of acetic acid, 6 female and 6 male healthy volunteers (age range 21–41) were exposed to 0 ppm (control exposure), 12.3, and 24.6 mg/m^3 acetic acid vapor for 2 h at rest (Ernstgard et al., 2006). In the qualitative, self-report portion of the study, the individuals indicated subjective ratings of nasal irritation, and smell increased significantly with exposure level using the visual analog scale (VAS). VAS is a psychometric response scale typically used in questionnaires to describe subjective characteristics that cannot be directly measured. Except for smell, all average ratings at 24.6 mg/m^3 were at the lower end of the 0–100 mm VAS and did not exceed the verbal expression “somewhat” (26 mm). Quantitative pulmonary function measurements included: vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak expiratory flow (PEF), and forced expiratory flow in 25%, 50%, and 75% of FVC (FEF25, FEF50, FEF75). The highest value of 3 measurements was used. Secondary parameters calculated from the spirogram were FEV1/FVC and FEV1/VC. The measurements were performed using a spirometer (Vitalograf 21210; Buckingham, UK) along with designated computer software (Spirotrac 3, v2.0). Pulmonary function parameters were measured prior to, immediately after, and at 3 h post-exposure. Measurements before and after all exposure concentrations demonstrated that there were no effects on pulmonary function, nasal swelling, nasal airway resistance, or plasma inflammatory markers (C-reactive protein, and interleukin-6). There was a non-significant tendency to increased blinking frequency, as measured continuously during exposure, after exposure to 24.6 mg/m^3 of acetic acid. Authors concluded that study data suggests a mild irritative effect at 24.6 mg/m^3 acetic acid, and no effects were observed at 12.3 mg/m^3 acetic acid. Therefore, the NOEC was determined to be the lowest exposure concentration of 12.3 mg/m^3.

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

- (12.3 mg/m3) (1m^3/1000 L) = 0.0123 mg/L
- Minute ventilation (MV) of 9 L/min for a human (on average) × duration of exposure of 120 min per day (min/day) = 1080 L/day
- (0.0123 mg/L) (1080 L/d) = 13.28 mg/day
- (13.28 mg/day)/(0.65 kg lung weight of human) = 20.43 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0018 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., 2015a). 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 0.0028 mg/kg lung weight/day resulting in a MOE of 7296 (i.e., [20.43 mg/kg lung weight/day]/[0.0028 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 0.0022 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

Additional References: Hoffman et al., 1991; NIOSH, 2006; Morris and Hubbs, 2009.

Table 1
Maximum acceptable concentrations for butyric acid that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.07%	0.01%
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.01%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.01%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.15%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Literature Search and Risk Assessment Completed On: 08/03/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of butyric acid 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, butyric acid 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 butyric acid as either being possibly persistent nor 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).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), butyric acid presents a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data

Butyric acid has been registered under REACH, and the following data is available.

Ready biodegradability of the test material was conducted according to the EU Directive 84/449/EEC C.3.

Method. Biodegradation of 100% was observed after 14 days.

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)**	880			1,000,000	0.88	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.0	1.0
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 0.880 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 5/1/18.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.030.

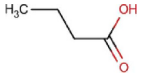
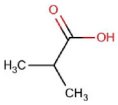
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 v4.11 (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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 v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Materials	
Principal Name	Butyric acid	Isobutyric acid	Acetic acid
CAS No.	107-92-6	79-31-2	64-19-7
Structure			
Similarity (Tanimoto Score)		0.7	0.6
Read-across Endpoint		• Genotoxicity	• Local respiratory toxicity
Molecular Formula	$C_4H_{10}O_2$	$C_4H_8O_2$	$C_2H_4O_2$
Molecular Weight	88.11	88.11	60.05
Melting Point (°C, EPI Suite)	3.02	−8.29	16
Boiling Point (°C, EPI Suite)	166.84	153.79	118
Vapor Pressure (Pa @ 25 °C, EPI Suite)	281	436	12.9
Log K_{OW}	0.79	0.98	0.09
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	6.6E+004	4.91E+004	475900
J_{max} (mg/cm^2/h, SAM)	907.164	3220	6283.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.72E-002	9.72E-002	5.477E-007
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	

Carcinogenicity (ISS)	• No alert found	• No alert found	
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	
Local respiratory toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	107-92-6.pdf	No metabolism possible.	No metabolism possible

Summary

There are insufficient toxicity data on butyric acid (CAS # 107-92-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, isobutyric acid (CAS # 79-31-2) and acetic acid (CAS # 64-19-7) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Isobutyric acid (CAS # 79-31-2) was used as a read-across analog for the target material butyric acid (CAS # 107-92-6) for the genotoxicity endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to a class of saturated aliphatic acids.
  - ○ The key difference between the target substance and the read-across analog is that the target substance is a straight chain acid while the read-across analog is a branched acid. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. 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 v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ There are no genotoxicity alerts for the target substance or the read-across analog. The alerts are consistent with the 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.
- Acetic acid (CAS # 64-19-7) was used as a read-across analog for the target material butyric acid (CAS # 107-92-6) for the local respiratory toxicity endpoint.
  - ○ The target substance and the read-across analog are structurally similar and belong to a class of saturated aliphatic acids.
  - ○ The key difference between the target substance and the read-across analog is that the target substance carbon chain is 2 carbons longer compared to the read-across analog. This structural difference makes the read-across analog more bioavailable and reactive.
  - ○ Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. 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 v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ There are no genotoxicity alerts for the target substance or the read-across analog. The alerts are consistent with the 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.

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