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RIFM fragrance ingredient safety assessment, methyl propionate, CAS Registry Number 554-12-1

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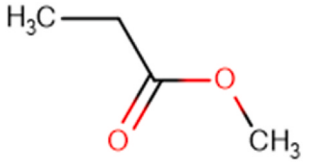
Name: Methyl propionate
CAS Registry Number: 554-12-1



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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 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 propionate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog ethyl acetate (CAS # 141-78-6) show that methyl propionate 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 show that there are no safety concerns for methyl propionate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl propionate is not expected to be photoirritating/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog ethyl acetate (CAS # 141-78-6). The environmental endpoints were evaluated; methyl propionate 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.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Methyl propionate; ECHA, 2018a; ECHA REACH Dossier: Ethyl acetate; ECHA, 2011)
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 = 126.12 mg/m^3.	(ECHA REACH Dossier: Ethyl acetate; ECHA, 2011)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical measured value: 77% (OECD 301F)	(ECHA REACH Dossier: Methyl propionate; ECHA, 2018a)
Bioaccumulation:	
Screening-level: 3.16 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 1164 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: 1164 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.164 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: not applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Methyl propionate
2. **CAS Registry Number:** 554-12-1
3. **Synonyms:** Methyl propanoate; Propanoic acid, methyl ester; Methyl propionate
4. **Molecular Formula:** $C_4H_8O_2$
5. **Molecular Weight:** 88.1 g/mol
6. **RIFM Number:** 984
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 79 °C (Fragrance Materials Association [FMA]), 77.91 °C (EPI Suite)
2. **Flash Point:** 6 °C (Globally Harmonized System), 43 °F; closed cup (FMA)
3. **Log K_{OW}:** 0.86 (EPI Suite)
4. **Melting Point**: 82.08 °C (EPI Suite)
5. **Water Solubility:** 24110 mg/L (EPI Suite)
6. **Specific Gravity: 0.915 (FMA)**
7. **Vapor Pressure:** 68.8 mm Hg at 20 °C (EPI Suite v4.0), 87.9 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 with very diffusive ethereal, rum-like odor, sweet and fruity tastes in concentrations higher than 20 ppm (Arctander, 1969)

3. Volume of use (Worldwide band)

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

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

1. **95**th **Percentile Concentration in Air Freshener Aerosol:** 0.12% (RIFM, 2021)

(No reported use in Fine Fragrance).

2. **Inhalation Exposure*:** 0.000041 mg/kg/day or 0.0030 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.00021 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

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

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

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:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Ethyl acetate (CAS # 141-78-6)
   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

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

Apple fresh (*Malus* species).
Coffee.
Durian (*Durio zibethinus*).
Honey.
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*).
Mussel.
Pineapple (*Aranas comosus*).
Plum brandy.

*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 (ECHA, 2018a); accessed on 01/25/22.

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 propionate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of methyl propionate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with methyl propionate in sterile ultra-pure water at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2018a). Under the conditions of the study, methyl propionate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of methyl propionate; however, read-across can be made to ethyl acetate (CAS # 141-78-6; see Section VI).

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. 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, 2011). Under the conditions of the study, ethyl acetate was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to methyl propionate.

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

Additional References: None.

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

22.

11.1.2. Repeated dose toxicity

The MOE for methyl propionate 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 propionate 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 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 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. 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, 2018a).

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 propionate was calculated by dividing the propyl propionate NOAEL (mg/kg/day) by the total systemic exposure to methyl propionate in mg/kg/day to be, 205.33/0.00021 or 977762.

In addition, the total systemic to methyl propionate (0.21 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 propionate 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 propionate. 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 propionate 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 propionate, 616/0.00021, or 2933333.**

In addition, the total systemic exposure to methyl propionate (0.21 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, methyl propionate does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, methyl propionate is not considered a skin sensitizer. The data are summarized in Table 1. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Methyl propionate was predicted not to be sensitizing in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens (ECHA, 2018a). In a human maximization test, no skin sensitization reactions were observed with 1380 μg/cm^2 methyl propionate (RIFM, 1977).

Based on weight of evidence (WoE) from structural analysis and *in vitro* and human studies, methyl propionate 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 propionate 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 propionate 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 propionate 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.

Table 1
Summary of existing data on methyl propionate.

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 Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
No evidence of sensitization[f]	NA	1380	NA	NA	NA	NA	NA
	***In vitro* Data[e]**				***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

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

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

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

11.1.6. Local respiratory toxicity

There are no inhalation data available on methyl propionate; however, in a 13-week inhalation exposure study for the analog ethyl acetate (CAS # 141-78-6; see Section VI), a NOAEC of 126.15 mg/m^3 was calculated for local respiratory effects (ECHA, 2011).

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 a 13-week study, 10 Crl:CD BR (Sprague Dawley) rats/sex/group were treated with 0, 1261.15, 2702.45, or 5404.91 mg/m^3 of ethyl acetate via whole-body inhalation exposures for 6 h/day, 5 days/week (ECHA, 2011). Standard observations included mortality, clinical signs, body weight, feed consumption, ophthalmological evaluations, hematology, clinical chemistry, urinalysis, sperm analyses, gross necropsy on all organs (including lung, trachea, larynx, pharynx, and nose), organ weights, and histopathology. Test substance-related local respiratory effects were limited to the degeneration of olfactory mucosa observed at all exposure concentrations and increased in incidence and severity with exposure. These effects were of minimal severity in 8 out 20 animals in the low-dose group. All animals in the mid- and high-dose groups showed minimal to moderate and minimal to severe olfactory mucosa degeneration, respectively. Based on the effects observed in the respiratory tract, the LOAEC for local respiratory effects was determined to be 1261.15 mg/m^3. By using a safety factor of 10, the NOAEC is estimated at 126.12 mg/m^3.

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

- (126.12 mg/m^3) × (1 m^3/1000 L) = 0.126 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
- (0.126 mg/L) × (61.2 L/d) = 7.7 mg/day
- (7.7 mg/day)/(0.0016 kg lung weight of rat**) = 4812.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0030 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 0.0046 mg/kg lung weight/day, resulting in a MOE of 1046196 (i.e., [4812.5 mg/kg lung weight of rat/day]/[0.0046 mg/kg lung weight of human/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 0.0030 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: None.

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

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl propionate 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 propionate 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) identified methyl propionate as not 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2019), methyl propionate does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.3. Ecotoxicity. No data available.

11.2.1.4. Other available data. Methyl propionate has been registered under REACH, and the following information is available (ECHA, 2018a):

The ready biodegradability of the test material was evaluated according to the OECD 301F method. Biodegradation of 77% was observed after 28 days.

An algae growth inhibition test was conducted according to the DIN 38 412, Part 9 method. Under the conditions of the study, the 72-h EC50 (growth rate) of the test material was >500 mg/L, and the 72-h EC10 (growth rate) was >500 mg/L. The 72-h EC50 (biomass) was >500 mg/L, and the 72-h EC10 (biomass) was 240 mg/L.

11.2.1.5. Risk assessment refinement. Since methyl propionate has 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	0.86	0.86
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. Additional assessment is not necessary.

The RIFM PNEC is 1.164 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
  - **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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1164			1000000	1.164	

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.2022.113345.

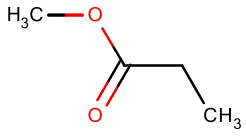
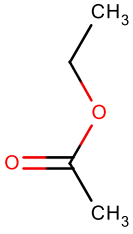
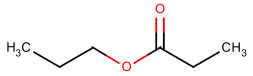
Appendix

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
Principal Name	Methyl propionate	Ethyl acetate	Propyl propionate
CAS No.	554-12-1	141-78-6	106-36-5
Structure			
Similarity (Tanimoto Score)		0.62	0.72
Endpoint		Genotoxicity (Clastogenicity) Local respiratory toxicity	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_4H_8O_2$	$C_4H_8O_2$	$C_6H_{12}O_2$
Molecular Weight (g/mol)	88.11	88.11	116.16
Melting Point (°C, EPI Suite)	−87.50	−83.60	−75.90
Boiling Point (°C, EPI Suite)	79.80	77.10	122.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	11199.05	12425.61	1853.18
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	62400.00	80000.00	5300.00
Log K_{OW}	0.84	0.73	1.85
J_{max} (μg/cm^2/h, SAM)	1024.60	1095.21	210.65
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	17.63	13.58	40.63
Genotoxicity			

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Shiff base formation after aldehyde release| AN2 ≫ Shiff 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)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized		Not categorized
Reproductive 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 (moderate reliability)		Toxicant (low reliability)
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 methyl propionate (CAS # 554-12-1). 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) and propyl propionate (CAS # 106-36-5) were identified as read-across materials 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 propionate (CAS # 554-12-1), for the genotoxicity (clastogenicity) and local respiratory toxicity endpoints.
  - o The target material and the read-across analog belong to the class of aliphatic esters.
  - o The key difference between the target and the read-across analog is that the target material is a propionate ester. whereas the read-across analog is an 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.
  - o According to the OECD QSAR Toolbox v4.2, the 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 AN2-type Schiff base formation (DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)). This alert is due to the presence of an acetate ester in the target material. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is 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 propionate (CAS # 106-36-5) was used as a read-across analog for the target material, methyl propionate (CAS # 554-12-1), for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog belong to the class of aliphatic esters.
  - o The key difference between the target and the read-across analog is that the target material is methyl ester, whereas the read-across analog is a propyl 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.
  - o According to the OECD QSAR Toolbox v4.2, the structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog are alerted for being toxicants for developmental toxicity by the CAESAR model. The data described in the developmental toxicity section confirm 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.

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