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RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, Terpinyl butyrate, CAS Registry Number 2153-28-8

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Name: Terpinyl butyrate
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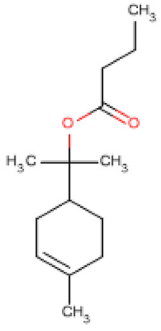

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

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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
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.
The material (terpinyl butyrate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on the read-across analog α-terpineol acetate (CAS # 80-26-2) show that terpinyl butyrate is not expected to be genotoxic. Data on read-across analog terpinyl acetate (isomer mixture; CAS # 8007-35-0) show that terpinyl butyrate is not a concern for skin sensitization and provided an MOE > 100 for the repeated dose toxicity endpoint. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The developmental and reproductive toxicity endpoint was completed using terpineol (CAS # 8000-41-7) and butyric acid (CAS # 107-92-6) as read-across analogs, which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; terpinyl butyrate was found not to be PBT as per the IFRA Environmental Standards; its risk quotients (i.e., PEC/PNEC) could not be calculated as no volume of use was reported in 2015 in North America or Europe.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 400 mg/kg/day.	(Hagan et al., 1967)
Developmental and Reproductive Toxicity: NOAEL = 200 and 250 mg/kg/day, respectively.	(ECHA Dossier: Terpineol)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 2012)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.6 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 1502 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Not applicable; no Volume of Use reported in 2015

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) Not Applicable

1. Identification

1. **Chemical Name:** Terpinyl butyrate
2. CAS Registry Number: 2153-28-8
3. **Synonyms:** Butanoic acid, 1-methyl-1-(4-methyl-3-cyclohexen-1-yl) ethyl ester; p-Menth-1-en-8-ol butyrate; p-Menth-1-en-8-yl butyrate; 1-Methyl-1-(4-methyl-3-cyclohexen-1-yl)ethyl butyrate; ｱﾙｶﾝ酸 (C = 1 ~ 5)ﾃﾙﾋﾞﾆﾙ; 1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl butyrate; Terpinyl butyrate
4. **Molecular Formula**: $C_{14}H_{24}O_2$
5. **Molecular Weight**: 224.34
6. **RIFM Number**: 5050
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 246 °C (FMA), 272.99 °C (EPI Suite)
2. **Flash Point:** > 212.00 °F. TCC (> 100.00 °C)*
3. **Log K_{OW}**: 5.32 (EPI Suite)
4. **Melting Point**: 42.76 °C (EPI Suite)
5. **Water Solubility:** 0.9352 mg/L (EPI Suite)
6. **Specific Gravity:** 0.940
7. **Vapor Pressure:** 0.00311 mm Hg @ 20 °C (EPI Suite v4.0), 0.00558 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Arctander Volume II 1969: Colorless oily liquid. Almost insoluble in water; soluble in alcohol and oils. Balsamic-floral, sweet and mild, slightly fruity-herbaceous odor of moderate tenacity. Peculiar fruity taste in concentrations lower than 40 ppm.

*http://www.thegoodscentscompany.com/data/rw1034831.html#tophyp, retrieved 7/29/2015.

3. Exposure

1 **Volume of Use (worldwide band):** < 0.1 metric ton per year (IFRA, 2015)

2 **95th Percentile Concentration in Hydroalcoholics:** 0.000033% (RIFM, 2015)

3 **Inhalation Exposure*:** 0.000013 mg/kg/day or 0.00093 mg/day (RIFM, 2015)

4 **Total Systemic Exposure**:** 0.00016 mg/kg/day (RIFM, 2015)

*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:** α-Terpineol acetate (CAS # 80-26-2)
   b. **Repeated Dose Toxicity:** Terpinyl acetate (isomer mixture; CAS # 8007-35-0)
   c. **Developmental and Reproductive Toxicity:** Terpineol (CAS # 8000-41-7); butyric acid (CAS # 107-92-6)
   d. **Skin Sensitization:** Terpinyl acetate (isomer mixture; CAS # 8007-35-0)
   e. **Phototoxicity/Photoallergenicity**: None
   f. **Local Respiratory Toxicity**: None
   g. **Environmental Toxicity**: None
3. **Read-across Justification**: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Terpinyl butyrate is reported to occur in the following foods*:

Mangerifera species

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 2/14/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Terpinyl butyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of terpinyl butyrate. However, read-across can be made to α-terpineol acetate (CAS # 80-26-2; see Section V). The mutagenic activity of α-terpineol acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-terpineol acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, α-terpineol acetate was not mutagenic in the Ames test, and this can be extended to terpinyl butyrate.

There are no studies assessing the clastogenic activity of terpinyl butyrate. However, read-across can be made to α-terpineol acetate (CAS # 80-26-2; see Section V). α-Terpineol acetate 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 α-terpineol acetate in DMSO at concentrations up to 225 μg/mL in the presence and absence of metabolic activation (S9) at the 3-h and 24-h time points. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at 58.3 μg/mL in the approximate 24-h treatment in the absence of S9. However, the %BNMN frequency (1.00%) at this concentration was within the historical control range. The percentage of cells with micronucleated binucleated cells in the test-substance tested groups was not significantly increased relative to the vehicle control at any dose level for the 3-h treatment in the presence or absence of S9 (RIFM, 2014b). Under the conditions of the study, α-terpineol acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to terpinyl butyrate.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on terpinyl butyrate. Read-across material terpinyl acetate (isomer mixture; CAS # 8007-35-0) has a dietary 20-week chronic toxicity study conducted in Osborne-Mendel rats. Groups of 10 rats/sex/dose were administered diets containing 0, 1000, 2500, or 10000 ppm terpinyl acetate (isomer mixture, equivalent to 0, 50, 250, or 500 mg/kg/day) for 20 weeks. No effects on growth, no alterations in hematology, and no macroscopic or microscopic changes were observed up to the highest dose of 10000 ppm. The animals exposed to 10000 ppm in the diet consumed between 400 and 500 mg/kg/day terpinyl acetate. Thus, the NOAEL for repeated dose toxicity was considered to be 10000 ppm or 400 mg/kg/day (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967; and ECHA Dossier: p-menth-1-en-8-yl acetate).

Therefore, the terpinyl butyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpinyl acetate NOAEL in mg/kg/day by the total systemic exposure to terpinyl butyrate, 400/0.00016 or 2500000.

In addition, the total systemic exposure to terpinyl butyrate (0.16 μg/kg/day) is below the TTC (30 μg/kg bw/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: 07/31/17.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on terpinyl butyrate. Terpinyl butyrate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see Section V) and butyric acid (CAS # 107-92-6; see Section V). The metabolite butyric acid has a developmental toxicity screening assay (Chernoff/Kavlock) conducted in rats. Decreased pup viability occurred only in the presence of significant maternal toxicity. The LOAEL for maternal toxicity was determined to be 100 mg/kg/day due to mortality and clinical signs at the higher dose level. The NOAEL for fetal toxicity was determined to be 133 mg/kg/day, the highest dose tested (Narotsky et al., 1994).

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main phase males and toxicity phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. There were no adverse effects towards the development of the fetus up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant. It was considered that the testicular and epididymal effects observed in males receiving 750 mg/kg/day would have been sufficient to prevent fertilization. Thus, the NOAEL for the developmental toxicity endpoint was considered to be 250 mg/kg/day (ECHA Dossier: Terpineol). In another study, terpineol multiconstituent diluted in corn oil was administered by gavage to groups of mated female Sprague Dawley rats (20/dose) at the dose levels of 0, 60, 200, or 600 mg/kg/day from days 6–19 after mating. The test was conducted according to the OECD 414 protocol. Embryo-fetal growth was slightly reduced by maternal treatment as evidenced by the reduced mean male and female fetal weight at 600 mg/kg/day. In addition, the mean placental weight in this dose group was slightly low with differences attaining statistical significance. Mean placental, litter and fetal weights at 60 or 200 mg/kg/day were unaffected by maternal treatment with terpineol. The incidence of major and minor abnormalities and skeletal variants showed no relationship to maternal treatment with terpineol. Thus, the NOAEL for the developmental toxicity was considered to be 200 mg/kg/day (ECHA Dossier: Terpineol). The most conservative NOAEL of 200 mg/kg/day was selected for the developmental toxicity endpoint.

Therefore, the terpinyl butyrate MOE for the developmental toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/

day by the total systemic exposure to terpinyl butyrate, 200/0.00016 or 1250000.

There are no reproductive toxicity data on terpinyl butyrate. Terpinyl butyrate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see Section V) and butyric acid (CAS # 107-92-6; see Section V). Metabolite butyric acid is expected to be directly excreted by phase II metabolism and hence does not contribute to the toxicity of terpinyl butyrate.

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main phase males and toxicity phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 5 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. Testis weight was markedly lower in males receiving 750 mg/kg/day (58% of controls), and there was also an indication of low epididymal weights at this dose. This effect was also seen in the recovery group males. At 750 mg/kg/day, reduced numbers or complete absence of spermatozoa, accompanied by the presence of degenerate spermatogenic cells in the duct(s) were observed in the epididymides and were still present following the 2-week recovery period. Spermatocele granuloma(ta) that were seen in 2 males receiving 750 mg/kg/day and 1 receiving 60 mg/kg/day were not seen at the end of the recovery period. The significance of this change in the single male receiving 60 mg/kg/day is uncertain as spermatocele granuloma(ta) can occur spontaneously in rats of this age and considering the absence of other degenerative changes in the testes or epididymides of this animal. Moderate to severe seminiferous tubular atrophy/degeneration was seen in the testes of all animals dosed at 750 mg/kg/day, accompanied by minimal to moderate spermatid giant cells and minimal to slight seminiferous tubular vacuolation. Similar findings were still evident following the 2-week recovery period but at a lower incidence and severity suggesting a degree of recovery. There were no alterations in the female reproductive cycles or the reproductive organs up to the highest dose tested. Thus, the NOAEL for the reproductive toxicity endpoint was considered to be 250 mg/kg/day, based on impairment of male fertility at 750 mg/kg/day (ECHA Dossier: Terpineol).

Therefore, the terpinyl butyrate MOE for the reproductive toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpinyl butyrate, 250/0.00016 or 1562500.

In addition, the total systemic exposure to terpinyl butyrate (0.16 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/31/17.

10.1.4. Skin sensitization

Based on the read-across analog terpinyl acetate (isomer mixture) (CAS # 8007-35-0), terpinyl butyrate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available on terpinyl butyrate. Based on the available data on read-across analog terpinyl acetate (isomer mixture) (CAS # 8007-35-0; see Section V), terpinyl butyrate does not present a concern for skin sensitization. The chemical structure of these materials would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v4.1). In a murine local lymph node assay, read-across analog terpinyl acetate (isomer mixture) was found to be negative up to maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 2.4 (RIFM, 2012). In guinea pigs, an open epicutaneous test with read-across terpinyl acetate (isomer mixture) did not present reactions indicative of sensitization (Klecak, 1979). In a human maximization test, no skin sensitization reactions were observed with 5% or 3450 μg/cm^2 read-across terpinyl acetate (isomer mixture) in petrolatum (RIFM, 1971). Based on weight of evidence from structural analysis and read-across terpinyl acetate (isomer mixture), terpinyl butyrate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/17.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, terpinyl 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 terpinyl butyrate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, terpinyl butyrate does not present a concern for phototoxicity or photoallergenicity.

There are no predictive studies available on terpinyl butyrate in experimental models.

10.1.5.2. UV spectra analysis. The available UV/Vis spectra (OECD TG 101) for terpinyl butyrate indicate no significant absorbance between 290 and 700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 $L \cdot mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/07/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for terpinyl butyrate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on terpinyl butyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.00093 mg/day. This exposure is 1505 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of terpinyl 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, terpinyl butyrate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (EPI Suite, 2012) identified terpinyl butyrate as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Not applicable.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data are available.

10.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 8/2/17.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.06.030.

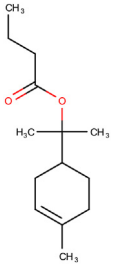
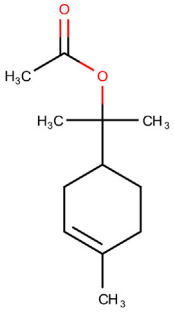
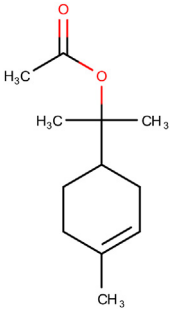
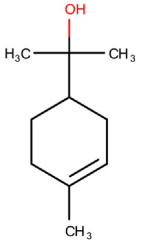
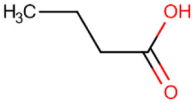
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity 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 was 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material			
Principal Name	Terpinyl butyrate	α-Terpineol acetate	Terpinyl acetate (isomer mixture)	Terpineol	Butyric acid
CAS No.	2153-28-8	80-26-2	8007-35-0	8000-41-7	107-92-6
Structure					
Similarity (Tanimoto Score)		0.93	0.93	NA	NA
Read-across Endpoint		• Genotoxicity	• Skin sensitization • Repeated dose	• Developmental and reproductive toxicity	• Developmental and reproductive toxicity
Molecular Formula	$C_{14}H_{24}O_2$	$C_{12}H_{20}O_2$	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$	$C_4H_8O_2$
Molecular Weight	224.35	196.26	196.26	154.25	88.11
Melting Point (°C, EPI Suite)	42.76	21.47	21.47	12.36	3.02
Boiling Point (°C, EPI Suite)	272.99	238.66	238.66	214.38	166.84
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.744	6.63	6.63	2.62	281
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	5.32	3.96	3.96	3.28	0.79
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.9352	18.97	18.97	1980	60000
J_{max} (mg/cm^2/h, SAM)	38.547	235.584	235.584	205.463	907.164
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.84E+002	1.04E+002	1.04E+002	1.60E+000	9.78E-002
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• Schiff base formation • Nucleophilic attack • Acylation			
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found			
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)			
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found			
Oncologic Classification	• Not classified	• Not classified			
Repeated dose toxicity					
Repeated Dose (HESS)	• Not categorized		• Not categorized		

Reproductive and Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2			• Non-binder, without OH or NH2	• Non-binder, without OH or NH2
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)			• Toxicant (good reliability)	• Toxicant (low reliability)
Skin Sensitization					
Protein binding by OASIS v1.1	• No alert found		• No alert found		
Protein binding by OECD	• No alert found		• No alert found		
Protein binding potency	• Not possible to classify		• Not possible to classify		
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found		• No alert found		
Skin Sensitization model (CAESAR) (version 2.1.6)	• No alert found		• No alert found		
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on terpinyl butyrate (CAS # 2153-28-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, α-terpineol acetate (CAS # 80-26-2), terpinyl acetate (isomer mixture) (CAS # 8007-35-0), terpineol (CAS # 8000-41-7) and butyric acid (CAS # 107-92-6) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- α-Terpineol acetate (CAS # 80-26-2) was used as a read-across analog for the target material terpinyl butyrate (CAS # 2153-28-8) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a butyrate acid fragment and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic unsaturate tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The read-across analog has an alert for Schiff base formation by DNA binding model by OASIS. This shows that the read-across analog is more reactive than the target substance. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genetic toxicity. Therefore the alert will be superseded by the availability of 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.
- Terpinyl acetate (isomer mixture) (CAS # 8007-35-0) was used as a read-across analog for the target material terpinyl butyrate (CAS # 2153-28-8) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a butyrate acid fragment and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven

by the cyclic unsaturated tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Terpinyl acetate (isomer mixture) (CAS # 8007-35-0) was used as a read-across analog for the target material terpinyl butyrate (CAS # 2153-28-8) for the repeated dose toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of terpene esters.
  - The target substance and the read-across analog share a cyclic unsaturated tertiary alcohol fragment.
  - The key difference between the target substance and the read-across analog is that the target substance has a butyrate acid fragment and the read-across analog has an acetate fragment. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the cyclic unsaturated tertiary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Metabolism

Metabolism of the target material terpinyl butyrate (CAS # 2153-28-8) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is metabolized to α-terpineol (CAS # 98-55-5) and butyric acid (CAS # 107-92-6) in the first step with 0.95 probability. α-terpineol is an isomer of terpineol (CAS # 8000-41-7). Hence, terpineol (CAS # 8000-41-7) and butyric acid (CAS # 107-92-6) can be used as read-across for the target material. Read-across terpineol (CAS # 8000-41-7) and butyric acid (CAS # 107-92-6) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and justification is provided.

- Read-across alcohol terpineol (CAS # 8000-41-7) and read-across acid butyric acid (CAS # 107-92-6) are used as read-across analogs for the target ester terpinyl butyrate (CAS # 2153-28-8) for the reproductive and developmental toxicity endpoint.
  - The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across analogs are toxicologically insignificant.
  - According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the read-across analog.
  - The read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. The data described in the developmental toxicity section above show that the read-across analogs have an adequate margin of exposure at the current level of use. Therefore the alert will be superseded by the availability of the data.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target substance.

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