Food and Chemical Toxicology 169 (2022) 113494

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, methyl butyrate, CAS registry number 623-42-7

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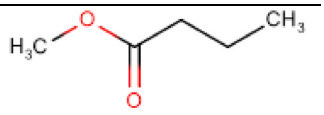
Version: 062222. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrance materialsafetyresource.elsevier.com.



Name: Methyl butyrate CAS Registry Number: 623-42-7

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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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)
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

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https://doi.org/10.1016/j.fct.2022.113494
Received 27 June 2022; Received in revised form 10 October 2022; Accepted 17 October 2022
Available online 21 October 2022

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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 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.

Methyl butyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl acetate (CAS # 141-78-6) show that methyl butyrate is not expected to be 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 methyl propionate (CAS # 554-12-1) show that there are no safety concerns for methyl butyrate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl butyrate is not expected to be photoirritating/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by read-across analog propyl acetate (CAS # 109-60-4). The environmental endpoints were evaluated; Methyl 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Ethyl acetate; ECHA, 2011a)

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Repeated Dose Toxicity: NOAEL = 205.33 mg/kg/day.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018b)
Reproductive Toxicity: NOAEL = 616 mg/kg/day.	(ECHA REACH Dossier: Propyl propionate; ECHA, 2018b)
Skin Sensitization: No concern for skin sensitization.	(ECHA REACH Dossier: Methyl propionate; ECHA, 2018a)
Photoirritation/ Photoallergenicity: Not expected to be photoirritating/ photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 626.56 mg/m^3.	(ECHA REACH Dossier: Propyl acetate; ECHA, 2011b)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 3.11 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.29 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 496.5 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: 496.5 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.4965 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Methyl butyrate
2. **CAS Registry Number:** 623-42-7
3. **Synonyms:** Butanoic acid, methyl ester; Methyl butanoate; Methyl butyrate
4. **Molecular Formula:** $C_5H_{10}O_2$
5. **Molecular Weight:** 102.13 g/mol
6. **RIFM Number:** 1027
7. **Stereochemistry:** Stereoisomer not specified. Stereocenter not present. Stereoisomers are not possible.

2. Physical data

1. **Boiling Point:** 103 °C (Fragrance Materials Association [FMA]), 102.3 °C (EPI Suite)
2. **Flash Point:** 10 °C (Globally Harmonized System), 50 °F; closed cup (FMA)
3. **Log K_{OW}:** 1.36 (EPI Suite)
4. **Melting Point**: −69.32 °C (EPI Suite)
5. **Water Solubility:** 9120 mg/L (EPI Suite)
6. **Specific Gravity:** 0.90 (FMA)
7. **Vapor Pressure:** 25.3 mm Hg at 20 °C (EPI Suite v4.0), 24 mm Hg at 20 °C (FMA), 33.2 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:** Colorless, mobile liquid. Very diffusive and penetrating sweet ethereal fruity odor. In extreme dilution reminiscent of apple peel with a slightly fatty peach-like undertone. Sweet but not very powerful taste in aqueous media. Apple-like or banana-pineapple-like in dilutions below 100 ppm (Arctander, 1969).

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Fine Fragrance::** 0.0098% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.000045 mg/kg/day or 0.0028 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00035 mg/kg/day (RIFM, 2021)

*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; 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 et al., 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

6.1. Cramer Classification: class I, low

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

6.2. Analogs selected

a. **Genotoxicity:** Ethyl acetate (CAS # 141-78-6)
b. **Repeated Dose Toxicity:** Propyl propionate (CAS # 106-36-5)
c. **Reproductive Toxicity:** Propyl propionate (CAS # 106-36-5)
d. **Skin Sensitization:** Methyl propionate (CAS # 554-12-1)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Propyl acetate (CAS # 109-60-4)
g. **Environmental Toxicity:** None

6.3. Read-across justification

See Appendix below.

7. Metabolism

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

8. Natural occurrence

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

Apple fresh (*Malus* species)	*Mangifera* species
Citrus fruits	Melon
Durian (Durio zibethinus)	Passion fruit (*Passiflora* species)
Guava and feyoa	Pineapple (Ananas comosus)
Kiwifruit (Actinidia chinensis, syn. A. deliciosa)	Strawberry (*Fragaria* 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. This is a partial list.

9. REACH dossier

Methyl butyrate has been pre-registered for 2010; no dossier available as of 06/22/22.

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, methyl butyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of methyl butyrate; however, read-across can be made to ethyl acetate (CAS # 141-78-6; see Section VI).

The mutagenic activity of ethyl acetate has been evaluated in a bacterial reverse mutation assay conducted following methods equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with ethyl acetate 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, 2011a). Under the conditions of the study, ethyl acetate was not mutagenic in the Ames test.

The clastogenic activity of ethyl acetate has been assessed extensively *in vitro* in rodent cell lines and human peripheral blood lymphocytes leading to varying results. However, these studies deviated significantly from regulatory guidelines. The clastogenic activity of ethyl acetate was evaluated in an *in vivo* micronucleus test conducted following methods equivalent to OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female Chinese Hamsters at a single dose of 2500 mg/kg body weight. Hamsters were euthanized at different time points of 12, 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011a). Under the conditions of the study, ethyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, ethyl acetate does not present a concern for genotoxic potential, and this can be extended to methyl butyrate.

Additional References: Loveday et al., 1990; Hayashi et al., 1988; Ishidate et al., 1984; Perocco et al., 1983; Basler (1986); Shirasu et al., 1976; Chen et al., 1984; Nonaka (1989); Zimmermann et al., 1985a; Zimmermann et al., 1985b.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no data on methyl butyrate to

support the repeated dose toxicity endpoint. 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 slightly lower in the mid- and high-dose groups during the study (statistically non-significant). Clinical chemistry analysis revealed a significant increase in AST levels in males of the high-dose group, but no correlated histopathological or functional changes of 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 (ECHA, 2018b; NTP, 2014). 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, 2018b).

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 methyl butyrate was calculated by dividing the propyl propionate NOAEL (mg/kg/day) by the total systemic exposure to methyl butyrate in mg/kg/day to be 205.33/0.00035, or 586657.

In addition, the total systemic to methyl butyrate (0.35 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: None.

Literature Search and Risk Assessment Completed On: 01/14/22.

11.1.3. Reproductive toxicity

The MOE for methyl 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 methyl 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- and GLP-compliant 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 in the 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, 2018b). **Therefore, the methyl 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 methyl butyrate, 616/0.00035, or 1760000.**

In addition, the total systemic exposure to methyl butyrate (0.35 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: 01/14/22.

11.1.4. Skin sensitization

Based on the existing data and read-across material methyl propionate, methyl butyrate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for methyl butyrate. Therefore, methyl propionate (CAS # 554-12-1; see Section VI) was used for the risk assessment of methyl propionate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, methyl 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). Read-across material, methyl propionate was predicted not to be skin sensitizing in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (ECHA, 2018a). In human maximization tests, no skin sensitization reactions were observed with methyl butyrate and read-across material methyl propionate at 5520 μg/cm^2 and 1380 μg/cm^2, respectively (RIFM, 1978; RIFM, 1977).

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

Additional References: None.

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

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, methyl 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 methyl 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, methyl 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 methyl butyrate; however, in a subchronic, 13-week inhalation study for the read-across analog propyl acetate (CAS # 109-60-4; see Section VI), a NOAEC of 626.56 mg/m^3

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

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm^2	NOEL-HMT (induction) µg/cm^2	LOEL[2] (induction) µg/cm^2	WoE NESIL[3] µg/cm^2	LLNA[4] Weighted Mean EC3 Value µg/cm^2	GPMT[5]	Buehler[5]
No evidence of sensitization[7]	NA	1380	NA	NA	NA	NA	NA
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative	NA		No alert found	No alert found	No alert found

was reported (ECHA, 2011ab).

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 from inhalation exposure when used in perfumery. In an OECD 413 Guideline 13-week study, 10 male and 10 female Wistar rats/group were exposed to propyl acetate via whole-body inhalation exposures at 0, 626.56, 2088.55, and 6265.64 mg/m^3 for 6 h/day, 5 days/week (ECHA, 2011ab). Standard observations included mortality, clinical observations, body weights, food consumption, ophthalmology, clinical pathology, clinical chemistry, and histopathology on all organs, including lungs, trachea, larynx, pharynx, and nasal cavity. Treatment-related effects were observed in the nasal cavity and larynx. Degeneration, necrosis, and/or regeneration of the olfactory epithelium were observed at different levels in the nasal cavity in 6 males and females in the 2088.55-mg/m^3 group and all animals from the 6265.64-mg/m^3 group. These effects were characterized by loss of sustentacular cells, increased intercellular spaces, irregular epithelial architecture, reduction of epithelial height, necrotic epithelium, and/or increased nuclear to cytoplasmic ratio; it was located at the dorsal septum, nasoturbinate, and/or ethmoturbinate. A minimal focal inflammation was observed in 3 males from the high-exposure group, which was caused by foreign bodies (2 of the 3 males showing inflammation had hairs within the inflammatory area) and therefore determined to be unrelated to the treatment. Based on the observations for local respiratory toxicity, the NOAEC was identified as 626.56 mg/m^3.

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

- (626.56 mg/m^3) × (1 m^3/1000 L) = 0.627 mg/L
- Minute volume of 0.17 L/min for a Wistar rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 50.4 L/day
- (0.627 mg/L) × (50.4 L/d) = 31.6 mg/day
- (31.6 mg/day)/(0.0016 kg lung weight of rat**) = 19750.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0028 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0043 mg/kg lung weight/day resulting in a MOE of 4593140 (i.e., [19750.5 mg/kg lung weight of rat/day]/[0.0043 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 0.0028 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: Helmig et al., 1999.

Literature Search and Risk Assessment Completed On: 01/20/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

11.2.2. Risk assessment

Based on the current Volume of Use (2019), methyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

No data available.

Ecotoxicity:

No data available.

11.2.2.2. Other available data. Methyl butyrate has been pre-registered under REACH, and no additional data is available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	496.5			1000000	0.4965	

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

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify methyl butyrate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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 ≥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).

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.36	1.36
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.4965 μg/L. The revised PEC/PNECs for EU and NA 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 VoU.

Literature Search and Risk Assessment Completed On: 05/24/22.

12. 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:** 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 06/22/22.

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.2022.113494.

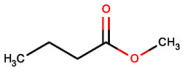
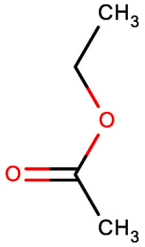
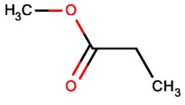
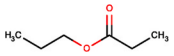
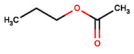
Appendix

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	Read-across Material
Principal Name	Methyl butyrate	Ethyl acetate	Methyl propionate	Propyl propionate	Propyl acetate
CAS No.	623-42-7	141-78-6	554-12-1	106-36-5	109-60-4
Structure					
Similarity (Tanimoto Score)		0.50	0.78	0.60	0.55
Endpoint		Genotoxicity	Skin sensitization	Repeated dose toxicity Reproductive toxicity	Local respiratory toxicity
Molecular Formula	$C_5H_{10}O_2$	$C_4H_8O_2$	$C_4H_8O_2$	$C_6H_{12}O_2$	$C_5H_{10}O_2$
Molecular Weight (g/mol)	102.13	88.11	88.11	116.16	102.13
	−85.80	−83.60	−87.50	−75.90	−93.00

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	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Melting Point (°C, EPI Suite)					
Boiling Point (°C, EPI Suite)	102.80	77.10	79.80	122.50	101.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	4306.30	12425.61	11199.05	1853.18	4786.26
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	15000.00	80000.00	62400.00	5300.00	18900.00
Log K_{OW}	1.29	0.73	0.84	1.85	1.24
J_{max} (μg/cm^2/h, SAM)	356.41	1095.21	1024.60	210.65	414.70
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	20.77	13.58	17.63	40.63	22.09
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters			
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found			
Carcinogenicity (ISS)	No alert found	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1	No alert found	No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**	0.00	0.00			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No skin sensitization reactivity domains alerts were identified	No skin sensitization reactivity domain alerts were identified			
Oncologic Classification	No alert found	No alert found			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not possible to classify according to these rules			Not possible to classify according to these rules	
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)	DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-Conjugated carboxylic acids and esters (non-reactive)		DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-Conjugated carboxylic acids and esters (non-reactive)		
Protein Binding (OECD)	Not possible to classify according to these rules (GSH)		Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Reaction at sp3 carbon atom (SN2)		
Protein Binding Potency	Not categorized		Not categorized		
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	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Metabolites (OECD QSAR Toolbox v4.2)					

Summary

There are insufficient toxicity data on methyl butyrate (CAS # 623-42-7). 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 acetate (CAS # 141-78-6), methyl propionate (CAS # 554-12-1), propyl propionate (CAS 106-36-5), and propyl acetate (CAS # 109-60-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl acetate (CAS # 141-78-6) was used as a read-across analog for the target material, methyl butyrate (CAS # 623-42-7), for the genotoxicity 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 formate ester, while the read-across analog is acetate 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 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 read-across analog has an alert for Schiff base formation and SN2 at the SP3 carbon. This is due to the fact that the ester is an acetate ester. The data described in the genotoxicity section confirm that the read-across analog does not present a concern for genetic toxicity. Therefore, the predictions are superseded by the data.
  - 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.
- Methyl propionate (CAS # 554-12-1) was used as a read-across analog for the target material, methyl butyrate (CAS # 623-42-7), 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 propionate ester, while the read-across analog is a butanoate 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 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 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, methyl butyrate (CAS # 623-42-7), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - o The target material and the read-across analog are ethyl esters.
  - o The key difference between the target material and the read-across analog is that the target ester is a buterate ester of methanol, while the read-across analog is the acetate ester of propenol. 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 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 read-across analog 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.
  - 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 acetate (CAS # 109-60-4) was used as a read-across analog for the target material, methyl butyrate (CAS # 623-42-7), for the local respiratory toxicity 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 propionate 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 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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