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Short review

RIFM fragrance ingredient safety assessment, 2-methylpropyl pentanoate, CAS Registry Number 10588-10-0

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

ABSTRACT

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

2-Methylpropyl pentanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl 2-methylbutyrate (CAS # 7452-79-1) show that 2-methylpropyl pentanoate is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for 2-methylpropyl pentanoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2-methylpropyl pentanoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-methylpropyl pentanoate 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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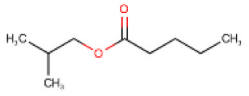

Name: 2-Methylpropyl pentanoate
CAS Registry Number: 10588-10-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017bib_Comiskey_et_al_2015; 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 Observable Effect Level
MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

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(*continued*)

2-Methylpropyl pentanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl 2-methylbutyrate (CAS # 7452-79-1) show that 2-methylpropyl pentanoate is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for 2-methylpropyl pentanoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2-methylpropyl pentanoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-methylpropyl pentanoate 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.	(RIFM, 2000; RIFM, 2014)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1000 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	RIFM (1987)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.29 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 64.39 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 17.45 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 17.45 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.01745 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Methylpropyl pentanoate
2. **CAS Registry Number:** 10588-10-0
3. **Synonyms:** Isobutyl pentanoate; Isobutyl valerate; Pentanoic acid, 2-methylpropyl ester; 2-Methylpropyl pentanoate
4. **Molecular Formula:** $C_9H_{18}O_2$
5. **Molecular Weight:** 158.24
6. **RIFM Number:** 21
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 178.41 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.25 (EPI Suite)
4. **Melting Point:** −32.06 °C (EPI Suite)
5. **Water Solubility:** 117.8 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1.01 mm Hg @ 25 °C (EPI Suite)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless mobile liquid

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Shampoo:** 0.008% (RIFM, 2017)

No reported use in hydroalcoholics

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00014 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017bib_Comiskey_et_al_2015; Safford, 2015, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_Comiskey_et_al_2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017bib_Comiskey_et_al_2015; Safford, 2015, 2017bib_Safford_et_al_2015bib_Safford_et_al_2017bib_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 v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
   b. **Repeated Dose Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
   c. **Reproductive Toxicity:** Ethyl 2-methylbutyrate (CAS # 7452-79-1)
   d. **Skin Sensitization:** Isoamyl acetate (CAS # 123-92-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   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 (discrete chemical) or composition (NCS)

2-Methylpropyl pentanoate is reported to occur in the following foods by the VCF*:
Apple processed (*Malus* species).
Cashew apple (*Anacardium occidentale*).
Cheddar cheese.
Rum.
Strawberry (*Fragaria* species).
Tomato (*Lycopersicon esculentum* Mill.)
Vanilla.
Wine.
*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

No dossier available as of 08/09/19.

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, 2-methylpropyl pentanoate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of 2-methylpropyl pentanoate; however, read-across can be made to ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI).

The mutagenic activity of ethyl 2-methylbutyrate 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with ethyl 2-methylbutyrate 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, 2000). Under the conditions of the study, ethyl 2-methylbutyrate was not mutagenic in the Ames test, and this can be extended to 2-methylpropyl pentanoate.

The clastogenic activity of ethyl 2-methylbutyrate 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 ethyl 2-methylbutyrate in DMSO at concentrations up to 1300 μg/mL in the presence and absence of S9 for 4 h and in the absence of S9 for 24 h. Ethyl 2-methylbutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic or maximum recommended concentrations in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, ethyl 2-methylbutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-methylpropyl pentanoate.

Based on the available data, ethyl 2-methylbutyrate does not present a concern for genotoxic potential, and this can be extended to 2-methylpropyl pentanoate.

Additional References: RIFM, 1999.

Literature Search and Risk Assessment Completed On: 09/03/19.

11.1.2. Repeated dose toxicity

The MOE for 2-methylpropyl pentanoate 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 2-methylpropyl pentanoate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient repeated dose toxicity data to support the risk assessment on 2-methylpropyl pentanoate. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days and females were treated for 40–51 days (maximum of 51 days; males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. No treatment-related adverse effects were reported for mortality, clinical signs, neurobehavior, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, pathological findings during necropsy, or histopathological examination. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the 2-methylpropyl pentanoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to 2-methylpropyl pentanoate, 333/0.00014, or 2378571.

In addition, the total systemic exposure to 2-methylpropyl pentanoate (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 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: 09/17/19.

11.1.3. Reproductive toxicity

The MOE for 2-methylpropyl pentanoate 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 2-methylpropyl pentanoate. Read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI) has sufficient reproductive toxicity data to support the risk assessment on 2-methylpropyl pentanoate. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days and females were treated for 40–51 days (maximum of 51 days; males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. There were no treatment-related effects on mating performance, fertility, conception, gestation length, parturition, survival, litter size, or litter weight. In the F1 generation, no treatment-related effects were reported for mortality, clinical signs, body weight, and bodyweight changes during necropsy. Furthermore, no gross abnormalities were reported in pups. Therefore, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the 2-methylpropyl pentanoate MOE for the reproductive toxicity endpoint can be calculated by dividing ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to 2-methylpropyl pentanoate, 1000/0.00014, or 7142857.

In addition, the total systemic exposure to 2-methylpropyl pentanoate (0.14 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 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: 10/10/19.

11.1.4. Skin sensitization

Based on the existing data and read-across material isoamyl acetate (CAS # 123-92-2), 2-methylpropyl pentanoate is not considered a skin sensitizer under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 2-methylpropyl pentanoate. Based on the *in silico* data for the target material and study data for read-across material isoamyl acetate (CAS # 123-92-2; see Section VI), 2-methylpropyl pentanoate is not considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.3). In a guinea pig maximization test, read-across material isoamyl acetate in a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne, 1986). Similarly, read-across material isoamyl acetate was found to be negative in a guinea pig open epicutaneous test (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm^2 read-across material isoamyl acetate (RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm^2 of read-across material isoamyl acetate in 75:25 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material isoamyl acetate, 2-methylpropyl pentanoate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: ECHA, 2011 [002 experimental result]; ECHA, 2011 [003 experimental result].

Literature Search and Risk Assessment Completed On: 09/13/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-methylpropyl pentanoate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-methylpropyl pentanoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2-methylpropyl pentanoate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/19.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-methylpropyl pentanoate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-methylpropyl pentanoate. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 14,000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/07/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methylpropyl pentanoate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA 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, 2-methylpropyl pentanoate 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 2-methylpropyl pentanoate 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-methylpropyl pentanoate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

2-methylpropyl pentanoate has been pre-registered for REACH with no additional information available at this time.

11.2.5. 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)**	<u>17.45</u>			1000000	0.01745	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.25	3.25
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No VoU
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.01745 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not Applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 09/18/19.

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**
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/31/20.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111730.

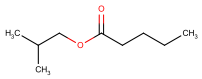
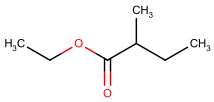
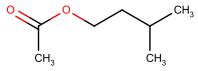
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	2-Methylpropyl pentanoate	Ethyl 2-methylbutyrate	Isoamyl acetate
CAS No.	10588-10-0	7452-79-1	123-92-2
Structure			
Similarity (Tanimoto Score)		0.70	0.57
Read-across Endpoint		• Genotoxicity • Reproductive Toxicity • Repeated Dose Toxicity	• Skin Sensitization
Molecular Formula	$C_9H_{18}O_2$	$C_7H_{14}O_2$	$C_7H_{14}O_2$
Molecular Weight	158.24	130.18	130.18
Melting Point (°C, EPI Suite)	−32.06	−56.05	−78.50
Boiling Point (°C, EPI Suite)	179.00	134.87	142.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	1.35 E+02	1.07 E+03	7.47 + E03
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.25	2.26	2.25
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	117.8	1070.0	2.00 E+03
J_{max} (μg/cm^2/h, SAM)	11.17	297.516	101.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.73 E+01	5.52 E+01	5.95 E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• Structural alert for nongenotoxic carcinogenicity| Substituted n-alkylcarboxylic acids (Nongenotox)	
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	• Urethane (renal toxicity) Alert	
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)	• Non-toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found		• No alert found
Protein Binding (OECD)	• No alert found		• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)		• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-methylpropyl pentanoate (CAS # 10588-10-0). 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 2-methylbutyrate (CAS # 7452-79-1) and isoamyl acetate (CAS # 123-92-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methylbutyrate (CAS # 7452-79-1) was used as a read-across analog for the target material 2-methylpropyl pentanoate (CAS # 10588-10-0) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - The target material and the read-across analog share saturated aliphatic acid and alcohol moieties.
  - The key difference between the target material and the read-across analog is that the target material has isobutanol and pentanoic acid moieties, whereas the read-across analog has ethanol and 2-methylbutyric acid moieties. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

- The read-across analog has a carcinogenicity alert for substituted *n*-alkylcarboxylic acids (nongenotoxic). Substances belonging to this chemical class are potentially reactive as peroxisome proliferators (PPs). PPs have been found to cause liver cancer when chronically administered to rats and mice. However, these chemicals are considered nongenotoxic agents, given generally negative results in genotoxicity assays. The data described in the genotoxicity section shows that there are no concerns for genotoxicity. Therefore, the predictions are superseded by the data.
- The read-across analog has a repeated dose (HESS) urethane (renal toxicity) alert. The read-across does not have any urethane group and, consequently, is out of the training set of this alert, so this alert can be ignored. The data described in the repeated dose toxicity section show that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Isoamyl acetate (CAS # 123-92-2) was used as a read-across analog for the target material 2-methylpropyl pentanoate (CAS # 10588-10-0) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - The target material and the read-across analog share saturated branched alcohol moieties and saturated straight chain acid moieties.
  - The key difference between the target material and the read-across analog is that the target material has isobutanol and pentanoic acid moieties, whereas the read-across analog has isoamyl alcohol and acetic acid moieties. This structural difference is toxicologically insignificant.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog 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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