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RIFM fragrance ingredient safety assessment, ethyl butyrate, CAS registry number 105-54-4

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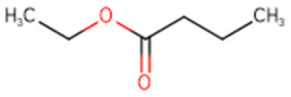

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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

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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., 2015a; Safford et al., 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 Observed 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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
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 , 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.

Ethyl butyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that ethyl butyrate is not genotoxic. Data on read-across analog propyl propionate (CAS # 106-36-5) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog pentyl propionate (CAS # 624-54-4) show that there are no safety concerns for ethyl butyrate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; ethyl butyrate is not expected to be photoirritating/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog butyl acetate (CAS # 123-86-4). The environmental endpoints were evaluated; ethyl butyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Ethyl Butyrate; ECHA, 2016)
Repeated Dose Toxicity: NOAEL = 205.33 mg/kg/day.	(ECHA REACH Dossier: Propyl Propionate; ECHA, 2018)
Reproductive Toxicity: NOAEL = 616 mg/kg/day.	(ECHA REACH Dossier: Propyl Propionate; ECHA, 2018)
Skin Sensitization: No concern for skin sensitization.	(ECHA REACH Dossier: Pentyl Propionate; ECHA, 2013)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)	
Local Respiratory Toxicity: NOAEC = 2375 mg/m^3.	(ECHA REACH Dossier: n-Butyl acetate; ECHA, 2011; David et al., 2001)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 63% (EU Method C.4-D)	RIFM (1992)
Bioaccumulation:	
Critical Measured Value: 8	(ECHA REACH Dossier: Ethyl Butyrate; ECHA, 2016)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 17.594 mg/L	(ECOSAR v2.0; 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, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 17.594 mg/L	(ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 1.7594 μg/L	
• Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** Ethyl butyrate
2. **CAS Registry Number:** 105-54-4
3. **Synonyms:** Butanoic acid, ethyl ester; Butyric ether; Ethyl n-butanoate; Ethyl normal butanoate; ﾌﾞﾀﾝ酸ｱﾙｷﾙ(C = 1～7); Ethyl butyrate
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16 g/mol
6. **RIFM Number:** 281
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 120 °C (Fragrance Materials Association [FMA]), 125.79 °C (EPI Suite)
2. **Flash Point:** 24 °C (Globally Harmonized System), 75 °F; closed cup (FMA)
3. **Log K_{OW}:** 1.73 (Abraham and Rafols, 1995), 1.85 (EPI Suite)
4. **Melting Point**: −56.83 °C (EPI Suite)
5. **Water Solubility:** 2745 mg/L (EPI Suite)
6. **Specific Gravity:** 0.872–0.879 (FMA), 0.870–0.877 (FMA)
7. **Vapor Pressure:** 10.9 mm Hg at 20 °C (EPI Suite v4.0), 11 mm Hg at 20 °C (FMA), 14.6 mm Hg at 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:** A colorless mobile liquid that has a powerful, ethereal-fruity odor suggestive of banana and pineapple and has a sweet, fruity taste.

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.26% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.00063 mg/kg/day or 0.046 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0049 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Propyl propionate (CAS # 106-36-5)
   c. **Reproductive Toxicity:** Propyl propionate (CAS # 106-36-5)
   d. **Skin Sensitization:** Pentyl propionate (CAS # 624-54-4)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Butyl acetate (CAS # 123-86-4)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Apple (*Malus* species)
Cheese, various types.
Citrus fruits.
Grape brandy.
Guava and feyoa
Mangifera species.
Passion fruit (*Passiflora* species)
Strawberry (*Fragaria* species)
Whisky.
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.

9. REACH dossier

Available; accessed on 01/27/22 (ECHA, 2016).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of ethyl butyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537 were treated with ethyl butyrate in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2016). In another bacterial reverse mutation assay, *Salmonella typhimurium* strains TA97 and TA102 were treated with ethyl butyrate in DMSO at concentrations up to 1000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2016). Under the conditions of the study, ethyl butyrate was not mutagenic in the Ames test.

The clastogenicity of ethyl butyrate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung cells (CHL/IU) were treated with ethyl butyrate in DMSO at concentrations up to 1200 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2016). Under the conditions of the study, ethyl butyrate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

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

Additional References: Ishidate et al., 1984

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

The MOE for ethyl butyrate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are limited repeated dose toxicity data on ethyl butyrate. Read-across material propyl propionate (CAS # 106-36-5; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422, EPA OPPTS 870.3650, and GLP-compliant study, 12 Crj:CD(SD)IGS rats/sex/dose were exposed to propyl propionate through whole-body inhalation at doses of 0, 50, 250, and 500 ppm (using the standard minute volume and body weights equivalent to 0, 61.6, 311, and 616 mg/kg/day, respectively). Treatment duration was 38 days in males and 48 days in females. No treatment-related mortality or clinical signs of toxicity were reported throughout the study. In addition, no treatment-related adverse effects were reported for organ weights, hematology, clinical chemistry, or urinalysis at any dose level. In females, body weight and food consumption were significantly lower in mid- and high-dose groups during the study. However, for both parameters, the decreases were <8% and therefore not considered to be of toxicological significance. Clinical chemistry analysis revealed a significant increase in AST levels in males of the high-dose group, but no correlated histopathological or functional changes in the liver were reported. Tension lipidosis, a pale focus in the right medial lobe of the liver, was observed in females of the high-dose group, but this was not considered to be a treatment-related adverse effect, as it is a commonly occurring lesion in rats. At all doses, several local respiratory effects were also reported. Since no systemic toxicity was reported at any dose, the NOAEL for this study was considered to be 500 ppm (616 mg/kg/day) (ECHA, 2018).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 studies (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 616/3 or 205.33 mg/kg/day.

Therefore, the MOE for ethyl butyrate was calculated by dividing the propyl propionate NOAEL (mg/kg/day) by the total systemic exposure to ethyl butyrate in mg/kg/day to be 205.33/0.0049, or 41904.

In addition, the total systemic to ethyl butyrate (4.9 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 1957.

Literature Search and Risk Assessment Completed On: 01/15/22.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on ethyl butyrate. Read-across material propyl propionate (CAS # 106-36-5; see Section VI) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. In an OECD 422/GLP study, groups of 12 Crl:CD(SD) rats/sex were administered test material n-propyl propionate via whole-body exposure at target concentrations of 0, 50, 250, and 500 ppm (equivalent to 0, 62, 308, and 616 mg/kg/day, respectively, as per standard minute volume and bodyweight parameters for Sprague Dawley rats) for 6 h per day, 7 days per week. Females were exposed for 2 weeks prior to breeding, through breeding (approximately 2 weeks), and continued through gestation day 20; the females were then subjected to gross necropsy on postpartum day 5. Males were exposed to the test material 2 weeks prior to breeding and continued through breeding (approximately 2 weeks) before being subjected to gross necropsy (day 38). In addition to systemic toxicity parameters, reproductive toxicity parameters and neurological function were also assessed. There were no treatment-related adverse effects on reproductive performance or survival and growth of pups. The NOAEL for fertility effects and the development of pups was considered to be 500 ppm or 616 mg/kg/day, the highest dose tested (ECHA, 2018). **Therefore, the ethyl butyrate MOE for the reproductive toxicity endpoint can be calculated by dividing the propyl propionate NOAEL in mg/kg/day by the total systemic exposure to ethyl butyrate, 616/0.0049, or 125714.**

In addition, the total systemic exposure to ethyl butyrate (4.9 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: None.

Literature Search and Risk Assessment Completed On: 01/15/22.

11.1.4. Skin sensitization

Based on the existing data and the read-across material pentyl propionate (CAS # 624-54-4), ethyl butyrate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for ethyl butyrate. Therefore, pentyl propionate (CAS # 624-54-4; see Section VI) was used for the risk assessment of propyl acetate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, ethyl butyrate is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material pentyl propionate was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (ECHA, 2013). In a human maximization test, no skin sensitization reactions were observed with 3450 μg/cm^2 ethyl butyrate (RIFM, 1972).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies on the read-across material as well as the target material, ethyl butyrate does not present a concern for skin sensitization.

Additional References: Klecak (1979); Klecak (1985).

Literature Search and Risk Assessment Completed On: 01/13/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, ethyl butyrate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for ethyl butyrate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, ethyl butyrate does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/22.

11.1.6. Local respiratory toxicity

There are no inhalation data on ethyl butyrate; however, in a sub-chronic, 13-week inhalation study for read-across analog butyl acetate

Table 1
Summary of existing data on pentyl propionate as a read-across for ethyl butyrate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	NA	NA	NA	NA	>25000 (negative up to 100%)	NA	NA
	***In vitro* Data**[f]				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

(CAS # 123-86-4; see Section VI), a NOAEC of 2375 mg/m^3 was reported (ECHA, 2011; David et al., 2001).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE for local respiratory toxicity. In a 13-week whole-body inhalation study conducted in rats, a NOAEC of 2375 mg/m^3 (500 ppm) was reported (ECHA, 2011; David et al., 2001). Whole-body inhalation exposure of read-across material butyl acetate was administered at target concentrations (0 [sham], 2375, 7126, and 14253 mg/m^3) to both male and female Sprague Dawley rats (15/sex/concentration). Clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross pathology, and histopathology were all considered. Body weights and food consumption decreased among animals in the mid- and high-dose treatment groups. Organ weight changes were also dependent upon treatment and concentration. Lung weights increased among males exposed to 14253 mg/m^3 butyl acetate compared to the control group. Additionally, histopathology for both the mid- and high-dose treatment groups demonstrated degenerated olfactory epithelial tissue as well as dorsal medial meatus and ethmotubinates of the nasal passages. The severity of the histopathological findings ranged from mild to moderate for the high-dose group but minimal to mild for the mid-dose group. As there were no observable adverse effects documented for the low-dose treatment group, the NOAEC was determined to be 2375 mg/m^3.

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

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

The 95th percentile calculated exposure to isobutyl acetate was reported to be 0.046 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 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, 2009) to give 0.071 mg/kg lung weight/day resulting in an MOE of 1279493 (i.e., [90844 mg/kg lung weight/day]/[0.071 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.046 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms, A.D. and Travis, C.C. (1988). Reference Physiological Parameters in Pharmacokinetic Modeling. EPA/600/6–88/004. Retrieved from https://nepis.epa.gov/Exe/ZyPDF.cgi/9100R7VE.PDF?Dockey=9100R7VE.PDF.

**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: Frederick et al., 2009.

Literature Search and Risk Assessment Completed On: 11/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of ethyl butyrate was performed following the RIFM Environmental Framework (Salvito, 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, ethyl 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 ethyl butyrate as possibly being 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). 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 $\geq$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.

11.2.1.1. Risk assessment. Based on the current VoU (2019), ethyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 1992: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to EU Method C.4-D. Biodegradation of 63% was observed after 28 days.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Ethyl butyrate is registered for REACH with the following additional data available (ECHA, 2016):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301 D Guideline. Biodegradation of 50% was observed after 42 days.

The bioaccumulation study in fish was conducted for estimating the BCF (bioaccumulation factor) value of the test chemical. The bioaccumulation factor (BCF) value was calculated using a log K_{ow} of 1.85 and a regression-derived equation. The estimated BCF (bioaccumulation factor) value of the test chemical was determined to be 8.

The acute fish (Zebrafish) toxicity test was conducted according to the OECD 203 Guideline under static conditions. The 96-h LC50 value, based on nominal concentrations, was reported to be $>$ 100 mg/L.

The *Daphnia* acute immobilization test was conducted according to the OECD 202 Guideline under static conditions. The 48-h EC50 value was reported to be 116.6 mg/L (95% CI: 84.9–164.1 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 Guideline under static conditions. The 72-h EC50 value was reported to be 100 mg/L.

11.2.1.5. Risk assessment refinement. Since ethyl butyrate passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.85	1.85
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	10–100
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 1.7594 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: 05/24/22.

Literature Search*

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>211.6</u>			1000000	0.2116	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	19.093	40.347	<u>17.594</u>	10000	1.7594	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	131.102	73.392	51.557			Neutral Organic SAR

- **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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 ChemView:** https://chemview.epa.gov/chemview/
- **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 06/21/22.

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.2022.113344.

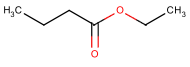
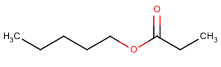
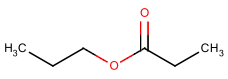
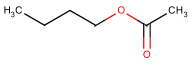
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- 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 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Ethyl butyrate	Pentyl propionate	Propyl propionate	Butyl acetate
CAS No.	105-54-4	624-54-4	106-36-5	123-86-4
Structure				
Similarity (Tanimoto Score)		0.68	0.71	0.77
Endpoint		• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity	• Local respiratory toxicity

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Molecular Formula	$C_6H_{12}O_2$	$C_8H_{16}O_2$	$C_6H_{12}O_2$	$C_6H_{12}O_2$
Molecular Weight (g/mol)	116.16	144.21	116.16	116.16
Melting Point (°C, EPI Suite)	−98.00	−73.10	−75.90	−78.00
Boiling Point (°C, EPI Suite)	121.50	168.60	122.50	126.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	1946.50	479.96	1853.18	1533.20
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4900.00	810.00	5300.00	8400.00
Log K_{OW}	1.85	2.83	1.85	1.78
J_{max} (μg/cm^2/h, SAM)	194.75	63.57	210.65	301.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	40.43	85.42	40.63	28.47
Repeated Dose Toxicity				
Repeated Dose (HESS)	Urethane (Renal toxicity) Alert		Not categorized	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure		Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)		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 were identified	No skin sensitization reactivity domain alerts were identified		
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

Summary

There are insufficient toxicity data on ethyl butyrate (CAS # 105-54-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, pentyl propionate (CAS # 624-54-4), propyl propionate (CAS # 106-36-5), and butyl acetate (CAS # 123-86-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Pentyl propionate (CAS # 624-54-4) was used as a read-across analog for the target material ethyl butyrate (CAS # 105-54-4) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target ester is a butyrate ester while the read-across analog is a propionate ester. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog do not have any toxicity-related alerts. The data are consistent with the prediction.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Propyl propionate (CAS # 106-36-5) was used as a read-across analog for the target material ethyl butyrate (CAS # 105-54-4) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to a class of aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target ester is a butyrate ester of ethanol, whereas the read-across analog is a propionate ester of propanol. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o 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 is alerted for being a toxicant for developmental toxicity by the CAESAR model. The data described in the developmental toxicity section confirms that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
- The target material has an alert of urethane (renal toxicity) by HESS categorization. This is due to more than 50% structural similarity of the target material with urethane. The reactive moiety in urethane is not present in the target material. Therefore, the target material is out of the structural domain of the alert system. The data described in the repeated dose toxicity section confirms that the MOE is adequate at the current level of use. Therefore, the predictions are 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 ethyl butyrate (CAS # 105-54-4) for the local respiratory toxicity endpoint.
  - The target material and the read-across analog belong to a class of aliphatic esters.
  - The key difference between the target material and the read-across analog is that the target ester is a butyrate ester while the read-across analog is an acetate ester. This structural difference is toxicologically insignificant.
  - 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 physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a 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 and the read-across analog do not have any toxicity-related alerts. The data are consistent with the prediction.
  - 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.

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