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Short Review

RIFM fragrance ingredient safety assessment, methyl valerate, CAS Registry Number 624-24-8

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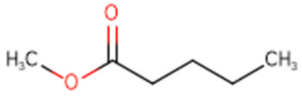

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Name: Methyl valerate

CAS Registry Number: 624-24-8

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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
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 valerate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl valerate is not genotoxic. Data on read-across analog butyl propionate (CAS # 590-01-2) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog propyl propionate (CAS # 106-36-5) provide a calculated MOE >100 for the reproductive toxicity endpoint. Data from read-across analog methyl propionate (CAS # 554-12-1) show that there are no safety concerns for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; methyl valerate is not expected to be photoirritating/photoallergenic. Data on read-across analog butyl acetate (CAS # 123-86-4) provide a calculated MOE >100 for the local respiratory toxicity endpoint. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, methyl valerate is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, methyl valerate was not able to be risk screened as there were no reported volumes of use (VoU) for either North America or Europe in the 2019 IFRA Survey.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 2016b; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 2071 mg/kg/day.	(Banton et al., 2000)
Reproductive Toxicity: NOAEL = 616 mg/kg/day.	(ECHA REACH Dossier: Propyl Propionate; ECHA, 2018c)
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 = 2375 mg/m^3.	(ECHA REACH Dossier: N-Butyl acetate; ECHA, 2011; David et al., 2001)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 57% (OECD 301F)	(ECHA REACH Dossier: Methyl Valerate; ECHA, 2018b)
Bioaccumulation:	
Screening-level: 9.124 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Not applicable	
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:
- Not applicable; No 2019 VoU reported

1. Identification

1. **Chemical Name:** Methyl valerate
2. **CAS Registry Number:** 624-24-8
3. **Synonyms:** Methyl pentanoate; Methyl valerianate; Pentanoic acid, methyl ester; Methyl valerate
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16 g/mol
6. **RIFM Number:** 1032
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 128 °C (Fragrance Materials Association [FMA]), 125.79 °C (EPI Suite v4.11)
2. **Flash Point:** 72 °F; closed cup (FMA), 22 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.85 (EPI Suite v4.11)
4. **Melting Point**: -56.83 °C (EPI Suite v4.11)
5. **Water Solubility:** 2196 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.875 (FMA)
7. **Vapor Pressure:** 8.33 mm Hg at 20 °C (EPI Suite v4.0), 11.2 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficients (N/A, 68, and 77 L mol^{-1} • cm^{-1} for neutral,

acidic, and basic conditions, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless mobile liquid, pungent ethereal green, fruity apple-like odor (Arctander, 1969)

3. Volume of use (Worldwide band)

1. No VoU reported in 2019 (IFRA, 2019)

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

1. **95**th **Percentile Concentration in Toothpaste:** 0.0015% (RIFM, 2020)
   (No reported use in Fine Fragrance)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.000092 mg/kg/day (RIFM, 2020)

*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:** None
b. **Repeated Dose Toxicity:** Butyl propionate (CAS # 590-01-2)
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:** Butyl acetate (CAS # 123-86-4)
g. **Environmental Toxicity:** None

3. **Read-across Justification**: See Appendix below

7. Metabolism

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

8. Natural occurrence

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

Acerola (*Malpighia*)	Kiwifruit (*Actinidia chinesis*, syn. *A. deliciosa*)
Asian pear (*Pyrus serotina*, *Pyrus pyrifolia*)	Mountain papaya (*C. candamarcensis*, *C. pubescens*)
Black currants (*Ribes nigrum* L.)	Passion fruit (*Passiflora* species)
Capsicum species	Pineapple (*Ananas comosus*) Coffee
Cherimoya (*Annona cherimolia* Mill.)	

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

9. REACH Dossier

Available; accessed on 01/27/22 (ECHA, 2018b).

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 valerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Methyl valerate was assessed in the BlueScreen assay and found negative for cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of methyl valerate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with methyl valerate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, methyl valerate was not mutagenic in the Ames test.

The clastogenic activity of methyl valerate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with methyl valerate in DMSO at concentrations up to 1160 μg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h. Methyl valerate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, methyl valerate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, methyl valerate does not present a concern for genotoxic potential.

Additional References: None
Literature Search and Risk Assessment Completed On: 01/21/22

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

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	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

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.
[1]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).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 87 (ECETOC, 2003).
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.
[7]Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl valerate. Read-across material butyl propionate (CAS # 590-01-2; see Section VI) has sufficient repeated dose toxicity data. In a GLP-compliant subchronic study, 15 Sprague Dawley rats/sex/dose were administered butyl propionate by inhalation at targeted concentrations of 0, 250, 750, and 1500 ppm (equivalent to 345, 1036, and 2071 mg/kg/day) for 13 weeks. In addition, 5 animals/sex/dose were maintained as recovery groups for 8 weeks after the end of the treatment period. Although several local microscopic effects were observed in the nasal cavity of animals in the mid- and high-dose groups, no treatment-related mortality or systemic toxicity was reported at these doses. In the high-dose group males, body weight, bodyweight gains, and feed consumption were significantly lower than the control group, but these changes were reversed at the end of the recovery period. Hence, these alterations were not considered to be treatment-related adverse effects. The NOAEL for the repeated dose toxicity endpoint was considered to be 2071 mg/kg/day (1500 ppm) based on the absence of systemic toxicity at the highest tested dose (Banton et al., 2000).

Therefore, the MOE can be calculated by dividing the butyl propionate NOAEL by the total systemic exposure for methyl valerate, 2071/0.000092, or 22510870.

In addition, the total systemic to methyl valerate (0.092 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.

Additional References: None

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

11.1.3. Reproductive toxicity

The MOE for methyl valerate 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 valerate. Read-across material propyl propionate (CAS # 106-36-5; see Section VI) has sufficient reproductive toxicity data that can

be used to support the reproductive toxicity endpoint. In an OECD 422/GLP study, groups of 12 Crl:CD(SD) rats/sex were administered test material *n*-propyl propionate via whole-body exposure at target concentrations of 0, 50, 250, and 500 ppm (equivalent to 0, 62, 308, and 616 mg/kg/day, respectively, as per standard minute volume and bodyweight parameters for Sprague Dawley rats) for 6 h per day, 7 days per week. Females were exposed for 2 weeks prior to breeding, through breeding (approximately 2 weeks), and continued through gestation day 20; the females were then subjected to gross necropsy on postpartum day 5. Males were exposed to the test material 2 weeks prior to breeding and continued through breeding (approximately 2 weeks) before being subjected to gross necropsy (day 38). In addition to systemic toxicity parameters, reproductive toxicity parameters and neurological function were also assessed. There were no treatment-related adverse effects on reproductive performance or survival and growth of pups. The NOAEL for fertility effects and the development of pups was considered to be 500 ppm or 616 mg/kg/day, the highest dose tested (ECHA, 2018c). **Therefore, the methyl valerate 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 valerate, 616/0.000092 or 6695652.**

In addition, the total systemic exposure to methyl valerate (0.092 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None

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

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Limited skin sensitization data are available for methyl valerate. Therefore, methyl propionate (CAS # 554-12-1; see Section VI) was used for the risk assessment of methyl valerate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, methyl valerate 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 valerate and read-across material methyl propionate at 1380 μg/cm^2 (RIFM, 1978; RIFM, 1977).

Based on the weight of evidence (WoE) from structural analysis and *in vitro* and human studies on the read-across material as well as the target material, methyl valerate 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 valerate 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 valerate in experimental models. UV/Vis absorption spectra indicate minor 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 valerate 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 minor absorbance in the range of 290–700 nm. The molar absorption coefficients (N/A, 68, and 77 L mol^{-1} • cm^{-1} for neutral, acidic, and basic conditions, respectively) are 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: 01/14/22

11.1.6. Local respiratory toxicity

There are no inhalation data on methyl valerate; however, in a subchronic, 13-week inhalation study for the read-across analog butyl acetate (CAS # 123-86-4; see Section VI), a NOAEC of 2375 mg/m^3 was reported (ECHA, 2011; David et al., 2001).

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

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

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

The 95th percentile calculated exposure to isobutyl acetate was reported to be < 0.0001 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 0.00015 mg/kg lung weight/day resulting in an MOE of 605626667 (i.e., [90844 mg/kg lung weight/day]/[0.00015 mg/kg lung weight/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 <0.0001 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 valerate 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, methyl valerate was not assessed as no VoU was reported.

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

11.2.1.1. Risk assessment. Not applicable.

11.2.1.2. Key studies. ***Biodegradation***:

No data available.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. Methyl valerate has been registered for REACH with the following additional data available (ECHA, 2018b):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to OECD 301 F Guideline. Biodegradation of 57% was observed after 28 days.

The *Daphnia* acute immobilization test was conducted according to OECD 202 guidelines under semi-static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be $>$ 61.8 mg/L.

The algae growth inhibition test was conducted according to the OECD 202 guidelines under static conditions. The 72-h EC50 value based on growth rate was reported to be $>$ 100 mg/L.

11.2.2. Risk assessment refinement

Not applicable.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/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.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

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.2023.114398.

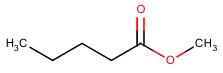
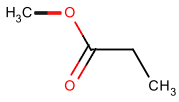
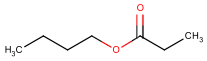
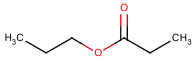
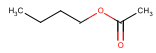
Appendix

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 Chemicals 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 valerate	Methyl propionate	Butyl propionate	Propyl propionate	Butyl acetate
CAS No.	624-24-8	554-12-1	590-01-2	106-36-5	123-86-4
Structure					
Similarity (Tanimoto Score)		0.64	0.55	0.51	0.53
Endpoint		• Skin sensitization	• Repeated dose toxicity	• Reproductive toxicity	• Local respiratory toxicity
Molecular Formula	$C_6H_{12}O_2$	$C_4H_8O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$	$C_6H_{12}O_2$
Molecular Weight (g/mol)	116.16	88.11	130.19	116.16	116.16
Melting Point (°C, EPI Suite)	−56.83	−87.50	−89.00	−75.90	−78.00
Boiling Point (°C, EPI Suite)	127.40	79.80	146.80	122.50	126.10
Vapor Pressure (Pa @ 25°C, EPI Suite)	2546.45	11199.05	589.28	1853.18	1533.20
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5060.00	62400.00	1500.00	5300.00	8400.00
Log K_{OW}	1.96	0.84	2.34	1.85	1.78
J_{max} (μg/cm^2/h, SAM)	235.51	1024.60	85.94	210.65	301.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	32.22	17.63	51.17	40.63	28.47
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized		Not categorized		
Reproductive Toxicity					

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure			Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Toxicant (low reliability)	
Skin Sensitization					
Protein Binding (OASIS v1.1	No alert found	No alert found			
Protein Binding (OECD)	No alert found	No alert found			
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Slightly reactive (GSH)| Slightly reactive (GSH) ≫ Reaction at sp3 carbon atom (SN2)			
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found			
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were identified			
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on methyl valerate (CAS # 624-24-8). 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, methyl propionate (CAS # 554-12-1), butyl propionate (CAS # 590-01-2), propyl propionate (CAS # 106-36-5), and butyl acetate (CAS # 123-86-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Methyl propionate (CAS # 554-12-1) was used as a read-across analog for the target material methyl valerate (CAS # 624-24-8) 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 material is a valerate ester of methanol, whereas the read-across analog is a propionate ester of methanol. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog 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.
- Butyl propionate (CAS # 590-01-2) was used as a read-across analog for the target material methyl valerate (CAS # 624-24-8) for the repeated dose 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 material is a valerate ester of methanol, whereas the read-across analog is a propionate ester of butanol. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no toxicological alerts for the read-across analog or the target material. Data are consistent with *in silico* alerts.
  - 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 valerate (CAS # 624-24-8) for the reproductive 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 material is a valerate ester of methanol, whereas the read-across analog is a propionate ester of propanol. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog is predicted to be a toxicant by the CAESAR model. The data described in the reproductive 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.
- Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material methyl valerate (CAS # 624-24-8) 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 material is a valerate ester of methanol, whereas the read-across analog is an acetate ester of butanol. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog do not have any toxicity-related alerts. The data are consistent with the prediction.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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