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Short Review

RIFM fragrance ingredient safety assessment, amyl butyrate, CAS Registry Number 540-18-1

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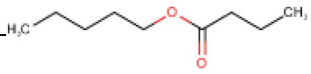

Name: Amyl butyrate
CAS Registry Number: 540-18-1

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
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level

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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
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Amyl butyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl hexanoate (CAS # 123-66-0) show that amyl butyrate is not expected to be genotoxic. Data on read-across analog butyl propionate (CAS # 590-01-2) provide a calculated MOE > 100 for the repeated dose and local respiratory toxicity endpoints. Data on read-across analogs butyl propionate (CAS # 590-01-2) and butyl acetate (CAS # 123-86-4) provide a calculated MOE > 100 for the reproductive toxicity endpoint. Data from read-across material pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for amyl butyrate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; amyl butyrate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; amyl butyrate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2015; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 2071 mg/kg/day.	(Banton et al., 2000)
Reproductive Toxicity: Developmental toxicity: NOAEL = 5638 mg/kg/day. Fertility: NOAEL = 2222 mg/kg/day.	(EPA HPVIS: Propanoic acid butyl ester; ECHA REACH Dossier: Butyl acetate; ECHA, 2011)
Skin Sensitization: Not sensitizing under the current, declared levels of use.	(ECHA REACH Dossier: Pentyl propionate; ECHA, 2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 1315.21 mg/m^3.	(Banton et al., 2000)

Environmental Safety Assessment

Hazard Assessment:

Persistence:	
Critical Measured Value: 91% (OECD 301 F)	RIFM (2009)
Bioaccumulation:	
Screening-level: 72 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-hour Algae EC50: 2.235 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-hour Algae EC50: 2.235 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.2235 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** Amyl butyrate
2. CAS Registry Number: 540-18-1
3. **Synonyms:** Amyl butanoate; Butanoic acid, pentyl ester; Pentyl butyrate; ﾌﾞﾀﾝ酸ｱﾙｷﾙ(C = 1～7); Amyl butyrate
4. **Molecular Formula:** $C_9H_{18}O_2$
5. **Molecular Weight: 158.**24
6. RIFM Number: 6146
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 178 °C (FMA), 190.83 °C (EPI Suite)
2. **Flash Point:** 57 °C (GHS), 135 °F; CC (FMA)
3. **Log K_{OW}:** log Pow = 3.5 and 3.6 (Givaudan, 2009t), 3.32 (EPI Suite)
4. **Melting Point:** 20.94 °C (EPI Suite)
5. **Water Solubility:** 101.9 mg/L (EPI Suite)
6. **Specific Gravity:** 0.863 (FMA)
7. **Vapor Pressure:** 0.473 mm Hg @ 20 °C (EPI Suite v4.0), 0.686 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless liquid with strong penetrating odor and sweet taste

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.075% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00032 mg/kg/day or 0.024 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0031 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:** Ethyl hexanoate (CAS # 123-66-0)
   b. **Repeated Dose Toxicity:** Butyl propionate (CAS # 590-01-2)
   c. **Reproductive Toxicity:** Butyl propionate (CAS # 590-01-2); butyl acetate (CAS # 123-86-4)
   d. **Skin Sensitization:** Pentyl propionate (CAS # 624-54-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Butyl propionate (CAS # 590-01-2)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

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

Amyl butyrate is reported to occur in nature in the following foods by the VCF*:

Apple fresh (*Malus* species).
Apple processed (*Malus* species).
Apricot (*Prunus armeniaca* L.)
Banana (*Musa sapientum* L.)
Beer.
Blue cheeses.
Capsicum species.
Passion fruit (*Passiflora* species).
Spineless monkey orange (*Strychnos madagasc*.)
Wine.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

8. REACH dossier

Pre-registered for 2010; no dossier available as of 04/19/19.

9. Conclusion

The existing information supports the use of this material as described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

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

There are no data assessing the mutagenic and clastogenic activity of amyl butyrate; however, read-across can be made to ethyl hexanoate (CAS # 123-66-0; see Section V).

The mutagenic activity of ethyl hexanoate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2uvrA were treated with ethyl hexanoate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, ethyl hexanoate was not mutagenic in the Ames test, and this can be extended to amyl butyrate.

The clastogenic activity of ethyl hexanoate 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 ethyl hexanoate in DMSO at concentrations up to 1442 μg/mL in a dose range finding (DRF) study. Micronuclei analysis was conducted at concentrations up to 824 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h. Ethyl hexanoate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl hexanoate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to amyl butyrate.

Based on the data available, read-across material ethyl hexanoate does not present a concern for genotoxic potential, and this can be extended to amyl butyrate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/11/19.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for amyl butyrate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on amyl butyrate. A subchronic toxicity study (non-guideline and non-GLP complaint) was conducted on 10 weanling Osborne-Mendel rats/sex/dose. Amyl butyrate was administered as a diet at doses of 0 (control: normal diet), 1000, 2500, and 10000 ppm (0, 50, 125, and 500 mg/kg/day) for 16 weeks. Since 35% of the treatment material was lost in 7 days, an accurate NOAEL could not be determined from the study (Hagan et al., 1967).

Read-across material butyl propionate (CAS # 590-01-2; see section V) has sufficient repeated dose toxicity data. In a GLP-compliant subchronic study, 15 Sprague Dawley rats/sex/dose were administered butyl propionate by inhalation at targeted concentrations of 0, 250, 750, and 1500 ppm (equivalent to 0, 345, 1036, and 2071 mg/kg/day) for 6 h/day, 5 days/week for 13 weeks. In addition, 5 animals/sex/dose were maintained as recovery groups for 8 weeks after the end of the treatment period. Although several local microscopic effects were observed in the nasal cavity of animals in the mid- and high-dose groups, no treatment-related mortality or systemic toxicity was reported during the study. In high-dose group males, body weight, bodyweight gains, and feed consumption were significantly lower than the control group, but these changes were reversed at the end of the recovery period. Hence, these alterations were not considered to be treatment-related adverse effects. **Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 2071 mg/kg/day (1500 ppm) based on the absence of systemic toxicity at the highest tested dose** (Banton et al., 2000).

Therefore, the MOE can be calculated by dividing the butyl propionate NOAEL by the total systemic exposure for amyl butyrate, 2071/0.0031 or 668065.

In addition, the total systemic to amyl butyrate (3.1 μg/kg/day) is below the TTC (30 μg/kg/day) 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: 06/05/19.

10.1.3. Reproductive toxicity

The MOE for amyl butyrate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on amyl butyrate. Read-across material butyl propionate (CAS # 590-01-2; see section V) has sufficient developmental toxicity data that can be used to support the developmental toxicity endpoint.

A GLP and EPA OTS 798.4900 guideline prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 24 rats were exposed to butyl propionate via whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm (mean analytical concentrations were 0, 495, 1011, and 2000 ppm; equivalent to 0, 698, 1425, and 2819 mg/kg/day, using standard minute volume and body weights for female Sprague Dawley rats) for 6 h/day on gestation days (GDs) 6–15. Dams were euthanized on GD 20. Clinical signs of toxicity included slightly drooping eyelids and salivation among the mid- and high-dose group dams in a dose-dependent manner. Body weights were significantly reduced in all treatment groups when compared to controls during GDs 7–20. The mean gravid uterine weight was not affected by the treatment. No treatment-related abnormalities were reported in any of the gestational and developmental parameters. There were statistically significant increases in the incidence of reduced ossification of the thirteenth rib(s) in all treatment groups and unossified sternebra(e) number 5 and/or 6 in the 1000 ppm litters; however, these skeletal variations were within the historical control data and were not considered biologically relevant. No teratogenic or embryotoxic effects were observed at any dose level. The NOAEL for maternal toxicity could not be established due to treatment-related effects on body weight and feed consumption in all dose groups. Therefore, the LOAEL for maternal toxicity was considered to be 495 ppm or 698 mg/kg/day. The NOAEL for developmental toxicity was considered to be 2000 ppm or 2819 mg/kg/day, the highest dose tested (Banton et al., 2000; Ulrich et al., 2000; data also available in ECHA, 2018).

In another GLP-compliant developmental toxicity study conducted in pregnant female Sprague Dawley rats, groups of 12 rats were exposed to butyl propionate (n-butyl propionate) via whole-body inhalation at concentrations of 0, 250, 500, 2500, or 4000 ppm (equivalent to 0, 352, 705, 3523, and 5638 mg/kg/day, using standard minute volume and body weights for female Sprague Dawley rats) for 6 h/day on GDs 6–15. All animals were euthanized on GD 20, and necropsy was performed. There was no treatment-related mortality reported throughout the study. Treatment-related clinical signs of toxicity reported in the 2500 and 4000 ppm groups included drooping eyelids and salivation during exposure and a red or brown material or staining around the nose and/or mouth 1 h following exposure. There were decreases in gravid uterine weights, body weights, and bodyweight gains in the 2500 and 4000 ppm dose groups (statistical significance not reported). No treatment-related changes were reported in any of the developmental parameters evaluated. The NOAEL for maternal toxicity was considered to be 500 ppm or 705 mg/kg/day, based on observed clinical signs of toxicity and decreased body weight and feed consumption at $\geq$2500 ppm. There was a decrease in the gravid uterine weights among the 2500 and 4000 ppm dose groups; however, intrauterine survival was not affected by exposure to n-butyl propionate in any of the treatment groups, and gestational and litters parameters (post-implantation loss, live litter size, numbers of corpora lutea, and implantation sites) were comparable to the control values. Therefore, the NOAEL for developmental toxicity was considered to be 2500 ppm or 5638 mg/kg/day, the highest dose tested (US EPA, 1996).

Since both developmental toxicity studies considered the NOAEL to be the highest dose tested, the NOAEL of 5638 mg/kg/day was selected for the developmental toxicity endpoint. **Therefore, the amyl butyrate MOE for the developmental toxicity endpoint can be calculated by dividing the butyl propionate NOAEL in mg/kg/day by the total systemic exposure to amyl butyrate, 5638/0.0031 or 1818710.**

There are no fertility data on amyl butyrate. Read-across material butyl acetate (CAS # 123-86-4; see section V) has sufficient fertility data that can be used to support the fertility endpoint. An OECD 416/GLP 2-generation reproduction toxicity study was conducted in Sprague Dawley rats. Groups of 30 rats/sex/dose were exposed via whole-body inhalation to butyl acetate at concentrations of 0, 750, 1500, or

2000 ppm (equivalent to 0, 833, 1667, or 2222 mg/kg/day, respectively, using standard minute volume and body weight of Sprague Dawley rats for chronic exposure) for 6 h/day, 7 days/week. All F0 and F1 animals were exposed for at least 70 days prior to mating. Exposure of F0 and F1 males continued throughout mating and up to the day prior to euthanasia. F0 and F1 females were exposed throughout gestation until day 20 and from lactation day (LD) 5 to the day prior to euthanasia. From GD 21 through LD 4, F0 and F1 females were treated via oral gavage at doses of 0 (control: deionized water), 1125, 2250, or 3000 mg/kg/day. Inhalation exposure for F1 and F2 rats was initiated on postnatal day (PND) 22 and continued up to 2–3 weeks. No treatment-related mortalities or clinical signs of toxicity were reported in the F0, F1, or F2 generations at any dose level. A significant decrease in bodyweight gain was reported in the mid- and high-dose groups in all generations throughout treatment in males except F2 males. A significant decrease in bodyweight gain was reported in females in the mid- and high-dose groups in all generations throughout treatment except F0 females during gestation. The decreased body weights were accompanied by significant decreases in feed consumption in the mid- and high-dose groups for all generations in both sexes throughout treatment, except for F0 females and F1 males, which showed occasional significant decreases in feed consumption during lactation (F0 females) and throughout treatment (F1 males). No treatment-related changes were reported in the reproductive parameters (estrous cycle evaluation, sperm analysis, gestation length, the process of parturition, and necropsy) in both males and females of the F0 and F1 generations at any dose level. No treatment-related changes were reported in litter parameters (number of pups born, live litter size, sex ratio, and postnatal survival) for both F1 and F2 generations at any dose level. No treatment-related mortalities or clinical signs of toxicity were reported in F1 and F2 pups at any dose level. A significant decrease in pup body weight was reported in the mid- and high-dose groups of both F1 and F2 litters, except F2 male litters, which reflected decreased pup body weight only at 2000 ppm. No treatment-related changes in sexual maturation were reported in the F1 and F2 generations in both sexes at any dose level. However, the average age of attainment of balanopreputial separation in F1 and F2 high-dose males was slightly higher than the controls. The average age of attainment of vaginal patency was slightly higher in the F2 high-dose females; this was attributed to the secondary effects of decreased body weights of their respective high-dose dams. No treatment-related changes were reported in the necropsy and developmental landmarks in both F1 and F2 generations at any dose level. Thus, the NOAEL for fertility effects was considered to be 2000 ppm or 2222 mg/kg/day, the highest dose tested (ECHA, 2011).

Butyl acetate did not induce any male or female fertility effects up to the highest tested dose of 2222 mg/kg/day in the 2-generation reproductive toxicity study (ECHA, 2011) and up to 3696 mg/kg/day in a 13-week toxicity study for males (David et al., 2001; see table for details). The most conservative NOAEL for fertility was considered to be 2222 mg/kg/day. **Therefore, the amyl butyrate MOE for the fertility endpoint can be calculated by dividing the butyl acetate NOAEL in mg/kg/day by the total systemic exposure to amyl butyrate, 2222/0.0031 or 716774.**

In addition, the total systemic exposure to amyl butyrate (3.1 μg/kg/day) is below the TTC (30 μg/kg/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: Hagan et al., 1967.

Literature Search and Risk Assessment Completed On: 06/11/19.

10.1.4. Skin sensitization

Based on the read-across material pentyl propionate (CAS # 624-54-4), butyl butyrate does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. No skin sensitization studies are available for butyl butyrate. Based on the read-across material pentyl propionate (CAS # 624-54-4; see section V), amyl butyrate is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material pentyl propionate was found to be not sensitizing when tested up to 100% (ECHA, 2013).

Based on weight of evidence (WoE) from structural analysis, animal studies, and read-across material pentyl propionate, amyl butyrate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/12/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, amyl 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 amyl 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 the lack of absorbance, amyl butyrate does not present a concern for phototoxicity or photoallergenicity.

10.1.6. 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 $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/19.

10.1.7. Local respiratory toxicity

There are no inhalation data on amyl butyrate; however, in a subchronic, 13-week inhalation study for the analog butyl propionate (CAS

Duration in detail	GLP/ Guideline	No. of animals/ dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
13 weeks, (-6 h/day)	Non-GLP and non-guideline	Male Sprague Dawley rats (15/group)	Inhalation	0, 500, 1500, or 3000 ppm (equivalent to 616, 1848, and 3696 mg/kg/day, as per standard minute volume and body-weight parameters for Sprague Dawley rats; US EPA, 1998)	Male fertility NOAEL = 3696 mg/kg/day	No reproductive effects (weight of testis, sperm count, number and concentration of testicular spermatids and epididymal spermatozoa) observed up to the highest tested dose	David et al., 2001

590-01-2; see section V), a NOAEC of 1315.21 mg/m^3 is reported by Banton et al., 2000).

10.1.7.1. 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 a 13-week subchronic study conducted in Sprague Dawley rats, a NOAEC of 247 ppm (1315.21 mg/m^3) was reported for butyl propionate (Banton et al., 2000). The rats were exposed to 0.0 (filtered air), 1315.21, 3977.58, and 8098.94 mg/m^3 of butyl propionate. Treatment-related microscopic findings were noted in the nasal cavity at 3977.58 and 8098.94 mg/m^3. Degenerative effects in the nasal cavity olfactory epithelium consisted of vacuolation, cell necrosis, and mucosal atrophy. There were no local respiratory effects observed at 1315.21 mg/m^3. Therefore, the NOAEC was determined to be 1315.21 mg/m^3 (247 ppm), the lowest concentration used for inhalation exposure.

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

- (1315.21 mg/m^3) × (1m^3/1000L) = 1.315 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (according to GLP study guidelines) = 61.2 L/day
- (1.315 mg/L) × (61.2 L/day) = 80.48 mg/day
- (80.48 mg/day)/(0.0016 kg lung weight of rat*) = 50300 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.024 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; 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 0.037 mg/kg lung weight/day resulting in an MOE of 1359459 (i.e., [50300 mg/kg lung weight/day]/[0.037 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 0.024 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.”

Additional References: Cain and Murphy, 1980.

Literature Search and Risk Assessment Completed On: 06/06/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of amyl 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, amyl 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 EPI Suite v4.11 (US EPA, 2012a) did not identify amyl 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 biodegradation, fate, and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), amyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. RIFM, 2009: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 93% was observed after 28 days.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.2.3. Other available data. Pentyl butyrate has been pre-registered for REACH with no additional data available at this time.

10.2.1.2.4. 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)**	8.66			1000000	0.00866	
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	3.587	6.474	2.235	10000	0.2235	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v1.11***	8.486	5.443	6.710			Neutral Organic SAR

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.6	3.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.2235 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/13/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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 09/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111343.

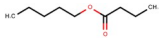
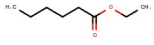
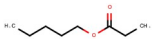
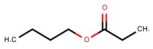
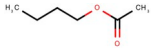
Appendix

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 Chemicals 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 material 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).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Amyl butyrate	Ethyl hexanoate	Pentyl propionate	Butyl propionate	Butyl acetate
CAS No.	540-18-1	123-66-0	624-54-4	590-01-2	123-86-4
Structure					
Similarity (Tanimoto Score)		0.71	0.95	0.82	0.71
Endpoint		• Genotoxicity	• Skin sensitization	• Reproductive toxicity • Repeated dose toxicity • Respiratory toxicity	• Reproductive toxicity
Molecular Formula	$C_9H_{18}O_2$	$C_8H_{16}O_2$	$C_8H_{16}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$
Molecular Weight	158.24	144.21	144.21	130.18	116.16
Melting Point (°C, EPI Suite)	−68.70	−67.00	−73.10	−89.00	−78.00
Boiling Point (°C, EPI Suite)	187.00	167.00	168.60	146.80	126.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.15E+02	2.40E+03	4.80E+03	5.89E+02	1.53E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	60.00	629.00	810.00	1.50E+03	8.40E+03
Log KOW	3.32	2.83	2.83	2.34	1.78
J_{max} (μg/cm^2/h, SAM)	39.24	49.36	63.57	85.94	301.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.73E+02	7.33E+02	8.54E+02	5.12E+01	2.85E+01
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found			
DNA Binding (OECD QSAR Toolbox v4.2)	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			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Valproic acid (Hepatotoxicity) Alert			Not categorized	
Reproductive and Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure			Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Non-toxicant (low reliability)	Non-toxicant (low reliability)
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 according to these rules (GSH)		Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (-OASIS v1.1)	No alert found		No alert found		

Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.		No skin sensitization reactivity domain alerts identified.		
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)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on amyl butyrate (CAS # 540-18-1). Hence, the *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, butyl acetate (CAS # 123-86-4), butyl propionate (CAS # 590-01-2), pentyl propionate (CAS # 624-54-4), and ethyl hexanoate (CAS # 123-66-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material amyl butyrate (CAS # 540-18-1) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a group of aliphatic esters.
  - The target material and the read-across analog share an ester functionality.
  - The target material and the read-across analog are structurally similar and belong to a group of aliphatic esters.The key difference between the target material and the read-across analog is that the target material is a butyrate ester of amyl alcohol while the read-across analog is a hexanoate ester of ethanol. This structural difference is toxicologically insignificant.
  - The target material and the read-across analog are structurally similar and belong to a group of aliphatic esters.The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The target material and the read-across analog are structurally similar and belong to a group of aliphatic esters.The physical–chemical properties of the target material 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 material and the read-across analog.
  - There are no toxicity alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
  - The target material 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.
- Pentyl propionate (CAS # 624-54-4) was used as a read-across analog for the target material amyl butyrate (CAS # 540-18-1) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - The target material and the read-across analog share an ester functionality.
  - The key difference between the target material and the read-across analog is the target material is a butyrate ester of amyl alcohol while the read-across analog is a propionate ester of pentanol. This structural difference is toxicologically insignificant.
  - Similarity between the target material 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 material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - There are no toxicological alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
  - The target material 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 propionate (CAS # 590-01-2) was used as a read-across analog for the target material amyl butyrate (CAS # 540-18-1) for the repeated dose, reproductive, and local respiratory toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - The target material and the read-across analog are ethyl esters.
  - The key difference between the target material and the read-across analog is that the target is a butyrate ester of amyl alcohol while the read-across analog is a propionate ester of butenol. This structural difference is toxicologically insignificant.
  - Similarity between the target material 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 material 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 material and the read-across analog.
  - The target material has a repeated dose toxicity alert of sodium valproate and valproic acid renal toxicity. This alert is due to more than 50% structural similarity via Dice score. The reactive moieties of C2 to C4 branched alkyl chain in valproic acid is not present in the target material. Therefore, the target material is out of the structural domain of the model. The data described in the repeated dose section confirm that the MOE for the read-across analog is adequate at the current level of use. Therefore, the alert is superseded by the data.
  - The target material 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 amyl butyrate (CAS # 540-18-1) for the reproductive

endpoint.

- The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
- The target material and the read-across analog share an ester functionality.
- The key difference between the target material and the read-across analog is that the target material is a butyrate ester of amyl alcohol while the read-across analog is an acetate ester of butenol. This structural difference is toxicologically insignificant.
- Similarity between the target material 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 material 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 material and the read-across analog.
- There are no toxicological alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
- The target material 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.

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Banton, M.I., Tyler, T.R., Ulrich, C.E., Nemec, M.D., Garman, R.H., 2000. Subchronic and developmental toxicity studies of n-butyl propionate vapor in rats. J. Toxicol. Environ. Health, Part A. 61 (2), 79–105.

Cain, W.S., Murphy, C.L., 1980. Interaction between chemoreceptive modalities of odour and irritation. Nature (London) 284 (20), 255–257.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

David, R.M., Tyler, T.R., Ouellette, R., Faber, W.D., Banton, M.I., 2001. Evaluation of subchronic toxicity of n-butyl acetate vapor. Food Chem. Toxicol. 39 (8), 877–886.

ECHA, 2011. *n*-Butyl Acetate Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15948/1.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2013. Pentyl Propionate Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/11188/1.

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

ECHA, 2018. Butyl Propionate Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/21655/1.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Chem. Toxicol. 5 (2), 141–157.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Ready Biodegradability of Amyl Butyrate. Unpublished report from Givaudan. RIFM report number 59272. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Amyl Butyrate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65455. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Ethyl Hexanoate (Ethylcapronat): Salmonella typhimurium and Escherichia coli Reverse Mutation Assay. Unpublished report from Symrise. RIFM report number 70288. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Ethyl Hexanoate (Ethylcapronat): Micronucleus Test in Human Lymphocytes in Vitro. Unpublished report from RIFM report number 71103. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey 16, May 2017.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

Ulrich, C.E., Nemec, M.D., Banton, M.I., Tyler, T.R., Garmon, R.H., 2000. Subchronic and developmental toxicity studies of n-butyl propionate vapor in rats. Toxicologist 54 (1), 292.

US EPA, 1996. High Production Volume Information System. Developmental Toxicity/Teratogenicity for Propanoic Acid. Butyl Ester (CAS # 590-01-2). Retrieved from: https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24966889&epcount=2&epname=Developmental+Toxicity/Teratogenicity&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null.

US EPA, 1998. Inhalation risk assessment at the environmental protection agency. In: Salem, H., Katz, S.A. (Eds.), Inhalation Toxicology, second ed. CRC Press 2005. Retrieved from: https://books.google.com/books?id=Fu7LBQAAQBAJ&printsec=frontcover#v=onepage&q&f=false.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows. United States Environmental Protection Agency, Washington, DC, USA v4.0–v4.11.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows. United States Environmental Protection Agency, Washington, DC, USA v1.11.