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Short Review

Rifm fragrance ingredient safety assessment, 2-methylpentyl 2-methylvalerate, CAS Registry Number 90397-38-9

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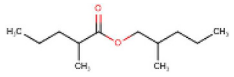
Version: 032718. This version replaces any previous versions.
Name: 2-Methylpentyl 2-methylvalerate
CAS Registry Number: 90397-38-9



Abbreviation/Definition List:

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

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

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits 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 use of this material under current conditions is supported by existing information.
2-Methylpentyl 2-methylvalerate 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-methylpentyl 2-methylvalerate is not expected to be genotoxic. Data from read-across analog isoamyl acetate (CAS # 123-92-2) show that this material is not expected to be a concern for skin sensitization. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 2-methylpentyl 2-methylvalerate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2000; RIFM, 2014)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: No safety concerns under the current, declared levels of use.	RIFM (1987)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.89 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 540 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 0.334 mg/L	(ECOSAR; US EPA, 2012b)
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: 96-h algae EC50: 0.334 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0334 µg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1	

1. Identification

1. **Chemical Name:** 2-Methylpentyl 2-methylvalerate
2. **CAS Registry Number:** 90397-38-9
3. **Synonyms:** Pentanoic acid, 2-methyl-, 2-methylpentyl ester; 2-Methylpentyl 2-methylvalerate
4. **Molecular Formula:** $C_{12}H_{24}O_2$
5. **Molecular Weight:** 200.22
6. **RIFM Number:** 5614
7. **Stereochemistry:** Isomer not specified. Two stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 225.84 °C (US EPA, 2012a)
2. **Flash Point:** 92 °C (GHS)
3. **Log K_{OW}:** 4.65 (US EPA, 2012a)
4. **Melting Point**: 8.81 °C (US EPA, 2012a)
5. **Water Solubility:** 4.696 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.85600 to 0.85900 @ 25.00 °C*
7. **Vapor Pressure:** 0.097 mm Hg @ 25 °C (US EPA, 2012a), 0.0634 mm Hg @ 20 °C (US EPA, 2012a)
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 liquid with a fruity, clean, sweet, pear, oily, jasmin natural odor (Luebke, William tgsc, 1987)*

*The Good Scents Company, accessed 09/14/17.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year@(IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.11% @(RIFM, 2016)
3. **Inhalation Exposure*:** 0.00045 mg/kg/day or 0.032 mg/day@(RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0036 mg/kg/day@(RIFM, 2016)

*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; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

2-Methylpentyl 2-methylvalerate is not reported to occur in foods by the VCF* and is not found in natural complex substances (NCS).

*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.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 03/22/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, 2-methylpentyl 2-methylvalerate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2-Methylpentyl 2-methylvalerate was assessed in the BlueScreen assay and found to be negative for genotoxicity, with and without metabolic activation (RIFM, 2013b). There are no studies assessing the mutagenicity of 2-methylpentyl 2-methylvalerate. The mutagenic activity of read-across material ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section 5) was evaluated in an Ames 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, TA102, TA1535, and TA1537 were treated with ethyl 2-methylbutyrate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of S9 metabolic activation. No increases in the number of revertant colonies were observed under any of the treatment conditions (RIFM, 2000). Under the conditions of the study, ethyl 2-methylbutyrate is not mutagenic, and this can be applied to 2-methylpentyl 2-methylvalerate.

There are no studies assessing the clastogenicity of 2-methylpentyl 2-methylvalerate. The clastogenic potential of ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section 5) was evaluated in an *in vitro* micronucleus assay conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocyte cell cultures were treated with ethyl 2-methylbutyrate in DMSO at concentrations up to 1300 μg/mL in the presence and absence of S9 metabolic activation for 4 or 24 h. No increases in the number of micronuclei in any of the treatment groups were observed (RIFM, 2014). Under the conditions of this study, ethyl 2-methylbutyrate was not considered to be clastogenic in cultured human lymphocytes, and this can be applied to 2-methylpentyl 2-methylvalerate.

Based on the available data, 2-methylpentyl 2-methylvalerate does not present a concern for genotoxic potential.

Additional References: RIFM, 1978; RIFM, 2013a.

Literature Search and Risk Assessment Completed On: 08/17/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-methylpentyl 2-methylvalerate or any read-across materials. The total systemic exposure to 2-methylpentyl 2-methylvalerate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-methylpentyl 2-methylvalerate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-methylpentyl 2-methylvalerate (3.6 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level

of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/08/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-methylpentyl 2-methylvalerate or any read-across materials. The total systemic exposure to 2-methylpentyl 2-methylvalerate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-methylpentyl 2-methylvalerate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 2-methylpentyl 2-methylvalerate (3.6 μg/kg/day) is below the TTC (30 μg/kg bw/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: 09/08/17.

10.1.4. Skin sensitization

Based on the read-across material isoamyl acetate (CAS # 123-92-2), 2-methylpentyl 2-methylvalerate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. There are insufficient data for 2-methylpentyl 2-methylvalerate. Based on the read-across analog isoamyl acetate (CAS # 123-92-2; See Section 5), 2-methylpentyl 2-methylvalerate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, read-across material isoamyl acetate was found to be negative in a guinea pig Open Epicutaneous Test (OET) (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm2 of read-across material isoamyl acetate (RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 20% or 23622 μg/cm2 of read-across material isoamyl acetate in 75:25 ethanol:DEP, no reactions indicative of sensitization were observed in any of the 197 volunteers (RIFM, 1987).

Based on the read-across material isoamyl acetate, 2-methylpentyl 2-methylvalerate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/17.

10.1.5. Phototoxicity/photoallergenicity

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

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

10.1.5.2. 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/17.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on 2-methylpentyl 2-methylvalerate. Based on the Creme RIFM Model, the inhalation exposure is 0.032 mg/day. This exposure is 43.8 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/11/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methylpentyl 2-methylvalerate 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, 2-methylpentyl 2-methylvalerate was identified as a fragrance material with the 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-methylpentyl 2-methylvalerate 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 based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), 2-methylpentyl 2-methylvalerate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 2-Methylpentyl 2-methylvalerate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	<u>1.475</u>			1,000,000	0.001475	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.763	1.195	<u>0.334</u>	10,000	0.0334	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.692	0.501	1.206			Neutral Organic

The RIFM PNEC is 0.0334 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 08/09/17.

11. Literature Search*

- **@RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **@ECHA:** http://echa.europa.eu/
- **@NTP:** https://ntp.niehs.nih.gov/
- @OECD Toolbox
- **@SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **@PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **@TOXNET:** http://toxnet.nlm.nih.gov/
- **@IARC:** http://monographs.iarc.fr
- **@OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **@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.

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

Exposure	Europe	North America
Log K_{ow} used	4.6	4.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.027.

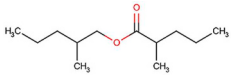
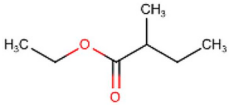
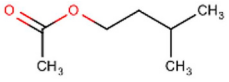
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was 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 substance 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material
Principal Name	2-methylpentyl 2-methylvalerate	Ethyl 2-methylbutyrate	Isoamyl acetate
CAS No.	90397-38-9	7452-79-1	123-92-2
Structure			
Similarity (Tanimoto Score)		0.67	0.73
Read-across Endpoint		• Genotoxicity	• Skin sensitization
Molecular Formula	$C_{12}H_{24}O_2$	$C_7H_{14}O_2$	$C_7H_{14}O_2$
Molecular Weight	200.32	130.19	130.19
Melting Point (°C, EPI Suite)	−8.81	−56.05	−56.05
Boiling Point (°C, EPI Suite)	225.84	134.87	134.87
Vapor Pressure (Pa @ 25 °C, EPI Suite)	12.9	1070	756
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.65	2.26	2.25
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4.696	1070	2000
J_{max} (mg/cm^2/h, SAM)	23.806	297.51	101.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.25E-003	5.45E-004	5.45E-004
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
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		• Not possible to classify
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 v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-methylpentyl 2-methylvalerate (CAS # 90397-38-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, 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 materials 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-methylpentyl 2-methylvalerate (CAS # 90397-38-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share a common branched saturated aliphatic acid portion on the ester.
  - o The key difference between the target material and the read-across analog is that the target has a branched aliphatic alcohol portion while the read-across analog has an aliphatic straight chain on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common branched saturated aliphatic acid portion on the ester. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - o The read-across analog and target material are predicted to be a carcinogen by ISS for genotoxicity. All other alerts are negative. Data superseded predictions in this case.
  - 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 endpoint 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-methylpentyl 2-methylvalerate (CAS # 90397-38-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share a common branched saturated aliphatic alcohol portion on the ester.
  - o The key difference between the target material and the read-across analog is that the target has a branched aliphatic acid portion while the read-across analog has an aliphatic straight chain on the acid portion of the ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common branched saturated aliphatic alcohol portion on the ester. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint 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 endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

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