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Short review

RIFM fragrance ingredient safety assessment, ethyl 3-hydroxybutyrate, CAS Registry Number 5405-41-4

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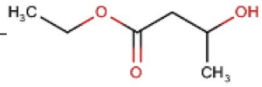
Version: 020618. This version replaces any previous versions.



Name: Ethyl 3-hydroxybutyrate
CAS Registry Number: 5405-41-4

Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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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 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.
Ethyl 3-hydroxybutyrate 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 (L)-lactate (CAS # 687-47-8) show that ethyl 3-hydroxybutyrate is not expected to be genotoxic. Data on ethyl (L)-lactate (CAS # 687-47-8) provide a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints. The fertility endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to ethyl 3-hydroxybutyrate is below the TTC (0.03 mg/kg/day). The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; ethyl 3-hydroxybutyrate is not expected to be phototoxic/photoallergenic. Data on read-across analog ethyl lactate (CAS # 97-64-3) provide a calculated MOE > 100 for the local respiratory endpoint. The environmental endpoints were evaluated; ethyl 3-hydroxybutyrate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Ethyl (S)-2-hydroxypropionate; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 13.47 mg/kg/day.	(ECHA REACH Dossier: Ethyl (S)-2-hydroxypropionate; ECHA, 2011)
Reproductive Toxicity: Developmental Toxicity: NOAEL = 3619 mg/kg/day. Fertility: No NOAEL available. Exposure is below the TTC.	(ECHA REACH Dossier: Ethyl (S)-2-hydroxypropionate; ECHA, 2011)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 150 mg/m^3.	(Clary et al., 1998)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 5264 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5264 mg/L	((RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 5.264 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

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1. Identification

1. **Chemical Name:** Ethyl 3-hydroxybutyrate
2. **CAS Registry Number:** 5405-41-4
3. **Synonyms:** Butanoic acid, 3-hydroxy-, ethyl ester; Ethyl-β-hydroxybutyrate; Ethyl 3-hydroxybutanoate; ﾋﾄﾞﾛｷｼｱﾙｶﾝ酸(C = 4 ~ 8)ｱﾙｷﾙ(C = 1–2); Ethyl 3-hydroxybutyrate
4. **Molecular Formula:** $C_6H_{12}O_3$
5. **Molecular Weight:** 132.15
6. **RIFM Number:** 6213
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 170 °C (Fragrance Materials Association [FMA]), 187.13 °C (EPI Suite)
2. **Flash Point:** 57 °C (Globally Harmonized System), 134 °F; CC (FMA)
3. **Log K_{OW}:** 0.31 (EPI Suite)
4. **Melting Point**: 16.01 °C (EPI Suite)
5. **Water Solubility:** 159200 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.7 mm Hg 20 °C (FMA), 0.115 mm Hg @ 20 °C (EPI Suite v4.0), 0.18 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Winey, fruity, rum and sherry characteristics*

*https://www.perfumerflavorist.com/flavor/rawmaterials/natural/123658534.html.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.098% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00076 mg/kg/day or 0.049 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl (L)-lactate (CAS # 687-47-8)
   b. **Repeated Dose Toxicity:** Ethyl (L)-lactate (CAS # 687-47-8)
   c. **Reproductive Toxicity:** Ethyl (L)-lactate (CAS # 687-47-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Ethyl lactate (CAS # 97-64-3)
   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)

Ethyl 3-hydroxybutyrate is reported to occur in the following foods by the VCF*:
Apple, fresh (*Malus* species).
Chinese quince (*Pseudocydonia sinensis* Schneid).
Citrus fruits.
Grape (*Vitis* species).
Guava fruit (*Psidium guajava* L.)
Mangifera species.
Red wine.
White wine.
Yuzu oil (*Citrus junos* Sieb. ex Tanaka).
*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. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 02/06/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, ethyl 3-hydroxybutyrate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of ethyl 3-hydroxybutyrate; however, read-across can be made to ethyl (L)-lactate (CAS # 687-47-8; see Section V).

The mutagenic activity of ethyl (L)-lactate has been evaluated in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with ethyl (L)-lactate in deionized, distilled grade water 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, 2011). Under the conditions of the study, ethyl (L)-lactate was not mutagenic in the Ames test (and this can be extended to ethyl 3-hydroxybutyrate).

The clastogenicity of ethyl (L)-lactate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with ethyl (L)-lactate in RPMI 1640 medium at concentrations up to 1180 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, 2011). Under the conditions of the study, ethyl (L)-lactate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay (and this

can be extended to ethyl 3-hydroxybutyrate).

Based on the data available, read-across ethyl (L)-lactate does not present a concern for genotoxic potential (and this can be extended to ethyl 3-hydroxybutyrate).

Additional References: ECHA, 2011.

Literature Search and Risk Assessment Completed On: 01/28/19.

10.1.2. Repeated dose toxicity

The margin of exposure (MOE) for ethyl 3-hydroxybutyrate 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 ethyl 3-hydroxybutyrate. Read-across material ethyl (L)-lactate (CAS # 687-47-8; see Section V) has sufficient repeated dose toxicity data. In an OECD 412 and GLP-compliant study, 5 Wistar rats/sex/dose were administered ethyl (L)-lactate (purity not reported) through whole body inhalation at concentrations of 0, 150, 600, and 2500 mg/m^3 (equivalent to 40.4, 161.7, and 673.8 mg/kg/day) 6 h/day, 5 days/week for 4 weeks. No treatment-related mortality was reported at any dose. No treatment-related effects were reported for clinical signs, hematology and clinical chemistry up to 2500 mg/m^3. Significant treatment-related effects were reported in the high-dose group animals, including reduced bodyweight gain throughout the study and decreased food consumption potentially inhibiting animal growth. Moreover, severe damage to the olfactory epithelium was reported with intensity increasing with increasing dose. Histopathological examinations demonstrated treatment-related effects in the nasal cavity, such as moderate to very severe atrophy of the olfactory epithelium with disarrangement, disappearing of cellular apices and flattening of the cells, and thinning of the olfactory layer. Furthermore, minimal recognizable epithelium remained in several high-dose animals. In the respiratory epithelium, goblet cell hypertrophy and moderate goblet cell hyperplasia were reported mainly in the epithelium of the nasal septum and ventrolateral parts of the nasal cavity, and nasoturbinates in severe cases. Based on decreased food consumption and growth retardation, the no observed adverse effect concentration (NOAEC) was considered to be 150 mg/m^3. Using standard minute volume and bodyweight values for Wistar rats, the calculated NOAEL for repeated dose toxicity is 40.42 mg/kg/day (ECHA, 2011).

In another OECD 412 and GLP-compliant study, 5 Wistar rats/sex/dose were administered ethyl (L)-lactate through whole body inhalation at concentrations of 0 (vehicle not reported), 25, 75 and 200 mg/m^3 (equivalent to 4.49, 13.48, and 35.94 mg/kg/day) for 6 h/day, 5 days/week for 4 weeks. The above dose levels were selected following excessive olfactory damage reported in animals treated at doses higher than 200 mg/m^3. During the study, recovery groups of 5 animals/sex were maintained for 4 weeks following a 4-week treatment. No treatment-related mortality, clinical signs, body weight, or histopathological changes were reported up to highest dose level. The NOAEC was considered to be 200 mg/m^3. Using standard minute volume and bodyweight values for Wistar rats, the calculated NOAEL for repeated dose toxicity is 53.90 mg/kg/day (ECHA, 2011).

Thus a conservative NOAEL of 40.42 mg/kg/day was determined for repeated dose toxicity. A default safety factor of 3 was used when deriving a NOAEL from the 28-day repeated dose study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 40.42/3 or 13.47 mg/kg/day. **Therefore, the ethyl 3-hydroxybutyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl (L)-lactate NOAEL in mg/kg/day by the total systemic exposure to ethyl 3-hydroxybutyrate, 13.47/0.0029 or 4645.**

In addition, the total systemic exposure to ethyl 3-hydroxybutyrate (2.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: NIWL, 1999.

Literature Search and Risk Assessment Completed On: 01/17/19.

10.1.3. Reproductive Toxicity

The MOE for ethyl 3-hydroxybutyrate is adequate for the developmental toxicity endpoint at the current level of use.

There are no fertility data on ethyl 3-hydroxybutyrate or on any read-across materials. The total systemic exposure to ethyl 3-hydroxybutyrate is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on ethyl 3-hydroxybutyrate. Read-across material ethyl (L)-lactate (CAS # 687-47-8; see Section V) has sufficient developmental toxicity data that can be used to support the developmental toxicity endpoint. A GLP dermal developmental toxicity study was conducted on pregnant female Crl:CD (SD) BR rats. Groups of 25 pregnant female rats/dose were exposed to 0, 0.517, 1.551, or 3.619 g/kg/day of ethyl lactate via percutaneous application during gestation days (GDs) 6–15 for 6 h per day. Females were examined daily for mortality, abortion, premature delivery, presence of skin reactions, body weight, food consumption, organ weight, and tissue lesions. The number of implantations, early/late resorptions, live/dead fetuses, and corpora lutea were evaluated. Fetuses were assessed for viability, body weight, and gross external morphology. Half of the fetuses from each litter were used for visceral or skeletal evaluations. One low-dose group dam was inadvertently euthanized on GD 18, and all other dams were euthanized and necropsied on GD 20. Females at the highest dose group exhibited increased incidences of slight erythema and/or desquamation as compared to the sham control group. These skin findings may be interrelated with incidental hyperactivity that was observed in 1 high-dose group dam. However, the incidences of these skin and clinical observations were not statistically significant. No treatment-related adverse developmental effects were reported for embryo-fetal viability, body weight, or morphology. The NOAEL for developmental toxicity was considered to be 3.619 g/kg/day or 3619 mg/kg/day, the highest dose tested (ECHA, 2011). **Therefore, the ethyl 3-hydroxybutyrate MOE for the developmental toxicity endpoint can be calculated by dividing the ethyl (L)-lactate NOAEL in mg/kg/day by the total systemic exposure to ethyl 3-hydroxybutyrate, 3619/0.0029 or 1247931.**

In addition, the total systemic exposure to ethyl 3-hydroxybutyrate (2.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on ethyl 3-hydroxybutyrate or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to ethyl 3-hydroxybutyrate (2.9 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/15/19.

10.1.4. Skin sensitization

Based on the existing data and the application of the dermal sensitization threshold (DST), ethyl 3-hydroxybutyrate does not present a concern for skin sensitization under the current, declared levels of use.

Table 1
Maximum acceptable concentrations for ethyl 3-hydroxybutyrate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	0.0052%
2	Products applied to the axillae	0.021%	9.5×10^{-7}%
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	0.098%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.045%
6	Products with oral and lip exposure	0.23%	0.012%
7	Products applied to the hair with some hand contact	0.79%	5.2×10^{-6}%
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.045%
10	Household care products with mostly hand contact	2.7%	0.080%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	1.0%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for ethyl 3-hydroxybutyrate. However, a human repeat insult patch test (HRIPT) was conducted with 50 female volunteer subjects, using 5% (2500 μg/cm^2) of the test material in specially denatured alcohol (SD39C). No skin sensitization reactions were observed in this study (RIFM, 1988). Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for ethyl 3-hydroxybutyrate that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, ethyl 3-hydroxybutyrate 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 ethyl 3-hydroxybutyrate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, ethyl 3-hydroxybutyrate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for ethyl 3-hydroxybutyrate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/19.

10.1.6. Local respiratory toxicity

There are insufficient inhalation data available on ethyl 3-hydroxybutyrate; however, in a subacute, 28-day inhalation study for the analog ethyl lactate (CAS # 97-64-3; see Section V), a NOAEC of 150 mg/m^3 was reported (Clary et al., 1998).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In an OECD TG 412/GLP-compliant subacute 28-day inhalation study, 5 Wistar rats/sex/treatment group were exposed to ethyl lactate vapors at 0, 150, 600, and 2500 mg/m^3 for 6 h/day, 5 days/week for 28 days (ECHA, 2011; also reported in Clary et al., 1998). The test animals were observed for treatment-related changes in body weight, food consumption, hematological, biochemical, organ weight, and gross and microscopic evaluations. Nasal tract effects were noted at the 600 mg/m^3 showing degenerative changes in the nasal olfactory epithelium showing atrophy with replacement by respiratory epithelium and hyperplasia in the nasal respiratory epithelium, including hyperplasia of the goblet cells, mainly in epithelium of the nasal septum and ventrolateral parts of the nasal cavity and, in more severe cases, also of the nasoturbinates. With these observations, the local respiratory toxicity NOAEC was set at 150 mg/m^3.

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

- (150 mg/m^3) (1m^3/1000 L) = 0.15 mg/L
- Minute ventilation (MV) 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
- (0.15 mg/L) (61.2 L/d) = 9.18 mg/day
- (9.18 mg/day)/(0.0016 kg lung weight of rat*) = 5737.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.049 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey et al., 2015; Safford et al., 2015a). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.08 mg/kg lung

weight/day resulting in an MOE of 71,718.75 (i.e., [5737.5 mg/kg lung weight of rat/day]/[0.08 mg/kg lung weight of human/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 0.049 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: ECHA, 2011.

Literature Search and Risk Assessment Completed On: 01/28/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of ethyl 3-hydroxybutyrate 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, ethyl 3-hydroxybutyrate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	5264			1,000,000	5.264	

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify ethyl 3-hydroxybutyrate 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 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 $\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).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), ethyl 3-hydroxybutyrate presents no risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.3. Other available data

Ethyl 3-hydroxybutyrate has been pre-registered for REACH, and no additional data is available at this time.

10.2.4. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.31	0.31
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	$<$ 1	$<$ 1
Risk Characterization: PEC/PNEC	**$<$ 1**	**$<$ 1**

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

The RIFM PNEC is 5.264 μg/L. The revised PEC/PNECs for EU and North America are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/22/19.

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 01/02/20.

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.2020.111264.

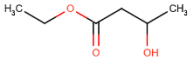
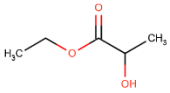
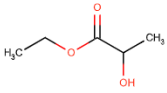
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target 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
Principal Name	Ethyl 3-hydroxybutyrate	Ethyl (L)-lactate	Ethyl lactate
CAS No.	5405-41-4	687-47-8	97-64-3
Structure			
Similarity (Tanimoto Score)		0.49	0.49
Read-across Endpoint		• Genotoxicity • Developmental Toxicity • Repeated Dose Toxicity	• Local Respiratory Toxicity
Molecular Formula	$C_6H_{12}O_3$	$C_5H_{10}O_3$	$C_5H_{10}O_3$
Molecular Weight	132.15	118.13	118.13
Melting Point (°C, EPI Suite)	−16.01	−27.76	−27.76
Boiling Point (°C, EPI Suite)	185	154	154
Vapor Pressure (Pa @ 25 °C, EPI Suite)	24.1	5.00E+002	5.00E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	0.31	−0.18	−0.18
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.592e+005	4.728e+005	4.728e+005
J_{max} (μg/cm^2/h, SAM)	376.14	2193.28	2193.28
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.52E-003	4.88E+000	4.88E+000
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)	• Non-carcinogen (low reliability)	• Non-carcinogen (good 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)	• H-acceptor-path3-H-acceptor	• H-acceptor-path3-H-acceptor	
Oncologic Classification	• Not classified	• Not classified	
Repeated Dose Toxicity			
Repeated Dose (Hazard Evaluation Support System [HESS])	• Urethane (Renal toxicity) Alert	• Urethane (Renal toxicity) Alert	
Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good reliability)	• Toxicant (good reliability)	
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

Summary

There are insufficient toxicity data on ethyl 3-hydroxybutyrate (CAS # 5405-41-4). 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, ethyl (L)-lactate (CAS # 687-47-8) and ethyl lactate (CAS # 97-64-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl (L)-lactate (CAS # 687-47-8) was used as a read-across analog for the target material ethyl 3-hydroxybutyrate (CAS # 5405-41-4) for the genotoxicity, repeated dose toxicity, and developmental toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated hydroxy esters.
  - The target material and the read-across analog share an ester functionality with a secondary alcohol group within the acid fragment and an ethyl alcohol fragment.
  - The key difference between the target material and the read-across analog is that the acid fragment in the target material is a 3-hydroxybutyric acid, whereas the acid fragment in the read-across material is a lactic acid. 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.
  - Both target and read-across materials have an *In Vivo* Mutagenicity (Micronucleus, ISS) alert for H-acceptor-path3-H-acceptor. This alert is due to the carbonyl functionality and the secondary hydroxyl group within 1–4 connectivity for the target and to the ester oxygen and the secondary hydroxyl group within the 1–4 connectivity for the read-across analog. The data described in the genotoxicity section shows that the margin of exposure is adequate at the current level of use. The predictions are superseded by data.
  - Both materials present a Repeated Dose (HESS) alert for urethane renal toxicity due to structural similarities of 53.3% with the target material and 57.1% with the read-across analog using the Dice score. Since both the target material and the read-across analog lack a urethane group, this alert can be ignored. The predictions are superseded by data.
  - Both target and read-across materials have a Developmental Toxicity (CAESAR v2.1.6) alert as toxicants. The data described in the developmental toxicity section shows that the margin of exposure is adequate at the current level of use. The predictions are superseded by 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.
- Ethyl lactate (CAS # 97-64-3) was used as a read-across analog for the target material ethyl 3-hydroxybutyrate (CAS # 5405-41-4) for the local respiratory toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated hydroxy esters.
  - The target material and the read-across analog share an ester functionality with a secondary alcohol group within the acid fragment and an ethyl alcohol fragment.
  - The key difference between the target material and the read-across analog is that the acid fragment in the target material is a 3-hydroxybutyric acid, whereas the acid fragment in the read-across material is a lactic acid. 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 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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